Hormone Replacement Therapy: A Critical Review

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Joseph Ragaz and Joshua Budlovsky

24.1 Introduction

The aim of this chapter is to review the most recent aspects of hormone replacement therapy (HRT), and to clarify its impact on associated health conditions amidst growing uncertainties. Special emphasis has been placed on its effect on cardiovascular conditions and breast cancer, the two most important outcomes affected by HRT, and on identifying ideal candidates for HRT as well as defining the optimum new HRT regimens.

Until the publication in 2002 of the first Women's Health Initiative (WHI) randomized trial [1], HRT was increasingly used to treat the variety of symptoms attributed to menopause, as well as to prevent most menopause-associated medical conditions. These policies were based largely on observational and case–control studies, providing evidence that HRT, besides providing control of menopausal symptoms, is also associated with cardiovascular, colon cancer, and bone fracture benefits. Most intriguing were data associating HRT with a significant all-cause mortality reduction [2–5], and paradoxically, despite increased breast cancer incidence rates, with improved rates of breast cancer mortality [5].

In 2002, the first WHI controlled randomized trial of HRT using estrogen plus progestin reported increased hazard rates from HRT for coronary heart disease (CHD) and strokes, as well as adverse effects on breast cancer and thromboembolism. While the previously seen HRT benefits for bones and against colon cancer were confirmed, the WHI group concluded that increased hazards outweighed the HRT benefits.

The first goal of this review is to identify the strengths and weaknesses of the published HRT data and especially to put into perspective all WHI HRT analyses. Special emphasis is placed on HRT indications for women who become menopausal as a result of a natural or iatrogenically-induced ovarian suppression, and who suffer with postmenopausal symptoms. These are mostly women aged 50–59 and/or <10 years from menopause.

The second objective of this review is to define the new generation of HRT regimens – agents of the lowest active dose that will palliate vasomotor and other menopausal symptoms effectively. This issue is important as the "classical" estrogen, the Premarin 0.625 tablets and Provera 2.5 mg used in most observational and in the WHI HRT trials, are considered more toxic, and thus likely associated with substantially more hazards.

24.2 The Women's Health Initiative (WHI) Hormone Replacement (HRT) Trials

The Women's Health Initiative (WHI) is perhaps the most extensive population research investigation undertaken in recent decades [6].

J. Ragaz (✉)
McGill University, Montreal, QC, Canada
e-mail: joseph.ragaz@mcgill.ca

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The WHI program included four randomized controlled clinical trials to evaluate the health benefits and risks among 68,132 postmenopausal women in the age range 50–79 at randomization. Enrollment into the WHI began in 1993 and concluded in 1998.

1. *TRIAL ONE* involved HRT testing in healthy women and with uterus intact the impact of conjugated equine estrogens (CEE, Premarin, 0.625 mg/day) plus progestin (medroxyprogesterone acetate 2.5 mg/day vs. placebo). The primary objective was to determine the HRT impact on CHD prevention, with breast cancer as an anticipated adverse effect. Additional HRT-related conditions constituted secondary objectives. Overall, 16,608 women were randomized to this trial.
2. *TRIAL TWO* was designed for women without uterus and randomized to conjugated equine estrogens (CEE, Premarin) *alone* vs. placebo, with the same objectives as TRIAL ONE. Altogether, 10,739 women were recruited to this trial.
3. *TRIAL THREE* tested low fat against conventional diet for breast and colorectal cancer prevention, with 48,835 women randomized.
4. *TRIAL FOUR* tested the impact of calcium and vitamin D supplementation. Hip fractures were the designated primary outcome, with other fractures and colorectal cancer as secondary outcomes. In total, 36,282 women were randomized to this trial.

The WHI program also includes an observational study (ObSt) that comprised 93,676 postmenopausal women recruited from the same population base as the randomized trials. The ObSt is intended to provide additional knowledge about risk factors for a range of diseases, including cancer, cardiovascular disease, and fractures. It has an emphasis on biological markers of disease risk and on risk-factor changes as risk modifiers.

Table 24.1 provides information on enrollment by age-group in the various WHI components.

The estrogen plus progestin trial ended early on July 8, 2002, when evidence had accumulated that the health risks exceeded the benefits for this study population, according to predefined WHI planning committee criteria. The second HRT trial in the estrogen-alone component was also halted early, on February 29, 2004, because of increased risks of stroke. The Dietary and Ca-D-Vitamin trials ended as planned on March 31, 2005. The follow-up of participating women is planned through 2010, which will give an average follow-up duration of 13 years in the four randomized trials and 12 years in the observational study.

Table 24.1 Age at trial start, and frequency of the vasomotor (postmenopausal) symptoms in women participating in the first Women's Health Initiative (WHI) Hormone Replacement Therapy (HRT) trial with estrogen plus progestin vs. placebo

Age categories	Estrogen ± progestin (*N*: 8,506)	Placebo (*N*: 8,102)
Mean age at trial start	63.2	63.3
Age 50–59	33.3%	33.1%
Age 60–69	45.3%	45.1%
Age 70–79	21.8%	21.7%
Years since menopause		
<10	32.7%	33.5%
10–19	21.7%	22.3%
>20	21.7%	22.3%
Vasomotor symptoms		
None	60.7%	60.8%
Mild	25.8%	26.1%
Moderate/severe	12.6%	12.0%

Trial participants, *N*: 16,608

According to Rossouw et al. [104]

With both WHI HRT trials ending prematurely, women already enrolled in the trials were asked to stop the allocated therapy. Soon afterwards, women worldwide were told to discontinue or to never start the HRT.

24.3 The WHI HRT Trials: Background

The WHI HRT trials were planned because of rising concerns that past HRT observational and case–controlled studies were based on small patient sample size or on study results with preselected participants who were in a better state of health than women who were not eligible for HRT. Thus, the objectives of the WHI studies were to determine, from large randomized trials, the individual HRT-related outcomes, in order to influence the clinical practice, whereby HRT was increasingly prescribed not only for the palliation of postmenopausal symptoms, but also for reduction of heart disease morbidity, cardiac mortality, and in general, to slow down the chronic degenerative conditions related to aging.

24.3.1 The First WHI Trial

The July 17, 02 JAMA article reported the results of the first of the two trials – the Estrogen plus Progestin (E2 + Prog) vs. placebo. Between 1993–1998, the WHI enrolled 16,608 women aged 50–79 with an intact uterus into the first HRT study, and randomized them into:

1. *ARM ONE,* 8,506 women receiving Premarin 0.625 mg/day (estrogen) + Provera 2.5 mg/day (progestin) vs.
2. *ARM TWO* with placebo pills.

The primary outcome measures were events related to *incident* cases of:

1. *Coronary heart disease – CHD* (EVENT 1)
2. *Invasive breast cancer* (EVENT 2)

Secondary outcomes included EVENT 3: Stroke; EVENT 4: thromboembolism defined as deep vein thrombosis or pulmonary embolism; EVENT 5: colon cancer; EVENT 6: endometrial cancer; and EVENT 7: skeletal fractures (hip, vertebral, or other osteoporotic).

Information on death was provided for cardiovascular causes, breast cancer, other cancers, and other known causes.

A "Global index" summarized the balance of the seven incidence events, as well as the "death due to other causes" and was defined as the definitive marker of benefit or hazard.

Each event as well as the Global index were expressed as absolute numbers/10,000 person-years, and as Hazard rates (with increased hazards defined as HR = 1.0; and benefits as HR = 1.0), with appropriate 95% confidence intervals (CI). Over 25% of cases were past or current HRT users, with over 30% of those having had HRT use of >5 years duration prior to randomization. Median age was 63.1 years, with only one third (33%) of the participants being less than 60 years of age.

Results

The first WHI HRT trial with Premarin + Provera versus Placebo was terminated on the advice of the independent Data and Safety Monitoring Board after a mean 5.2 years of follow-up because of an increased risk of breast cancer and an overall assessment of harms exceeding benefits for chronic disease prevention.

A summary of the most *complete trial results* published (Table 24.2–24.3) ending July 7, 2002 (mean follow-up 5.6 years), confirmed the interim findings. Specifically reported were a 26% increase in breast

Table 24.2 Clinical outcome by the randomization assignment. The first WHI HRT trial. Annaul event %, and hazards (HR) with appropriate 95% confidence limits (C.I.)

	HRT (*N:* 8506) (%)	Placebo (*N:* 8102) (%)	HR	95% confidence intervals
CHD – any event	0.37	0.30	1.29	0.85–1.97
CHD deaths	0.07	0.06	1.18	0.47–2.98
Nonfatal MI	0.30	0.23	1.32	0.82–2.13
Stroke – any	0.29	0.21	1.41	0.86–2.31
Fatal	0.04	0.03	1.20	0.32–4.49
Nonfatal	0.21	0.14	1.50	0.83–2.70
Thromboembolism	0.34	0.16	2.11	**1.26–3.55**
Pulmonary embolism	0.16	0.08	2.13	0.99–4.56
Cancer				
Invasive breast cancer	0.38	0.30	1.26	0.83–1.92
Endometrial cancer	0.05	0.06	0.83	0. 29–2.32
Colorectal cancer	0.10	0.16	0.63	0.32–1.24
Fractures	1.47	1.91	0.76	**0.63–0.92**
Total deaths	0.52	0.53	0.98	0.95–1.39

95% Confidence intervals in bold and underline indicate statistical significance, "*P*"<0.05
According to Rossouw et al. [104]

Table 24.3 WHI HRT first and second trials: impact on HRT on total mortality, coronary heart disease, and strokes

Age	HRT %	Placebo %	RR	95% CI
Total mortality				
50–59 (*N:* 8,832)	0.24	0.31	**0.70**	**0.51–0.96**
60–69 (*N:* 12,362)	0.76	0.74	1.05	0.87–1.26
70–79 (*N:* 6,153)	1.52	1.36	1.14	0.94–1.37
CHD – incidence				
50–59 (*N:* 8,832)	**0.26**	**0.28**	**0.93**	**0.65–1.33**
60–69 (*N:* 12,362)	0.56	0.58	0.98	0.79–1.21
70–79 (*N:* 6,153)	1.05	0.86	1.26	**1.00–1.59**
Strokes – incidence				
Years since menopause				
50–59 (*N:* 8,832)	**0.20**	**0.17**	**1.13**	**0.73–1.76**
60–69 (*N:* 12,362)	0.50	0.33	1.50	1.17–1.92
70–79 (*N:* 6,153)	0.82	0.66	1.21	0.93–1.58

Annual event %, analysis according to age (50–59 vs. 60–69 vs. 70–79)Based on WHI first HRT trial, Rossouw et al. [104], p. 1471, Table 4

cancer incidence, 29% increase of CHD, 41% increase in risk of stroke, and a doubling of the rates of thromboembolism. None of these hazards, with the exception of thromboembolism, were increased with statistical significance. There was also a significant 25% *reduction* of skeletal fracture rates, a 37% reduction of colorectal cancer, a 17% reduction of endometrial cancer, and a 2% reduction of deaths from any cause.

However, despite these benefits, the Global index was increased (HR = 1.15, 95%CI: 0.95–1.39).

In absolute terms, the results of the first WHI HRT trial confirmed in the estrogen plus progestin arm *excess* of CHD (excess of 0.07%); breast cancer (excess of 0.08%), stroke (excess of 0.08%), pulmonary embolism (excess of 0.08%); but *reduced events* of skeletal fractures (reduction by 0.44%); colorectal cancer (reduction by 0.06%); endometrial cancer (reduction by 0.01%); and of *total deaths* (reduced by 0.01%/year). Blood lipid levels showed favorable profile, with reductions in low-density lipoprotein cholesterol (−12.7%) and increases in high-density lipoprotein cholesterol (+7.3%) and triglycerides (+6.9%).

Thus, authors concluded that for an average 5.2 years follow time:

1. Overall health risks of combined estrogen plus progestin exceeded benefits among healthy postmenopausal U.S. women.
2. All-cause mortality was not different between the two groups.
3. The risk-benefit profile is not consistent with the requirements for an intervention for primary prevention of chronic diseases such as CHD.

The Data and Safety Monitoring Board *(DSMB)* reviewing the interim May 31, 2002 analyses found adverse effects in cardiovascular disease within the monitoring boundaries (i.e., not requiring the stopping of the trial). However, the increased risks for invasive *breast cancer* necessitated a premature termination of the trial. All investigators, trial participants, and public at large were informed about these results and their interpretation, and trial participants randomized to the HRT were asked to stop their allocated hormones.

24.3.2 The Second WHI HRT Trial

Despite the early termination of the first WHI estrogen plus progestin trial in 2002, the second WHI estrogen-alone trial was continued. In this trial, women after hysterectomy were randomized into *ARM ONE*, of HRT with estrogen alone (conjugated estrogen, [CEE, Premarin 0.625 mg/day continuously]) without the progestin (5,310 women), vs. *ARM TWO* of placebo (5,429 women).

Of all participants, only less than one third (30.8%) were <60 years of age; and over 47% were past or current HRT users before enrollment. Approximately, 40% of all participants had oophorectomy with hysterectomy (39.5 vs. 42% in arm of CEE vs. Placebo, respectively). Forty eight percent of women in the trial had been treated for hypertension and 15% had therapy for elevated cholesterol. Overall, 86% of all patients had no first-degree relative with breast cancer, and 74.5% had no benign breast disease in the past.

Estimated hazard ratios (with adjusted 95% confidence intervals) for CEE vs. placebo for the major clinical outcomes available through February 29, 2004 are shown in Table 24.5. Overall, there was a 9% reduction of CHD, a 33% (nonsignificant) increase in thromboembolism, a 39% increase in strokes, and an 8% increase in colorectal cancer; reduced were rates of breast cancer, by 23%; overall skeletal fractures by a significant 30%, and significant 39% reduction of hip fractures. Total death rate was increased nonsignificantly, by 4%; and so was the global index, by 1%.

For the outcomes significantly affected by CEE, there was an absolute excess risk of 12 additional strokes per 10,000 person-years and an absolute risk reduction of six fewer hip fractures per 10,000 person-years. The estimated risk for all monitored events in the global index was a nonsignificant excess of two events per 10,000 person-years.

On account of these results, the second WHI trial on CEE alone vs. placebo concluded that the use of CEE, in women after hysterectomy, after follow-up of 6.8 years:

a. Increases the risk of strokes.
b. Decreases the risk of hip fracture.
c. Does not affect the CHD incidence.
d. With a possible reduction in breast cancer risk requiring further investigation.
e. The sum of combined events was equivalent in the CEE and placebo groups, indicating no overall benefit and no hazards.
f. Thus, CEE should not be recommended for chronic disease prevention in postmenopausal women.

As a result of these data, after reviewing data through November 30, 2003, the National Institutes of Health (NIH) decided in February 2004 to end the intervention phase of the second WHI HRT trial early, with results published in the April 14, 2004 issue of the *Journal of American Medical Association* [89].

Consequences of the WHI reports. The recommendations to stop HRT resulted, in subsequent years, in millions of women in the Western world discontinuing HRT, even if they were in the age-group of 50–59, and suffering with vasomotor symptoms. By then, approximately 38% of postmenopausal women in the United States used HRT. In the year 2000 alone, just prior to the WHI HRT trial publication, 46 million prescriptions were written for Premarin (conjugated estrogens), making it the second most frequently prescribed medication in the United States and accounting for more than $1 billion U.S. in sales [90].

By the end of 2002, the use of hormone-replacement therapy had decreased by 38% in the United States, with approximately 20 million fewer prescriptions written in 2003 than in 2002. By the year 2005, the decrease was by 71%, and the drop continues [16].

This move represents one of the most dramatic health policy shifts registered in the recent medical history. HRT benefits from most past case–control and observational studies were in question, and most publications of the WHI trials and editorials universally agreed on more harm than benefits of HRT.

Thus, at the start of the critique, we ask several questions, specifically about the age of participants as over 2/3rd were >age 60; also questioned is the possible adverse impact of HRT using progestins, as estrogen alone had more beneficial breast cancer profile. Lastly, questioned is appropriateness of HRT agents – in the era when high-dose Premarin and Provera both used in WHI HRT trials are agents considered more toxic than the newer regimens based on lower hormone dose or nonoral use.

24.4 Overview of the WHI HRT Trial

24.4.1 Analyses According to Age (Table 24.3)

Overall, when all women are analyzed, the WHI first HRT trials showed more CHD, strokes, and thromboembolism. Also, higher breast cancer incidence rates were seen in the first WHI HRT trial but not in the second trial. These hazards were highlighted in most WHI publications since 2002. However, if one takes the results for younger women – those aged 50–60 or those

<10 years since menopause – the results look different (Table 24.3).

Table 24.3 shows that relative risks for *total mortality* of women aged 50–59 at the time of enrollment to the first WHI HRT trial is substantially reduced, with a statistically significant 30% reduction of all-cause mortality (HR = *0.70*; 95% CI: 0.51–0.96).

Similarly, CHD for women aged 50–59 was not adversely affected (HR = 0.93, 95% CI: 0.65–1.33), and for women <10 years since menopause, the CHD showed a nonsignificant reduction, by 24% (HR = *0.76*, 95% CI: 0.50–1.16).

Importantly, incidence rates of strokes were also not affected in the younger women, with hazards moderately elevated but without statistical significance (HR = 1.13, 95% CI: 0.73–1.76). It was only in the older age-groups, age 60+, that stroke hazards were increased more substantially (Table 24.3). However, even in the elderly age-group, the absolute rates of strokes in association with HRT are considerably lower than the risks due to potentially avoidable life style factors such as smoking, lack of exercise, overweight, and/or alcohol consumption.

Specifically, the actual rates of strokes taking women of all ages from the first WHI trial – figures which do matter when individual decisions are made for a given woman suffering with menopausal symptoms – were 0.19% in the HRT group vs. 0.11% for women in the placebo group, for an absolute increase of +0.08% of stroke incidence. The corresponding increase in women in 50–59 age-group is +0.02%.

24.4.2 Breast Cancers: Analyses According to Past Hormone Use

Taking all participants in the first WHI HRT trial, breast cancer incidence rates were increased nonsignificantly (when *HR = 1.26*, 95% adjusted CI: 0.83–1.92). However, Table 24.4 shows that 74.1% of all women who were without the past HRT use prior to the study enrolment had no increase of invasive breast cancer (HR = 1.06). It was only in women with past hormone intake and in particular for those with >5 years that the HRT was associated with a significant increase in breast cancer rate (Table 24.4).

24.4.3 Impact of HRT and Duration of Follow-Up

With the follow-up duration of patients enrolled in the first WHI HRT trials, further interesting observations were noted for CHD [91]. While in the first years of the trial there was a fluctuation of cardiac hazards (ranges 0.99–1.78), in the subsequent follow-up (years of 6–8+), the hazard rates were reduced, with CHD reduced by 22% (HR = 0.78). Similarly, for strokes, in years 1–3, the hazard rates fluctuated between 0.99–1.79; however in years 6–8+, the stoke rates were reduced by 34% (HR = 0.66) [1, 73, 76].

Table 24.4 Breast cancer rates, according to prior use of progestin

Panel A: WHI first HRT trial with estrogen + progestin, vs. placebo (according to JAMA, 2002, pp. 328–329)				
Prior use of HRT (*N*)	Estrogen + progestin (*N*: 8,506)	Placebo (*N*: 8,102)	HR	95% CI
All (*N*:16,604)	166 (0.38%)	124 (0.30%)	**1.26**	0.83–1.92
No prior use of menopausal hormones (*N*: 12,304)	114 (0.34%)	102 (0.33%)	**1.06**	0.7–1.97
Prior use <5 years (3,005)	32 (1.4%)	15 (0.8%)	**2.13**	1.15–3.94
Prior use 5–10 years (783)	11 (0.59%)	2 (0.1%)	**4.61**	1.01–21.02
Prior use >10 years (515)	9 (0.66%)	5 (0.38%)	**1.81**	0.60–5.43
Panel B: WHI second trial estrogen (CEE) alone vs. placebo (according to JAMA, 2006, Vol. 295, N 14, Table 2, p. 1650; and Fig. 3, p. 1653)				
Prior use of HRT (N)	Estrogen (*N*: 5,310)	Placebo (*N*: 5,429)	**HR**	**95% CI**
All	104 (0.28%)	124 (0.30%)	**0.80**	0.62–1.04
No prior use of menopausal hormones (7,802)	52 (0.27%)	79 (0.40%)	**0.65**	0.46–0.92
Yes prior use of menopausal hormones (2,937)	52 (0.29%)	54 (0.28%)	**1.02**	0.70–1.50

Noted are higher hazards of breast cancer seen in the first WHI HRT trial (progestin added to estrogen) compared to the second HRT trial (estrogen alone)

24.5 Overview of the Second WHI HRT Trial

24.5.1 Analyses According to Age (24.5)

The second WHI trial was halted in 2004, due to the perceived excess of overall hazards over benefits. However, the analysis restricted to the age-group 50–69 (Table 24.5) showed a 44% reduction of CHD events approaching statistical significance (*HR = 0.56,* 0.30–1.03). This compares, also in this trial, to much less CHD protection of HRT for women aged 60–69 (HR = 0.92) and basically no effect among women aged 70–79 (HR = 1.04).

A nonsignificant increase of thromboembolism was seen, with HR = 1.22, 1.31 and 1.44, respectively, for ages 50–59, 60–69, and 70–79.

As with the first WHI trial, strokes were also not increased among *young women aged 50–69* (HR = 1.08, 95% CI: 0.57–2.04), although the rates were increased nonsignificantly among participants aged 60–69 and 70–79 (HR = 1.65 and 1.25, respectively, Table 24.5).

Surprisingly, and in contrast to the first WHI trial, breast cancer rates after CEE alone were not increased, and (Table 24.6 a-c) outlines that most subsets of the second WHI trial actually experienced a substantial reduction of invasive breast cancers in association with CEE. That reduction reached statistical significance in the sizable subset of women *without* underlying breast cancer risk factors (see below).

Also confirmed in this trial were reductions of colorectal cancer, with the rates reduced more so in younger women aged 50–59 (HR = 0.59), with less CRC benefit with increasing age (HR = 0.88 and 2.09, respectively for age-groups 60–69 and 70–79, respectively).

Bone fractures, among all participants (except the women <age 60 with very few events) were reduced consistently, with trends for more protection among younger women (*HR = 0.33*, for the ages 60–69 vs. *HR = 0.62*, for ages 70–79).

Total death rates were reduced nonsignificantly by 27% among young women aged 50–69 – more so when compared to women aged 60–69 and 70–70 (HRs = 1.01, and 1.20 respectively).

Table 24.5 Impact of HRT on estrogen-related outcomes, in the second WHI HRT trial (estrogen alone vs. placebo), according to age groups

	CEE (%)	Placebo (%)	HR	95% CI
Coronary heart disease				
Age 50–69	0.14	0.24	**0.56**	0.30–1.03
Age 60–69	0.54	0.59	0.98	0.69–1.23
Age 70–79	0.88	0.84	1.04	0.75–1.44
Stroke				
Age 50–69	0.16	0.16	**1.08**	0.57–2.04
Age 60–69	0.49	0.30	1.65	**1.16–2.36**
Age 70–79	0.71	0.57	1.25	0.85–1.82
Venous thromboembolism				
Age 50–69	0.15	0.13	**1.22**	0.62–2.42
Age 60–69	0.31	0.23	1.31	0.86–2.00
Age 70–79	0.40	0.28	1.44	0.86–2.44
Invasive breast cancer				
Age 50–69	0.21	0.29	**0.72**	0.43–1.21
Age 60–69	0.26	0.36	0.72	0.49–1.07
Age 70–79	0.32	0.34	0.94	0.56–1.60
Colorectal cancer				
Age 50–69	0.07	0.12	**0.59**	0.25–1.41
Age 60–69	0.16	0.19	0.88	0.52–1.48
Age 70–79	0.32	0.15	2.09	**1.08–4.04**
Total deaths				
Age 50–69	0.29	0.39	**0.73**	0.47–1.13
Age 60–69	0.79	0.79	1.01	0.79–1.29
Age 70–79	1.54	1.30	1.20	0.93–1.54

According to Anderson et al. [105], modified from Fig. 5, p. 1709

24.5.2 Analysis of Invasive Breast Cancer

The unexpected yet potentially most important aspect of the WHI second HRT trial involved invasive breast cancer analyses. Taking all trial participants, the hazard rates of invasive breast cancer were reduced by 20% – a reduction approaching statistical significance (*HR = 0.80,* 95% CI: 0.62–1.04).

As seen in Table 24.6, women with no past history of breast disease (79.6% of the participants) had a significant 43% reduction of invasive breast cancer by HRT (*HR = 0.57*, 95% CI: 0.41–0.78). Similarly, women without a history of first-degree relative with breast cancer (86% of the trial population) had a statistically significant 32% reduction of invasive breast cancer with estrogen alone (Table 24.6, *HR = 0.68,* 95% CI: 0.50–0.92).

Table 24.6 **a-c** Rates of invasive breast cancer, second WHI HRT trial, CEE vs. placebo, in women with hysterectomy: impact of prior risk factors (conditions)

Past benign breast disease (*N*)	CEE (5,310) (% event)	Placebo (429) (% event)	HR	95% CI
Panel A: Risk of invasive breast cancer, as determined by history of benign breast disease				
All patients (10,739)	0.28	0.34	**0.80**	0.62–1.04
No (7,681)	**0.23**	**0.39**	**0.57**	**0.41–0.78**
Yes, 1 biopsy (1,439)	0.45	0.29	1.60	0.82–3.14
Yes, >1 biopsy (545)	0.41	0.19	2.54	0.73–8.86
Panel B: Prior risk for breast cancer determined by first-degree relative with breast cancer				
First-degree relative with breast cancer	**CEE (%)**	**Placebo (%)**	**HR**	**95% CI**
None (8,554)	**0.23**	**0.34**	**0.68**	0.50–0.92
>1 (1,382)	0.41	0.19	2.54	0.73–8.86
Panel C: Rates of invasive breast cancer prior risk for breast cancer as determined by Gail score				
5-year Gail risk score	**CEE (%)**	**Placebo (%)**	**HR**	**95% CI**
<1.25 (4,278)	**0.24**	**0.32**	**0.76**	0.54–1.17
1.25–1.74 (3,308)	**0.18**	**0.39**	**0.45**	**0.26–0.76**
>1.75 (3,153)	0.43	0.34	1.28	0.83–1.97

95% confidence intervals in bold and underline indicate statistical significance, "*P*"<0.05

According to JAMA, 2006, vol 295, N 14, Table 2, p. 1650, Fig. 3 on p. 1653

Related to these data are the results according to the Gail score at the time of randomization (Table 24.6c), showing similar trends: a substantial 24-55% reduction of breast cancer in low/medium risk subsets, with a nonsignificant increase in those with a high Gail risk score. Also, women with no prior estrogen or progestin use (i.e., no "prior menopausal hormone use," Table 24.7) had a statistically significant 35% reduction of the rates of new invasive breast cancer (*HR = 0.65*, 95% CI: 0.46–0.92).

24.6 HRT and Breast Cancer Incidence: Changing Trends after WHI Trial Reports?

The data from the WHI HRT trials as published in the year 2002 had a strong impact on the previous HRT use, worldwide. Within months, the medical community and population at large were alerted about the HRT hazards. By the year 2003 – within 1 year of the first WHI HRT trial publication – only 65% of the previous year's HRT prescriptions were filled in North America, with the HRT use reduction representing one of the most substantial shifts of medical policies ever recorded.

In 2007, Ravdin et al. published data indicating a *reduction of breast* cancer incidence in 2003 in USA – associating these trends with the HRT policy shifts [16]. Specifically, data from SEER showed that the age-adjusted incident rates of women's breast cancer in the USA fell between the years 2002 and 2003 by 6.7%. However, the rates in 2004 subsequently showed a leveling relative to the 2003 rates, with little additional decrease. The decrease of new breast cancer rates was evident only in women 50 years of age or older and was more evident in cancers that were estrogen-receptor positive than in those that were estrogen-receptor negative. According to the authors, the decrease in breast cancer incidence seems to be related to the first WHI trial report – and to the ensuing HRT use reduction among the postmenopausal women in the United States.

These data were subsequently updated, and reinforced by Chlebowski et al. [17], showing from the WHI update of the first HRT trial, a firm association between discontinuation of estrogen plus progestin combination, and decrease, with 1–2 years, of new breast cancers. No data regarding breast cancer rate dynamics are available from the second HRT trial.

Table 24.7 Invasive breast cancer in the second WHI HRT trial: impact of HRT with CEE alone, according to prior estrogen or progesterone (hormone) exposure

	CEE (*N:* 5,310) (%)	Placebo (*N:* 5,429) (%)	HR	95% CI
All women (*N*: 10,739)	0.28	0.34	0.80	0.62–1.04
Prior estrogen use: no (5,763 women)	0.27	0.40	**0.68**	**0.48–0.96**
Prior estrogen use: yes (any length, (4,976 women))	0.29	0.30	**0.98**	0.67–1.44
Prior estrogen + progestin use: yes (468 women)	0.44	0.16	**2.35**	0.60–9.14

According to JAMA Apr. 2006, Vol. 295, Table 2, p. 1650, Fig. 3, p. 1653

24.7 Comments Regarding HRT Policy Shift and Reduced Breast Cancer Incidence Rates

The data linking the primarily estrogen receptor-positive breast cancer incidence rate reduction with HRT discontinuation are of great interest. However, it has also been identified that the downward trends of breast cancer incidence rates started before the year 2002, already evident from the mid- to late 1990s.

After the implementation of screening mammography, there was an increase of Breast cancers among postmenopausal women. Screening mammography reached maximum in the late 1990s, with 70.1% of women having biennial mammograms [92]. In parallel, postmenopausal breast cancer rates according to SEER's data declined, and began to shift from older into younger ages at onset, probably because prevalent older screened breast cancer patients were removed from the general population [92]. Recent declines in HRT usage after the July 2002 WHI announcement have likely accelerated this decreasing incidence trend among older women.

Other data such as lifestyle factor including increased exercise, better diet, and DCIS (ductal carcinoma in-situ) management provide factors. Of interest, is the DCIS guideline changes in the late 1980s and throughout the 1990s – with the more aggressive management leading to more frequent excisions of the DCIS lesions, which could have also been an additional factor contributing to the subsequent reduction in invasive breast cancer, independent of the HRT [93].

Also, data from Europe have shown that, between the years 2002 and 2005, breast cancer incidence rates were stable in Norway and Sweden despite the sharp decline in the use of HRT, contrasting the results reported by Ravdin's et al. [94, 95].

These opinions do indicate that while there may have been an accelerated rate of breast cancer reduction observed related to the year 2002 WHI HRT publication, the reductions when projected over long time, are continuous since the 1990s – and thus not restricted to the recent times since the year 2002.

Thus, while a continuous drop in breast cancer incidence is evident over the last 10–15 years, Ravdin and Chlebowski data are nevertheless compatible with the changing HRT use policies contributing after the year 2002 toward other largely multifactorial epidemiology factors, cumulatively resulting in an ongoing breast cancer incidence reduction in the Western world.

Correlations of the fluctuating incidence trends with the breast cancer mortality trends will be very important. Breast cancer mortality reduction has been noted in most Western countries from the early 1990s – and in some pockets of the Western world already in the early 1980s [96], a time era with well established and/or *increasing* HRT intake. Thus, the long-term follow-up of HRT impact on breast cancer mortality will be needed to clarify the complex issue of hormonal impact on human carcinogenesis.

24.8 Estrogen Breast Cancer Protective and Progestin A Breast Cancer Carcinogen? Identification of a New Paradigm

The analyses of the WHI HRT trials showing invasive breast cancer reduction with CEE alone implicate differentiating estrogen effect as possible protective chemopreventive activity for breast cancer.

However, review of the first WHI HRT randomized trial has shown estrogen *plus* progestin combination a substantial breast cancer rate increase, significant statistically in some subgroups. While the magnitude of invasive breast cancer rate increase after combined estrogen *plus* progestin vary among subsets such as those with differing duration of prior hormone use, the rates of the estrogen–progestin combinations were almost never decreased.

Table 24.4 show these results. Table 24.4 shows breast cancer rates from the first HRT trial, all increased, with rates for all participants increased by 26% (HR = 1.26, 95% CI: 0.83–1.92); of particular increases are rates in subgroups with prior hormone use, with HR ranges 2.13–4.61. Noted is that even in those with no prior hormone use, the incidence was increased by 6% (HR = 1.06, 95% CI: 0.7–1.97).

As seen in Table 24.7, the breast cancer incidence rates from the second HRT trial are reduced by 20% in all participants (HR = 0.80, 95% CI: 0.62–1.04), with rates statistically significantly lower among women with prior use of hormones (HR = 0.65, 95% C: 0.46–0.92); furthermore, Table 24.7 shows breast cancer rates according to prior estrogen or progestin, with no rate increase in women taking prior estrogen (HR = 0.98, 95% CI: 0.67–1.44); however a more substantial (although not statistically significant) increase when progestin is also added (HR = 2.35, 95% CI: 0.60–9.14).

The emerging concepts of progestin contributing to the carcinogenic effect of breast cancer, and estrogen *alone* being potentially breast cancer protective, are new and require urgent confirmation in both epidemiology and molecular biology studies. However, in the absence of new HRT trials, there is evidence that estrogen, in women with hysterectomy used alone without progestin, as randomized in the second WHI HRT trial is not only safe with regard to breast cancer carcinogenesis, but in appropriately selected subsets, may be protective.

24.9 Summary

Overall, three main observations from the WHI randomized HRT trials are contributory and new:

First, that the CHD and overall mortality endpoints of chronic disorders will not be positively affected by HRT in the trial participants who were >60-years old, many over the age of 70. These more elderly women are therefore poor candidates to initiate HRT.

Second, that women without a history of significant risk factors for breast cancer may have a significant protection for subsequent incidence of invasive breast cancer using estrogen alone, without progestin.

Third, this review based on the WHI HRT trials shows that in *younger women* the decision-generating algorithm for HRT use will be substantially different than in more elderly postmenopausal women, not only as the intensity of menopausal symptoms is typically more severe, but also as most HRT-associated hazards are substantially lower, and benefits higher.

Thus, as identified in this chapter, the WHI trial data when applied to *appropriate candidates*, do confirm some of the conclusions generated in the past decades of large observational studies with long follow-up: that HRT will improve the quality of life in most women entering menopause, and in addition may have all-cause mortality benefits most evident among younger women aged 50–69. After estrogen alone, HRT may be associated with reduced breast cancer rates. Thus, in well selected candidates, HRT-associated hazards are small, and have to be viewed in perspective with quality of life benefits of HRT due to reduction of menopausal symptoms for women suffering these symptoms, and in view of other avoidable risk factors.

24.10 Concluding Remarks

There is no doubt that HRT issues remain complex, even after a thorough research as demonstrated in this chapter. Our knowledge of hormones and their impact on benefit and hazard in humans continues to evolve.

It would be fair to conclude that the WHI trials, as did the prior observational studies, contributed greatly by generating large amounts of essential data. These indicate that no single answer with regard to HRT recommendations do exist for *all* women.

When considering HRT, individual heterogeneity based on age and the known risk factors for each condition affected by HRT will need to be taken into consideration. To add to the complexity and thus challenges of clinicians and women dealing with HRT, these factors are influenced by an array of largely unknown genetic predispositions affecting most HRT-associated conditions.

It is very likely, as with most therapies of human conditions, that some women will derive a great deal of benefit from HRT with few hazards; some will have some benefit, and some none. Some even in the younger age category, if genetically predisposed, may suffer more hazards than benefits – the inevitable outcome of most classes of medications for some individuals.

It remains without saying that all HRT benefits and hazards will have be to monitored on an on-going basis, with women and their practitioners kept fully informed at all times about the complex HRT therapy as its research continues to evolve. This issue is important, primarily in view of the fact that the WHI trial reanalyses as illustrated in our review confirm that the perception of the HRT facts and the recommendations of today may not necessarily apply to tomorrow.

Accepting an HRT program is ultimately the decision of each individual woman, who should make the final decision, at times accepting small hazards for a substantial improvement in the quality of her life. The important condition in this decision process, however, is a full knowledge of all facts – those fully emphasized as well as those in small print. This is the goal of this review.

24.11 Appendix I

24.11.1 Observational and Case–Control HRT Studies Prior to the Publications of the 2002 WHI HRT Trials. Breast Cancer

The collaborative Group on Hormonal Factors in Breast Cancer collected and reanalyzed individual data on over 50,000 breast cancer cases and over 100,000 healthy women, as seen from 51 different epidemiological studies OG HRT [7]. It thus represented, until the year 2002, the most comprehensive overview of HRT ever published.

The results of this meta-analysis were that for current or recent HRT users, when compared to nonusers, the relative risk for breast cancer was increased, with Hazards rates (HR) = 1.023/year, translating into a 2.3% increase of annual incidence of breast cancer. The overall risk increased with the duration of HRT use, so that in users of over 15 years, cumulative Hazard rates (HR) of 1.3 for incidence was observed.

A 2002 review on the subject [8], summarized these results and indicated that while a breast cancer risk increase has been observed, it should be assessed in relation to other epidemiological causes for breast cancer risk increase [9].

For instance, much higher rates in the range of 40–60% (HR = 1.4–1.6) have been reported due to other conditions such as moderate alcohol consumption [10], absence of exercise [11, 12], nulliparity, or high caloric intake [13].

The past HRT policies are also to be viewed in conjunction with data showing that in the population of women at large, up to 45% mortality is from cardiovascular disease and less than 5% from breast cancer. Thus, the moderate increase of breast cancer rates related to HRT will result in lesser absolute added risk than the cardiovascular mortality – considered in the years before 2002 to benefit from HRT. Thus, the breast cancer hazards were acceptable for those women who suffer with severe menopausal symptoms, as in absolute terms, a small increase in the risk of breast cancer would be tolerable because the overall risk benefit ratio would favor HRT. Indeed, all-cause mortality was improved by HRT, shifting the HRT equation in favor of overall benefits [3, 14].

24.11.1.1 HRT and Carcinogenesis vs. Promotional Effect

The surprisingly short time period of recorded breast cancer events in relation to HRT – i.e., fluctuations of breast cancer rates are seen within 1–2 years of HRT start or discontinuation – negate the HRT effect on *carcinogenesis* and shift the emphasis to tumor *promotion*. These data are obtained not only from the past observational trials [15], but also from the recent WHI HRT analyses [1] and related epidemiology reports [16, 17].

The promotional rather than carcinogenic mechanisms would implicate the HRT effect primarily on the preformed malignant lesions, with resulting increased cell division of hormone sensitive clones. The accelerated formation of microcalcifications, and subsequently, earlier diagnosis through mammogram or physical examination would follow. In those women, however, the carcinogenic events presumably had occurred earlier and most likely with no connection with HRT. Thus, the *promotional* effect of HRT should be distinguished from any causative role.

These data also indicate a possibility that in the absence of HRT, the same tumor could develop later in time, but would present with a biologically more aggressive disease, and at a more advanced stage clinically. The data from the old literature described in either bacteria [18] or in cancer clones [19] indicate that with time, as a result of random ongoing mutations during cellular divisions in either bacteria or malignant tumor clones, there will be an exponential increase of mutants with aggressive, therapy-resistant phenotypes. Thus, tumors diagnosed later in their history would be more aggressive and less sensitive to hormonal, chemotherapy, or radiation treatments [19].

Several large observational studies indeed confirmed lower tumor aggressiveness in HRT users [5, 20–26], which may explain the observations of reduced breast cancer mortality in HRT users compared to nonusers, despite increased incidence [5, 21, 22, 24]. For instance, Grodstein et al. reported in the update of Nurse's health study [5] a significant reduction of breast cancer mortality (adjusted RR > 0.76) in women taking HRT for less than 10 years, despite the moderately increased breast cancer incidence rates (RR > 1.09–1.4). In addition, the HRT users in this study had a significant reduction of overall all-cause mortality (adjusted RR > 0.63), with a similar survival improvement in cases with a strong family history of breast cancer (RR > 0.65) or in cases who had HRT after oophorectomy (RR > 0.71).

Chlebowski et al. however were unable to confirm these observations from the recent WHI trial [27]. Estrogen plus progestin increased the rates of total and invasive breast cancers compared with placebo (199 vs. 150 cases; HR, 1.24, $P > 0.003$). The invasive breast cancers diagnosed in the estrogen plus progestin group were similar in histology and grade but were larger (mean 1.7 cm vs. 1.5 cm, respectively; $P > 0.04$) and were at more advanced stage (regional/metastatic 25.4 vs. 16.0%, respectively; $P > 0.04$) compared with those diagnosed in the placebo group.

In favor of Nurse's health study results, however, are data from the second WHI trial showing overall, reduced breast cancer incidence rates, after the use of HRT with estrogen alone (Tables 24.2–24.4). In this trial, women were randomized to estrogen (conjugated equine estrogen, CEE) without progestin, vs. placebo. In women with CEE, the incidence rates of invasive breast cancer were significantly reduced in the majority of participants (80%) *without* the past history of benign breast disease or without a first-degree relative with breast cancer, or similarly, significantly reduced were the breast cancer rates in participants without the past use of estrogens or progestins [28].

In view of these new data, the HRT association with breast carcinogenesis and biology is becoming more complex. The long-term follow-up outcomes of the WHI HRT trials with emphasis for a possible protective role of estrogen-alone on the rates of both breast cancer incidence and mortality.

Ravdin et al. recently reported a possible link between decreasing breast cancer incidence rates – as documented in U.S. – and *reduced HRT use* after the year 2002 – the year when the first results of the WHI HRT were published indicating excess of hazards over benefits. While comments regarding this association have been raised [29], a careful evaluation of not only incidence but also of mortality rates will be required, in order to clarify the important interactions of HRT use and breast cancer outcome.

24.11.2 Nononcological Aspects of HRT: Cardiac and Cardiovascular Events. Data Evaluation Before the 2002–2004 WHI HRT Trials

24.11.2.1 Estrogens and Lipids

Several longitudinal studies of postmenopausal women have shown a strong effect of estrogen on lipid metabolism [30], resulting in reduction of the plasma low density lipoproteins (LDL) and an increase in the high density lipoproteins (HDL). As the HDL/LDL ratio is one of the best predictors of future cardiovascular outcomes [31], it is plausible that in the long-term there could be significant benefit of estrogen use due to reduced atherogenesis. This mechanism may explain the long-term HRT benefits in the primary prevention of cardiac events [32–34], which exceeds its short-term hazards attributed, in all likelihood, to the HRT-associated increase in the rates of thromboembolism.

The most convincing evidence for the beneficial effects of HRT on lipid metabolism comes from the Postmenopasual Estrogen/Progestin Interventions, the PEPI trial [15], showing a significant reduction, at 3 years follow-up, of LDL-cholesterol (LDL-C) in HRT users, with HDL-cholesterol (HDL-C) levels increased compared to pretreatment levels. The PEPI trial is the

first placebo controlled *randomized* study to document that estrogen either alone or in combination with progestin significantly improves the serum lipid profile, thus confirming number of reports from *nonrandomized* studies. The results of the study also suggest that the effect on lipids may be comparable between estrogen alone and estrogen/progestin combination, particularly, using the newly available micronized progestin. The significance of these data for prevention of cardiac mortality is yet to be determined. The *long-term* follow-up of the ongoing randomized WHI trial [35] will provide a definitive answer to this issue. The PEPI trial is particularly important in view of other studies in which a modest incremental HDL-C increase (4–5 mg/dL) was associated with a 20–25% reduction of CHD. These findings are in line with the long-term follow-up of the observational HRT studies.

More recently, Darling et al. studied HRT and simvastatin in comparative lipid analyses [36] documenting that while the effect of simvastatin was greater than that of hormone therapy with regard to LDL-C reduction, the plasma concentration of Lp(a) lipoprotein – a known risk factor for CHD – *decreased* with hormone therapy (mean decrease, 27%; 95% confidence interval, 20–34%), but not with simvastatin [36].

24.11.2.2 Estrogen Effects on Vessels: Biochemical Effects

Other mechanisms indicate possible favorable vascular effect of estrogen. Thus, uptake of LDL is reduced by coronary arteries of monkeys fed with atherogenic diets randomized to estrogens [37, 38]. Also, estrogens are known to modulate the prostacycline-mediated vasodilating effect [39] and interact with calcium channel blockers [40] and Lp(a) [30, 41–44]. Furthermore, estrogen therapy significantly increased the catabolism of LDL [45]; estrogens also lowered the tissue concentration of adhesion molecules such as E-selectin, ICAM-1, and VCAM-1, yet another mechanism that may be known to reduce atherogenesis [46].

24.11.2.3 Direct Estrogen Effect on Vessel Wall

Another line of evidence suggestive of a protective effect of estrogens involves studies of direct effects of HRT on vessel walls. Estrogen receptors (ER) are present in the muscularis layer of arteries, and improved blood flow through the coronaries, documented upon estrogen exposure, is probably ER mediated [47, 48]. Consistent with these observations is the finding that in ovariectomized female monkeys, estrogen protected vessels from vasoconstriction after exposure to acetylcholine [49]. In other trials estrogen exposure led to a reduction of systemic vascular resistance [47, 49, 50]. Similar observations were also subsequently made in postmenopausal women [51, 52], where in one study estrogen reduced arterial impedance and vascular tone after 6 weeks of treatment [53].

Other investigators confirmed increased hyperemic response and vasodilatation after estrogen administration [54]. Pines et al. found improved flow velocity and improvement of the mean cardiac ejection fraction in estrogen users, as measured by aortic sonograms [55]. Finally, estrogen was found, in a placebo-controlled trial [55], to improve performance of women on a treadmill and to decrease symptoms of coronary artery disease [56] – effects which may be explained by the above-outlined estrogen effects on vessel vasculature.

24.11.2.4 Epidemiological Data on Estrogen and Heart Disease: HRT and Primary Prevention of Cardiovascular Disease

Most population-based studies examining HRT in the primary prevention of cardiac events have shown a strong risk reduction in users with cardiac mortality rates reduced between 20–60% [52, 57–62]. The magnitude of the HRT effect is similar between case–control and cross sectional studies [50]. While several hypotheses were offered to explain these observations, the most favored concern the favorable effects of estrogen on lipid metabolism [32, 38, 56, 63–65] and endothelial function [40, 47, 51, 53, 66, 67]. There is a possible bias due to the participation in the HRT cohort of healthier women, who may also undergo cardiac screening more effectively [60] as none of these studies were randomized. While these biases may exist, they do not fully account for the strong association of HRT with improved lipid profile and estrogen favorable vessel effect, both emerging as long-term surrogates for improved cardiac outcomes [32, 57, 62, 68].

24.11.2.5 Epidemiological Data on Estrogen and Heart Disease: Secondary Prevention

Once the atherosclerotic plaques and/or coronary occlusions produce clinical symptoms, therapy is usually not curative. Indeed, most interventions for the secondary prevention are expected to relieve symptoms, slow down progression, but not to completely reverse the lesions. Although the favorable lipid changes are seen early, the effects of HRT on the cardiovascular outcomes may take decades. It has also been predicted that, compared to its effect in primary prevention, hormonal therapy will have lower impact once the process of atherosclerosis has already advanced.

Indeed, the only randomized trial of secondary prevention, the HERs study, showed little cardiovascular protection. HERS trial was first published in the late 1990s [69] and updated recently [70]. A total of 2,763 women, 65 years or older (mean age: 66.7 years), with a history of myocardial infarction, were randomized in a double-blind placebo-controlled design, to be treated with either HRT (conjugated equine estrogen, CEE, 0.635 mg, plus daily medroxyprogesterone acetate, MPA, 2.5 mg/day) or placebo. At 4 years of follow-up, the authors reported no significant differences in deaths from CHD or myocardial infarction between the two arms (RR > 0.99, 95% CI: 0.80–1.22). The lack of an overall effect was seen despite a reduction of LDL levels and increase of HDL levels. More women in the HRT group had thromboembolic events (TEs) (RR > 2.89, 95% CI 1.50–5.58) and gallbladder disease (RR > 1.38, CI 1.00–1.92). There was no difference in cancer rates or overall mortality. For the latter two parameters, however, the power of the study was greatly limited. The authors' conclusion was that HRT does not reduce the overall rate of CHD in postmenopausal women with established coronary disease, and that the risk of thromboembolism and of gall stones is increased.

Examining the interaction of relative risk over time, interesting trends were observed. In the first year of the study, more cardiac events were seen in the users (RR > 1.52). In the second year, however, that increase was not seen any more, with the incidence of cardiac mortality or of the nonfatal infarctions among users vs. nonusers being equal (RR > 1.0). Subsequently, in years three and four, the risk of these events in HRT users was actually reduced (RR of 0.87 and 0.67, respectively), consistent with the degree of risk reduction seen in long-term follow-up observational primary prevention studies. The updated 2002 study showed, after the follow-up ranging 4–8 years, overall, no effect (RR > 0.99–1.0). However, the proportions of patients with at least 80% adherence to HRT declined from 81% in the first years, to only 45% in the year 6 [70].

Overall, these data indicate that in women with advanced atherosclerosis, the HRT may temporarily increase the morbidity, or even mortality, but in long-term, HRT plays no role in improving cardiac outcome once arterial occlusions occur. However, even in this population, HRT showed favorable effects on serum lipids, similar to the results of the primary prevention trials.

The increased event rate in the first years in the cohort of elderly women with established atherosclerosis exposed to HRT could be due to initial precipitating events such as thromboembolism or minor blood pressure fluctuations, not uncommon in the population of patients with advanced vessel disease. These complications would be, however, of lesser consequence in younger women without coronary disease. In these women, not only substantial improvements in the quality of life, but in long-term follow-up, also beneficial effect on lipid metabolism, and thus cardiac disease prevention, can be anticipated.

The analyses of the WHI HRT trials mirror these observations. Manson et al. [71] reported in the WHI ancillary substudy of 1,064 women aged *50–59* years at randomization of the second HRT trial (women with hysterectomy) results of estrogen (0.625 mg/day) impact on coronary-artery calcium scores as measured by computed tomography. The CT scans were carried out at 8.7 years after randomization, with the coronary-artery calcium scores measured at a central reading center without knowledge of randomization status.

The results showed the mean coronary-artery calcium score after trial completion to be significantly lower among the women aged 50–59 receiving estrogen than among those receiving placebo ($P > 0.02$ by rank test). After adjustment for coronary risk factors, the multivariate odds ratios for coronary-artery calcium scores in the group with at least 80% adherence to the study (estrogen or placebo) were reduced by 36% (HR = 0.64, $P > 0.01$).

Authors concluded that among women 50–59 years old at enrollment, the calcified-plaque burden in the

coronary arteries after trial completion was lower in women assigned to estrogen than in those assigned to placebo.

Our review of the WHI data [72] in women below age 60 shows early trends toward reduced CHD hazards (Table 24.3), with a significant all-cause mortality reduction in women aged 50–59. It is only among women over 60 and in particular in those over 70 that a nonsignificant trend is seen for increased CHD events. These data mirror the HERs trial: HRT has no impact on cardiac events in elderly women and failure of HRT in secondary prevention – yet they attest to the HRT potential benefit in primary prevention in women <60.

24.11.2.6 HRT and the "Timing" Hypothesis

Clarkson et al. published a series of analyses where they tested in primates the impact of immediate vs. delayed administration of estrogen in conjunction with atherosclerogenic diet [33]. Compared to controls, HRT showed a substantial reduction of the atherosclerotic plaques at the time of autopsy – but only if administered at the same time as atherogenic diet. Delayed HRT administration, late into starting the high-fat diet, had outcomes similar to animals who never received HRT.

More recently, Grodstein et al. [74] have prospectively examined the relation of HRT to CHD, according to the timing of hormone initiation, relative to age and time since menopause. Participants were postmenopausal women in the Nurses' Health Study, with follow-up extending from 1976 to 2000. The study showed that women beginning HRT near menopause had a significantly reduced risk of CHD – by 36% for estrogen alone (RR > 0.66, 95% CI: 0.54–0.80), and 28% for estrogen with progestin (RR > 0.72, 95% CI: 0.56–0.92). On the other hand, in the elderly women, at least 10 years after menopause – a subgroup demographically similar to those in the WHI – they found no significant relation between HRT and CHD among women who initiated therapy (HR = 0.87, 95% CI: 0.69–1.10 for estrogen alone; RR > 0.90, 95% CI: 0.62–1.29 for estrogen with progestin).

These data, same as the HERs trial [70, 75] confirm that no cardio-protective HRT effects are demonstrated when HRT is delivered after a more prolonged exposure of estrogen deficit state, and after the atherosclerotic plaques have formed.

Willet and Colditz, the principal authors of the Nurse's Health Study (NHS) – which showed substantial and significant cardioprotection by HRT – summarized the differences between the two trials recently [76]. In the WHI trial, women were eligible up to the age of 79 years, whereas in the NHS – and most observational studies showing cardiac benefits – more than 80% of the women initiated HRT use within 10 years of menopause.

Second, the NHS included women with much longer follow-up who had already been using hormone therapy for years. Thus, the effect mediated by improved lipid profile could have emerged in the NHS, but less likely in the WHI trial, with much shorter time of both HRT exposure, and follow-up duration.

Third, as in the HERS trial [69] where a transient risk elevation soon after HRT start is followed by risk reduction, the increased CHD risk is limited to the short interval soon after the initiation of HRT even in the WHI trials: For estrogen plus progestin, the relative risks for CHD were 1.68 for <2 years, 1.25 for 2–5 years, and 0.66 for 5 or more years [1, 76]. Prentice et al in the commentary on the WHI HRT trial [77] confirmed that when stratified by year from initiation of hormone therapy, the findings for CHD from the Nurses' Health and the WHI trials did not differ appreciably.

Hence the reanalysis of the WHI data according to age of participants – reflecting the "timing" of HRT start – and length of follow-up, may after all support the decades-long HRT research, which confirms both biochemical and lipid surrogate protection, but also a reduction of cardiac events in association with HRT.

24.11.3 Nononcological Aspects of HRT: Thrombo-Embolism (TE)

Estrogens are known to increase blood clotting, due to their effects on several clotting factors including fibrinogen, factors VII, X, and antithrombin III [78]. As a result, HRT is known to moderately increase the incidence of thromboembolism with HR ranging from 1.1–4.00 [3, 58, 69, 79–81]. However, despite these trends, no increase in mortality with HRT has been reported [82].

Abnormalities of clotting factors, however, may contribute to the HRT-associated complications [83–87]. It has been shown that a genetic variant of Factor V Leiden (especially the Factor V G1691A variant) is

responsible for the majority of TEs in users of birth control pills [84]. In women with established coronary disease, as reported in two clinical trials, the Leiden mutation was present in 8 (16.7%) of 48 cases with TEs compared with only 7 (6.3%) of 112 without TEs. In women with the factor V Leiden mutation who were treated with HRT, the estimated absolute incidence of TEs was 15.4 in 1,000 per year compared with 2.0 in 1,000 per year in women without the mutation who were taking a placebo (HR = 7.7) [87]. Van de Water [85] confirmed that in patients with myocardial infarction, the frequency of factor V Leiden mutation was 14.6% in patients <50 years old in the study group compared with 3.6% in patients in the control group [83].

With regard to strokes, a meta-analysis of 3,399 patients with stroke [86] showed a statistically significant association with factor VG 1691A variant (Leiden) [86].

The problem of thrombembolism in HRT users may be further complicated by other confounding factors, especially smoking. In a group with high Factor V or high Factor VII levels, smoking or high blood pressure increased the relative risk for myocardial infarction up to 50-fold [88].

Thus thromboembolism in the first years of HRT exposure could be responsible for vascular events leading to strokes and CHD, with genetic factors affecting coagulation in the first time exposure raising the risk. The first exposure to hormones will thus select the individuals prone on genetic grounds to thromboembolism, increased by other risk factors such as age, smoking, or hypertension. Subsequently, women continuing on HRT would experience fewer TEs, and may benefit, in long-term, from HRT. The "timing" hypothesis (see below) suggests that more adverse CVS events are related to thromboembolism in the first years of HRT exposure, followed by reduced hazard rates. This is confirmed in most observational trials by the dynamics of the HERs study, which is now also emerging in the WHI reports [1, 73, 76].

These data indicate that preventative measures in individuals prone to TE selected for HRT have to be considered. These should include interventions ranging from life style changes (i.e., emphasis on regular exercise, less sedentary activities, smoking cessation, reduced alcohol intake), to more targeted anti-TE interventions such as regular dose ASA (aspirin) – or in extreme cases where HRT is clearly required due to severity of menopausal symptoms, low doses of warfarin.

24.12 Appendix II

24.12.1 New HRT Agents

24.12.1.1 Clinical Equivalence of Intranasal and Oral 17β-Estradiol for Symptoms of Menopause [97]

This study confirmed that intranasal administration of 300 μg/day estradiol was at least as effective as oral administration of 2 mg/day estradiol in alleviating postmenopausal symptoms, with less frequent mastalgia and uterine bleeding and without the metabolic consequences of the first-pass effect.

24.12.1.2 A Prospective Randomized Comparative Study of the Effects of Intranasal and Transdermal 17β-Estradiol on Postmenopausal Symptoms and Vaginal Cytology [98]

Intranasal and transdermal 17β-estradiol combined with vaginal progesterone gel as a continuous HRT caused a similar decrease in vasomotor symptoms and did not have any significant effect on vaginal maturation index after 12 weeks of treatment in this study population.

Results of this study have shown that intranasal administration of 17β -estradiol (E2) is at least as effective as oral administration of 2 mg/day E2 in alleviating postmenopausal symptoms, with less frequent mastalgia and uterine bleeding and without the metabolic consequences of the first-pass effect.

Also, it is well-tolerated and provides a reproducible, easily adjustable dosing mechanism. Sustained-release vaginal progesterone gel ensures high endometrial protection and avoids the side-effects and possible risks linked to oral progesterones.

24.12.1.3 Efficacy and Acceptability of Intranasal 17β-Oestradiol for Menopausal Symptoms: Randomized Dose-Response Study. Aerodiol Study Group [99]

A third study documenting that intranasally administered 17β-oestradiol is significantly better than placebo

in reducing menopausal symptoms, and is similar to that of oral oestradiol. It was well-tolerated. Intranasal administration avoids first-pass metabolism and provides a reproducible, easily adjustable dosing mechanism that represents a new option for HRT.

24.12.1.4 Efficacy and Tolerability of Pulsed Estrogen Therapy: A 12-Week Double-Blind Placebo-Controlled Study in Highly Symptomatic Postmenopausal Women [100]

Pulsed estrogen therapy, achieved by intranasal estradiol 150 μg/day and 300 μg/day, significantly reduced the incidence of moderate to severe vasomotor symptoms, compared with placebo. *The 300-μg/day dose* demonstrated a greater and more rapid therapeutic effect, with no clinically significant difference in tolerability, compared with the 150-μg/day dose, and therefore offers the best efficacy/safety ratio when initiating treatment with intranasal estradiol.

24.12.1.5 Twice-Weekly Transdermal Estradiol and Vaginal Progesterone as Continuous Combined HRT in Postmenopausal Women: A 1-Year Prospective Study [101]

Transdermal estradiol and a twice-weekly administration of the vaginal progesterone gel Crinone constitutes a new, viable HRT regimen. It represents a practical option for a no-bleed treatment, ensuring both high endometrial protection and the inherent safety linked to administrating physiologic hormones nonorally.

24.12.1.6 Vaginal Progesterone in Menopause: Crinone 4% in Cyclical and Constant Combined Regimens [102]

This study also shows that vaginal progesterone can be used to maintain normal uterine morphology with a decrease in systemic side effects and when used in combination with estrogen without bleeding.

24.12.1.7 Relationship Between Long Durations and Different Regimens of Hormone Therapy and Risk of Breast Cancer [103]

Women using unopposed estrogen replacement therapy (ERT) (exclusive ERT use), even for 25 years or longer, had no appreciable increase in risk of breast cancer. Ever users of HRT (includes HRT users who also had used ERT) had a 1.7-fold increased risk of breast cancer, including a 2.7-fold increased risk of invasive lobular carcinoma.

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