

# The Women's Health Initiative Reports: Critical Review of the Findings

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The world of prescribing physicians and postmenopausal hormone users was turned upside down in the summer of 2002 with the media blitz over the publication of the Women's Health Initiative (WHI) findings.<sup>1</sup> Women's concerns about hormone use increased sharply following early termination of the estrogen/progestogen arm of the WHI. Prior to the report in July 2002, it was estimated that 15 million postmenopausal women were using estrogens because multiple studies and decades of use seemed to demonstrate a favorable balance of benefits and risks. With the wide media coverage, however, it was estimated that up to 50% of hormone users stopped them. Many women discontinued therapy without even discussing it with their physicians. And many clinicians, not understanding the methodology of the study, advised their patients to discontinue hormone therapy (HT).

## INTERPRETING THE FINDINGS

This panic was unnecessary, because careful perusal of these findings reveals that they were of borderline statistical significance. The findings that provoked discontinuation of the trial of continuous combined estrogen plus progestogen (CCHT)—specifically the estimated hazard ratio (HR) for breast cancer of 1.26, 95% confidence interval (CI) 1.00-1.59—are actually unlikely. When adjusted for risk factors of breast cancer, the 95% CI becomes insignificant (0.83-1.92). The mean of 5.2 years of follow-up was too short, and even the planned duration of 8.5 years was not long enough to reach significance. Based on doubling times of 7 to

8 years for carcinoma of the breast, the majority of the 290 cases in 16,608 participants had malignant cells in their mammary tissues at entry into the study. Although it might be argued that the estrogen/progestogen hormones could accelerate the growth of existing malignant cells, there are no data to support this concept.<sup>2</sup> In fact, one recent report indicated that estrogen therapy (ET) could safely be given to women with a history of breast cancer, with fewer recurrences than in nonusers.<sup>3</sup>

In a review of 55 studies about estrogen and breast cancer, Bush et al<sup>2</sup> observed that all 11 of the investigations looking at the prognosis of breast cancer developing in estrogen users reported prolonged survival and decreased mortality, with none to the contrary (Figure 1). They concluded that in the 45 studies of unopposed estrogen use, the data did not support the conclusion that estrogen use raises the risk of breast cancer (Figure 2). The estrogen/progestogen studies are listed in Figure 3, which also shows that combined HT does not increase the risk of breast cancer. Thus, while a small increase in breast cancer risk with HT, or an increased risk with long-term use (15 years or more), cannot be discounted, the likelihood is probably small given the large number of studies performed.<sup>2</sup> The WHI was too short (5.2 years, with some women using HT only 2 to 3 years) to draw conclusions about breast cancer, especially because mammography detects cancers some 2 to 3 years earlier than physical examination.<sup>3</sup> There are now more than 60 published studies indicating that estrogen can be safely given to women with a history of breast cancer.<sup>4</sup> This review cites 21 studies with sufficient data for comparison, showing that 152 of the 1,612 estrogen users with previous breast cancer had recurrences (9.4%), while 739 of the 3,640 controls had either recurrences or new breast cancer (20.3%) (Table 1).

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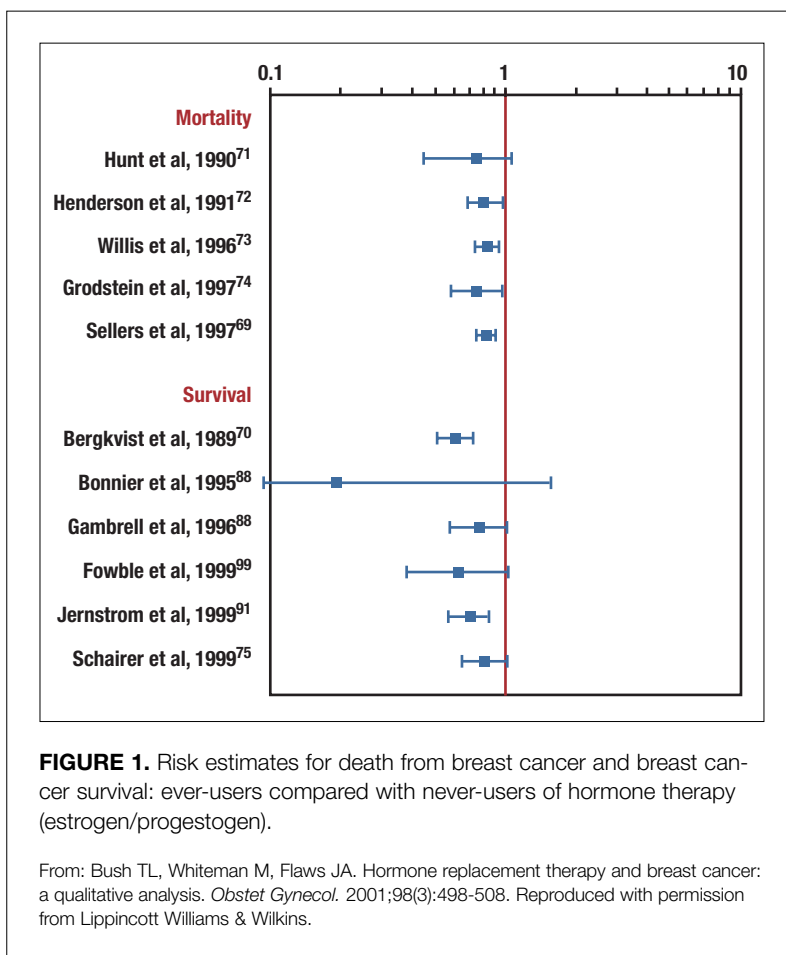
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The CCHT regimen chosen for this study was ill-advised—not because it increased the risk of breast cancer, which has not been shown—but because it may not fully protect women from endometrial cancer.<sup>5</sup> There were 27 cases of endometrial cancer in the CCHT users compared with 31 in the controls (HR = 0.81; 95% CI, 0.48-1.36). This 19% decrease is far less than that seen in the 1990s with sequential HT.<sup>5</sup> Because continuous progestogen use may cause downregulation of progesterone receptors in the endometrium, sequential HT, cyclic-combined HT (estrogen plus progestogen for the first through the 25<sup>th</sup> of the month),<sup>5,6</sup> or interrupted-progestogen HT (continuous estrogen with progestogen added 3 days out of every 6)<sup>7</sup> would allow upregulation of progesterone receptors in the endometrium, and thus be more protective. Cyclic-combined HT and interrupted-progestogen HT also produce more amenorrhea than CCHT.<sup>5</sup>

### CONSEQUENCES

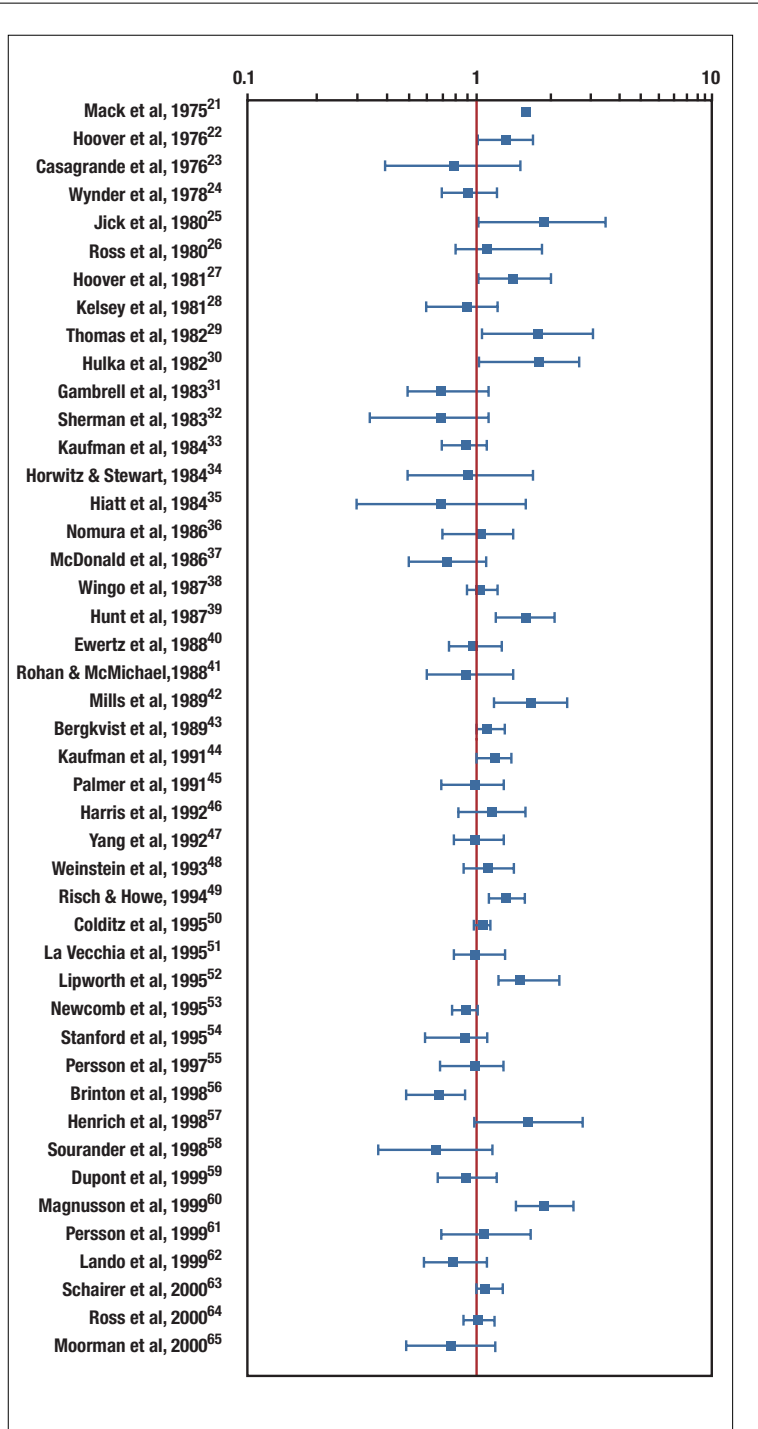
The report by the WHI investigators was preempted by a press conference that prejudged the meaning of the data for patients and physicians.<sup>8</sup> Media reports glossed over the protection offered by HT against osteoporosis, colon cancer, and mortality in users versus controls to emphasize the risks of breast cancer and cardiovascular disease (CVD). It was a classic case of hype fomenting hysteria. Where it had been thought that women who stopped HT after using it for 10 years would have a 10-year delay in developing hip fracture, a current report from The National Osteoporosis Foundation indicates otherwise.<sup>9</sup> In a study of 140,584 women who had discontinued HT for less than 5 years, the past users have almost the same fracture rate as matched never-users—odds ratio (OR) = 0.93; 95% CI, 0.63-1.38. Thus, women who have discontinued estrogen use for 5 years or longer have an excessive risk for hip fracture (OR= 1.65; 95% CI, 1.05 to 2.59) compared with never-users. Because of the misleading reports from the WHI, millions of users have stopped estrogen or will never use it despite the confirmed 34% decrease in hip fracture. This may result in millions more hip fractures.

What is the WHI, and why is it generating so many adverse reports from the National Heart, Lung, and Blood Institute? The WHI was designed 10 years ago



in 1992 as a primary prevention trial with a planned duration of 8.5 years. It sought to compare estrogen use alone (conjugated estrogens, 0.625 mg—the estrogen arm), or continuous combined estrogen/progestogen therapy (conjugated estrogens, 0.625 mg, plus medroxyprogesterone acetate, 2.5 mg—the HT arm) with placebo. Outcomes included development of heart disease, breast cancer, stroke, blood clots, endometrial cancer, colorectal cancer, and deaths due to other cancers.

A data safety monitoring board (DSMB) set statistical risk levels for the two primary endpoints—breast cancer and CVD. The DSMB set safety thresholds that were very conservative so that if one of these critical values was observed, the committee was obliged to stop the study. The breast cancer HR or relative risk (RR) of 1.26, with 95% CI of 1.00-1.59, exceeded the board's predetermined threshold, and hence the study was halted. It should be pointed out that the HR was not statistically significant, as the 95% CI included 1.00. The press conference and report stated that the



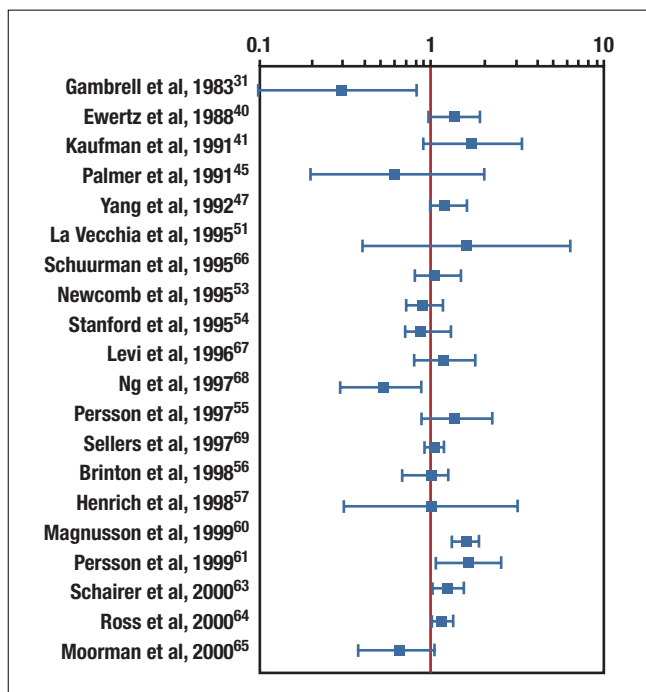
**FIGURE 2.** Risk estimates for incident breast cancer: ever-users compared with never-users of estrogen therapy (unopposed estrogen).

From: Bush TL, Whiteman M, Flaws JA. Hormone replacement therapy and breast cancer: a qualitative analysis. *Obstet Gynecol.* 2001;98(3):498-508. Reproduced with permission from Lippincott Williams & Wilkins.

trial was stopped early because the health risks exceeded the health benefits. However, most patients and many physicians believed that the trial was stopped because it showed that hormones caused breast cancer. These are not even new data; a collaborative group on hormonal factors in breast cancer had reported an increased risk after 5 years of estrogen use (RR = 1.115; 95% CI, 1.011-1.180) in 1997.<sup>10</sup>

A recent report estimated that where there were 91,000,000 new HT prescriptions in the United States in 2001, only 57,000,000 new HT prescriptions were written in 2003—a 42% decrease.<sup>11</sup> Of this decrease, 80% were for conjugated estrogens or conjugated estrogens combined with a daily progestogen. While transdermal and vaginal estrogen prescriptions remained steady because of a slight increase in vaginal estrogen use, these only account for 10% of all new HT prescriptions. The WHI was thought to be so well designed that it would answer any remaining questions about estrogen use, but with its many flaws, the WHI has generated more questions than answers. The information gleaned from multiple studies of so many different hormones and methods of administration for the past 50 years should not be discounted because of a single study, no matter how large—especially when only two hormone preparations and one method of administration were used (continuous-combined).

The report also listed the risks of stroke (HR = 1.41; 95% CI, 1.07-1.85) and pulmonary embolism (HR = 2.13; 95% CI, 1.39-3.25), but these ratios did not trigger the predetermined safety threshold that would have halted the study. All that can really be said is that at the end of the 5.2-year observation period, statistical analyses for these occurrences implied harm. Because the study was never completed (ie, the duration on which the initial hypotheses were built was not fulfilled), the primary outcome measure—a benefit or lack of benefit from estrogen/progestogen for nonfatal myocardial infarction and CVD—was neither proved nor disproved.<sup>8</sup>



**FIGURE 3.** Risk estimates for incident breast cancer: ever-users compared with never-users of hormone therapy (estrogen/progestogen).

From: Bush TL, Whiteman M, Flaws JA. Hormone replacement therapy and breast cancer: a qualitative analysis. *Obstet Gynecol.* 2001;98(3):498-508. Reproduced with permission from Lippincott Williams & Wilkins.

**OTHER CONSIDERATIONS**

Total mortality was decreased in the HT users (HR = 0.98; 95% CI, 0.82-1.18). In the women with breast cancer, there were three deaths in the hormone users and two in the controls. The 29% increase in heart disease (seven more events per 10,000 women per year) is probably valid as this has been shown elsewhere<sup>12</sup> and is also biologically explainable—whereas breast cancer is not. Although estrogens have cardiovascular benefits in that they increase high-density lipoprotein (HDL) cholesterol and decrease low-density lipoprotein (LDL) cholesterol, the major benefit is through the direct effects of estrogen on the coronary arteries. Most hormones work through receptors in target tissues. Estrogen increases its receptors in coronary arteries, whereas progestogens decrease the estrogen receptors—particularly when taken continuously as with CCHT. This may leave fewer sites for the beneficial action of estrogen, including increased blood flow, dilation of coronary arteries, reduced vascular resistance, increased velocity of blood flow, inhibition of atherosclerosis

progression, decreased platelet adhesiveness, and increased peripheral vasodilation.

The WHI findings do not apply to most HT users. Because of the characteristics of the WHI study populations, results cannot be compared with typical HT users—ie, women who are seeking relief from menopausal symptoms. Indeed, women with significant menopausal symptoms, especially hot flashes, were excluded from the WHI. In addition, the average age of women in the WHI was 63 years, so many already had an increased risk for heart disease (such as progressive atherosclerosis), with some even having prior angioplasty or coronary bypass surgery. Studies in younger postmenopausal women with an average age of 53 years, although using this CCHT or other estrogen/progestogen regimens, do not find any increase in heart disease. It should be emphasized that in the WHI, the study in the estrogen-only users was not stopped until February 2004 because they had no increase in either breast cancer or heart disease. They were to remain on estrogen alone for at least another 3 years, but were stopped after 7 years of use at an average age of 70 years because there was no increased risk for heart disease or breast cancer.

Even with the purported findings of increased breast cancer and heart disease, several benefits were demonstrated by the WHI, where absolute risk reductions per 10,000 patients were six fewer colorectal cancers, five fewer hip fractures, and fewer deaths in HT users compared with nonusers. Relative to osteoporosis, not only did HT decrease vertebral fractures in the WHI, it also significantly

**TABLE 1. Early Termination of the Estrogen/Progestogen Arm of the Women’s Health Initiative\***

	HR	95% CI
Coronary heart disease	1.29	1.02-1.63
Breast cancer	1.26	1.00-1.63
Stroke	1.41	1.07-1.85
Hip fractures	0.66	0.45-0.98
Endometrial cancer	0.81	0.48-1.36
Colorectal cancer	0.63	0.45-0.98
Total deaths	0.98	0.82-1.18

\*Results at 5.2 years.

HR = hazard ratio; CI = confidence interval.

**TABLE 2. Osteoporotic Fracture Rates**

	HR	95% CI
Hip	0.66	0.45-0.98
Vertebral	0.66	0.44-0.99
Other fractures	0.77	0.69-0.88
Total fractures	0.76	0.69-0.85

HR = hazard ratio; CI = confidence interval.

reduced hip fractures (Table 2). While up to 50% of the 15 million estrogen users stopped taking hormones after the WHI report, some have resumed therapy, so it is now estimated that 7 million to 8.5 million US women are now taking estrogens. Many resumed estrogen use because of unbearable symptoms.

The report of the WHI Memory Study (WHIMS) in May 2003 may have had the most devastating impact on postmenopausal health of all the WHI reports.<sup>13</sup> Contrary to multiple previous studies of ET and Alzheimer disease (AD), the WHI observed a 105% increase in AD with estrogen use. The age at initiation of ET is paramount. If ET is started at menopause and used for more than 10 years, there is a reduction of up to 83% in the lifetime risk of AD (HR = 0.41; 95% CI, 0.17-0.86).<sup>14</sup> In contrast, current users who initiated estrogen after age 60 years and continued for 3 to 10 years experienced an 112% increase in AD. In the WHIMS, all of the women were aged 65 years or older when estrogen was initiated. They did not have overt AD at the beginning of the study, but changes were already occurring in the brain. Because of the misleading WHIMS report, women may stop estrogen use, and some postmenopausal women will never use estrogen and miss the “window of opportunity” to have a significant impact on lifetime AD risk (which may be limited to the menopausal transition). This could result in millions of more cases of AD.

Older women without menopausal symptoms were chosen for the WHI so that the placebo users would not develop hot flashes and leave the study. These data were not new; a secondary prevention trial had already shown an increased risk of heart disease in CCHT users,<sup>12</sup> and was stopped early after 4 years because there were more cardiovascular events in the hormone users than in the controls. Nearly all of these events occurred in the first year of the study (RR = 1.52; 95% CI, 1.01-2.29). In the fourth and final year of the study, the RR had dropped to 0.60 (95% CI, 0.36-0.98).

The Nurses' Health Study, a very large study of more

**TABLE 3. Mortality Data From the Nurses' Health Study<sup>16</sup>**

Group	RR	CI
Current HT users	0.63	0.56-0.70
Long-term use (> 10 yr)	0.80	0.67-0.96
Heart disease in current users	0.51	0.45-0.57
Stroke in current users	0.68	0.39-1.16
All cancers in current users	0.71	0.62-0.81
Breast cancer in current users	0.76	0.56-1.02

RR = relative risk; CI = confidence interval; HT = hormone therapy.

than 100,000 nurses who were followed by questionnaire for over 20 years, observed decreased death from heart disease and even cancer in estrogen-only users (Table 3).<sup>15</sup> In a retrospective secondary prevention trial of cardiovascular mortality, Sullivan<sup>16</sup> observed an almost 100% survival for 10 years in estrogen users compared with 60% in nonusers.

There is little controversy that HT has a beneficial impact on postmenopausal quality of life, but the WHI findings did not reflect this. Again, this is because the WHI results do not apply to the majority of HT users. In the WHI, the women were aged 63 years on average (ie, 18 years postmenopause) and had no significant symptoms to avoid a high dropout rate. The WHI was a study of older women who were a relatively homogeneous group with a good quality of life on entry. This excludes quality-of-life considerations in more typical HT users, who initiate estrogen use at the menopausal transition due to intolerable symptoms.

Postmenopausal women must continue ET in adequate dosages for many years to achieve the maximum benefits. The lowest effective dosage for the shortest period of time is invalid, as the benefits of long-term HT far exceed the risks—the WHI notwithstanding. The benefits of HT are summarized in Table 4.

### ESTROGEN-ONLY THERAPY

The estrogen-only arm of the WHI was terminated early in February 2004 by the National Institutes of Health (NIH). This action was not undertaken by the DSMB, as was the halt to the estrogen/progestogen arm in July 2002.<sup>17</sup> Apparently, there was a debate between the NIH and the DSMB because the global index of risk/benefit was only increased by 1% (HR = 1.01; 95% CI, 0.91-1.12).<sup>17</sup> It was concluded that the use of conjugated equine estrogens increased the risk of stroke, decreased the risk of hip fracture, and did not

**TABLE 4. Benefits of Estrogen/ Estrogen/Progestogen Therapy**

- Relief of vasomotor symptoms
- Prevention of urogenital atrophy
- Alleviation of psychogenic manifestations
- Improved quality of life
- Prevention of osteoporosis
- Prevention of cardiovascular disease
- Prevention of Alzheimer disease
- Reduction in macular degeneration
- Reduction in cataracts

affect CVD incidence over an average of 6.8 years. It was further concluded that there was a possible reduction in breast cancer risk, but that conjugated estrogens should not be recommended for chronic disease prevention in postmenopausal women. In the discussion of the risk of stroke, there was no mention that the subjects were many years postmenopausal, had never used estrogen, and possibly already had other risk factors for stroke. The HRs are listed in Table 5.

When stratified by age, some of the risk factors become more obvious, especially for CVD and breast cancer. In this arm of the study, though, there was almost a significantly decreased risk for breast cancer with estrogen use. Almost all of the clinical outcomes increased with each decade of age (Table 6). The estrogen-alone WHIMS trial<sup>18</sup> confirms the earlier findings by Zandi et al,<sup>14</sup> with the WHIMS reporting that approximately 45% of the women in that trial had previously used HT and that the HR was reduced to 0.87 (95% CI, 0.32-2.39) compared with never-users, whose HR increased to 1.95 (95% CI, 0.94-4.04).

Overall, a theme has emerged from the epidemiologic confusion of the last few years.<sup>19</sup> It takes healthy tissue to allow an effective response to estrogen and maintenance of health. Experimental evidence indicates that

**TABLE 5. Early Termination of the Estrogen-only Arm of the Women’s Health Initiative<sup>18</sup>**

	HR	95% CI
Coronary heart disease	0.91	0.75-1.12
Breast cancer	0.77	0.59-1.01
Stroke	1.39	1.10-1.77
Hip fracture	0.61	0.41-0.91
Colorectal cancer	1.08	0.75-1.15
Dementia	1.49	0.83-2.66

HR = hazard ratio; CI = confidence interval.

as vessels become atherosclerotic and neurons are affected by AD, the beneficial response to estrogens decreases. Maximum benefit may require early initiation of treatment, near the time of menopause.

**CONCLUSION**

There is very little new information in the WHI, as the Collaborative Study on Hormone Factors in Breast Cancer showed a minimally increased risk after 5 years.<sup>10</sup> The HERS study indicated an increased risk of heart disease in the CCHT users with preexisting cardiovascular disorders.<sup>12</sup> In the estrogen-only arm of the WHI, there was no increase in CVD, and a decreased risk of breast cancer of borderline statistical significance. The Cache County study indicated that ET initiated after age 60 years increased the risk of AD, but decreased it by 83% when initiated at the menopausal transition and used for more than 10 years.<sup>14</sup> The daily progestogen in the CCHT users decreased the estrogen receptors in the coronary arteries, minimizing the beneficial cardiovascular effects of estrogen. It also down-regulated the progesterone receptors in the endometrium, minimizing the protection from uterine cancer. The WHI findings were contrary to those of previous studies of ET because women with specific menopausal symptoms were excluded and older

**TABLE 6. Stratification of Risk Factors by Age<sup>17</sup>**

Age Range (y)	Coronary Heart Disease		Breast Cancer		Colorectal Cancer	
	HR	95% CI	HR	95% CI	HR	95% CI
50-59	0.56	0.30-1.03	0.72	0.43-1.21	0.59	0.25-1.41
60-69	0.92	0.69-1.23	0.72	0.49-1.07	0.88	0.52-1.48
70-79	1.04	0.75-1.44	0.94	0.56-1.60	2.09	1.08-4.00

HR = hazard ratio; CI = confidence interval.

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women were chosen. These older women already had increased risks for heart disease and AD. Maximum benefit from HT may require early initiation of treatment at perimenopause. However, it is never too late to arrest the progression of osteoporosis and decrease the risk of fracture.

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