dryness, itching, burning, and dyspareunia is well demonstrated, regardless of the route of administration.[3,6,7] A fall in vaginal pH from 6.0 to 5.0 after estrogen administration has been documented,[8] as has the increase in the number of superficial cells of the vagina with exogenous estrogen.[9]

These physical changes are associated with improvement of symptoms, especially dyspareunia.

3. HRT maintains or increases bone mineral density (BMD). Most estrogen preparations on the US market have been shown to improve BMD.[10-15] "Improvement" means no significant loss, or an increase, in BMD. In the WHI, both vertebral and nonvertebral fractures diminished unequivocally in women using estrogen—alone or with a progestin.[16,17] Other clinical trials also have shown increased BMD, as well as decreased urinary and serum markers of bone turnover.

Do new data link progestin to cancer?

Although compelling evidence supports the use of progestational agents in addition to estrogen to prevent endometrial hyperplasia and endometrial cancer,[18] a 2005 report[19] suggests that chronic, long-term use of estrogen with a progestin may increase the risk of endometrial carcinoma. Because this is the only study in which this risk has been found, corroboration is required.

Until then, give progestin at a sufficient dose and duration to inhibit endometrial hyperplasia.[20-25]

Effects on heart disease may be age-related

With notable exceptions, the overall conclusion of clinical trials and observational studies to date is that estrogen helps prevent coronary heart disease (CHD).[26-30] This finding was first observed in the late 1980s with evidence that estrogen increases high-density lipoprotein (HDL) cholesterol and reduces total and low-density lipoprotein (LDL) cholesterol.[31]

Some experts argue that these observational trials are biased because many of the women taking estrogen had modified their lifestyles to maintain their weight, control their diet, and exercise regularly.[32] Indeed, the randomized, placebo-controlled Heart and Estrogen Replacement Study (HERS) and both arms of the WHI trial found no evidence for a significant increase or decrease in CHD events.[33-35]

Time from menopause to HRT may be key

Both the HERS and WHI trials enrolled older women who had entered menopause a few months to several years before starting HRT.[36] In addition, the estrogen-progestin arm of the WHI trial lacked sufficient power to detect a significant difference in CHD outcomes.[37]

The WHI findings contrast those of the large, ongoing, observational Nurses Health Study, which has shown a consistent decrease in CHD incidence in women who began HRT with the onset of menopausal symptoms.[27-30] The most recent data suggest that the interval between menopause and the start of HRT may explain the different findings in randomized, controlled trials and observational studies.[38] The WHI data support this theory: CHD was lower in women who began taking HRT within 5 years of menopause, compared with women who initiated HRT more than 5 years afterward.[36] In addition, data from the estrogen-only arm of the WHI show fewer CHD events in women younger than 60.[34]

Several other studies support this hypothesis:

- The surgically postmenopausal cynomolgus macaque had a lower rate of atherosclerotic plaque development when estrogen was given, with or without a progestin.[39,40]
- In the Rancho Bernardo study, women who had used HRT had less cardiac calcification documented by computed tomography, compared with nonusers.[41]
- Estrogen has been shown, by

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Women who began HRT within 5 years of menopause had less heart disease than women who started HRT more than 5 years after menopause

measurement of carotid intimal medial thickness, to inhibit atherosclerotic plaque in humans.[42]

- Older women with established atherosclerosis do not undergo any significant change in plaque size with the use of exogenous estrogen.[43]

Although these findings support the use of estrogen or estrogen-progestin early after menopause as a way of preventing CHD, further clinical trials are needed.[44]

Stroke risk is small but real

Both arms of the WHI found an increased incidence of stroke in women using hormones, compared with nonusers.[16,36] The exact mechanisms underlying this increased risk are unclear.

The actual attributable risk was an increase of 0.7 cases of stroke per 1,000 women per year over placebo in the estrogen-progestin arm,[36] and 1.2 cases per 1,000 in the estrogen-only arm.[16] The relative hazards were 1.31 (95% confidence interval [CI] 1.02–1.68) and 1.30 (95% CI 1.10–1.77), respectively.

Note that women in the estrogen-only arm had a greater incidence of hypertension and diabetes mellitus—known risk factors for stroke—than did women in the estrogen-progestin arm.[16,36]

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In the Women's Health Initiative, the risk of VTE increased by 1.8 cases per 1,000 women using HRT

VTE risk is twice as high in HRT users

Postmenopausal women who take estrogen have a higher risk of venous thromboembolism (VTE) than those who do not. This risk translated into a relative hazard of 2.06 (1.57–2.70) in the WHI estrogen-progestin arm, or an attributable risk of 3.6 cases per 1,000 women, compared with 1.8 cases per thousand in the control group.[36]

The absolute increased risk is 1.8 cases per 1,000 women, or, as expressed in the study itself, 18 cases per 10,000 women per year.

I have deliberately reduced the attributable risk to the number of cases per thousand because I believe this number is more easily understood by the patient and accurately demonstrates the low risk.

In the estrogen-only arm of the WHI, the hazard ratio for VTE was 1.33 (0.99–1.79), or an absolute increased risk of 0.7 cases per thousand—although this finding was not significant. The attributable risk was 2.7 cases per 1,000 women, compared with 2.0 cases per thousand among controls.[16]

Like stroke, the risk of VTE may be confounded by other factors besides use of exogenous estrogen.

No cause and effect for HRT and breast cancer

Nothing frightens women as much as breast cancer, and articles focusing on the relationship between breast cancer and HRT have drawn widespread attention. However, despite voluminous literature, the etiology of breast cancer remains elusive—and there is no evidence that either estrogen or progestins cause the disease.[45,46] Rather, there is only an association between the use of estrogen, progestin, and breast cancer. Linking the finding of an increased risk with an implication of causality would be inappropriate.

Breast cancer risk with HRT is not consistently elevated, in studies

In fact, a qualitative review of observational studies from 1975 to 2000 found no significant increase or decrease in the risk of breast cancer with estrogen or estrogen-progestin in 80% of the reports.[47]

Risk factors for breast cancer (**TABLE 1**) include family history, obesity, late childbirth, and hormone therapy—but obesity and family history have higher relative risks than the use of HRT.[48]

WHI arms find different risks

In the widely publicized WHI, women in the estrogen-progestin arm had an overall relative hazard for breast cancer of 1.24 (95% CI 1.01–1.54), but there was no

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increased risk in women who had never before used hormones.[36] Women who had previously used hormones for 5 years or more did have an increased risk.[36] The incidence of breast cancer in the study population was 3 cases per 1,000 women, and the excess number was 0.7 more cases with the use of estrogen-progestin (**TABLE 2**).

Conversely, in the estrogen-only arm of the WHI,[16] the relative hazard for breast cancer was 0.77 (95% CI 0.59–1.01), and the reduction in risk was almost statistically significant. There are at least 2 potential explanations for the lower incidence of breast cancer in this arm:

- Without a progestin, estrogen increases breast density only minimally, allowing for easier mammographic interpretation.
- Women susceptible to breast cancer because of their previous use of estrogen may not have been present in the at-risk population in sufficient numbers to cause an increase.

Neither explanation—separate or combined—fully explains the lowered risk in this population. Each population studied appears to have a different level of risk based on multiple factors that cannot be controlled completely in clinical trials and observational studies.

HRT may promote, rather than induce, breast cancer

The role of hormones in the etiology of breast cancer is difficult to assess. The Million Women Study[49] found that the elevated risk of breast cancer disappeared within 1 year of stopping HRT. This finding implies that hormones may be a promoter, rather than inducer, of neoplasms in the breast.

Breast cancer may be present in many women, but apparent in few

When autopsies were performed on women in their 40s who had died from other diseases, the incidence of breast cancer was 39%, but the clinical detection rate was only 1% for this population.[50] This discrepancy suggests that neoplastic cells may be present in the body at any time, but become clinically apparent only under certain conditions.[51]

More recent data suggest that undifferentiated stem cells in the breast become dysfunctional and result in cancer.[52] This theory is supported by the various histologic types of cancer found in the breast.

TABLE 1

Relative risk of breast cancer

CHARACTERISTIC	RELATIVE RISK
2 family members with breast cancer	14
1 family member with breast cancer	2.2
Obesity	1.8
Young age at menarche	1.6
Hormone therapy <5 years	1.3
>30 years of age at birth of first child	1.3
Menopause <49 years of age	0.7

A weak link

Although it may be compelling to link hormone use with breast cancer, the association is weak and the incidence is lower than in other known relationships such as obesity. At present, the cause of breast neoplasia appears to be multifactorial. ■

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Autopsies done on women in their 40s who died from other diseases found that 39% had breast cancer—but the clinical rate was only 1%

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TABLE 2

Extra cases of breast cancer, by risk factor

RISK FACTOR	BREAST CANCERS DIAGNOSED OVER 20 YEARS FROM AGES 50 TO 70 (PER 1,000)	EXTRA BREAST CANCERS (PER 1,000)
Never used HRT	45	-
>5 years HRT	47	2
>10 years HRT	51	6
>15 years HRT	57	12
Late menopause (age 60)	59	14
Alcohol (2 drinks/day)	72	27
No daily exercise	72	27
Weight gain (>20 kg)	90	45

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Top 3 risk factors for breast cancer:

- **Obesity**
- **No daily exercise**
- **More than 2 alcoholic drinks daily**

symptoms in highly symptomatic menopausal patients. The Esclim Study Group. Am J Obstet Gynecol. 1999;181:71–79.

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EXAMINING THE EVIDENCE — CLINICAL IMPLICATIONS OF KEY TRIALS

Q Do atypical glandular cells on Pap require aggressive follow-up?

A Yes. "Atypical glandular cells are markers for cancer in a high proportion of cases, yet I see clinicians merely repeating the sample, or quitting after a negative colposcopy." —*Kenneth L. Noller, MD*

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Undifferentiated stem cells in the breast may become dysfunctional and result in cancer

OBG MANAGEMENT

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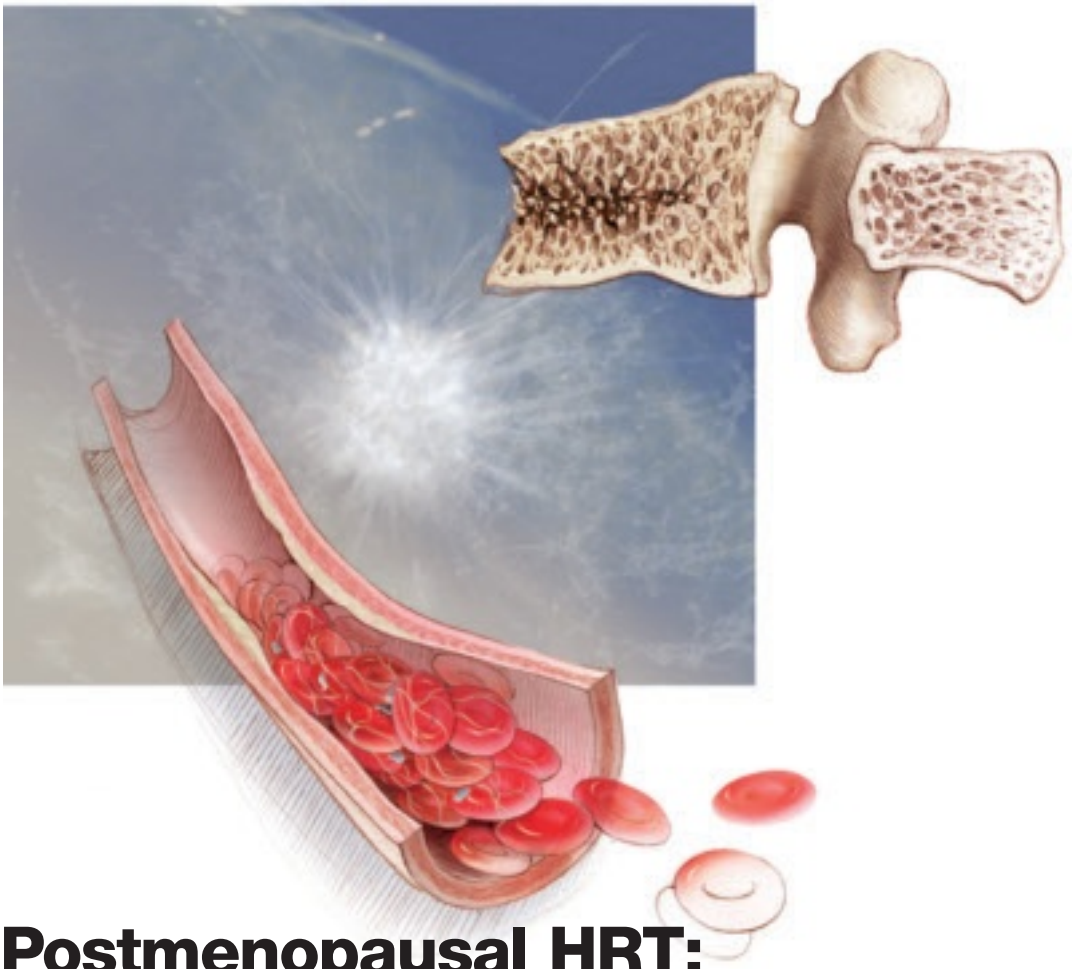

The mammogram depicts a typical stellate image of carcinoma. The artery section represents plaque, stroke, and/or venous thromboembolism—all by implication due to the thickened arteriole wall, and embolism clogging the lumen. The fractured vertebra relates to postmenopausal bone loss

IMAGE: KIMBERLY MARTENS

IN THIS ARTICLE

Postmenopausal HRT: What is fact, what is fiction?

What the evidence to date does and does not confirm

Now that the dust is settling from the Women's Health Initiative (WHI), our patients are again asking reasonable questions about hormone replacement therapy (HRT). I remind them of estrogen's proven advantages in menopause, as well as its risks. Although most women are generally aware of these risks and benefits, considerable misunderstanding persists. This article reviews what the evidence to date does and does not confirm, particularly regarding breast cancer and coronary heart disease, where most of the uncertainty remains.

HRT stops vaginal atrophy, hot flashes, and bone loss

Three applications form the basis for HRT in postmenopausal women:

1. Hot flashes subside. Hot flashes occur with varying intensity in about 85% of women, and are effectively treated with estrogen, whether given orally, transdermally, or vaginally.[1,2] As long as an appropriate blood level of the hormone is reached, hot flashes diminish.[3-5] This reduction is dose-related.

2. Measurable improvements in vaginal atrophy. Estrogen's efficacy in relieving