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Menopausal Hormone Therapy, Age, and Chronic Diseases: Perspectives on Statistical Trends

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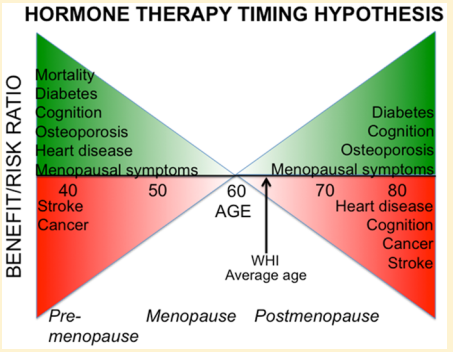
ABSTRACT: The release of the Women's Health Initiative (WHI) study in 2002 was a shock to the medical community. Hormone therapy (HT) had generally been considered to be highly beneficial for postmenopausal women since it was the gold standard for relief of menopausal symptoms (hot flashes, night sweats, vaginal atrophy) and it was thought to protect women from osteoporosis, heart disease, and cognitive decline and to generally improve quality of life. However, WHI showed a statistically significant increase in a number of disease states, including breast cancer, cardiovascular disease, and stroke. One problem with the WHI study was that the average age of women in the study was 63, which is considerably older than the age at which most women enter menopause (about 51). The timing hypothesis attempts to rationalize the effect of age on response to HT and risk of various diseases. The data suggests that younger women (50−60) may be protected from heart disease with only a slight increase in breast cancer risk. In contrast, older women (>65) are more susceptible to breast cancer and heart disease and should avoid HT. This Perspective on Statistical Trends evaluates the current data on HT and risk for chronic diseases as a function of age.



INTRODUCTION

Before the release of the Women's Health Initiative (WHI) in 2002, hormone therapy (HT) was the gold standard for treatment of menopausal symptoms.[1] Primary symptoms, such as hot flashes and night sweats, were dramatically reduced with HT in most women, and health care providers believed there were additional health benefits including protection from osteoporosis, heart disease, and dementia. As a result, worldwide use of HT increased dramatically from 1980 to 2002.[2] The WHI trials were designed to test the hypothesis that HT protected women from heart disease and osteoporosis.[3] The Prempro arm was a large randomized double-blind clinical trial (16 600 postmenopausal women, 50−79 years old) in which 8506 women with an intact uterus received Prempro [Figure 1, conjugated equine estrogens (0.625 mg/day), medroxyprogesterone acetate (2.5 mg/day), Wyeth-Ayerst, Philadelphia, PA] and 8102 women received placebo.[1,3] The progestin was needed to protect women with a uterus from endometrial cancer risk.[4] Another trial was set up for women (10 739 postmenopausal women, 50−79 years old) who had previously undergone a hysterectomy where the medroxyprogesterone was eliminated. The estrogen-alone trial [Premarin, conjugated equine estrogen (0.625 mg/day), Wyeth-Ayerst, Philadelphia, PA] consisted of 5310 women and a placebo group of 5429.[5,6] Instead of seeing protective effects, the WHI trials showed a worrisome increase in some disease states, causing both trials to be terminated earlier (2.5 years early, Prempro; 0.9 years early, Premarin) than the original 8 year plan.[1,5] As a direct consequence of the WHI report in 2002, the number of HT prescriptions dispensed declined dramatically.[2,7] Reanalysis of the WHI data suggests that age could significantly change the beneficial and/or adverse effects of HT.[8] The average age of women in the WHI trials was 63 to avoid recruitment of younger menopausal symptomatic subjects and increase recruitment of older women who were more likely to have cardiovascular events.[9] This study design has been extensively criticized since it specifically limited participation from younger women that were more likely to be taking HT.[10] The timing, critical window, or window of opportunity hypotheses suggest that HT, if initiated before 60 years of age, may protect (or has no adverse effect on) younger women from coronary heart disease, osteoporosis, diabetes, and/or dementia without increasing cancer risk (Figure 2).[9,11−17] This Perspective on Statistical Trends summarizes the effect of hormone therapy on women's health as a function of age (Table 1).

MENOPAUSAL SYMPTOMS

Most women are prescribed HT initially to deal with menopausal symptoms, especially hot flashes, night sweats, and vaginal dryness, that can be quite debilitating for some women.[18] Prior to the release of WHI, women in the U.S. were routinely taking Prempro or Premarin if they had undergone a hysterectomy. HT is still the most efficacious regime for relieving menopausal symptoms, and low-dose short-term use for women under 60 years of age is generally considered safe.[19] Exceptions include women with a history of, or risk factors for, heart disease, breast cancer, and/or stroke. Women who are

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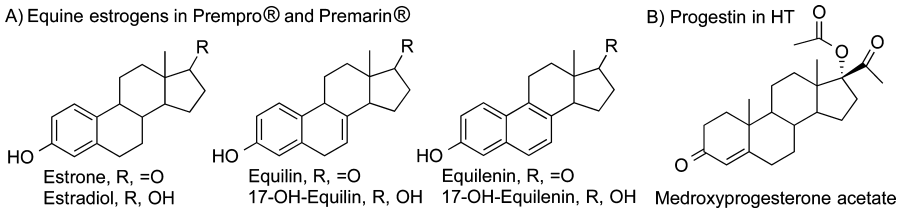

Figure 1. Structures of estrogens and progestins in HT.

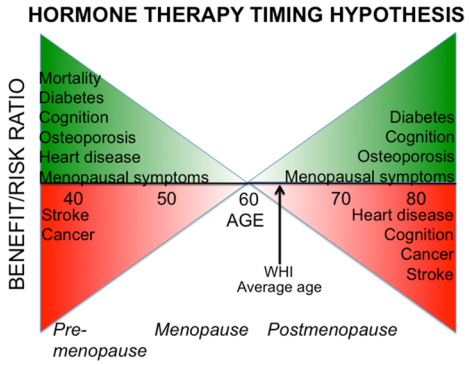

Figure 2. Timing hypothesis (modified from ref 17).

over 60 with hot flashes and night sweats, which significantly impact quality of life, should be prescribed the lowest dose of transdermal 17β-estradiol HT.[19,20]

OSTEOPOROSIS

The decrease in estrogen levels at menopause is associated with rapid bone loss due to increased bone resorption, which may result in osteoporosis.[21] Prior to release of WHI, HT was routinely prescribed for osteoporosis.[22] In both the Prempro and Premarin arms of WHI and the Million Women Study, HT reduced hip and vertebral fracture risk.[1,5,23−25] However, HT is no longer a first-line approach for the treatment of osteoporosis in postmenopausal women over 60 because of increased risk factors described below.[22] For younger women closer to menopause, HT may still be an effective treatment for osteoporosis prevention, especially for women at increased risk for fracture, although other alternative treatments should be considered.[14,22]

CARDIOVASCULAR DISEASE

Heart disease is the number one cause of morbidity and mortality for all women in developed countries; one in every four female deaths are due to heart disease.[26] For women over 70, cardiovascular disease represents 54% of all deaths, and for younger women (50−69), the mortality rate is 31%.[26,27] The Nurses Health Study, started in 1976, was a large observation study (121 700 female nurses, 30−55 years) where nurses were asked about their HT use and medical history.[28] On the basis of a 20-year analysis of 70 533 postmenopausal women, their data suggests that HT was associated with a significant decrease in risk for a major coronary event (RR = 0.61, 95% CI, 0.52−0.71).[29] On the basis of this study and others,[30−32] the major hypothesis of the WHI was that HT (Prempro, conjugated estrogens plus progestin) would protect women from cardiovascular disease. However, the data from the WHI showed the opposite effect and was one of the major reasons that the trial was stopped early.[1] One explanation for the increase in cardiovascular disease observed in the Prempro group was the advanced average age of the WHI women (average age 63 years old).[9] In addition, the WHI women had an average BMI of 28, one-third had hypertension, and one-half had a history of smoking.[33] These older, sicker women were more likely to show signs of atherosclerotic disease, which was aggravated by estrogen plus progestin therapy. Interestingly, estrogen therapy alone did not increase cardiovascular events regardless of age, leading to speculation that progestins might be responsible for the adverse effects, although the underlying mechanism is not known. A reanalysis of WHI data trends suggested that HT did not increase heart disease if HT was started close to menopause, which, for most women, is about 51 years old (i.e., younger women <60 years old).[8] A relatively small randomized, double-blind, placebo controlled trial (ELITE, Early versus Late Interventional Trial with Estradiol, 248 early postmenopausal women and 348 women at least 10 years past menopause) that was designed to test the timing hypothesis showed that HT taken within 6 years of menopause can slow age-related thickening of heart arteries compared to placebo.[34] The rate of heart disease progression after 5 years was significantly lower in the estradiol group compared to the placebo group in younger women closer to menopause. However, in older women who were 10 or more years past menopause, no cardioprotective effect was observed. It is important to note that this trial was done with a different HT regimen (1 mg/day oral estradiol, 45 mg progesterone vaginal gel, Teva Pharmaceuticals, Watson Pharmaceuticals, Inc., Abbott Laboratories) as compared to WHI (oral daily dose of Prempro). The current data may or may not support the HT timing hypothesis as far as cardiovascular disease is concerned; however, the evidence seems to suggest that HT early in menopause is not harmful to the heart and may slow the progression of atherosclerosis.[13] At present, HT is not recommended for the purpose of preventing adverse cardiovascular events.[35]

BREAST CANCER

Breast cancer is the most common cancer and the second leading cause of cancer deaths in the U.S in 2016, as reported by the American Cancer Society.[36] The most troubling finding from the WHI for most women and their doctors was the small but statistically significant increase in breast cancer incidence in the Prempro group (26%).[1] Similar data was reported in the Million Women Study cohort (50−64 years old, average age 56) where users of HT had increased breast cancer risk (RR = 1.66; 95% CI = 1.60−1.72) compared to nonusers.[37] Breast cancer risk also increases with the duration of HT use.[38] Since the release of the results from these large HT trials, there have been a number of reports linking the decline in breast cancer incidence with the decreased use of HT, suggesting a causal relationship.[7,39−44] In contrast, in the estrogen alone trial, a possible reduction in breast cancer risk was reported (RR = 0.77; 95% CI = 0.59−1.01).[5] The current data seems to suggest

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Table 1. Influence of HT on Women's Health as a Function of Age

Health Effect	Age < 60	Age > 60	References
Menopausal Symptoms	Effective (low dose, < 2 years)	Effective (transdermal E_2)	19, 20
Osteoporosis E and E+ P	↓ fracture risk	↓ fracture risk	1, 5, 23-25
Cardiovascular Disease E and E+ P	↓ heart risk	↑ heart risk	8, 34
Breast Cancer			
E	≈ no effect	↓ cancer risk	5, 45, 46
E + P	↑ cancer risk	↑ cancer risk	1, 37, 45, 47
Colorectal Cancer			
E + P	≈↓ cancer risk	≈↓ cancer risk	1, 51-53, 55
E	≈ no effect	≈ no effect	5, 55
Endometrial Cancer			
E + P	↓ cancer risk	↓ cancer risk	58, 59
E	↑ cancer risk	↑ cancer risk	4
Lung Cancer E and E+ P	≈↓ cancer risk	≈↓ cancer risk	1, 60, 63, 65
Ovarian Cancer E and E + P	↑ cancer risk	↑ cancer risk	67, 69, 71
Diabetes E and E + P	≈↓ diabetes risk	≈ no effect	72, 74, 76
Cognition E and E + P	≈↓ cognitive decline	≈↑ cognitive decline	78, 80-82, 84
Stroke E and E + P	≈↑ stroke risk	↑ stroke risk	15, 85, 86, 88
Death			
E	≈↓ death rate	≈↑ death rate	14-16, 90
E + P	≈ no effect	≈ no effect	15, 16

that estrogens alone have no effect on breast cancer risk in younger women and may decrease risk in older women.[45] The protective effect of estrogens in older women might be due to estrogen-induced apoptosis in breast tumors.[45,46] These tumors might not be detectable by mammography at the beginning of the study. Both younger and older women have increased breast cancer risk when taking estrogens plus a progestin, which implicates progestin as the risk agent.[45,47] Interestingly, it has been reported that women taking HT consisting of estradiol and micronized progesterone showed no increased breast cancer risk, which may imply that medroxyprogesterone acetate is mainly to blame.[48] On the other hand, the equine estrogens in Premarin could be responsible for the increased breast cancer incidence. It is known that equine estrogens equilin and equilenin are metabolized differently from estradiol, forming highly redox active quinones that might have a variety of adverse biological effects.[49] It remains difficult to evaluate the exact impact of the drop in HT use on the decrease in breast cancer incidence as a function of age since the various studies are not usually based on detailed patient questionnaires and often do not indicate the type of HT used or the duration of use and/or specify the specific type of breast cancer.[42,50] Other confounding factors, such as obesity, smoking, alcohol use, prescription medications, reproductive history, etc., could also alter the importance of the link between HT use and breast cancer risk.[42]

■ COLORECTAL CANCER

Colorectal cancer is the third most common cancer and the third leading cause of cancer deaths in the U.S in 2016, as reported by the American Cancer Society.[36] One positive result from the WHI was the protective effects of Prempro (conjugated estrogens plus progestin) on colorectal cancer incidence (RR = 0.63; 0.43−0.92, 95% CI), and these data are supported by more recent trials.[1,51−53] It is possible that the progestin is responsible for the protective effect in the WHI study through an unknown mechanism.[52,54] However, a reanalysis of the WHI data did not support a clinically relevant colorectal cancer protective effect with either estrogen alone or estrogen plus progestin.[55] Data from prospective cohort studies suggest that circulating estrogen levels are correlated with colorectal cancer risk (1.5-fold).[54] For example, the New York University Women's Health Study showed a 60% increase in colorectal cancer for women with high levels of serum

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estrogens compared to those with low levels.[56] Currently, HT is not recommended for prevention of colorectal cancer.

■ ENDOMETRIAL CANCER

It has long been known that unopposed estrogen therapy increases endometrial cancer risk and that progestins protect women.[4] The concerns about endometrial cancer led to a reduction in HT prescriptions until the introduction of estrogen plus progestin therapies.[38] The results from the Million Women Study showed a protective effect with HT (RR = 0.71, 95%, CI = 0.56−0.90) for endometrial cancer compared to women that had never used HT.[57] More recent studies have continued to show a small protective effect against endometrial cancer for continuous combined HT users.[58,59]

■ LUNG CANCER

Lung cancer is the leading cause of cancer deaths among women in the U.S.[36] The data from WHI showed no increase in the risk of lung cancer with HT.[1,60] However, reanalysis of these data suggested that HT increased lung cancer mortality.[61] In contrast, the use of conjugated estrogen therapy alone did not increase deaths from lung cancer.[62] A meta-analysis of 25 studies seemed to suggest that HT could protect from lung cancer.[63] A decrease in lung cancer for HT users was also observed in a small study with Chinese women.[64] Another case-control study showed a 34% reduction in lung cancer risk with HT use after controlling for age, ethnicity, tobacco use, and body mass index.[65] However, the authors cautioned about over interpretation of the data since dose and duration of HT was not controlled. Additional prospective studies are necessary before the relationship (positive or negative) between HT and lung cancer incidence is fully understood.

■ OVARIAN CANCER

The link between HT and ovarian cancer risk is much more tenuous.[66] The Million Women study did report a slight increase in ovarian cancer for HT users; over 5 years, the standardized incidence rates represent one extra ovarian cancer in 2500 users.[67] WHI did not analyze for ovarian cancer risk; however, similar to breast cancer, an overall decline in ovarian cancer incidence might be related to the reduction in the use of HT.[68] Most studies that have looked for a causal relationship between HT use and ovarian cancer have been small and/or retrospective. A meta-analysis of 52 epidemiological studies found that women who used HT even for a short time were 20% more likely to develop ovarian cancer compared to those who never used HT.[69] The longer the time since last use of HT, the lower the ovarian cancer risk. The risk was with both estrogen only and estrogen−progestin combination regimens. It should be noted that the conclusions of this study have been labeled as misleading and alarmist.[66,70] Another more recent meta-analysis found similar increased ovarian cancer risk, although the increased risk was seen only for serous ovarian cancer.[71] The findings of these two studies may support adding ovarian cancer to health risks associated with HT, although the risk is probably small.

■ DIABETES

HT seems to have no effect or be beneficial toward diabetes.[72] For example, the Heart and Estrogen−Progestin Replacement Study (HERS) of postmenopausal women with documented coronary heart disease reported 6.2% of women developed diabetes in the HT group compared to 9.5% in the placebo group (RR = 0.65; 95% CI, 0.48−0.89).[73] Similarly, in WHI, 3.5% of women in the Prempro group developed diabetes compared to 4.2% in the placebo group (RR = 0.79; 95% CI, 0.67−0.93).[74] A protective effect was also observed in the estrogen only arm of WHI with women without a uterus (RR = 0.88; 0.77−1.01).[75] As with cardiovascular disease, younger women under the age of 60 may derive benefit from reduction in type 2 diabetes, whereas older women do not.[74,76] The protective mechanism may involve estrogen-mediated protection of insulin production and β-cell survival.[77] Currently, HT is not recommended for treatment or prevention of diabetes.[76]

■ COGNITIVE FUNCTION

The effect of HT on dementia and Alzheimer's disease has been controversial.[78] Some studies have shown that HT has no effect on prevention of cognitive diseases and should be avoided in older women.[79] In fact, the WHI results showed increased cognitive decline with HT, probably because the majority of women were over the age of 60.[78,80−82] On the other hand, younger women (under 60 years old) could benefit from the protective effects of HT on the brain.[83] Administration of estrogen during a critical window close to the onset of menopause is hypothesized to delay or prevent age-associated cognitive decline. There is some evidence to suggest that short-term HT around the age of menopause can translate to long-term cognitive protection.[81] A recent clinical trial designed to test the timing hypothesis on the cognitive effects of estradiol showed no effect on verbal memory, executive functions, or global cognition for early (within 6 years of menopause) or late (10+ years) menopause groups.[84] Currently, there is insufficient evidence to recommend HT after menopause for the prevention of cognitive decline.[14]

■ STROKE

The WHI estrogen alone HT trial showed a significant increase in the risk for stroke in the Premarin group compared to placebo (RR = 1.37; 1.09−1.73, 95% CE).[85] The NIH terminated this trial 1 year early due to concern over increased risk of stroke. Similar data were reported for the WHI estrogen plus progestin trial (RR = 1.31; 1.02−1.68, 95% CE).[86] The stroke hazard ratios did not appear to depend on age, and stroke risk may apply to younger women.[87] However, it is important to note that stroke risk is rare among women receiving HT when they are less than 60 years old.[8] The Danish Osteoporosis Prevention Study (DOPS, 1006 women, 10 years HT, total follow-up 16 years, open label, randomized, controlled), which was designed to examine clinical outcomes of HT [2 mg of estradiol plus sequential norethisterone acetate (1 mg), or estradiol (2 mg) alone for hysterectomized women] in younger women (50 years average age) found a decrease in the incidence of stroke in the HT group relative to placebo group (RR = 0.89; 95% CI, 0.48−1.65).[15,88] The Women's Estrogen for Stroke Trial (WEST), which was specifically designed to examine the effect of HT on stroke risk, looked at 664 postmenopausal women at high risk for stroke (average age 71 years). No difference was detected between the HT (1 mg oral estradiol) group and the placebo group.[15,89] The majority of observational studies do not support an association between HT use and stroke risk, especially for younger women.[15]

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MORTALITY

There is some evidence that HT delivered early in menopausal women reduces total mortality, especially for women who have had a hysterectomy and received estrogen alone.[14,15,90] For women 50−59 years old in the estrogen only WHI trial, a significant reduction in total mortality was observed (RR = 0.73; 95% CI, 0.53−1.00).[6] However, another reanalysis of the WHI data for younger women failed to show a significant reduction in total mortality for either the estrogen alone trial or the Prempro trial.[87] Similarly, women who were more than 60 years old showed no reduction in overall mortality with HT relative to placebo.[15,16]

CONCLUSIONS AND FUTURE DIRECTIONS

It is quite clear that menopausal therapies have changed significantly since the release of WHI and the Million Women Study.[91,92] Current recommendations for women whose hot flashes and night sweats are significantly impacting quality of life are the lowest dose of HT that provides relief for the shortest period of time.[93,94] It is generally accepted that HT is safe in younger women close to menopause without risk factors (breast cancer, heart disease, stroke).[14,15] In these women, the benefits derived from HT including prevention of osteoporosis, and potentially coronary artery disease, and diabetes may override the risks.[91,92] The results from the recently released ELITE trial in particular support the hypothesis that the benefits from HT depend on the time of initiation of HT and are limited to women who start therapy close to menopause.[34,35] However, other studies provided little support for the beneficial effects of HT in younger women.[87] For older women (over 60), HT should be avoided unless menopausal symptoms impact quality of life. Alternative delivery mechanisms for HT such as low-dose transdermal applications and different drugs such as tibolone and raloxifene may be helpful for some women.[95] Botanical dietary supplements such as black cohosh, red clover, soy, hops, and *Angelica sinensis* may also provide some relief.[96] Women and their healthcare providers should personalize clinical decisions with respect to risk/benefit of HT for chronic disease prevention, overall mortality, and quality of life, especially since the world population of postmenopausal women is steadily increasing.

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ABBREVIATIONS

DOPS, Danish Osteoporosis Prevention Study; ELITE, Early versus Late Interventional Trail with Estradiol; E, estrogen; ER, estrogen receptor; HERS, Heart and Estrogen-Progestin Replacement Study; HT, hormone therapy; MWS, Million Women Study; P, progestin; WEST, Women's Estrogen for Stroke Trial; WHI, Women's Health Initiative

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