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HORMONE THERAPY AND THE TIMING HYPOTHESIS

A POTENTIALLY NEW PARADIGM FOR THE PRIMARY PREVENTION OF CORONARY HEART DISEASE

By Howard N. Hodis, MD

In the public health arena, there are very few potential therapies with such consistent data for reducing coronary heart disease (CHD) and overall mortality as postmenopausal hormone therapy (HT). Over the past 5 decades, approximately 40 observational studies consistently show that HT is associated with a 30–50% reduction in CHD and overall mortality in postmenopausal women.[1-10] On the other hand, randomized controlled trials (RCTs) with the exception of the Estrogen in the Prevention of Atherosclerosis Trial (EPAT)[11] have shown a null effect of HT on CHD. This unexpected discordance between observational studies and RCTs led to the "timing hypothesis" that posits that the benefits of HT are dependent upon timing of initiation of HT relative to menopause. Formulation of the "timing hypothesis" resulted in part from the realization that the characteristics of women randomized to RCTs are significantly different from those of women who were studied in observational studies *(Table 1)*.[12] The "timing hypothesis" or "window-of-opportunity" has become one of the most provocative hypotheses of the 21st

Table 1.
Differences in Study Populations between Randomized Controlled Trials and Observational Studies of Postmenopausal Hormone Therapy

	Randomized Controlled Trials	Observational Studies
Mean age or age range at enrollment (years)	>62	30–55
Time-since-menopause at enrollment (years)	>10	<6 (<2)*
Duration of therapy (years)	<7	>10
Menopausal symptoms (flushing)	excluded	predominant
Body mass index (mean)	~29 kg/m^2	~25 kg/m^2

**>80% of the women initiated hormone therapy at the time of menopause.*

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century with implications that could alter the current paradigm for the primary prevention of CHD for women, and potentially for men.[13] More recently, it has become evident that the "timing hypothesis" is applicable to soy isoflavones and other agents that bind to the estrogen receptor besides HT.[14]

RCTS Supporting The Timing Hypothesis

EPAT showed a reduction in subclinical atherosclerosis progression in healthy postmenopausal women who were randomized to unopposed estradiol versus placebo.[11] Since women randomized to EPAT were younger than those randomized to other RCTs, and the time from menopause to randomization was 10 years earlier in EPAT, the divergence in outcomes between EPAT and other RCTs was hypothesized to be dependent upon timing of HT initiation; particularly when initiated early in the intervention of atherosclerosis progression at the start of menopause as the key to preventing CHD with HT.[13] This hypothesis, further supported by EPAT's sister study, the Women's Estrogen-progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART) and animal studies later became known as the "timing hypothesis" or the "window-of-opportunity" for the reduction of CHD with HT in postmenopausal women.[15]

The beneficial HT effect on CHD according to timing of HT initiation has been shown in a large meta-analysis of 23 RCTs (191,340 patient-years of follow-up).[16] Over all ages, the HT effect on CHD was null whereas a statistically significant 32% reduction in CHD was found for women younger than 60 years of age or within 10 years-since-menopause when randomized to HT relative to placebo (Table 2). Magnitude of CHD reduction for women younger than 60 years of age or within 10 years-since-menopause when randomized to HT was similar to observational studies.[1-10] This large meta-analysis of cumulated RCTs of HT clearly demonstrates two distinct populations of women who respond differently to HT according to timing of HT initiation relative to age and/or time-since-menopause.

Other Estrogen Receptor-Binding Agents And The Timing Hypothesis

Broadening support for the timing hypothesis are accumulating data that show products other than mammalian hormones that bind to the estrogen receptor exert similar CHD beneficial effects as HT in young postmenopausal women. In the Raloxifene Use for the Heart (RUTH) trial (10,101 postmenopausal women), raloxifene, a selective estrogen receptor modulator had no effect on CHD incidence over all ages after a median treatment of 5.6 years. However, among women younger than 60 years of age when randomized to raloxifene, CHD was statistically significantly reduced 41% relative to placebo[17] a finding similar to the meta-analysis of HT RCTs of CHD *(Table 2)*.

In the Women's Isoflavone Soy Health (WISH) study, a RCT examining the effects of high-dose isoflavone soy protein supplementation on the progression of subclinical atherosclerosis, women who were randomized within 5 years of menopause to isoflavone soy protein supplementation had a significant reduction in progression of subclinical atherosclerosis relative to placebo whereas women more than 5 years beyond menopause when randomized had no significant effect.[14]

Overall Mortality Of HT

The beneficial HT effect on overall mortality according to age has also been demonstrated in a large meta-analysis of 30 RCTs (119,118 patient-years).[18] Over all ages, the HT effect on overall mortality was null whereas a statistically significant 39% reduction in overall mortality was found for subjects younger than 60 years of age (mean age 54 years) when randomized to HT relative to placebo *(Table 2)*—a reduction similar to observational studies.[1-10] Age at HT initiation among women in observational studies and age of younger women randomized to RCT's examined in the meta-analysis is similar. On the other hand, in this meta-analysis the HT effect on overall mortality in women who were older than 60 years of age (mean age 66 years) when randomized was null as reported over all ages in RCTs.

Benefit-Risk Of HT

To address benefit-risk of HT, a Bayesian meta-analysis was conducted using RCTs and observational studies to evaluate the HT effect on overall mortality in young postmenopausal women who initiated HT in close proximity to menopause.[19] Results from this meta-analysis

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Send comments or questions to:
The Soy Connection
P.O. Box 237
Jefferson City, MO 65102
Email: stevev@communiqueinc.com

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using 19 RCTs with 16,283 women (mean age 54.5 years) followed for 83,043 patient-years over 5.1 years (range, 1–6.8 years) showed an overall mortality reduction of 27% (RR, 0.73; 95% credible interval (CrI), 0.52–0.96) among women randomized to HT relative to placebo. The 95% CrI used in the Bayesian analysis is comparable to the 95% CI used in traditional meta-analyses. Using pooled data from eight prospective observational studies in which a total of 212,717 women were followed for 2,935,495 patient-years over a mean of 13.8 years (range, 6–22 years), overall mortality was reduced 22% (RR, 0.78; 95% CrI, 0.69–0.90) in HT users relative to non-users. Overall mortality was reduced 28% (RR, 0.72; 95% CrI, 0.62–0.82) with the RCT and prospective observational data combined. Results from this study indicate a convergence of evidence from several sources that support a beneficial HT effect on overall mortality in women who initiate HT in close proximity to menopause. Further, results from this meta-analysis indicate that RCTs and observational studies are similar, each with an overall mortality reduction of approximately 25%.

Initiation of HT at Younger Age Cost Effectively Extends Life

A cost-effectiveness analysis indicates that compared with no therapy, HT given to postmenopausal women in their 50s for 5–30 years results in a substantial increase of 1.5 quality-adjusted life-years (QALYs) at a cost of $2,438 per QALY gained.[20] Net gains gradually increase with treatment durations of 5–30 years and results for younger women are robust to all sensitivity analyses with HT remaining highly cost effective (defined as <$10,000 per QALY gained). At $2,438 per QALY gained, these data indicate that HT is a highly cost-effective strategy for improving quality-adjusted life. The substantial increase in QALYs in younger women is due to a net benefit in quality of life and reduced overall mortality compared with no therapy. On the other hand, for 65-year old postmenopausal women initiating HT there is a smaller net gain of 0.11 QALYs at a cost of $27,953 per QALY gained.[20]

Test of the Estrogen Cardioprotective Timing Hypothesis

In the wake of early trial results showing discordance between RCTs and observational studies, the Early versus Late Intervention Trial with Estradiol (ELITE; clinicaltrials.gov NCT00114517) was funded by the National Institutes of Health; enrollment initiated in 2004. Designed to specifically test the timing hypothesis, 643 postmenopausal women have been randomized to a 2x2, double-blind, placebo-controlled, single-center trial according to time-since-menopause. Women without pre-existing clinical cardiovascular disease <6 years- and >10 years-since-menopause were randomized to oral estradiol (1 mg/d) or placebo (with vaginal progesterone gel or placebo for 10 days each month) in each stratum. The primary trial end point is CIMT progression measured every 6 months. The secondary trial end point is rate of cognitive decline. Based on the wealth of evidence

Table 2.
Number of Participants and Relative Risks of Coronary Heart Disease and Mortality for Hormone Therapy and Raloxifene Compared to Placebo by Age and Years-Since-Menopause at Randomization

STUDY	RELATIVE RISK	NUMBER OF PARTICIPANTS	P-VALUE FOR TREND
CORONARY HEART DISEASE			
HT Meta-analysis[16]	OR (95% CI)		
All ages	0.99 (0.88–1.11)	39,049	
<60 years old or <10 YSM	0.68 (0.48–0.96)	not given	
≥60 years old or ≥10 YSM	1.03 (0.91–1.16)	not given	
RUTH[17] (age, years)	HR (95% CI)		0.01
<60	0.59 (0.41–0.83)	1,670	
60–69	1.06 (0.88–1.28)	4,534	
≥70	0.98 (0.82–1.17)	3,897	
MORTALITY			
HT Meta-analysis[18] (age, years)	OR (95% CI)		
All ages	0.98 (0.87–1.18)	26,708	
<60	0.61 (0.39–0.95)	not given	
≥60	1.03 (0.90–1.18)	not given	

YSM = Years-since-menopause   OR = Odds ratio (95% Confidence Interval)   HR = Hazard ratio (95% Confidence Interval)   HT = Hormone therapy that accumulated since 2003 in support of the initial ELITE proposal to the NIH of the timing hypothesis,[11–15, 21–23] a 3-year extension of the trial was awarded. The three specific aims of the ELITE extension include:

1. increased randomized treatment for an average of 5 years

2. addition of a secondary vascular end point using non-contrast and contrast cardiac computed tomography to non-invasively measure coronary artery calcium and coronary artery lesions

3. addition of a third cognitive assessment to extend measurement of cognitive decline over an average of 5 years. Primary trial results from ELITE are expected in 2013.

overall mortality. The "window-of-opportunity" for maximal expression of HT beneficial effects on CHD and overall mortality while minimizing the risks appears to occur with HT initiation before 60 years of age and/or within 10 years of menopause

Conclusion

The totality of data show that the postmenopausal HT effect on CHD and overall mortality is modified by duration of therapy and by age and/or time-since-menopause when initiated. HT appears to exert its greatest benefit when initiated in women before 60 years of age and/or within 10 years of menopause. RCTs are supported by approximately 40 observational studies that also indicate that HT initiation early in the postmenopausal period and continued for a prolonged period of time results in a significant reduction of CHD and overall mortality. Comparison of RCT and observational data indicates that selection bias does not explain the consistent evidence that HT is associated with a duration- and time-dependent lowering of CHD and overall mortality. Analyses of the subgroups of women within RCTs that resemble women from observational studies indicate a consistency between the two study designs with similar HT benefit on the reduction of CHD and and continued for 6 years or more.[13] Due to reduced overall mortality there is a substantial increase in QALYs in younger postmenopausal women who initiate HT in close proximity to menopause supporting HT as a highly-cost effective strategy for improving quality-adjusted life.[18,19] Additionally, the "timing hypothesis" appears to extend to other agents that bind to the estrogen receptor.

In the final analysis, discordance in the association of HT with CHD and overall mortality between RCTs and observational studies is a function of differences in study design and characteristics of the populations studied. As such, the cardioprotective hypothesis requires appropriate testing with RCTs in a cohort of women with characteristics like those women from whom the hypothesis was generated. ELITE is a 2x2 factorial RCT designed specifically to study the estrogen cardioprotective hypothesis through the timing hypothesis.

ABOUT THE AUTHOR

Dr. Howard Hodis is currently the Harry J. Bauer and Dorothy Bauer Rawlins Professor of Cardiology and Professor of Medicine and Preventive Medicine in the School of Medicine and Professor of Molecular Pharmacology and Toxicology in the School of Pharmacy at the University of Southern California (USC). Dr. Hodis is an internationally recognized leader in atherosclerosis and vascular research and cardiovascular disease prevention and is the Director of the USC Atherosclerosis Research Unit. His work includes the endocrine aspects of vascular disease including insulin, estrogen and testosterone actions in both men and women.

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ISOFLAVONES INHIBIT THE PROGRESSION OF SUBCLINICAL ATHEROSCLEROSIS

By Mark Messina, PhD

As discussed in the lead article by Howard Hodis, MD, the estrogen "timing hypothesis" maintains that exposure to estrogenic compounds soon after menopause leads to marked reductions in the risk of coronary heart disease.[1] Because isoflavones are classified as phytoestrogens it is reasonable to speculate that isoflavone exposure during the early years of menopause is protective against heart disease. However, isoflavones differ from the hormone estrogen.[2] Numerous clinical studies demonstrate this to be the case; for example, in contrast to estrogen, isoflavones have no effect on the vaginal maturation index (a measure of estrogenicity)[3] and appear not to affect postmenopausal bone mineral density,[4-6] whereas both molecules alleviate hot flashes[7] and improve endothelial function.[8]

The Women's Isoflavone Soy Health (WISH) study provides the first true test of whether isoflavones act in a manner consistent with the "timing hypothesis." In this three year randomized clinical trial, which involved 350 healthy postmenopausal women ages 45 to 92, participants were randomly assigned to groups consuming either 25 grams of isolated soy protein per day or 25 grams of milk protein.[9] The soy protein provided 99 milligrams of isoflavones (expressed in aglycone equivalent weight). The primary outcome of interest was progression of subclinical atherosclerosis as assessed by the change in carotid intima-media thickness (CIMT).

Subclinical atherosclerosis can be assessed using ultrasound to measure the thickness of the carotid arteries, which are located on both sides of the neck beneath the jawline and provide the main blood supply to the brain. The thickness of the carotid artery is referred to as CIMT. In most people, the CIMT increases or progresses over time; the extent of progression reflects risk of future coronary events.

At study termination, progression among the women consuming soy protein was 16% lower than the milk group. Although the difference was not statistically significant (p=0.35), the results are intriguing nevertheless, if a 16% decrease in the progression of CIMT translates into a 16% decrease in the risk of future coronary events. Equally important, because the difference between groups increased steadily over the three-year study period, the results suggest a longer period of soy exposure would have produced even greater benefit. Furthermore, subgroup analysis of the results according to the number of years the participants were beyond menopause shows the effects of isoflavones to be consistent with the "timing hypothesis."

Among women who were fewer than 5 years, 5 to 10 years, and more than 10 years post-menopause, CIMT progression was reduced by 68 (p=0.05), 17 (p=0.51) and 9% (p=0.77), respectively. The fact that progression was reduced so significantly in early postmenopausal women is notable for two reasons. First, because the results are consistent with those predicted by the timing hypothesis, the credibility of the findings is enhanced. Second, the results clearly implicate isoflavones as the soy component responsible for the beneficial effects.

The results of this three-year study provide the strongest evidence to date that menopausal women, especially those in the early years of menopause, benefit by consuming isoflavones. In regard to the effective dose, 99 mg isoflavones is within the accepted dietary range as it is the amount provided by about four servings of traditional soyfoods. Furthermore, since only one dose of isoflavones was used, it is possible that a lower dose would have produced a comparable benefit.

ABOUT THE AUTHOR

Mark Messina, PhD is the co-owner of Nutrition Matters, Inc., a nutrition consulting company, and is an adjunct professor at Loma Linda University. His research focuses on the health effects of soyfoods and soybean components. He is chairperson of *The Soy Connection* Editorial Board.

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SOY AND BREAST CANCER: POINT/COUNTERPOINT

By Mark Messina, PhD

The relationship between soy intake and breast cancer, which has been rigorously investigated for more than two decades, is controversial as there exists evidence suggesting soyfoods may both increase and decrease risk. Initial interest in this area of research[1] was fueled by the historically low breast cancer incidence rates in soyfood-consuming countries, especially Japan,[2] and animal data showing that adding soybean isoflavones to the diets of laboratory rats inhibited chemically-induced mammary cancer.[3] Recent evidence suggests that to derive protection against breast cancer, soy needs to be consumed during childhood and/or adolescence.[4-5] Although isoflavone exposure early in life may reduce breast cancer risk, one widely used mouse model shows that isoflavones can stimulate the growth of existing estrogen-sensitive mammary tumors.[6] Conversely, however, recent epidemiologic data show post-diagnosis soy consumption improves the prognosis of breast cancer patients.[7, 8] The point-counterpoint below highlights the most relevant data related to the issue of soy consumption by breast cancer patients and women at high risk of developing breast cancer.

Point ▶ Estrogen increases breast cancer risk therefore isoflavones increase risk because they are phytoestrogens.[9] Soyfoods increase breast cancer risk because they are uniquely rich sources of isoflavones.[10]

◀ Counterpoint Isoflavones are phytoestrogens but they are also classified as selective estrogen receptor modulators (SERMs).[11] SERMs, which include the breast cancer drug tamoxifen, can have effects similar to and opposite to those of estrogen or no effects at all in tissues that are affected by estrogen.

The effect of estrogen therapy on breast cancer risk is unclear. In the Women's Health Initiative trial, the largest trial of its kind, estrogen therapy actually decreased risk.[12] In epidemiologic studies, estrogen use is associated with a very modest increase in risk.[13] According to a recent commentary in the *Journal of the National Cancer Institute* by Chlebowski and Anderson " . . . the effect of estrogen-only formulation use on breast cancer risk in postmenopausal women, even with longer-term hormone use, still stands unanswered."[14]

Point ▶ Genistein (the primary soy isoflavone) increases the growth of estrogen-sensitive human breast cancer cells (MCF-7) in vitro[15] and stimulates the growth of mammary tumors in athymic (lacking an immune system) ovariectomized (lacking ovaries) mice implanted with these cells.[15]

◀ Counterpoint In vitro results often poorly predict in vivo effects.[16]
Athymic mice metabolize isoflavones much differently than humans so their value for understanding the effects of soyfoods in humans is unclear.[17, 18]

Recent research failed to find that genistein stimulated mammary tumor growth in athymic ovariectomized mice.[19] (The estrogen concentration of the media in which the MCF-7 cells are placed prior to implantation determines how they are affected by genistein in vivo).

Point ▶ In athymic ovariectomized mice implanted with MCF-7 cells, genistein inhibits the efficacy of tamoxifen[20] and the aromatase inhibitor letrozole.[21]

◀ Counterpoint In epidemiologic studies from China[7, 22] and the United States,[8, 23] post-diagnosis soy intake improves the prognosis (reduces recurrence and improves survival) of breast cancer patients, has no impact on the efficacy of tamoxifen[7, 8, 23] and in the one study to examine this relationship, enhanced the efficacy of the aromatase inhibitor, anastrozole.[22]

Point ▶ Clinical studies show hormone therapy (estrogen plus progestin) increases markers of breast cancer risk (breast tissue density[24] and breast cell proliferation[25, 26]) and increases breast cancer risk.[27]

◀ Counterpoint Clinical studies show neither soyfoods nor isoflavone supplements affect markers of breast cancer risk including breast tissue density and breast cell proliferation.[28]

Complete references for this article can be found at ***www.soyconnection.com***

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