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An Ecological Analysis of Menopausal Hormone Restoration

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Abstract

Background: *The Women's Health Initiative (WHI) generated lasting restrictions on menopausal hormone therapy (MHT), largely through a framework in which breast cancer incidence functioned as a surrogate for clinical harm. This framework has been applied broadly across hormone formulations and has shaped two decades of clinical policy despite significant evidentiary limitations.*

Evidence Review: *This article provides a narrative review and conceptual analysis that integrates evidence from randomized controlled trials, large observational cohorts, chemoprevention research, meta-analyses, and bone-marrow niche studies. It focuses on how these data inform: (1) the relationship between breast cancer incidence and mortality in MHT and chemoprevention; (2) 20-year WHI breast cancer mortality outcomes; (3) formulation-specific distinctions between synthetic progestins and micronized progesterone; (4) the timing hypothesis as investigated in KEEPS and ELITE; (5) late-initiation effects reported in the Baik Medicare analysis; (6) systemic harms of estrogen deficiency, including bone marrow disruption; and (7) recognition of menopause as an endocrine insufficiency.*

Findings: *Breast cancer incidence has not been consistently validated as a reliable surrogate for breast cancer mortality in the MHT or chemoprevention literature, and in several large datasets reductions in incidence have not been accompanied by clear reductions in mortality. The adverse incidence signals from WHI are attributable primarily to the CEE plus MPA combination. To date, no study has yet demonstrated an increased breast cancer mortality signal specifically attributable to tE2+MP and current evidence repeatedly demonstrates a superior cardiovascular, metabolic, skeletal, and neurocognitive profile. The 2019 Collaborative Group meta-analysis, while large, cannot distinguish tE2+MP from other formulations because the number of micronized progesterone cases was too small to permit formulation-specific conclusion. Estrogen deficiency disrupts bone marrow niche function in ways that affect hematopoiesis, immune surveillance, and tumor dormancy regulation. Menopause appears to be the only common endocrine insufficiency in which physiologic hormone restoration is systematically time-limited and discouraged on the basis of age. This is a striking contrast to lifelong restoration norms in other endocrine conditions.*

Conclusions*: Current MHT policy reflects a sex-stratified therapeutic double standard. It is the only endocrine insufficiency affecting exclusively women, managed by normalizing deficiency rather than restoring*

physiology. Restriction of tE2+MP lacks formulation-specific evidentiary justification. The persistence of a restrictive MHT therapeutic framework, based on methodologically compromised and formulation-nonspecific evidence, exemplifies an asymmetric evidentiary standard that obstructs the full implementation of ecological women's health.

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Overview

Ecological medicine views the body as an integrated system rather than a collection of organ-specific risk profiles. In women's health, it treats estrogen and progesterone as systemic hormones with regulatory roles across the cardiovascular, skeletal, bone marrow, neurocognitive, genitourinary, metabolic and immune signaling systems, and it comprehensively evaluates interventions by the long-term consequences of hormonal deprivation versus restoration.

An ecological women's health-oriented analysis of the menopause hormone therapy literature suggests that the central error of the past two decades rests on a reductive framework which conceptualizes menopausal hormone deficiency as a neutral baseline and treats breast cancer incidence as if it were a validated proxy for breast cancer mortality.

Within an ecological framework, Women's Health Initiative (WHI) findings become less paradoxical and more clarifying. At 20-year followup, conjugated equine estrogen (CEE) alone was associated with lower breast cancer incidence and lower breast cancer mortality, while CEE plus medroxyprogesterone acetate (MPA) increased incidence without a statistically significant increase in breast cancer mortality.

This pattern matters because it challenges the evidentiary logic used to restrict access to menopause hormone therapy (MHT) and physiologic dosing in older women, and to frame decades of estrogen and progesterone deficiency as a safer therapeutic practice than hormone restoration. Essentially, menopause is being managed through an anatomically reductive paradigm that isolates organ-specific risk signals while neglecting the systemic harms of prolonged endocrine deprivation, including disruption of the bone marrow microenvironment.

This raises a deeper structural question about medical institutions. The restriction of physiologic hormone restoration in menopause represents a therapeutic anomaly with no equivalent in other endocrine insufficiency conditions. It is an anomaly whose persistence is difficult to reconcile on biological or evidentiary grounds.

WHI Signal Reconsidered

The 20-year WHI follow-up reported 200 breast cancer deaths across the combined 27,347 participants from the two hormone therapy trials, including 71 and 53 deaths in the CEE plus MPA and placebo groups, respectively, and 30 and 46 deaths in the CEE-alone and placebo groups. The cohort had a mean baseline age of 63.4 years, substantial obesity prevalence, and meaningful

smoking exposure, making it older and clinically more burdened than the typical recently menopausal woman seeking hormone therapy. Annualized breast cancer mortality rates were 0.045% in the CEE+MPA group and 0.031% in the CEE-alone group, demonstrating very low absolute mortality even in this higher-risk cohort. In younger, healthier, recently menopausal women these figures represent an upper bound on expected risk—a risk-ceiling that incidence-based cautions have systematically obscured.

This salient WHI result demonstrates a dissociation between breast cancer incidence and breast cancer mortality. In women with an intact uterus, CEE plus MPA increased breast cancer incidence (HR 1.28) yet breast cancer mortality was not significantly different (HR 1.35 CI 0.94–1.95, non-significant). In women with prior hysterectomy, CEE alone reduced breast cancer incidence and reduced breast cancer mortality, with a mortality HR of 0.60 (CI 0.37 to 0.97).

WHI authors explicitly noted that CEE alone represented, to their knowledge, the first pharmacological intervention demonstrated to reduce deaths from breast cancer in a primary prevention context. This remarkable finding has received far less clinical attention than the breast cancer incidence results. This evidence supports a cautious but important inference: breast cancer incidence is not a stable or validated surrogate for breast cancer mortality in this setting. A rise in diagnosed breast tumors did not yield a clearly demonstrable rise in deaths, outcomes depended on formulation and context.

Why Incidence is a Weak Proxy for Mortality

The broader prevention literature reinforces the WHI insight. IBIS-I reporter long-term reduction in breast cancer incidence without differences in breast cancer-related mortality between tamoxifen and placebo. ASCO guidance has stated that raloxifene is not known to reduce breast cancer-specific mortality despite lowering breast cancer diagnoses. Pooled data across three tamoxifen prevention trials (N=23,360; Royal Marsden, NSABP P-1, IBIS-I) showed 226 fewer breast cancer diagnoses but 9 more breast cancer deaths in the tamoxifen groups [1]. This suggests an important conceptual separation between reducing the number of breast cancer diagnoses and reducing the number of breast cancer deaths. The epidemiological implication is that incidence is at best a partial marker and at worst a misleading surrogate when used to justify restrictions on hormone restoration. For clinical and shared decision-making, absolute mortality risk, all-cause mortality, fracture risk, cardiovascular outcomes, symptom burden, cognitive effects and quality of life are more meaningful endpoints than breast cancer incidence in isolation.

The Timing Hypothesis: KEEPS and ELITE Trial Evidence

The conventional post-WHI framing treated all hormone therapy as equivalent regardless of timing of initiation relative to menopause onset. The KEEPS and ELITE trials were specifically designed to test whether initiation of MHT close to the time of menopause produces different vascular and cognitive outcomes from late initiation.

The 2014 KEEPS (Kronos Early Estrogen Prevention Study) randomized 727 recently postmenopausal women (within 3 years of last menstrual period) to oral CEE plus progesterone, transdermal estradiol plus progesterone, or placebo, and followed carotid artery intima-media thickness (CIMT) as the primary atherosclerosis endpoint over 4 years. Neither MHT arm significantly increased CIMT progression compared with placebo, demonstrating that hormone therapy initiated early in menopause does not accelerate subclinical atherosclerosis. This finding directly contradicted the extrapolation of adverse WHI cardiovascular findings to recently menopausal women. KEEPS additionally found that neither formulation produced adverse cognitive outcomes at four years.

The 2016 ELITE (Early versus Late Intervention Trial with Estradiol) randomized 643 postmenopausal women to oral estradiol or placebo, stratified by time since menopause, and followed CIMT over a median of five years. The primary cardiovascular finding was a significant interaction between treatment and timing: among women within 6 years of menopause, estradiol was associated with significantly less CIMT progression (0.0044 mm/year) versus placebo (0.0078 mm/year, p=0.008); among women 10 or more years past menopause, no protective effect was observed.
ELITE thus provided direct RCT evidence for the timing hypothesis: estrogen initiated close to menopause confers vascular protection that is lost when initiation is

delayed. Baik 2024 Medicare analyses showed lesser though substantial systemic preventive benefits with late initiation >65. Current policies that discourage MHT initiation, restrict hormone restoration or recommend discontinuation at older ages may therefore be eliminating a therapeutic window during which cardiovascular protection is achievable.

Late MHT Initiation Analysis: BAIK 2024

The 2024 Medicare analysis by Baik, Baye, and McDonald is important because it directly addresses a question that post-WHI medicine has often treated as settled: whether menopausal hormone therapy (MHT) continued beyond, or initiated after age 65 can still confer measurable systemic benefits. In a cohort of 10 million senior Medicare women, the use of estrogen monotherapy after age 65 was associated with lower all-cause mortality and lower risks of several major outcomes, including breast cancer, lung cancer, colorectal cancer, congestive heart failure, atrial fibrillation, venous thromboembolism, acute myocardial infarction, and dementia. The authors also reported that combined estrogen-progestogen therapy showed outcome differences by formulation, route, and dose, with generally more favorable results for low-dose transdermal or vaginal preparations and estradiol rather than conjugated estrogen.

The Baik study is useful because it suggests that the net clinical effect of MHT in older women may be more favorable than long-standing age cutoffs imply.

Limitations of the Medicare Analysis

The Baik analysis is best interpreted as a large observational signal, not as definitive formulation-specific causal evidence. Baik supports the possibility of clinically meaningful benefit from MHT beyond age 65. Yet, the effect size for modern bioidentical regimens may be understated because Medicare Part D does not cover compounded hormones and imposed coverage restrictions for Prometrium (micronized progesterone).

During the Medicare coverage landscape of the 2007-2020 Baik study period, when Prometrium was under patent (2007-2012) and expensive, it required prior authorization. Thus, access barriers created a plausible under-reporting of women using compounded micronized progesterone and self-pay Prometrium, who would be misclassified as "estrogen-only" users rather than combined therapy users. The study's findings that effects vary by type, route, and dose provide strong evidence for nuanced late-life treatment. However, the automated Medicare structure is too coarse to resolve the exact risk-benefit profile of modern bioidentical hormone restoration, particularly for compounded formulations used in integrative medicine.

The American Geriatric Society: Beers Criteria

The American Geriatric Society (AGS) Beers Criteria list systemic estrogen as potentially inappropriate in adults 65 and older, and the 2023 update says initiation of oral and transdermal estrogen should be avoided in older women, with deprescribing considered for those already using nonvaginal estrogen.Beers Criteria are intended to reduce potentially inappropriate medication exposure in adults age 65 and older, but they are not a menopause-specific evidence framework and do not distinguish physiologic hormone restoration from symptom-directed endocrine management.

In practice, Beer's logic has been used to reinforce age-based caution around menopausal hormone therapy. This matters because the geriatric safety orientation and the menopause medicine orientation answer different questions. Geriatric medicine asks whether a medication is potentially inappropriate in older adults in general, while menopause medicine asks whether a specific formulation, route, and dose can restore endocrine physiology with a favorable benefit-risk balance in a given woman. When those frameworks are collapsed together, MHT can be swept into a broad age-based caution category that was never designed to separate bioidentical progesterone from synthetic progestins or to evaluate restoration against the harms of untreated estrogen and progesterone deprivation.

The result is a familiar evidentiary asymmetry with contemporary clinical implications. Once bioidentical hormone therapy becomes associated in aggregate with the older formulations tested in WHI trial data and referenced in USPSTF prevention-oriented recommendations, subsequent claims-based analyses and geriatric safety frameworks perpetuate class-wide caution, even when the actual exposure is modern bioidentical transdermal estradiol with micronized progesterone—the formulation with the most favorable safety profile.

The Bone Marrow as Ecological Hub

Current menopause policy fails to reflect the full biology of estrogen deficiency. One of its most important but least acknowledged effects is the disruption of the bone marrow microenvironment.

The bone marrow is exactly the kind of tissue a reductive organ-system framework tends to overlook. It belongs to the skeleton anatomically, to the immune system functionally, to the hematopoietic system developmentally, and maintains the dormancy state of disseminated tumor cells. The dependence of the bone marrow environment on estrogen signaling has direct implications for the risk calculus applied to hormone deprivation.

The mechanistic evidence for estrogen's role in hematopoiesis is well-characterized at the molecular level. The Nature 2014 and Haematologica 2012 articles together establish that the bone marrow niche requires estrogen not as a permissive background condition but as an active regulatory input. Estradiol maintains hematopoietic stem cell (HSC) frequency in the vascular niche through stromal cell mechanisms independent of skeletal effects. ERα-mediated signaling drives HSC self-renewal and erythropoiesis directly. In the ecological framework this article advances, these findings mean that menopause-associated estrogen deficiency reorganizes one of the body's most consequential microenvironments—not as a side effect of bone loss, but as a primary consequence of removing a direct regulatory signal.

A reductive medical framework evaluates estrogen deficiency one tissue at a time. An ecological framework sees what that conceptual orientation misses: a hormone that simultaneously generates immune effector cells, calibrates immune surveillance, and maintains the microenvironmental signals that can sustain disseminated tumor cell (DTC) dormancy. Estrogen supports B-cell lymphopoiesis, natural killer cell function, and the balance of immune tolerance. When estrogen is lost and osteoclastic remodeling increases, stromal and osteoblast-lineage signals that help maintain dormancy in the marrow niche are also disrupted. This is best understood not as separate organ-level losses, but as a simultaneous compromise of two linked tumor-suppressive systems. This raises a testable hypothesis that current trial designs cannot yet directly test or exclude: menopause-associated estrogen deprivation may destabilize dormant disseminated tumor cells and create a microenvironment permissive to metastatic outgrowth.

An ecological accounting of menopause-associated estrogen deficiency must include what an anatomically reductive model omits: the reorganization of a bone marrow microenvironment that supports blood cell production, immune defense, and tumor dormancy None of these consequences appear in the guideline frameworks that restrict MHT on the basis of breast cancer incidence. The selective omission of deprivation harms from a risk-focused literature is structural, and in menopausal women's health it consistently operates in the direction of restriction.

Systemic Benefits of Modern MHT

The evidence for tE2+MP does not merely differ from WHI CEE+MPA findings—it differs systematically and consistently across every organ system for which comparative data exist, with tE2+MP showing superior or equivalent benefit and lower risk across cardiovascular, metabolic, skeletal, neurocognitive, and breast cancer endpoints.

Table 1: MHT Formulations and Key Endpoints

Endpoint	CEE+MPA (oral)	CEE alone (oral)	Transdermal estradiol (tE2) + micronized progesterone (MP)
Breast cancer incidence	Increased incidence vs placebo in WHI	Decreased incidence vs placebo in WHI hysterectomy arm	No significant increase in E3N overall; small ↑ with >5y use
Breast cancer mortality	No statistically significant increase vs at 20-yr follow-up	Reduced mortality vs placebo (HR 0.60) at 20-yr follow-up	No study showing increased mortality; data sparse and largely observational
VTE	Clear ↑ VTE risk with oral route	↑ VTE risk with oral route	VTE risk similar to background in route-stratified studies; MP adds no VTE burden
CVD	In older, late initiating cohort: adverse signals (MI, stroke) drove cautions	Some neutral / beneficial signals in older, higher-risk women; not designed for early-initiation test	Early postmenopausal estradiol in ELITE: slower CIMT progression; transdermal avoids first-pass prothrombotic effects
Fracture/skeletal outcomes	Reduces fractures while on therapy; benefit lost with discontinuation	Reduces fractures; skeletal benefit recognized but overshadowed by perceived cancer / CVD risks	Robust skeletal protection; aligns with estrogen's known anti-resorptive effects and osteoporosis prevention
Cognition / dementia	WHIMS cognitive harm signal with late initiation in older women	Similar late-initiation concerns; not a clean test of early neutral / favorable effects.	KEEPS/ELITE: no cognitive harm with early initiation over several years; possible memory benefit; long-term dementia impact still uncertain
Data type and strength	Large RCT (WHI) with long follow-up, but older, higher-risk population and non-physiologic formulation	Large RCT (WHI hysterectomy arm), same limitations of age and formulation	Mix of RCTs (KEEPS, ELITE for vascular / cognitive endpoints, large cohorts (E3N, Baik) and mechanistic data

Cardiovascular: Transdermal delivery resolves the principal cardiovascular safety objections to estrogen therapy. A fourfold VTE elevation associated with oral estrogen (OR 4.2) is not replicated with transdermal estradiol (OR 0.9), the stroke risk of oral formulations disappears with route change, and early initiation is associated with significantly reduced atherosclerosis progression in the ELITE trial. Micronized progesterone carries no VTE burden and does not raise blood pressure—a profile that makes the continued application of oral CEE+MPA cardiovascular risk data to tE2+MP pharmacologically implausible.

Metabolic: Menopausal hormone therapy is associated with a reduced incidence of new-onset type 2 diabetes and with favorable effects on visceral fat distribution and insulin sensitivity in postmenopausal women.

Skeletal: The protective effect of MHT against osteoporosis and osteoporotic fracture is among the most consistently replicated findings in the menopause literature, demonstrated across randomized controlled trials, observational cohorts, and meta-analyses. Guidelines that restrict MHT use withdraw a well-established skeletal protection intervention from the postmenopausal population most exposed to fracture risk.

Neurocognitive: KEEPS and ELITE suggest that menopausal hormone therapy initiated near menopause does not impair cognition over several years, and KEEPS-related data suggest transdermal estradiol may be associated with better verbal or episodic memory. This directly contradicts the generalization of the WHIMS (CEE±MPA) cognitive harm signal to this population. Whether early tE2+MP reduces long-term dementia risk remains an open research question that neither trial was powered or followed long enough to answer.

Breast cancer: In the E3N prospective cohort, estrogen combined with micronized progesterone (MP) was not associated with significantly increased breast cancer risk (RR 1.00 CI 0.83–1.22), in contrast to estrogen combined with synthetic progestins (RR 1.69 CI 1.50–1.91). E3N data also suggested that longterm (>5 years) of MP use was associated with a small increase in breast cancer incidence (HR 1.31 CI 1.15-1.48). The 2019 Collaborative Group meta-analysis included only a very small number of women using micronized progesterone—too few to permit formulation-specific conclusions.

An Endocrine Double Standard

A core principle of endocrine replacement therapy is to replace deficient hormones and aim for physiologic or near-physiologic levels and effects. This principle is applied without controversy to hypothyroidism, adrenal insufficiency, male hypogonadism, and insulin deficiency. Its application to estrogen and progesterone deficiency in postmenopausal women is an outlier.

This asymmetry is not derived from the biology of the conditions, but rather from a historical framework of how endocrine conditions are culturally and institutionally classified.

Table 2: Endocrine Insufficiency: Comparative Analysis

Endocrine Insufficiency	Physiologic Restoration	Restriction by Age
Type 1 diabetes (insulin deficiency)	Yes, universal	No
Hypothyroidism (T4/T3 deficiency)	Yes, universal	No
Adrenal insufficiency (cortisol deficiency)	Yes, universal	No—intensified with age
Male hypogonadism (testosterone deficiency)	Yes, routine	No—older men actively treated
Premature ovarian insufficiency (<40 yrs)	Yes, strongly endorsed to age 51	No
Menopause (estrogen/ progesterone deficiency)	Symptom control with subphysiologic doses, age-based restrictions	Yes—older age explicitly cited

Clinical guidelines recommend physiologic hormone restoration in premature ovarian insufficiency (POI) on the grounds that estrogen deficiency before the age of natural menopause carries well-documented risks to

cardiovascular, skeletal, neurological, and overall health. Those same risks (bone loss, cardiovascular disease, immune dysregulation, bone marrow microenvironment disruption) are present in a woman who becomes estrogen-deficient at 51 or 52, yet the management standard shifts to subphysiologic dosing oriented toward symptom relief and age-based discontinuation, rather than physiologic restoration. The biological basis for this asymmetry does not exist in the endocrinology of estrogen deficiency. It exists in a clinical and cultural classification bias which conceptualizes a reproductive-age woman's hormone insufficiency as an important treatable condition, and a post-reproductive-age woman's hormone insufficiency as a natural state to be managed palliatively with subphysiologic dosing.

This pattern reflects an institutional asymmetry in evidence evaluation. The original therapeutic restrictions were adopted on the basis of evidence that subsequent analyses revealed to be formulation-specific and methodologically limited. Yet the evidence threshold required to revise those restrictions remains substantially higher than the threshold used to impose them. The primary question of what sustained estrogen deprivation costs the female body across multiple organ systems was unimplemented as a designated a primary endpoint in MHT trial methodology.

Although the FDA removed breast cancer, cardiovascular, and dementia boxed warnings from MHT products in early 2026, clinical guidelines remain unchanged and rely on outdated, formulation-blind restrictions.

- ACOG Practice Bulletin 141 (reaffirmed 2024) continues to recommend "lowest dose for shortest duration", based on outdated CEE/MPA risk data.
- USPSTF maintains its 2022 Grade-D recommendation against MHT for chronic disease prevention using WHI data.
- Endocrine Society upholds its 2015 stance against MHT for primary prevention.
- American Geriatrics Society's 2023 Beers Criteria recommends avoiding initiation of systemic estrogen and considering deprescribing in adults over 65 already using it.

The Burden of Proof and Evidentiary Logic

Current MHT prescribing restrictions are grounded in a chain of inference from the available evidence. That chain contains logical errors that have not been systematically addressed in the clinical literature sustaining those restrictions.

Absence of Evidence of Harm ≠ Evidence of Harm

The logical error at the center of the evidence-gap reasoning for MHT restriction is the argument from ignorance. Inferring that tE2+MP is unsafe because its long-term safety has not been confirmed by RCT data is not a precautionary inference—it's a logical fallacy. Absence of confirmatory safety data is not evidence of harm; it is evidence of incomplete data. That incomplete data problem is equally applicable to the alternative: no adequately powered RCT has examined the impact of sustained estrogen deprivation on women's all-cause mortality over decades.

Burden of Proof

Estradiol is an essential endogenous molecule with broad systemic and reproductive functionality. Its designation as a hazardous exogenous agent is not an evidence-based biological conclusion but an inferential one requiring affirmative evidentiary support. The therapeutic restriction extends risk signals from a non-physiologic formulation (CEE+MPA) to a bioidentical formulation (tE2+MP) that was not studied in WHI trials. The burden of demonstrating that this extrapolation is valid rests with those who originated and continue to defend MHT restrictions, not with clinicians whose practice reflects physiologic hormone restoration principles or with women whose values and treatment preferences are oriented toward an integrated ecological health framework.

Symmetrical Assessment of Harm

Any future risk signal for tE2+MP must be assessed against the full clinical burden of the untreated hormone insufficiency. The consequences of prolonged estrogen deficiency are well-established. They include skeletal demineralization, cardiovascular and metabolic deterioration, urogenital atrophy, vasomotor morbidity, sleep disruption, sexual dysfunction, depression, and cognitive decline. A benefit-risk calculation that counts treatment harms while excluding deprivation harms is not a neutral assessment of evidence. This asymmetry in how treatment risks and deprivation harms are

accounted for in women's health is not a feature of the evidence—it's a feature of the framework applied to the evidence.

Ecological Women's Health

An ecological women's health paradigm recognizes estrogen and progesterone as systemic hormones with reproductive functionality. Instead of asking only whether hormone exposure increases organ-specific risk, it asks what systemic functions are impaired by long-term deprivation of ovarian hormones within the cardiovascular, skeletal, bone marrow, neurocognitive, metabolic, genitourinary, thermoregulatory, connective tissue and immune signaling ecologies. This changes what counts as evidence and what counts as harm, and it reframes the unit of analysis from isolated organ risks to a woman's integrated physiology, and orients hormone restoration within a comparative risk/benefit analysis.

Two clinical paradigms generate two different questions. The reductive paradigm treats postmenopausal estrogen deficiency as a natural neutral state and asks what risks are added by pharmaceutical intervention. The ecological paradigm treats deficiency as a biologically consequential deviation from a woman's optimal hormonal environment and asks what comparative outcomes are produced by restoration versus deprivation over the long term. WHI was not designed within an ecological framework. It compared a specific pharmaceutical formulation against a deprivation baseline, treating female hormone deficiency as the neutral comparator rather than as the condition under investigation.

Implications for Women's Health Equity

Current menopause policy embeds a structural inequity: it normalizes prolonged estrogen and progesterone deprivation in midlife and older women while treating other endocrine insufficiencies with lifelong physiologic restoration. The result is a sex-stratified therapeutic double standard in which a condition affecting only women is managed by accepting systemic deficiency as "natural" and scrutinizing treatment harms, while the harms of deprivation—fracture, cardiovascular disease, neurocognitive decline, immune dysregulation, and bone marrow niche disruption—remain largely unmeasured and absent from guidelines.

This evidentiary asymmetry functions as a form of institutional bias: lower-quality, formulation-nonspecific data (WHI CEE+MPA) were sufficient to restrict access to hormone restoration, but higher-quality, formulation-specific and timing-sensitive evidence has not been granted equal power to revise those restrictions. Women's autonomy is further constrained when breast cancer incidence is used as a proxy for mortality without acknowledging its failures as a surrogate or the ecological consequences of untreated hormone deprivation [1-29].

Conclusion

An ecological women's health assessment of the evidence relocates uncertainty to where it belongs: not simply in the question of whether hormones carry any risk, but in the much larger question of the biological costs of prolonged estrogen and progesterone deficiency on untreated women across the post-reproductive lifespan. Multiple independent lines of evidence—WHI 20-year follow-up, the E3N cohort formulation-stratified analyses, the KEEPS and ELITE trials, the Canonico route-of-administration VTE data, the chemoprevention trial mortality record, and the logic of comparative endocrinology—converge on conclusions that the current therapeutic framework has not adequately incorporated: (1) breast cancer incidence is not a validated mortality surrogate; (2) synthetic progestins are the primary driver of adverse MHT signals; (3) bioidentical tE2+MP carries a distinct and more favorable risk profile; (4) transdermal delivery appears not to increase thrombotic risk and, in pooled analyses, has a VTE risk indistinguishable from background levels; and (5) population-level restrictions on physiologic hormone restoration lack proportionate formulation-specific justification in evidence. The timing of MHT initiation determines the magnitude of systemic protective benefit—with the greatest effects associated with initiation within ten years of menopause, and with potential systemic benefits persisting with later initiation.

There is no other endocrine insufficiency in medicine managed by systematically withholding physiologic restoration on the evidentiary basis applied here: evidence from a non-physiologic formulation, generalized across formulation classes without justification, within a framework that scrutinizes treatment risks but not deprivation harms. The corrective framework

is ecological: evaluate restoration against deprivation, distinguish formulations, treat the whole woman as the unit of analysis, optimize timing, and apply the burden of proof symmetrically. Women's health policy that falls short of this standard does not meet the criteria of evidence-based medicine.

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