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Use of Menopausal Hormone Therapy Beyond Age 65 Years
(and Its Effects on Women's Health Outcomes Summary)

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BACKGROUND:

The US Centers for Medicare and Medicaid Services **(CMS**) and the Virtual Research Data Center **(VRDC**)[9] provided 14 years of prescription claims, 21 years of diagnosis claims and vital status for almost all U.S. women aged 65 years or older. VRDC provides hormone therapy (**HT**) exposure data as well as outcomes data about death, dementia, cardiovascular (**CV)**, and cancer, conditions like those studied by the Women's Health Initiative **(WHI**) trials. Given that at least 2%-7% of elderly women still use hormone therapy (HT) after age 65 years, the VRDC data is large enough to shed light on the consequences of HT use after 65 years.

Goal of Study: Describe the usage of HT in women age ≥65 years and to determine the influence of such usage on the survival and on the occurrence of *WHI-like* outcomes (five cancers, six CV conditions, dementia and all-cause mortality).[1,4] The five cancer outcomes included breast, lung, endometrial, colorectal, and ovarian cancers. The six CV outcomes included ischemic heart diseases (**IHD**), heart failure **(HF**), venous thromboembolism (**VTE**), stroke, atrial fibrillation (**AF**), and acute myocardial infarction (**AMI**).

Over 14 years of follow-up (2007-2020), the proportion of senior women taking any form of estrogen dropped by half, from **11.4% to 5.5%.** Over the years Estradiol **(E2)** tended to replace conjugated equine estrogens (**CEE)** (Premarin). Estrogen/progesterone therapy **(EPT**) plummeted from 1.4% to a minuscule 0.2%. The vaginal route tended to replace the oral route. Overall, the number of estrogen (**ET**) users was *>10 times* greater than that of EPT or progestogen alone users. Among ET users, the predominant route was vaginal. Twice as many women were on vaginal and one-third as many on transdermal as oral estrogen preparations.

DISCUSSION

For decades, menopausal HT after age 65 years was considered to be unnecessary because symptoms due to estrogen withdrawal rarely persisted beyond age 65. However, a growing body of evidence suggests that some vasomotor symptoms do persist in many elderly women,[7] and thus HT can benefit them. Recognizing this reality, in 2022, The *Menopause Society* changed their position about use of HT in women aged 65 years and older,[8] suggesting that the "decision to start or continue HT beyond age 65 years should be individualized and highlighted the use of lower doses and nonoral preparation to minimize risks of adverse effects". In this study, we explored the initiation and continuation of menopausal HT beyond age 65 years and the effects of 40 different HT preparations on 13 different health outcomes.

Compared with *never used or discontinuation of HT after 65 years*, **Estrogen Therapy use beyond age 65 was associated with *significant risk reductions* in:**

- **Mortality**
- **Cancer:** Breast, Lung, and Colorectal
- **Cardiovascular**: Heart failure, Blood Clots, A-Fib, and Heart Attack
- **Dementia**.

Generally, risk reduction was greater for estradiol (E2) preparations, vaginal and transdermal, and low or medium doses (vs high dose). For EPT use, E+progestin marginally exhibited risk reductions in endometrial and ovarian cancers, IHD, CHF, and VTE, whereas E+ progesterone exhibited risk reduction only in CHF.

Association with All-Cause Mortality

Oral CEE 0.625 mg, [the only estrogen-only preparation studied in the WHI trials], exhibited a significant *6% mortality reduction* in the 18-year cumulative follow-up of the WHI trials. The *19% mortality reduction* we observed with ET overall is consistent with the results from a meta-analysis of 31 other observational and RCT (random controlled trials) studies that reported reduced mortality among HT users. Additionally, reanalysis of the *Prostate, Lung, Colorectal, and Ovarian Cancer Screening RCT,* reported a *23% decrease in all-cause mortality* among current users of any HT. Medium (0.625 mg) dose of oral CEE+progestin exhibited no mortality risk reduction in both our study and the 18-year cumulative follow-up of the WHI trials. However, our study found significant mortality reduction associated with different EPT preparations, including low dose of oral CEE+progestin, CEE+progesterone, E2+progestin, and medium dose of oral and transdermal E2+progestin, confirming the *Menopause Society's 2022* position statement advice on mitigation of risk through use of the low dose, non-oral route of administration, and different types of estrogen and progesterone.

Associations with Cancers

Breast:

Overall ET and medium dose of oral CEE, in our study, were associated with *16% and 26% reductions* of breast cancer risk, respectively. Overall EPT and medium dose oral CEE+ progestin (Provera) were associated with the opposite - a *10%-19% increase* in breast cancer risk. The WHI Study reported a significant, and similarly sized, 21% decreased risk of breast cancer with CEE alone and a *28% increase* with CEE+medroxyprogesterone (Provera), giving credence to our results. Importantly, our study found an insignificant, but numerically reduced risk of breast cancer associated with two EPT (low dose of transdermal and vaginal E2+ progestin).

Lung and Colo-Rectal:

On average, ET use was also associated with significant *13% and 12% risk reductions* for lung and colorectal cancers, but EPT had no association with these two cancers. In contrast, the WHI postintervention study only reported insignificant associations for lung and colorectal cancers. However, our results were based on at least 100,000 cases of *each cancer*, 1,000 times more cases than that of the WHI postintervention study, providing much greater statistical power to see associations. A few observational studies support our findings of reduced lung cancer risk in association with HT use. Two observational studies and a reanalysis of the Prostate, Lung, Colorectal, and Ovarian trial data[28] support our protective associations between HT use and colorectal cancer. The greater incidence of colorectal (79%) and lung cancer (26%) among women with lower levels of estrogen due to oophorectomy as part of their hysterectomy compared with hysterectomized women without ovary removal also supports our results of ET use by implying that estrogen protects against these two cancers.

Associations with CV Diseases and Dementia

Similar to the results of oral CEE 0.625 mg in the WHI postintervention study,[5] our medium dose of oral CEE exhibited no risk reductions in either six CV conditions or dementia. Our results also suggest significant risk increases for IHD and stroke associated with medium dose of oral CEE. However, low-dose ET was associated with significant risk reductions for all CV conditions and dementia. Transdermal and vaginal ET which should avoid the procoagulant and proinflammatory effects ascribed to liver passage exhibited reduced risk of both dementia and stroke, in accord with the results of other studies.

When used alone, (natural) progesterone was associated with significantly decreased risks of three CV conditions (CHF, VTE, and AMI), whereas progestin exhibited no risk reductions at all. However, when combined with estrogen, CEE+progestin did exhibit significant risk reductions in IHD, CHF, and VTE, whereas CEE+progesterone exhibited risk reduction for CHF alone.

Strengths and limitation

Our data availability only began at age 65 years, and information on hysterectomy and other health conditions before Medicare year was unavailable, and thus we did not have a way to correct for them. We depended on claims for encounter diagnoses and could not validate them through chart review. As is true for all observational studies, differential influences of unmeasured confounders, such as adherence to healthy behavior among HT users, could have been present.

One strength was the **use of filled prescription records**, rather than (memory) recall, to ascertain HT use. Another strength was its sample size ***(>10 million women***), including almost all menopausal women aged ≥65 years and the incidence of each outcome (up to 1.6 million women)—nearly an order of magnitude greater than any previous HT study. Its massive sample size and incidence enabled us to estimate differential effects of 40 different HT type, route, and dose combinations on study outcomes.

CONCLUSIONS

Our study suggests the possibility of important health benefits with use of menopausal HT beyond age 65 years. The use of ET, mostly prescribed to women without intact uterus, can protect against risks of all-cause mortality, developing cancers (breast, lung, and colorectal), CHF, VTE, AF, AMI, and dementia. The benefits of EPT for women who still have their uterus are less clear. The use of EPT (does not increase risks for almost all conditions but does increase the risk of breast cancer (using Provera).

Our follow-up review began when women entered Medicare at about age 65 years, but it is likely that many of them started taking HT closer to the time of onset of their menopausal symptoms and continued it into their Medicare years. If so, our positive results align with the timing hypotheses that asserts that HT use *early* in menopause is better than later and extends it by reporting positive effects with usage continued into Medicare years. Our findings offer important insights into the variations among different menopausal hormone therapies, which could assist in tailoring postmenopausal HT on an individual basis.