OXFORD

Journal Of The National Cancer Institute, 2023, **115(2)**, 222–223
https://doi.org/10.1093/jnci/djac213
Advance Access Publication Date: 21 November 2022
Correspondence

RE: Systemic or vaginal hormone therapy after early breast cancer: a Danish observational cohort study

Rowan T. Chlebowski, MD, PhD,[1,*] Aaron K. Aragaki, MS,[2] Kathy Pan, MD[1]

[1]The Lundquist Institute, Torrance, CA, USA
[2]Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, WA, USA

*Correspondence to: Rowan T. Chlebowski, MD, PhD, The Lundquist Institute, 1124 W. Carson St, Torrance, CA 90502, USA (e-mail: rowanchlebowski@gmail.com).

Cold and colleagues (1) report findings by menopausal hormone therapy (MHT) use without providing the hormone therapy category. Both estrogen plus progestin and estrogen alone are described as increasing breast cancer incidence and mortality in women without breast cancer history, citing 2 large observational studies published in 2019. However, not cited was a 2020 report from 2 Women's Health Initiative randomized placebo-controlled trials with 27 347 postmenopausal women with no prior breast cancer and mammogram clearance, evaluating estrogen plus progestin and estrogen alone (for women with prior hysterectomy). After 20 years of follow-up and 1565 incident breast cancers, estrogen plus progestin increased breast cancer incidence, whereas estrogen alone decreased breast cancer incidence and breast cancer mortality (2). Against such randomized trial findings, it is inappropriate to report findings without describing the MHT therapy category because differential effects on breast cancer outcomes could be anticipated. The authors should provide this information.

Regarding the randomized trial evidence of MHT safety in breast cancer survivors, Cold and colleagues (1) report that, in the HABITS trial, "MHT increased risk of recurrence" whereas the "association was not reproduced" in the Stockholm report. However, individual outcomes are instructive (see Table 1 provided below, therapy category details provided in citations). Including a feasibility randomized trial from The Royal Marsden, a total of 920 women were randomized, and there were 167 breast cancer recurrences (3,4). Pooling data across the 3 trials yields a relative risk of 1.53 (95% confidence interval = 1.15 to 2.03) based on the usual asymptotic formula for a 2 × 2 contingency table (5). Against such randomized clinical trial evidence suggesting approximately 50% more breast cancer recurrences with MHT use, Cold and colleagues (1) conclude that MHT "was not associated with an increased risk of recurrence" based on findings in only 117 women who chose to use MHT (out of the 8143 diagnosed over 8 years in their breast cancer survivor cohort) and suggest the findings "contrast somewhat" with the randomized trial evidence.

The safety of MHT use in breast cancer survivors has been a concern for decades. In 2005, this issue was examined in a meta-analysis including 2 randomized trials and 8 observational studies. Findings then suggested that, in randomized trials, MHT increased breast cancer recurrence risk, whereas in observational studies, MHT use was associated with lower recurrence risk (6). Perhaps it should not be surprising that 17 years later, with updated findings, the same discordance is seen, with findings from randomized trials suggesting harm and an observational study suggesting safety. Continuation of observational studies, despite contrary randomized trial evidence, has been described as "circular epidemiology" (7). In what other setting are clinical breast cancer recommendations based on observational studies when randomized clinical trial evidence is available? Clinicians, and especially breast cancer survivors, should be aware of the limitations of the conclusions of Cold and colleagues (1) regarding MHT safety for use after breast cancer, especially in consideration of the mortality risk associated with breast cancer recurrence.

Funding

Supported by National Cancer Institute grants R01 CA119171 and R01 CA10921.The Women's Health Initiative was funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts The Women's Health Initiative program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. R25CA203650 also supported this manuscript.

Notes

Role of the funder: The funders had no role in the concept, design, preparation, writing, or review of this correspondence.

Disclosures: Rowan T Chlebowski reported receiving personal fees from Novartis, AstraZeneca, and Up-To-Date and reported receiving grant support from the National Institutes of Health. No other authors reported conflicts.

Received: August 19, 2022. **Accepted:** November 08, 2022

Table 1. Randomized trials: recurrence risk among women with early-stage breast cancer by menopausal hormone therapy[a]

	Hormone therapy use		No hormone	
	Total	Breast cancer recurrence	Total	Breast cancer recurrence
Marsden (Col 2005) (6)	51	2	49	1
HABITS (Holmberg 2008) (3)	221	39	221	17
Stockholm (Fahlen 2013) (4)	188	60	190	48
Total	460	101	460	66

[a] Pooling data across the 3 trials yields a relative risk of 1.53 (95% confidence interval = 1.15 to 2.03).

Author contributions: Conceptualization: RTC, KP, AKA. Methodology: RTC, KP, AKA. Validation and Formal analysis: AKA. Resources: RTC. Writing—Original Draft: RTC. Writing—Review & Editing: RTC, KP, AKA. Funding acquisition: RTC.

Prior presentations: An abstract of some of the findings was presented at the San Antonio Breast Cancer Symposium, December 7, 2021.

Data availability

Data are from previous publications which are cited in this correspondence. No new data were generated or analyzed in this correspondence.

References

1. Cold S, Cold F, Jensen MB, et al. Systemic or vaginal hormone therapy after early breast cancer: a Danish observational cohort study. *J Natl Cancer Inst*. 2022;114(10):1347-1354.
2. Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative Randomized Clinical Trials. *JAMA*. 2020;324(4):369-380.
3. Holmberg L, Iversen OE, Rudenstam CM, et al.; HABITS Study Group. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst*. 2008;100(7):475-482.
4. Fahlén M, Fornander T, Johansson H, et al. Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial. *Eur J Cancer*. 2013;49(1):52-59.
5. Altman DG. *Practical Statistics for Medical Research*. London, UK: Chapman & Hall; 1990.
6. Col NF, Kim JA, Chlebowski RT. Menopausal hormone therapy after breast cancer: a meta-analysis and critical appraisal of the evidence. *Breast Cancer Res*. 2005;7(4):R535-40.
7. Kuller LH. Circular epidemiology. *Am J Epidemiol*. 1999;150(9):897-903.