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Menopausal hormone therapy: assessing associations with breast and colorectal cancers by familial risk

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Abstract

Menopausal users of hormone replacement therapy (HRT) are at increased breast cancer risk and decreased colorectal cancer (CRC) risk compared with individuals who have never used HRT, but these opposing associations may differ by familial risk of breast cancer and CRC. We harmonized data from 3 cohorts and generated separate breast cancer and CRC familial risk scores based on cancer family history. We defined moderate or strong family history as a risk score of 0.4 or higher, where 0.4 was equivalent to a 50-year-old woman with 1 parent diagnosed with either breast cancer or CRC at 55 years of age. Of 24 486 women assessed, 1243 and 405 were diagnosed with incident breast cancer and CRC, respectively. For breast cancer, menopausal HRT ever use versus never use hazard ratios were 1.27 (95% CI = 1.11 to 1.45) for a breast cancer familial risk score below 0.4 and 1.01 (95% CI = 0.82 to 1.25) for a breast cancer familial risk score of 0.4 or higher ($P_{\text{difference}} = .08$). For CRC, menopausal HRT hazard ratios were 0.63 (95% CI = 0.50 to 0.78) for a CRC familial risk score below 0.4 and 1.21 (95% CI = 0.73 to 2.00) for a CRC familial risk score of 0.4 or higher ($P_{\text{difference}} = .03$). Associations with menopausal HRT use that apply to the general population may not hold for women at moderate or strong familial risk of these cancers.

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Epidemiological studies have found that women who have ever used menopausal hormone therapy, commonly referred to as hormone replacement therapy (HRT), are at approximately 20% increased risk of breast cancer but at approximately 20% decreased risk of colorectal cancer (CRC) compared with women of the same age who have never used HRT,^{1,2} although only a small proportion of women in these studies had a family history of these cancers. When counseling patients about risk, a common approach to estimate the overall risk from family history and menopausal HRT is to multiply the 2 relative risks, then multiply the product by the absolute risk for people without a family history and who do not use menopausal HRT.³ Studies using polygenic risk scores show that both breast cancer and CRC associations were strongest in the highest quintile of risk,^{4,5} but these polygenic risk scores explain less than 20% of the familial relative risk.^{6,7} As we observed differences in breast cancer risk for other exposures due to family history,^{8,9} we examined whether these menopausal HRT associations also applied to women at higher baseline risk because of their family history of cancer—a key clinical issue for risk management in such individuals seen in cancer genetic clinics because most of them are found not to carry high-risk genetic variations.¹⁰

We harmonized data from 3 international cohorts: the Prospective Family Study Cohort (ProF-SC) baseline data from 1992 to 2011, the Colon Cancer Family Registry Cohort (CCFRC) baseline data from 1997 to 2012, and the Melbourne Collaborative Cohort Study (MCCS) follow-up visit 2 data from 2003 to 2007. The ProF-SC comprises baseline and follow-up data from the Breast Cancer Family Registry Cohort, formed by a collaboration among 6 centers in the United States, Canada, and Australia and the Kathleen Cuninghame Foundation Consortium for Research into Familial Breast Cancer.¹¹ The CCFRC was formed by a collaboration among 7 sites in the United States, Canada, and Australia.¹² The MCCS is a prospective study of participants recruited in Melbourne, Australia.¹³ All participants provided written informed consent before enrollment, and the study protocols were approved by institutional review boards. We harmonized cancer risk factor data collected using questionnaires, which captured demographic characteristics; height and weight; reproductive history; lifestyle factors; and first-degree family history of breast cancer and CRC, including age at diagnosis. Information about vital status, with date or age of death (where applicable), was obtained from population registries and proxy reports. We sought confirmation of all reported invasive breast cancer and CRC diagnoses and ages at diagnosis for participants using pathology reports, medical records, cancer registry reports, and death certificates, where possible.^{11,13}

Eligible participants included women aged 45 to 75 years at baseline without a personal history of any cancer and not known to have pathogenic (or likely pathogenic) variants in *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, or *PMS2*. For breast cancer and CRC, we generated the following:

familial risk score = $\log((\text{individual 5-year risk calculated by Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm}^{14} \text{ and CRISP}^{15,16} \text{ risk tools, respectively}) / \text{population average risk for each age})$

We modeled risk associations with the breast cancer and CRC familial risk scores as continua, and they did not diverge appreciably from linearity ($P > .05$). As the median familial risk score in these cohorts was 0.4 for women with a family history of either disease, we defined moderate to strong family history as a risk score of 0.4 or above, where 0.4 was equivalent to a 50-year-old

woman with 1 parent diagnosed with either cancer before 55 years of age. Time at risk of breast cancer or CRC started at 2 months after the baseline questionnaire (to exclude undetected cancers at baseline) and continued to the first of date of diagnosis of invasive breast cancer or CRC, date last known to be undiagnosed with breast cancer or CRC, date of death, or (for breast cancer) date of bilateral mastectomy. We used Cox regression, with age as the time scale, to estimate hazard ratios and 95% confidence interval (CI) for menopausal HRT use, stratified by study and adjusted for body mass index, parity, education level, alcohol consumption, smoking status, oral contraceptive use, and country of residence. We evaluated menopausal HRT use by never or ever use; secondary analyses included never, former, or current use; age at baseline (<60 or ≥ 60 years); duration of menopausal HRT use (<5 or ≥ 5 years); and whether women had had a hysterectomy, all measured at baseline. We assumed that women on menopausal HRT were using a combined therapy unless they reported having had a hysterectomy, in which case we assumed the use of estrogen alone. For all analyses, the referent group was women who reported never on menopausal HRT. Tests of the proportional hazards assumption were based on Schoenfeld residuals. A robust variance estimator was used to account for multiple family members within the cohorts. We specified cross-product terms to test for multiplicative interactions of menopausal HRT with breast cancer and CRC familial risk scores. Statistical significance was determined as P less than .05 for a 2-sided hypothesis test. Analyses were conducted using Stata, version 16.1, statistical software (StataCorp LP).

There were 310 789 person-years of observation of 24 488 women (ProF-SC, $N = 6181$; CCFRC, $N = 6726$; MCCS, $N = 11 581$), of which 1243 individuals were diagnosed with incident breast cancer and 405 with incident CRC (Table S1). Hazard ratio estimates for ever use vs never use of menopausal HRT, not stratified by family history, were 1.20 (95% CI = 1.07 to 1.34) for breast cancer and 0.73 (95% CI = 0.59 to 0.90) for CRC. Menopausal HRT ever use vs never use hazard ratios by continuous variables of breast cancer–specific and CRC–specific familial risk scores show that the confidence intervals cross 1.0 at a familial risk score of approximately 0.4 for both breast cancer and CRC (Figure 1). For breast cancer, menopausal HRT hazard ratios were 1.28 (95% CI = 1.12 to 1.46) for a breast cancer–specific familial risk score less than 0.4 and 1.02 (95% CI = 0.83 to 1.27) for a score of 0.4 or higher ($P_{\text{difference}} = .08$). For CRC, menopausal HRT hazard ratios were 0.66 (95% CI = 0.53 to 0.83) for a CRC–specific familial risk score below 0.4 and 1.21 (95% CI = 0.74 to 1.98) for a score of 0.4 or higher ($P_{\text{difference}} = .03$).

Breast cancer risk secondary analyses did not find any major differences (all $P_{\text{interaction}} > .05$), except for family history of breast cancer (Figure 2)—that is, there was no evidence for multiplicative risk of menopausal HRT use by family history. For women without a family history of CRC, there was no evidence of differences in the negative risk associations by subgroups (all $P_{\text{interaction}} > .05$). For women with a family history of CRC, there was no evidence of an association with decreased risk for any of the subgroups of menopausal HRT use, although hazard ratios were imprecise.

Using a pooled analysis of 3 large prospective cohorts, we demonstrated the utility of examining the associations of menopausal HRT use across 2 common cancers, stratifying on cancer family history. Just as breast cancer and CRC have distinct etiologies, as reflected in the different directions of their associations with menopausal HRT use, these results suggest that they may also be the distinct etiologies within a given cancer for women

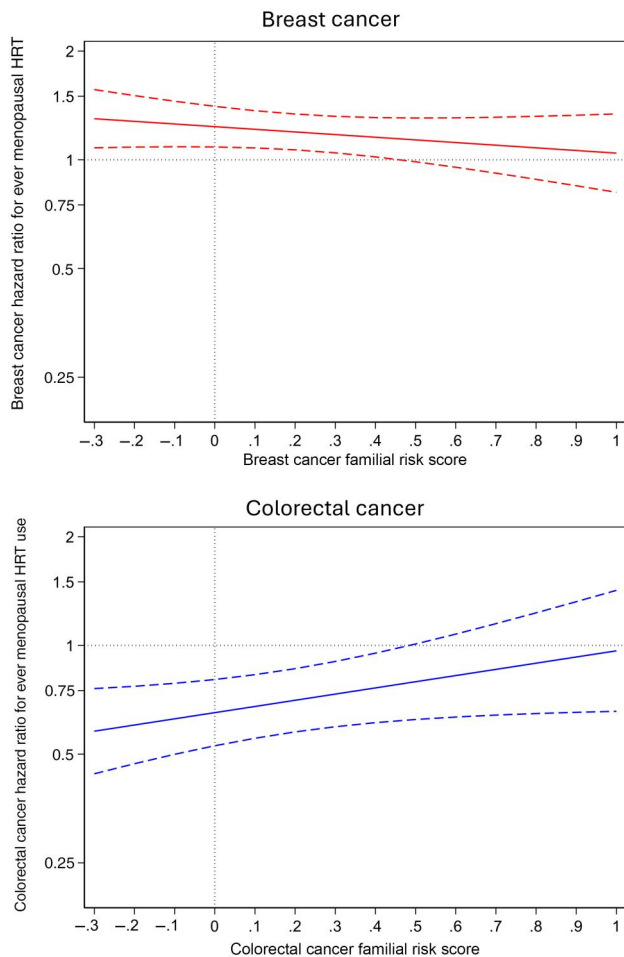


Figure 1. Hazard ratios (solid lines) and 95% confidence intervals (dashed lines) of breast and colorectal cancer risk in relation to ever vs never use of menopausal HRT by their cancer-specific familial risk score. A familial risk score of 0 denotes the population average. Analyses were stratified by study and adjusted for body mass index (continuous), parity (0, 1, 2, 3, ≥ 4 live births), education level (high school or less, some college or university, bachelor's degree or higher), smoking status (never, former, current), oral contraceptive use (never, ever), and country of residence (Australia, Canada, United States). HRT = hormone replacement therapy.

with a family history of that cancer. Cancer risks for individuals with a moderate to strong family history may be influenced more by early-life exposures rather than hormone exposures such as menopausal HRT later in life.¹⁷ It is, however, currently unknown how menopausal HRT use could influence the risk of CRC.¹⁸

A key strength of this study was that we collected data to estimate a woman's absolute risks of breast cancer and CRC based on the number of relatives with these cancers as well as the relatives' ages at cancer diagnosis. Given our oversampling of cancer families, we were able to informatively study risk estimates for women across the continuum of familial risk scores as well as stratify the results based on no, minimal, or moderate to strong family history; there were at least 50 incident breast or colorectal cancer cases for most subanalyses. Further, we adjusted for several potential confounders measured in similar ways and data harmonized. Some women with moderate to strong family history may have chosen not to take menopausal HRT because of worries of their risk being further increased, but most of the participants were exposed before the landmark Women's Health Initiative

clinical trial results were published in 2002.¹⁹ Time-updated menopausal HRT use data were not available in our cohorts to explore this issue further.

Our results suggest that the potentially harmful and beneficial associations of menopausal HRT observed for breast cancer and CRC, respectively, for women in the general population may not apply to women with a first-degree family history of either cancer. Specifically, we found that use of menopausal HRT may not affect breast cancer or CRC risk for women with moderate to strong family histories. If replicated, these results support the need to understand mechanistically why the associations with menopausal HRT differ according to a woman's family history of cancer.

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Author contributions

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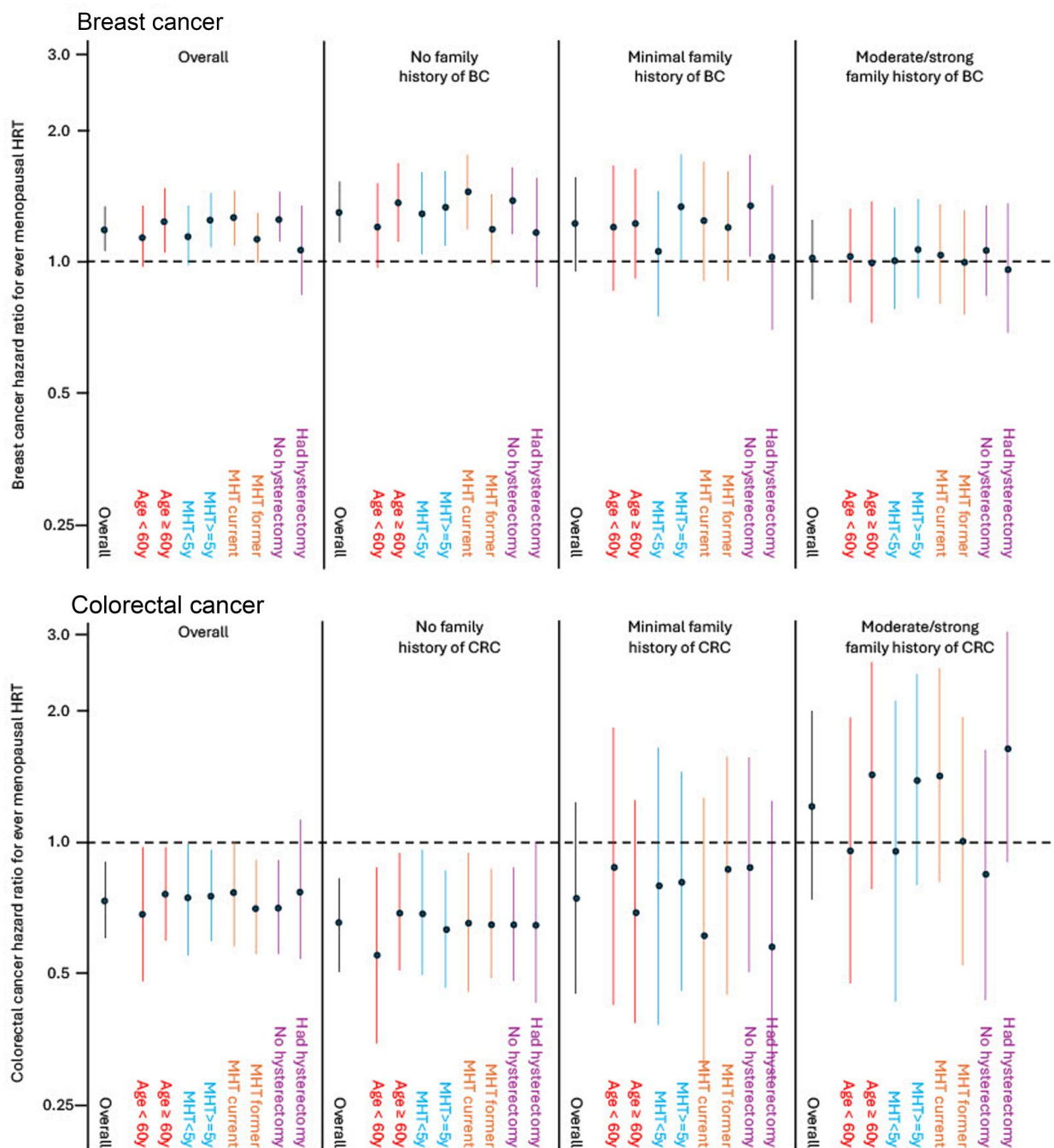


Figure 2. Hazard ratios (dots) and 95% confidence intervals (lines) of breast cancer and CRC risk in relation to subgroups of menopausal HRT use, by groups' cancer-specific familial risk score. Minimal family history was defined as having a familial risk score greater than 0 and less than 0.4; moderate to strong family history was defined as having a familial risk score of 0.4 or higher. Analyses were stratified by study and adjusted for body mass index (continuous), parity (0, 1, 2, 3, ≥ 4 live births), education level (high school or less, some college or university, bachelor's degree or higher), smoking status (never, former, current), oral contraceptive use (never, ever), and country of residence (Australia, Canada, United States). CRC = colorectal cancer; HRT = hormone replacement therapy.

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Methodology; Project administration; Resources; Supervision; Writing—original draft).

Supplementary material

Supplementary material is available at *JNCI Cancer Spectrum* online.

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Conflicts of interest

Kelly-Anne Phillips has an unpaid advisory role with AstraZeneca and research funding (to Kelly-Anne Phillips's institution) from AstraZeneca. The other authors declared no conflicts of interest during the conduct of this study outside the grant funding listed in the "Funding" section.

Data availability

For information about how to collaborate with the ProF-SC cohort in making further use of the data and resources and with the Breast Cancer Family Registry, please see <http://www.bcfamilyregistry.org>. For access to kConFab resources, see www.kconfab.org. The data generated in this study can be accessed by request to the CCFR (<https://www.coloncfr.org/collaboration>). The MCCS data can be made available on request to pedigree@cancervic.org.au.

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