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Breast Cancer Research

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Plasma prolactin and postmenopausal breast cancer risk: a pooled analysis of four prospective cohort studies

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Abstract

Background Prolactin, a hormone produced by the pituitary gland, regulates breast development and may contribute to breast cancer etiology. However, most epidemiologic studies of prolactin and breast cancer have been restricted to single, often small, study samples with limited exploration of effect modification.

Methods The Biomarkers in Breast Cancer Risk Prediction consortium includes 8,279 postmenopausal women sampled from four prospective cohort studies, of whom 3,441 were diagnosed with invasive breast cancer after enrollment. Prolactin concentrations were measured for all study participants on plasma samples collected when all women were postmenopausal and before any breast cancer diagnosis using ELISA assays. Pooled, unconditional logistic regression models, adjusted for confounders, estimated odd ratios (OR) for associations of prolactin and postmenopausal breast cancer risk overall and stratified by breast cancer risk factors.

Results Higher plasma prolactin concentrations were positively associated with postmenopausal breast cancer risk (> 13.2 ng/mL vs. < 7.9 ng/mL, OR: 1.20, 95% CI: 1.06, 1.36; P-trend < 0.001). Although associations did not appear to vary by time since blood draw or most breast cancer risk factors, associations were primarily observed in current users of postmenopausal hormones at blood draw (> 13.2 ng/mL vs. < 7.9 ng/mL, current users, OR: 1.58, 95% CI: 1.27, 1.96, P-trend < 0.001; non-current users, OR: 1.08, 95% CI: 0.93, 1.27, P-trend = 0.11; P-heterogeneity = 0.06).

Conclusion Prolactin may be a risk factor for postmenopausal breast cancer, particularly in the context of postmenopausal hormone use. Investigations of prolactin interactions with other hormonal factors may further inform breast cancer etiology.

Jacob K. Kresovich and Catherine Guranich: co-first authorship.

Jacob K. Kresovich, Catherine Guranich, Serena Houghton, Jing Qian, Micheal E. Jones, Shelley S. Tworoger and Susan E. Hankinson: Writing group.

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Keywords Breast cancer, Prolactin, Consortium, Postmenopausal breast cancer, Cohort study

Introduction

Prolactin, a hormone produced by the pituitary gland, regulates breast development and has been proposed to contribute to breast cancer etiology [1, 2]. Experimental studies of breast cancer cell lines demonstrate that prolactin promotes cellular differentiation [3] and proliferation [4–10] while inhibiting apoptosis [9–11]. In human studies, circulating prolactin levels are associated with traditional breast cancer risk factors, including menopause status, parity, and breast density [12–16].

Several prospective epidemiologic studies have reported a positive association between blood prolactin concentrations and breast cancer risk [17–25]. Specifically, women with the highest blood prolactin levels were at a 5–30% greater risk of breast cancer compared to those with lower levels [20–22]. However, most epidemiologic studies have been restricted to single, often small, study samples with limited information on breast cancer risk factors that might influence these associations. To improve our understanding of prolactin as a risk factor for breast cancer, well-powered studies are needed to investigate how various participant characteristics might modify this association. Identifying the groups of women for whom prolactin is most strongly associated with breast cancer risk will advance our understanding of breast cancer etiology and clarify how prolactin might be used to improve clinical breast cancer risk assessment models.

Here, we conduct the largest and most comprehensive study to date on prolactin and breast cancer risk in postmenopausal women. To accomplish this, we utilized the resources of the Biomarkers in Breast Cancer Risk Prediction (B2Risk) consortium. This international consortium includes 8,279 postmenopausal women, of whom 3,441 were diagnosed with invasive breast cancer after study enrollment, from the Breast Cancer Now Generations Study (BGS), Mayo Mammography Health Study (MMHS), Melbourne Collaborative Cohort Study (MCCS), and Nurses' Health Study (NHS). These studies provided plasma prolactin measurements on samples collected from all women when they were postmenopausal and breast cancer-free, along with extensive data on participant characteristics and tumor features.

Methods

Parent cohorts and study design

A detailed description of each study cohort is provided in the supplementary methods. Briefly, data for this analysis came from four prospective cohort studies: BGS, MMHS, MCCS, and NHS. Each cohort collected participant information via study questionnaires and medical records. For a subset of participants, blood samples (collected once or twice over time) and screening mammograms were also collected. Female participants have been followed since study enrollment for incident invasive breast cancer diagnoses. In each cohort, a nested-case control study (all four cohorts) or a case-cohort study (for the second MCCS blood collection) was created for women who were postmenopausal at enrollment with an available plasma sample. Participants provided written informed consent upon enrollment into their parent cohort, and all research was performed in accordance with the Declaration of Helsinki. Institutional review board approval for this project was obtained at each cohort's institution and at the coordinating center, the University of Massachusetts–Amherst.

Data collection and harmonization

Each cohort provided participant-level data that were harmonized centrally to ensure uniform variable definitions for those selected for prolactin assessment. Questionnaire-reported covariates included date of birth, past and current weight, adult height, fasting status at blood collection, family history of breast cancer, alcohol use, body mass index (BMI), parity, and breastfeeding history; young adult weight was not collected in MMHS, and fasting status at blood draw was not collected in BGS and MMHS. Mammographic density data were obtained from women who had consented to have their screening mammograms made available to their respective study centers and where mammograms could be traced. Each cohort measured breast density using CUMULUS software, and the percent mammographic density was standardized across cohorts [26, 27]. DNA was extracted from the collected blood sample and genotyped, and a 313-single nucleotide polymorphism polygenic risk score (313-SNP PRS) for breast cancer was calculated [28].

In the nested case-control study samples, matching factors varied slightly between cohorts (detailed in the supplement) and included age, postmenopausal hormone use, fasting status, and blood collection timing (time of day and calendar year). MCCS and NHS each conducted two blood collections approximately 10 years apart. In MCCS, one blood sample per participant was assayed for prolactin; the baseline blood draw was used for participants selected into the nested case-control sample, and the second blood draw was used for those selected into the case-cohort sample. To investigate the stability of prolactin concentrations over time, a subset of women from MCCS (n=98) had prolactin measured at both time points. In NHS, women diagnosed with breast cancer after their second blood draw (and their matched

controls) had both their first and second blood draws assayed simultaneously for prolactin (n=786).

Prolactin assays

Plasma prolactin concentrations were measured using validated, commercially available enzyme-linked immunosorbent assay (ELISA) kits in four processing laboratories across 17 batches. All laboratories were blinded to the case status of the samples. For the nested case-control samples, plasma samples from matched case-control sets were assayed together, with the case-control order randomized within the set. For the case-cohort sample, the plasma samples were randomized between laboratory batches, with an equal number of cases distributed in each batch. 10% masked quality control samples were randomly included in all batches.

All NHS prolactin levels from 1990 to 2010 were previously assayed, and their association with breast cancer was published [21]. Nine batches were assayed at Massachusetts General Hospital using the ARCHITECT chemiluminescence system (Abbot Diagnostics), and four batches at the University of Massachusetts Medical Center using the IMx system (Abbot Laboratory). The lower limit of quantification for both assays is 0.6 ng/mL, the correlation between the two laboratories was 0.91, and the average coefficient of variation (CV) was 7.8% [21]. Prolactin in the other three cohorts was newly assayed using ELISA kits from ALPCO (Salem, NH). BGS and MMHS samples were assayed at McGill University, while MCCS samples were assayed at the International Agency for Research on Cancer (IARC; Lyon, France). The lower limit of quantification was 0.35 ng/mL. For BGS, the within-plate and between-plate CVs of 1.5% and 2.0%, respectively and for MCCS, the within-plate and between-plate CVs were 3.5% and 14.5% (case-cohort) and 4.1% and 12.1% (case-control). Four sets of fifteen quality control samples previously assayed in the NHS datasets, selected to represent the range of postmenopausal prolactin levels, were reassayed at both the McGill and IARC laboratories; the overall between laboratory CV was 28.2%. To account for this variation, prolactin levels were adjusted for batch as previously described [29]. Briefly, linear regression was used to apply a correction factor to recalibrate prolactin measurements across batches to a consistent overall average. The regression accounted for characteristics that may cause true variation in prolactin levels, such as case status, age, PMH use at blood draw, parity, family history of breast cancer, fasting status, and time of blood collection. NHS data were treated as 13 batches; BGS, MMHS, and MCCS case-cohort and MCCS case-control samples were treated as one batch each.

The within-person intraclass correlation coefficient for the subset of women with repeated blood samples approximately 10 years apart (n=884, from NHS and MCCS) was 0.45 (95% confidence interval: 0.43, 0.47).

Disease outcome and classification

Cases were defined as women diagnosed with incident invasive breast cancer after study enrollment, which was then confirmed by medical record review. Tumor estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor-2 (HER2) receptor status were abstracted from medical records or determined by fluorescence assay using archival formalin-fixed paraffin-embedded breast tumor tissue blocks. Using these data, incident breast cancers were categorized by ER status (ER-positive vs. ER-negative) and molecular subtypes (luminal A vs. luminal B vs. triple negative). Further details on cohort-specific case and tumor subtype ascertainment methods are provided in the supplementary methods.

Statistical analysis

After correcting for laboratory and batch effects, prolactin outliers (n=16) were detected using a generalized extreme studentized deviation procedure [30]. Missing covariate data was imputed using the 'mice' R package and the MIANALYZE procedure in SAS [31]. Nearly all covariates had less than 5% missing data. The supplemental methods report additional details of the multiple imputation.

Univariate associations between breast cancer risk factors and plasma prolactin concentrations in women who remained breast cancer-free were estimated by calculating median prolactin levels by characteristic categories and performing Kruskal-Wallis analysis of variance tests. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate multivariate associations between prolactin concentrations and postmenopausal breast cancer risk. In the nested case-control studies, results from conditional and unconditional logistic regression analyses were similar. We, therefore, applied unconditional logistic regression models to allow pooling across the different sample designs (nested case-control, case-cohort) and inclusion of cases or controls where, for practical reasons, the prolactin measurement for the matched participant was missing (e.g., inadequate sample volume). Study-specific analyses were performed, and a test for heterogeneity across cohorts was conducted using the SAS macro %METAANAL(https://ysph.yale.edu/cmips/research/software/meta-analysis/metaanal/). Although the total combined data set provides the most reliable results, because the NHS nested case-control data were previously published [21], we performed a sensitivity analysis excluding NHS women from this sample. In all analyses, prolactin concentrations were investigated as continuous (scaled per 1-standard

deviation [SD] increase, SD = 6.5 ng/mL), and categorized into quartiles, with cut-points defined by the control/non-case distribution in the pooled sample (<7.91 ng/mL, 7.91–10.08 ng/mL, 10.09–12.15 ng/mL, and >13.15 ng/mL). To account for potential confounding, models were adjusted for a priori covariates used in previous studies of prolactin and breast cancer and included age (years), fasting status (fasting, non-fasting, not reported), current postmenopausal hormone (PMH) (yes/no), adult height (<162.5 cm, 162.5–172.5 cm, >127.5 cm), young adult weight (continuous, kg), and first-degree family history of breast cancer (yes/no). Subsequent analyses were performed, additionally adjusting for parity (nulliparous, 1–2 births, 3+births), breastfeeding (ever/never), alcohol use (grams/week), current BMI (kg/m^2), and circulating estradiol (in non-PMH users only; pg/mL). Tests for trend across quartiles were performed by modeling the medians of the pooled quartiles as a continuous variable and calculating the Wald statistic. Given the large sample size of this study, breast cancer associations were further evaluated across prolactin deciles to better examine the shape of the association.

To examine the influence of blood collection timing, stratified associations were estimated by the time between blood draw and index dates (<10 years vs. 10+years), where index dates were defined as the date of cancer diagnosis for cases and their matched controls in the nested case-control samples and censoring date for non-cases in the case-cohort sample. In the NHS nested case-control sample, which had two prolactin measurements available for a subset of women, we used the plasma sample that was taken closest in time and before the index date in the primary analysis. A secondary analysis was performed using only the baseline plasma samples.

Effect modification of prolactin and breast cancer associations by participant characteristics was evaluated through stratified analyses. Modifiers of interest were: PMH use at blood draw (yes/no), BMI at blood draw (<25, 25–30, 30+kg/m^2), germline breast cancer risk as measured by the 313-SNP PRS (tertile), first-degree family history of breast cancer (yes/no), circulating estradiol levels (tertile), percent mammographic density (tertile), breastfeeding history (among parous, yes/no), and parity (nulliparous, 1–2 births, 3+births). Tests for heterogeneity were performed by calculating likelihood ratio test statistics and corresponding p-values comparing the full (including the interaction term of continuous prolactin and the modifier of interest) and reduced (no interaction term) models. Given suggested non-linearity and a possible threshold in the association, Wald tests were used to examine differences in top quartile point estimates across modifier strata. Analyses were additionally stratified by tumor characteristics (ER status and molecular subtype). Tests for heterogeneity by tumor characteristics were conducted using polytomous logistic regression and conducting a likelihood ratio test. In the primary analyses, two-sided P-values for main effects and statistical interaction were considered statistically significant if ≤0.05. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and R software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Sample characteristics

The B2Risk consortium includes 8,279 postmenopausal women from four parent cohort studies: NHS (1,205 cases, 2,006 controls), BGS (992 cases, 998 controls), MMHS (257 cases, 257 controls), and MCCS (nested case-control study: 432 cases, 429 controls; case-cohort study: 555 cases, 1,148 subcohort). Participant characteristics after imputation, overall and by study sample, are detailed in Table 1. Mean ages at blood draw ranged between 60 and 67 years and, by design, were similar for the cases and controls in the nested case-control samples. There was variability in the timing of the blood draws and index dates across the samples, with NHS and BGS having the largest proportions of participants (>78%) with blood collected within ten years of the index event. Most blood samples in NHS and MCCS were collected while fasting, whereas fasting status was unavailable for BGS and MMHS. In the combined dataset, 19% of cases and 13% of controls had a first-degree relative with breast cancer. In addition, breast cancer cases had higher BMI at enrollment, breast cancer PRSs, and mammographic density compared to controls. Imputation of missing covariate information did not appreciably alter the distributions of participant characteristics across any of the study samples (Supplemental Table 1).

Prolactin distributions and associations with participant characteristics

The distributions of plasma prolactin concentrations after batch correction were similar across all five samples (Fig. 1). In the participants who remained breast cancer-free, prolactin concentrations were associated with PMH use (median concentrations, non-users: 9.96 ng/mL, users: 10.47 ng/mL; $P<0.001$), parity (median concentration, nulliparous: 10.86 ng/mL, 1–2 births: 10.07 ng/mL, 3+births: 9.96 ng/mL; $P<0.001$), breastfeeding history (median concentration, yes: 10.05 ng/mL, no: 10.19 ng/mL; $P=0.04$), and breast density (median concentrations, < 9.23%: 9.68 ng/mL, 9.23–19.51%: 10.05 ng/mL, > 19.51%: 10.56 ng/mL; $P=0.01$) (Fig. 2). There were also notable differences in prolactin concentrations by fasting status (median concentration, fasting: 10.25 ng/mL,

Table 1 Participant characteristics by cohort and case-control status ($N = 8,279$)

	NHS		BGS		MMHS		MCCS case-control		MCCS case-cohort		Total	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Subcohort	Case	Non-case
	n = 1,205	*n* = 2,006	*n* = 992	*n* = 998	*n* = 257	*n* = 257	*n* = 432	*n* = 429	*n* = 555	*n* = 1,148	*n* = 3,441	*n* = 4,838
Age at blood draw (years)												
Mean (SD)	62.8 (7)	62.5 (7)	60.8 (5)	60.8 (5)	63.1 (7)	63.1 (7)	61.7 (5)	61.2 (5)	67.2 (7)	66.9 (7)	62.8 (7)	63.1 (7)
Time between blood draw and index (years)												
Mean (SD)	6.4 (4)	6.8 (5)	4.9 (3)	5.0 (3)	7.7 (4)	7.7 (4)	9.0 (6)	8.9 (6)	7.3 (4)	13.5 (3)	6.5 (5)	8.3 (5)
<10 years (%)	82.2	78.0	93.5	93.0	64.6	63.8	61.6	61.5	69.4	8.6	79.5	62.4
Fasting status at sample collection (%)												
Not Reported	0	0	100	100	100	100	0	0	0	0	36.3	25.9
Fasting	69.0	70.4	0	0	0	0	72.7	73.9	88.6	88.2	47.6	56.7
Non-fasting	31.0	29.6	0	0	0	0	27.3	26.1	11.4	11.8	16.1	17.4
Weight at age 18–20 (kg)												
Mean (SD)	57.0 (8)	57.4 (9)	57.1 (7)	56.7 (8)	59.8 (9)	59.0 (9)	54.9 (7)	54.1 (8)	55.1(8)	54.9 (7)	56.6 (8)	56.4 (8)
BMI at blood (kg/m^2) (%)												
<25	53.7	54.7	49.6	53.8	33.4	38.0	31.1	29.8	33.5	36.4	45.0	47.1
25–30	31.9	32.1	34.1	33.6	36.2	33.6	39.6	45.0	37.0	38.4	34.6	35.1
30+	14.4	13.2	16.3	12.6	30.4	28.4	29.3	25.2	29.6	25.2	20.4	17.8
Adult height (%)												
<162.5 cm	33.5	32.8	34.3	41.6	28.6	35.8	69.7	76.0	58.6	63.9	42.0	46
162.5–172.5 cm	56.1	57.0	54.5	50.0	55.8	49.4	28.9	22.4	37.7	34.2	49.2	46.7
>172.5 cm	10.4	10.2	11.3	8.4	15.6	14.8	1.4	1.6	3.8	1.9	8.8	7.3
First-degree family history of breast cancer (%)												
Yes	16.3	12.2	25.4	16.9	30.0	19.8	11.6	8.6	14.8	11.3	19.1	13.1
Standardized PRS												
Mean (SD)	0.29 (1.0)	-0.07 (1.0)	0.41 (1.0)	0.00 (1.0)	0.39 (1.1)	-0.03 (1.0)	0.54 (0.9)	0.01 (1.0)	0.45 (1.0)	0.09 (1.0)	0.39 (1.0)	-0.01 (1.0)
% Mammographic density												
Mean (SD)	20 (15)	17 (14)	20 (15)	17 (13)	20 (14)	18 (15)	18 (13)	18 (14)	20 (15)	18 (14)	20 (15)	17 (14)
Parity (%)												
Nulliparous	7.8	6.5	11.6	11.6	10.9	11.4	12.5	13.1	16.9	12.4	11.2	9.8
1–2 Births	31.1	29.0	62.5	61.7	42.7	37.1	34.7	37.8	39.1	39.7	42.8	39.5
3 + Births	61.1	64.5	25.9	26.7	46.3	51.5	52.8	49.2	44.0	47.9	46.0	50.7
History of breastfeeding (%)												
Ever breastfed	65.5	63.0	82.0	82.1	45.6	44.4	80.8	81.9	79.1	82.0	72.9	72.1

Abbreviations: NHS, Nurses' Health Study; BGS, Breakthrough Generations Study; MMHS, Mayo Mammography Health Study; MCCS, Melbourne Collaborative Cohort Study; SD, standard deviation; BMI, body mass index; PRS, polygenic risk score

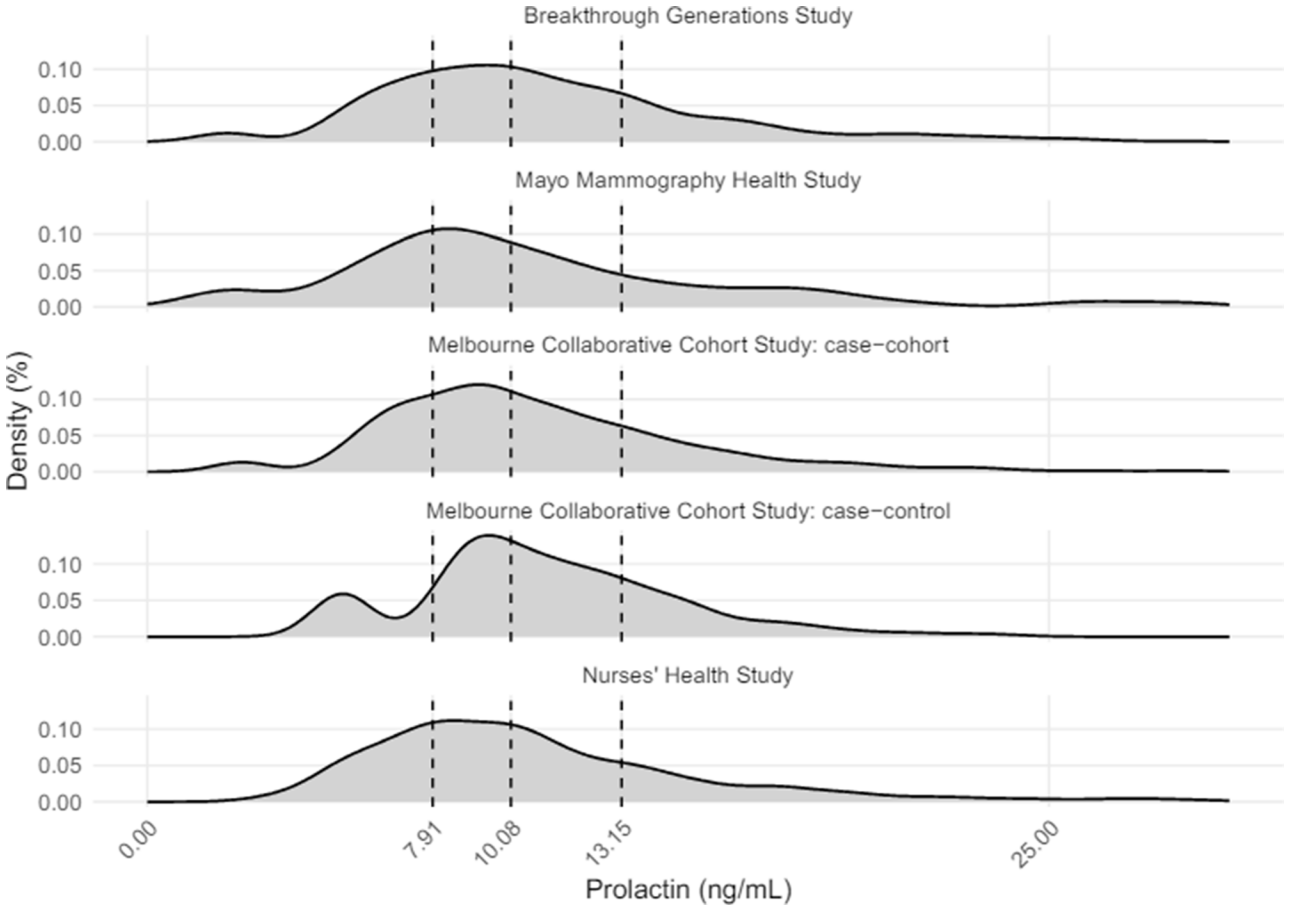

Fig. 1 Plasma prolactin distributions by study sample. Density plots displaying the distributions of plasma prolactin (ng/mL) by study sample. Dotted vertical lines denote the prolactin concentration cut-points for quartile analyses (defined by the distribution of prolactin among all non-cases)

non-fasting: 9.37 ng/mL, not reported: 10.11 ng/mL; $P<0.001$).

Prolactin associations with breast cancer risk overall and stratified by time since blood draw

In the pooled sample, compared to women with prolactin concentrations below 7.91 ng/mL, women with plasma prolactin concentrations greater than 13.15 ng/mL showed higher breast cancer risk (quartile 4 vs. quartile 1; OR: 1.20, 95% CI: 1.06, 1.36; P-trend < 0.001) (Fig. 3). Lower prolactin concentrations were not statistically associated with breast cancer risk (compared to quartile 1; quartile 3, OR: 1.07, 95% CI: 0.94, 1.21; quartile 2, OR: 0.95, 95% CI: 0.84, 1.08). In a pooled sample excluding the NHS, associations were somewhat attenuated (quartile 4 vs. quartile 1, OR: 1.11, 95% CI: 0.94, 1.30; P-trend = 0.10) (Supplemental Fig. 1). Cohort-specific associations appeared to vary modestly (Supplemental Fig. 1). However, there was limited statistical evidence for heterogeneity across study samples (P-heterogeneity = 0.15). Associations were also unchanged after additional model adjustments for parity, breastfeeding, alcohol use, current BMI, and circulating estradiol in non-PMH users (data not shown). In an analysis of prolactin deciles, associations were primarily observed among the top two deciles (compared to decile 1; decile 9, OR: 1.21, 95% CI: 1.00, 1.47; decile 10, OR: 1.22, 95% CI: 1.00, 1.48) and a test for non-linearity was significant (P-non-linearity = 0.01), suggesting a threshold effect (Supplemental Fig. 2).

In an analysis stratified by timing of blood collection relative to the index date, the magnitude of the association appeared stronger in those with blood collected within ten years of the index date (quartile 4 vs. quartile 1; < 10 years, OR: 1.24, 95% CI: 1.08, 1.43, P-trend < 0.001; 10 + years, OR: 1.11, 95% CI: 0.86, 1.43, P-trend = 0.42) (Fig. 3). However, there was limited evidence of statistical heterogeneity (P = heterogeneity = 0.44). In sensitivity analyses using only the baseline blood samples from the NHS, the time-dependent differences again appeared different, but the test for heterogeneity was not statistically significant (quartile 4 vs. quartile 1; < 10 years, OR: 1.17, 95% CI: 1.00, 1.36, P-trend = 0.01; 10 + years, OR: 0.96, 95% CI: 0.77, 1.19, P-trend = 0.80; P-heterogeneity = 0.58) (Supplemental Fig. 3).

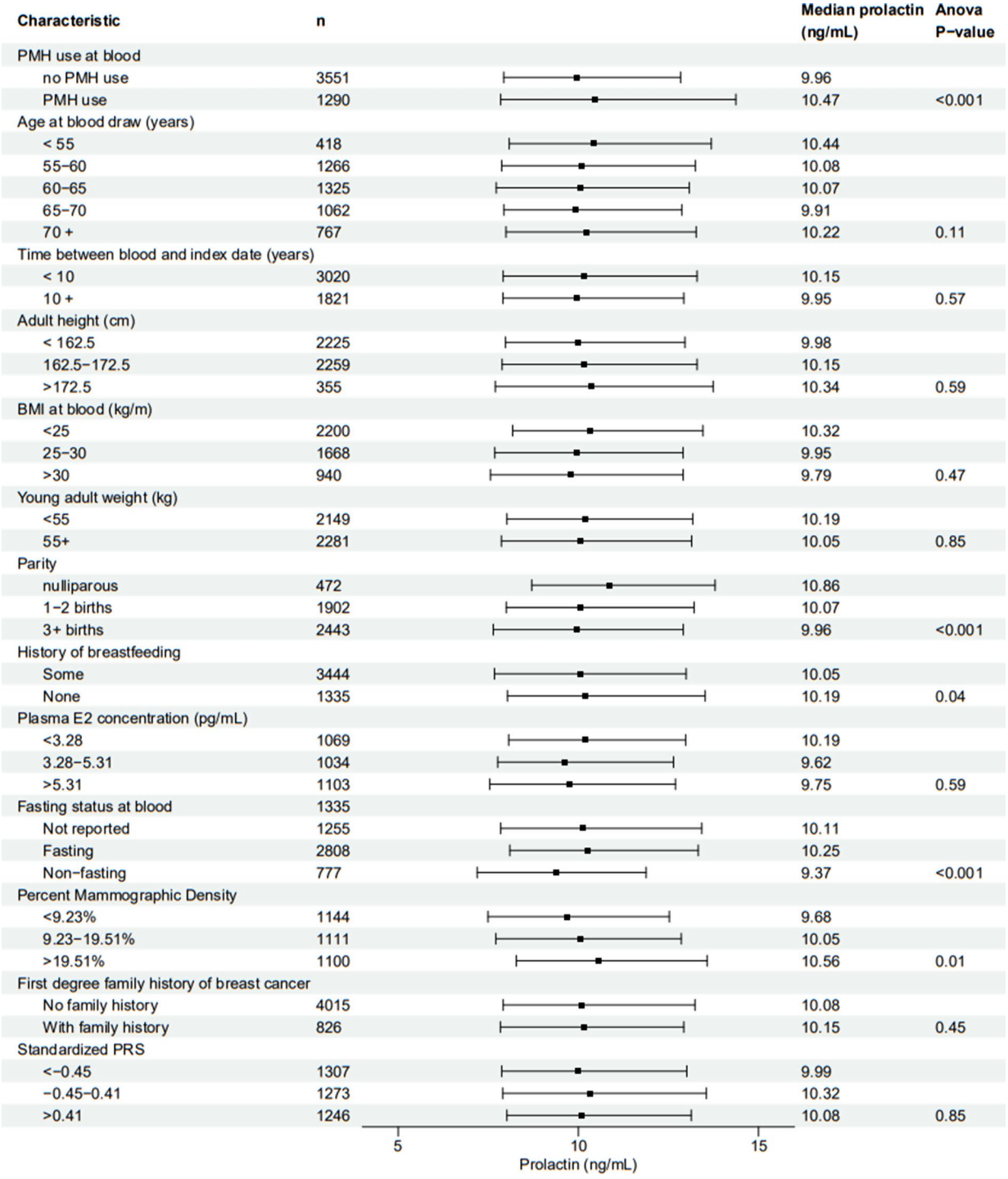

Fig. 2 Non-case distribution of prolactin by participant characteristics. Tests for differences were performed using Kruskal-Wallis analysis of variance tests. Abbreviations: IQR, interquartile range; PMH, postmenopausal hormone; BMI, body mass index; E2, estradiol; PRS, polygenic risk score

Effect modification by participant characteristics and tumor features

The association of prolactin and postmenopausal breast cancer risk appeared stronger in PMH users than non-users. PMH users with the highest plasma prolactin levels had over 50% higher risk of breast cancer compared to PMH users with the lowest levels (quartile 4 vs. quartile 1, PMH users, OR: 1.58, 95% CI: 1.27, 1.96, P-trend < 0.001), with weaker differences observed in non-users (quartile 4 vs. quartile 1, OR: 1.08, 95% CI: 0.93, 1.27, P-trend = 0.11) (P-heterogeneity = 0.06) (Fig. 4). A Wald test for differences in the top quartile point

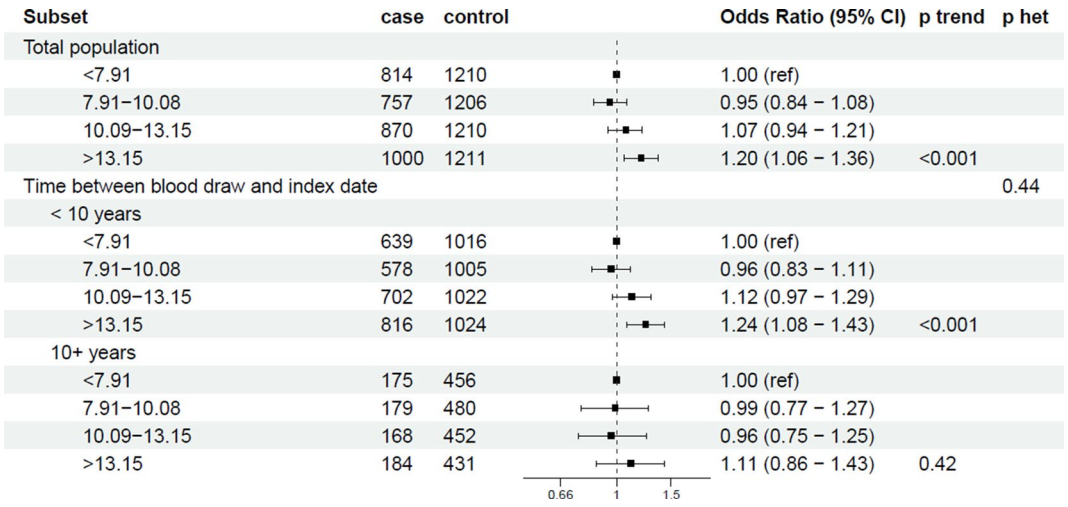

Fig. 3 Multivariate-adjusted associations between plasma prolactin (ng/ml) and invasive breast cancer in the pooled sample overall and stratified by time since blood draw. Models adjusted for age, fasting status, PMH use at blood draw, young adult weight, and family history of breast cancer. Abbreviations: CI, confidence interval; SD, standard deviation; p het, p heterogeneity; PMH, postmenopausal hormone

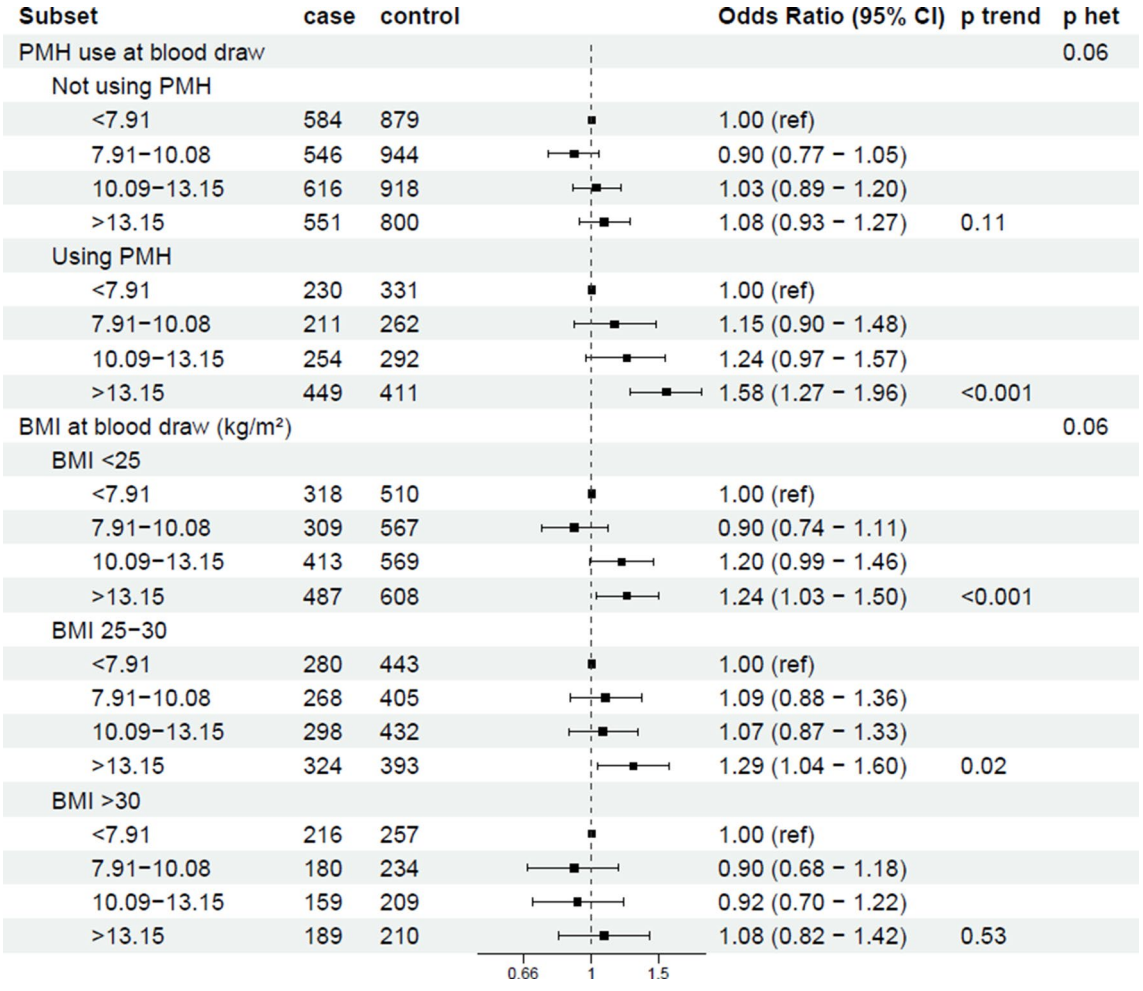

Fig. 4 Multivariable-adjusted associations between plasma prolactin (ng/ml) and invasive breast cancer, stratified by PMH use and BMI at blood draw. Models adjusted for age, fasting status, and PMH use at blood draw (BMI-stratified models only), young adult weight, and family history of breast cancer. Abbreviations: PMH, postmenopausal hormone; BMI, body mass index; CI, confidence interval; p het, p heterogeneity; SD, standard deviation

estimates comparing PMH users and non-users was statistically significant (P=0.017). Associations were similar in magnitude among never and former PMH users (data not shown), and there was insufficient sample size to examine associations by PMH composition. BMI also appeared to modify the association, with stronger associations observed in those with lower BMIs at blood draw (quartile 4 vs. quartile 1, BMI<25 kg/m^2, OR: 1.24, 95% CI: 1.03, 1.50, P-trend=<0.001; BMI 25–30 kg/m^2, OR: 1.29, 95% CI: 1.04, 1.60, P-trend=0.02; BMI>30 kg/m^2, OR: 1.08, 95% CI: 0.82, 1.42, P-trend=0.53; P-heterogeneity=0.06) (Fig. 4). However, compared to those with BMI<25, there was limited statistical evidence for differences in point estimates across the two other BMI strata (BMI 25–30, P=0.97; BMI>30, P=0.33). Prolactin associations also appeared to vary by polygenic breast cancer risk, with associations primarily observed in those with the highest polygenic risk (quartile 4 vs. quartile 1; lowest PRS tertile, OR: 1.11, 95% CI: 0.85, 1.44, P-trend=0.25; middle PRS tertile, OR: 0.99, 95% CI: 0.79, 1.24, P-trend=0.90; highest PRS tertile, OR: 1.35, 95% CI: 1.10, 1.65, P-trend<0.001; P-heterogeneity=0.08) (Supplemental Fig. 4). There was a significant difference in the top quartile point estimates comparing women with PRS values in the middle tertile with those in the highest tertile (P=0.03). The prolactin association with breast cancer did not vary across categories of other breast cancer risk factors, including family history of breast cancer (P-heterogeneity=0.74), circulating estradiol level tertiles(P-heterogeneity=0.18), mammographic density tertiles (P-heterogeneity=0.38), breastfeeding history (P-heterogeneity=0.45), or parity (P-heterogeneity=0.14) (Supplemental Figs. 4–6).

Prolactin and breast cancer associations did not vary for ER-positive and ER-negative tumors (P-heterogeneity=0.58) (Supplemental Fig. 7). In the analysis of molecular subtypes, although the association appeared stronger for the subset of women diagnosed with triple-negative breast cancer, the test for heterogeneity did not reach statistical significance (quartile 4 vs. quartile 1, Luminal A OR: 1.15, 95% CI: 0.97, 1.36, P-trend=0.04; Luminal B, OR: 1.11, 95% CI: 0.80, 1.54, P-trend=0.39; Triple-Negative OR: 1.54, 95% CI: 1.04, 2.27, P-trend=0.04; P-heterogeneity=0.38) (Supplemental Fig. 7).

Discussion

In an international consortium of four prospective studies of 8,279 postmenopausal women, of whom 3,441 were diagnosed with invasive breast cancer after enrollment, we found that plasma prolactin concentrations were positively associated with postmenopausal breast cancer risk. Associations appeared strongest in women with the highest circulating levels of prolactin, such that those with prolactin levels above 13 ng/mL had a 20% higher risk of breast cancer compared with those with the lowest levels. Notably, the association was primarily observed in current PMH users. These findings support prolactin as a risk factor for postmenopausal breast cancer, particularly among PMH users.

Considerable research has examined the relationship between prolactin and breast cancer risk [17–25, 32–35]. Multiple early studies suggested a positive relationship, but the associations did not reach statistical significance, likely due to small sample sizes [32–35]. In a study of 1,738 invasive postmenopausal breast cancer cases and matched controls from the European Prospective Investigation into Cancer and Nutrition cohort, prolactin levels in the top (vs. bottom) quartile were significantly associated with a 29% higher risk of postmenopausal breast cancer [20]. A similar positive association was found in a nested case-control study of 1,992 cases from the NHS and NHSII cohorts (NHS data were included in this study) [21]. The current analysis, which included nearly twice the number of postmenopausal cases compared to any previous study, provides further clarity that postmenopausal women with higher plasma prolactin concentrations are at modestly increased breast cancer risk.

Despite the fairly consistent findings from previous studies demonstrating a positive association between prolactin and breast cancer risk in postmenopausal women [19–21], associations by PMH use have been inconsistent. In the European Prospective Investigation into Cancer and Nutrition cohort, the prolactin and breast cancer association appeared stronger in PMH users [20]. However, there was no evidence of heterogeneity in the NHS and NHSII cohorts [21]. In this much larger study, we found the association between prolactin and postmenopausal breast cancer risk to be primarily observed in current PMH users, with limited evidence of association in non-PMH users. Interestingly, we also found potential modification by BMI, a factor that correlates with sex hormone levels in postmenopausal women [36], further suggesting that prolactin may interact with other hormones to influence breast cancer risk [2, 37]. For instance, prolactin and progesterone both regulate several signaling pathways implicated in breast carcinogenesis (e.g., JAK/STAT) [37, 38]. In addition, studies have linked adipocyte prolactin production with circulating levels of adiponectin, interleukin-6, and leptin [39], proteins that have previously been associated with PMH use and BMI [40]. Notably, in our study, the association between prolactin and breast cancer was similar by tumor ER status and across tertiles of circulating estradiol levels, suggesting that hormones beyond estrogen may play a key role. Additional studies investigating prolactin and breast cancer interactions by PMH composition and other circulating proteins may provide additional insights into breast cancer etiology.

This study is not without limitations. The study population was comprised of women of European ancestry. Future studies should include more racially and ethnically diverse samples to improve generalizability. Similarly, the study sample was restricted to postmenopausal women. Although these design features limit the generalizability of the study, they play a key role in reducing potential confounding and providing valid association estimates. We additionally had only one blood measurement of prolactin for most study participants. Our data from over 800 participants from two cohorts with prolactin assessed longitudinally over 10 years showed an ICC of 0.45, indicating that a single measure reasonably reflects longer-term levels. Of note, this ICC is lower than those reported for sex steroids such as estradiol and testosterone over the same time period [41, 42]. Despite these limitations, this study is strengthened by its large prospective sample population, precise prolactin assays and comprehensive harmonization techniques, and detailed investigation of effect modifiers, several for the first time.

In summary, we found that women with the highest plasma prolactin concentrations had approximately 20% higher breast cancer risk, with associations primarily observed in women reporting current PMH use. This study contributes to the substantial body of evidence linking prolactin to postmenopausal breast cancer risk and helps identify specific groups of women for whom this association is particularly relevant. Identifying these groups improves our understanding of breast cancer etiology and can help inform how prolactin might be used to enhance clinical breast cancer risk assessment models.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Author contributions

C.G., S.H., and S.E.H. conceptualized the research question. C.G. and J.Q. performed the data analysis. J.K.K., C.G., S.H., J.Q., M.E.J., S.S.T, and S.E.H. drafted the manuscript. All authors aided in the interpretation of the study findings, provided additional edits, and approved of the manuscript.

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Data availability

Data requests for replication purposes can be made directly to the senior author and/or the corresponding cohort coordinating centers (NHS, MCCS, MMHS, BGS).

Declarations

Competing interests

The authors report no competing interests.

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