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Inclusion of Endogenous Plasma Dehydroepiandrosterone Sulfate and Mammographic Density in Risk Prediction Models for Breast Cancer

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ABSTRACT

Background: Endogenous hormones and mammographic density are risk factors for breast cancer. Joint analyses of the two may improve the ability to identify high-risk women.

Methods: This study within the KARMA cohort included prediagnostic measures of plasma hormone levels of dehydroepiandrosterone (DHEA), its sulfate (DHEAS), and mammographic density in 629 cases and 1,223 controls, not using menopausal hormones. We evaluated the area under the receiver-operating curve (AUC) for risk of breast cancer by adding DHEA, DHEAS, and mammographic density to the Gail or Tyrer–Cuzick 5-year risk scores or the CAD2Y 2-year risk score.

Results: DHEAS and percentage density were independently and positively associated with breast cancer risk ($P = 0.007$ and $P < 0.001$, respectively) for postmenopausal, but not premenopausal, women. No significant association was seen for DHEA. In postmenopausal women, those in the highest tertiles of both DHEAS and density were at greatest risk of breast cancer (OR, 3.5; 95% confidence interval, 1.9–6.3) compared with the lowest tertiles. Adding DHEAS significantly improved the AUC for the Gail (+2.1 units, $P = 0.008$) and Tyrer–Cuzick (+1.3 units, $P = 0.007$) risk models. Adding DHEAS to the Gail and Tyrer–Cuzick models already including mammographic density further increased the AUC by 1.2 units ($P = 0.006$) and 0.4 units ($P = 0.007$), respectively, compared with only including density.

Conclusions: DHEAS and mammographic density are independent risk factors for breast cancer and improve risk discrimination for postmenopausal breast cancer.

Impact: Combining DHEAS and mammographic density could help identify women at high risk who may benefit from individualized breast cancer screening and/or preventive measures among postmenopausal women.

Introduction

Breast cancer is the most commonly diagnosed cancer in women, and numerous risk prediction models have been developed to identify women at greater risk of developing the disease. Previous studies show that addition of endogenous hormones to existing risk models may to some extent improve the predictive power, particularly for invasive breast cancers in postmenopausal women (1–3). Current models use lifestyle factors (4), family history of breast cancer (5), mammographic density (6), mammographic features (7), and genetic determinants (8). The well-validated Gail and Tyrer–Cuzick models are based on confirmed risk factors and predict the 5-year risk of breast cancer (4, 9). In contrast, the in-house–developed computer-aided detection 2-year risk (CAD2Y) risk model predicts the shorter 2-year risk based on mammographic density and other imaging features and is suitable for predicting the risk of breast cancer between two mammography visits (7). Mammographic density is one of the strongest risk factor for breast cancer and reflects the radiographically dense fibroglandular tissue, which appears light on the mammogram.

We (10), and others (11), recently found that combining endogenous hormones, such as estrogen, testosterone, or prolactin, with mammographic density can improve risk prediction by current models. Findings also suggest that sex hormones from the androgen and estrone pathways and mammographic density may represent different etiology and are independent risk factors for breast cancer (12). Dehydroepiandrosterone (DHEA) and its sulfate analog DHEAS are multifunctional metabolic intermediates in the biosynthesis of the androgenic and estrogenic steroid pathways (13). DHEAS has been repeatedly associated with increased breast cancer risk among postmenopausal women (1, 14–17). DHEAS is the most abundant steroid hormone in adult women, although circulating concentrations decline with age (18, 19). However, though estrogen and testosterone have been abundantly studied in association with breast cancer, no study to our knowledge has examined if DHEA or DHEAS acts independently of mammographic density as risk factors for breast cancer, or if combining these biomarkers can improve risk prediction.

We thus used the large, prospective KARMA study (20) to evaluate the independence of DHEA/DHEAS with mammographic density as risk factors for breast cancer as well as the joint and independent contribution of the hormones and density to the Gail, Tyrer–Cuzick, and CAD2Y risk prediction models.

Materials and Methods

Study population

In this study, we used data from the KARMA (Karolinska Mammography project for risk prediction for breast cancer) study, a

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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population-based prospective cohort study initiated in 2011 comprising 70,877 women attending mammography screening or clinical mammography in Sweden (20, 21). The overarching goal of KARMA is to reduce the incidence and mortality of breast cancer by focusing on individualized prevention and screening. This current study only included prediagnostic blood samples. As described previously (10), all available KARMA participants diagnosed with breast cancer after study entry and initial blood draw but before August 1, 2015, and who were not using menopausal hormone therapy (MHT) at time of blood draw were included. Mean time to diagnosis was 12.2 months (SD 13.0) and 12.5 months (SD 13.6) for premenopausal and postmenopausal cases, respectively. Controls were age-matched 2:1 for each case.

All participants completed a comprehensive KARMA baseline questionnaire and donated nonfasting EDTA plasma samples of peripheral blood at study entry (20, 21). All variables included in the analyses were generated through the questionnaire at baseline, and body mass index (BMI) was self-reported. All blood samples were processed in the Karolinska Institutet high-throughput biobank and handled in accordance to a strict 30-hour cold-chain protocol. Full-field digital mammograms from the medio lateral oblique and cranio caudal views of the right and left breasts were collected at study enrolment (20, 21), and used to measure mammographic density using the area-based STRATUS method (7). Percentage mammographic density was calculated as the mean percentage densities of left and right breasts.

Each study participant signed a written-informed consent form and accepted linkage to national breast cancer registers at study entry. The Stockholm ethical review board approved the study (2010/958-31/1).

Laboratory assays

Hormones were measured in blinded peripheral blood plasma as described previously (22). Briefly, sample preparation for the analysis of DHEA was carried out through liquid–liquid extraction with tert-butyl methyl ether (MTBE) followed by derivatization with methoxyamine, whereas DHEAS was analyzed directly, after the extraction with MTBE. The analysis was performed by ultra-performance supercritical fluid chromatography-tandem mass spectrometry (UPSFC-MS/MS) system (Waters Corporation). Separation of DHEA and DHEAS was accomplished using the Acquity-UPC^2 BEH and CSH-fluoro-phenyl columns (3.0 mm $\times$ 100 mm, 1.7 μm), respectively (Waters). DHEA methoxyamine derivative was separated using 0.1% formic acid in methanol isopropanol (1:1, v/v; 2 mL/min) as modifier, whereas DHEAS was separated using 10 mmol/L ammonium acetate in methanol with 3% (v/v) water (1.5 mL/min) using respective columns. Mass spectrometric detection was performed using electrospray ionization in the dual ionization mode (ESI^+ for DHEA and ESI^- for DHEAS) with nitrogen and argon serving as desolvation and collision gas, respectively. Data acquisition range was 100 to 600 m/z. Quantification was based on a multiple reaction monitoring method with suitable deuterated internal standards; collision energy and cone voltage were set according to Supplementary Table S1. MS/MS conditions and methods were confirmed by individual analysis of standard DHEA and DHEAS (50 ng/mL). The limit of quantification and coefficient of variation of DHEA and DHEAS assays were 0.1 and 0.01 ng/mL and 4.8% and 3.2%, respectively. The recovery of the DHEA and DHEAS assays was 96% and 97%, respectively. Total testosterone was measured using the same method as DHEA and DHEAS, as described previously (22). Linear rage of quantification for testosterone was 0.05 to 30 ng/mL, and the absolute recovery was 87.1%. All data were acquired, analyzed, and processed using the MassLynx 4.1 software (Waters).

Risk scores

The 2- or 5-year risk of breast cancer was estimated using the CAD2Y, Gail, and Tyrer–Cuzick risk scores (4, 7, 9), as previously described (10). None of the models uses endogenous hormones or, with the exception of the CAD2Y risk score, mammographic density. The major determinants included are reproductive history and family history of breast cancer.

The Gail model includes risk factors of age, age at menarche, age at first live birth, number of previous breast biopsies, atypical hyperplasia, and first-degree family history of breast cancer (4). The Tyrer–Cuzick model (version 7) includes age, age at menarche and age at first child, menopause, height, weight, use of MHT, hyperplasia, atypical hyperplasia, lobular cancer *in situ*, and first-/second-degree family history of breast cancer (9).

The CAD2Y risk model includes age, menopausal status, BMI, current use of MHT, family history of breast cancer, percentage mammographic density, number of microcalcifications, and masses (7). It also includes breast side differences of breast density, microcalcifications and masses, and an interaction term between mammographic density and number of masses.

Statistical analyses

All analyses were stratified by menopausal status defined at baseline. For DHEA, values were missing for 23.0% of premenopausal cases and 22.8% controls, and 29.0% postmenopausal cases and 28.0% controls, respectively. Values for DHEAS were missing for 6.3% of premenopausal cases and 8.1% controls, and 5.7% postmenopausal cases and 6.4% controls, respectively. Associations of quartiles of percentage mammographic density (determined from the distribution among controls) with hormone levels among controls were assessed using linear regression in multivariable-adjusted analyses with density as dependent categorical variable. ORs and 95% confidence intervals (CI) for breast cancer were determined using logistic regression, adjusting for matching factor (age at blood draw), comparing sex hormone levels by quartiles of mammographic density. Tests for trend were based on natural log-transformation for sex hormones and square root transformation for mammographic density as continuous variables and calculated using Wald statistic. For combined ORs of breast cancer by hormones and density, tertiles were determined from distribution among controls. Multiplicative interaction between tertiles of hormones and density was tested with a likelihood ratio test comparing a model including the main effects and interactions with a model including only the main effects. All models were adjusted for age and BMI at blood draw (continuous), history of benign breast disorder (no, yes), smoking status (never, past, current smoker), alcohol consumption (g/day), time of day of blood draw, and MHT (never, previous use; postmenopausal only).

To assess improvement in risk discrimination, we compared the area under the receiver-operating curve (AUC) for different risk models, adjusting for age, before and after adding hormones and mammographic density. Significance of improvement was tested by adding linear terms for natural log-transformed hormones and square root–transformed density and likelihood ratio tests (23). Secondarily, we tested improvement of the Gail, Tyrer–Cuzick, and CAD2Y risk models by mammographic density and hormones using stepwise regression.

All P values were two sided and considered statistically significant if <0.05. Analyses were conducted using SPSS (version 25; IBM corporation).

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Results

We had 222 premenopausal and 407 postmenopausal cases with 381 and 842 age-matched controls, respectively. Cases were more likely to have a history of benign breast disease and a family history of breast cancer compared with controls, irrespective of menopausal status (**Table 1**). Postmenopausal cases had significantly higher BMI, consumed more alcohol, and were more likely smokers, compared with controls. Breast cancer risk probability using the Gail model was higher for cases than controls irrespective of menopausal status, as was the CAD2Y risk. Postmenopausal cases had significantly increased risk by the Tyrer–Cuzick model. Both premenopausal and postmenopausal cases had significantly greater percentage mammographic density. Median DHEA and DHEAS concentrations were significantly higher for postmenopausal, but not premenopausal, cases compared with controls. Total percentage mammographic density was inversely associated with DHEAS, but not DHEA, among premenopausal women, whereas there was no association between density and DHEA or DHEAS among postmenopausal women (Supplementary Table S2).

Incidence of breast cancer was not significantly associated with DHEA in neither premenopausal nor postmenopausal women, nor was DHEAS among premenopausal women (**Table 2**). In contrast, greater concentrations of DHEAS were positively associated with increased incidence of postmenopausal breast cancer (OR, top vs. bottom quartile 1.75; 95% CI, 1.19–2.57, $P_{trend} = 0.006$). Addition of

Table 1. Baseline characteristics for patient cases and matched controls not currently using menopausal hormone replacement therapy.

	Premenopausal women					Postmenopausal women				
	Cases ($n = 222$)		Controls ($n = 381$)			Cases ($n = 407$)		Controls ($n = 842$)		
Characteristic	*N*	Mean (SD), or %	*N*	Mean (SD), or %	*P* value[a]	*N*	Mean (SD), or %	*N*	Mean (SD), or %	*P* value[a]
Age at blood draw, y	222	46.7 (4.4)	381	46.6 (4.2)	0.881	407	63.9 (6.4)	842	64.1 (6.5)	0.501
BMI at study entry, kg/m^2	222	24.8 (3.8)	380	24.8 (4.0)	0.713	407	26.3 (4.4)	839	25.6 (4.0)	0.009
Age at menarche, y	222	12.9 (1.5)	381	13.0 (1.4)	0.255	407	13.1 (1.5)	842	13.3 (1.5)	0.105
Alcohol consumption, g/d	220	6.7 (7.3)	380	6.4 (7.8)	0.070	402	8.4 (10.0)	837	7.1 (8.5)	0.031
Smoking status, %					0.084					0.031
Never smoked	111	50.5	214	56.2		156	38.9	379	45.2	
Past smoker	76	34.5	127	22.3		183	45.6	354	42.2	
Current smoker	33	14.9	40	10.5		62	15.5	106	12.6	
Ever use of MHT[b]	9	4.1	16	4.2	0.931	144	35.4	280	33.3	0.457
Ever use of oral contraceptives, %	199	90.1	355	93.2	0.177	295	74.3	644	78.1	0.145
Age at first birth and parity, %					0.304					0.317
Nulliparous	33	14.9	55	14.5		48	11.9	81	9.6	
<25 years/1–2 children	30	13.5	35	9.2		91	22.6	190	22.6	
<25 years/≥3 children	15	6.8	31	8.2		54	13.4	133	15.8	
25–29 years/1–2 children	53	23.9	79	20.8		109	27.1	221	26.3	
25–29 years/≥3 children	13	5.9	44	11.6		26	6.5	75	8.9	
≥30 years/≥1 children	77	34.7	136	35.8		74	18.4	141	16.8	
Total lifetime breastfeeding, %					0.503					0.505
≤6 months	49	23.7	91	26.0		128	33.6	257	31.7	
7–12 months	83	40.1	149	42.6		194	50.9	420	51.9	
≥13 months	75	36.2	110	31.4		59	15.5	133	16.4	
History of benign breast disease, %	58	26.1	69	18.4	0.011	123	31.1	191	23.1	0.003
Family history of breast cancer, %	50	22.5	54	14.6	0.008	101	25.3	145	17.1	0.002
Mean 2-year breast cancer risk score										
CAD2Y	138	0.4 (0.5)	376	0.3 (0.3)	<0.002	250	0.9 (0.0)	829	0.6 (0.4)	<0.001
Mean 5-year breast cancer risk score										
Gail	220	1.1 (0.4)	381	1.0 (0.4)	0.036	403	1.6 (0.6)	842	1.1 (0.4)	0.002
Tyrer–Cuzick	220	1.3 (1.0) Median (10th–90th percentile)	381	1.2 (0.6) Median (10th–90th percentile)	0.139	403	2.4 (1.4) Median (10th–90th percentile)	842	1.9 (0.0) Median (10th–90th percentile)	<0.001
DHEA, ng/mL	171	19.6 (1.8–64.4)	294	19.4 (1.8–56.2)	0.720	289	13.2 (1.1–44.4)	606	9.5 (1.1–42.8)	0.038
DHEAS, μg/mL	208	2.0 (0.7–4.1)	350	1.9 (0.9–3.7)	0.575	384	1.4 (0.6–3.1)	788	1.2 (0.5–2.8)	0.002
Mammographic density, %	214	36.6 (9.5–67.1)	373	30.7 (4.2–60.8)	<0.001	401	10.9 (1.3–36.3)	831	9.0 (0.8–32.7)	0.004

[a]*P* value for test of means, or χ^2 test of proportions between cases and controls.
[b]Current users not included.

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DHEA, percentage mammographic density, or total circulating testosterone to the model did not substantially affect these associations (**Table 2**).

Incidence of breast cancer was positively associated with mammographic density among both premenopausal (OR, top vs. bottom quartile 2.55; 95% CI, 1.39-4.68, $P_{trend} < 0.001$) and postmenopausal women (OR, top vs. bottom quartile 2.55; 95% CI, 1.66–3.92, $P_{trend} < 0.001$; **Table 3**). Additional inclusion of DHEA or DHEAS did not materially alter the results. Joint exposure analyses of incidence of breast cancer by combined effects of percentage mammographic density and DHEA or DHEAS levels did not reveal any significant interactions between density and hormone concentrations, independent of menopausal status (Supplementary Table S3).

Individual hormone levels were added to the Gail, Tyrer–Cuzick, and CAD2Y risk models. Adding either hormone to any model in premenopausal women did no significantly change the AUC (Supplementary Table S4). In postmenopausal women however, adding DHEAS, but not DHEA, significantly improved the AUC by 2.1 units for the Gail model and by 1.3 units for the Tyrer–Cuzick model (**Table 4**). Similarly, the predictive power of the CAD2Y model was significantly improved by adding DHEAS, but not DHEA, although the overall AUC was not improved (**Table 4**).

Adding mammographic density to Gail or Tyrer–Cuzick models significantly improved the AUC for both premenopausal (4.7 and 8.8 units, respectively; Supplementary Table S4) and postmenopausal women (2.1 and 1.2 units, respectively; **Table 4**). Similarly, adding DHEA or DHEAS and mammographic density simultaneously to the Gail or Tyrer–Cuzick model significantly improved the AUC for postmenopausal women. The Gail model improvement in AUC ranged from 2.5 to 3.3 units, with the greatest gain by adding both DHEAS and mammographic density. For the Tyrer–Cuzick model, improvement in AUC ranged from 0.9 to 1.5 units, with the greatest gain by adding DHEAS and mammographic density.

When testing model improvement by stepwise regression, both the postmenopausal Gail and Tyrer–Cuzick models including mammographic density were significantly improved by further adding DHEAS ($P = 0.006$ and $P = 0.007$, respectively; **Table 4**). Among premenopausal women, there was no significant gain by adding DHEA or DHEAS to either the Gail or the Tyrer–Cuzick risk models model already including density (**Table 4**; Supplementary Table S4).

Combining mammographic density and DHEAS in postmenopausal women significantly improved the discriminatory power of the Gail and the Tyrer–Cuzick models in early detected (<2 years) ER-positive and ER-negative tumors, grade 1–2, and grade 3 tumors (**Table 5**). Adding DHEAS to the CAD2Y model significantly improved the predictability

Table 2. ORs for incidence of breast cancer in relation to quartiles of plasma DHEA (ng/mL) or DHEAS (μg/mL) among women not currently using menopausal hormone replacement therapy.

		Plasma hormone levels, quartiles[a]				
		1st	2nd	3rd	4th	
	N cases/controls	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P* value trend[b]
Premenopausal women						
DHEA						
Model 1	153/280	1.0	1.09 (0.62–1.94)	0.89 (0.49–1.59)	1.03 (0.58–1.82)	0.864
Model 2	142/255	1.0	1.30 (0.72–2.35)	0.89 (0.48–1.63)	1.05 (0.56–1.95)	0.970
Model 3	146/275	1.0	1.03 (0.57–1.87)	0.92 (0.50–1.67)	0.95 (0.52–1.71)	0.759
Model 4	150/271	1.0	1.16 (0.64–2.10)	0.93 (0.52–1.69)	1.03 (0.58–1.85)	0.984
Premenopausal women						
DHEAS						
Model 1	188/336	1.0	0.35 (0.20–0.61)	0.61 (0.37–1.01)	0.84 (0.52–1.37)	0.341
Model 2	142/255	1.0	0.28 (0.14–0.56)	0.50 (0.28–0.92)	0.80 (0.43–1.48)	0.777
Model 3	181/328	1.0	0.37 (0.21–0.66)	0.58 (0.35–0.99)	0.87 (0.53–1.45)	0.377
Model 4	153/266	1.0	0.31 (0.16–0.59)	0.58 (0.33–1.02)	0.80 (0.46–1.40)	0.562
Postmenopausal women						
DHEA						
Model 1	269/571	1.0	0.80 (0.50–1.26)	1.15 (0.75–1.75)	1.25 (0.82–1.89)	0.154
Model 2	249/528	1.0	0.80 (0.50–1.29)	1.13 (0.72–1.76)	1.05 (0.66–1.67)	0.590
Model 3	267/564	1.0	0.83 (0.52–1.33)	1.18 (0.77–1.81)	1.30 (0.85–2.00)	0.132
Model 4	264/561	1.0	0.83 (0.52–1.32)	1.21 (0.79–1.85)	1.29 (0.84–2.00)	0.127
Postmenopausal women						
DHEAS						
Model 1	359/745	1.0	1.40 (0.95–2.07)	1.50 (1.01–2.22)	1.75 (1.19–2.57)	0.006
Model 2	249/528	1.0	1.59 (0.96–2.63)	1.74 (1.05–2.87)	2.04 (1.23–3.40)	0.019
Model 3	356/735	1.0	1.43 (0.90–2.00)	1.50 (1.01–2.23)	1.70 (1.14–2.52)	0.009
Model 4	276/578	1.0	1.61 (1.01–2.56)	1.57 (0.99–2.49)	2.00 (1.25–3.12)	0.028

Note: Model 1: Adjusted for age and BMI at blood draw (continuous), history of benign breast disorder (no, yes), family history of breast cancer (no, yes), smoking status (never, past, current smoker), alcohol consumption (g/d), time of day of blood draw, and menopausal hormone therapy (never, previous use; postmenopausal women only). Model 2: as Model 1, with addition of DHEA/S (log-transformed, continuous), respectively. Model 3: as Model 1, with addition of percentage mammographic breast density by STRATUS (square root–transformed, continuous). Model 4: as Model 1, with addition of total testosterone (ng/mL, continuous).
[a]DHEA premenopausal: 1st: <5.2 ng/mL, 2nd: 5.2–18.6, 3rd: 18.6–34.7, 4th: ≥34.8; postmenopausal: 1st: <2.6 ng/mL, 2nd: 2.6–9.0, 3rd: 9.0–22.3, 4th: ≥22.4. DHEAS premenopausal: 1st: <1.4 μg/mL, 2nd: 1.4–1.9, 3rd: 1.9–2.7, 4th: ≥2.8; postmenopausal: 1st: <0.7 μg/mL, 2nd: 0.7–1.2, 3rd: 1.2–1.8, 4th: ≥1.9.
[b]*P* value based on Wald test of natural log-transformed hormone, treated as a continuous variable.

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Table 3. ORs for incidence of breast cancer in relation to quartiles of mammographic density (%) among women not currently using menopausal hormone replacement therapy.

		Mammographic density, quartiles[a]				
	N cases/controls	1st OR (95% CI)	2nd OR (95% CI)	3rd OR (95% CI)	4th OR (95% CI)	*P* value trend[b]
Premenopausal women						
Mammographic density						
Model 1	194/355	1.0	1.11 (0.62–2.00)	1.59 (0.89–2.91)	2.55 (1.39–4.68)	<0.001
Model 2	146/275	1.0	1.20 (0.62–2.31)	1.53 (0.76–3.07)	2.13 (1.08–4.23)	0.006
Model 3	181/328	1.0	1.27 (0.69–2.34)	1.84 (0.97–3.49)	2.69 (1.41–5.14)	<0.001
Postmenopausal women						
Mammographic density						
Model 1	379/787	1.0	1.64 (1.11–2.41)	2.17 (1.45–3.24)	2.55 (1.66–3.92)	<0.001
Model 2	367/564	1.0	1.93 (1.21–3.09)	2.29 (1.39–3.75)	2.40 (1.42–4.06)	0.001
Model 3	356/735	1.0	1.60 (1.07–2.38)	2.15 (1.42–3.26)	2.46 (1.58–3.85)	0.009

Note: Model 1: Adjusted for age and BMI at blood draw (continuous), history of benign breast disorder (no, yes), family history of breast cancer (no, yes), smoking status (never, past, current smoker), alcohol consumption (g/d), time of day of blood draw, and menopausal hormone therapy (never, previous use; postmenopausal women only). Model 2: as Model 1, with addition of DHEA (log-transformed, continuous). Model 3: as Model 1, with addition of DHEAS (log-transformed, continuous).
[a]Mammographic density (%), premenopausal: 1st: <13.6, 2nd: 13.6–30.3, 3rd: 30.3–43.3, 4th: ≥43.4, postmenopausal: 1st: <2.9, 2nd: 2.9–9.1, 3rd: 9.1–20.6, 4th: ≥20.7.
[b]*P* value based on Wald test of square root–transformed mammographic density (%), treated as a continuous variable.

of early detected tumors (**Table 5**). There was no model improvement for breast cancers detected ≥2 years.

Discussion

In this large prospective study, circulating DHEAS was associated with an increased risk of postmenopausal breast cancer that was independent of mammographic density. Inclusion of DHEAS to current risk prediction models improved breast cancer discrimination among postmenopausal women not currently using MHT. Adding mammographic density along with DHEAS further improved risk prediction using the Gail and Tyrer–Cuzick models. DHEA and DHEAS did not improve either of the models in premenopausal women.

Few have studied the combined effects of density and endogenous hormones on breast cancer risk, and to our knowledge, none have included DHEA or DHEAS. Most studies, including ours, have failed to find a positive association between DHEA and DHEAS with premenopausal breast cancer risk (24–30), although some previous associations have been reported (1, 28, 31). In contrast, and consistent with most prior studies, we show that DHEAS was positively associated with increased breast cancer risk among postmenopausal women and with a similar magnitude of risk (1, 14–17). Besides the potential role as an androgen precursor, DHEAS is hypothesized to influence breast cancer risk through the androgen receptor (AR), although, to our knowledge, the association between endogenous sex hormone levels and breast cancer risk in AR-positive tumors remains unstudied. To test for any potential

Table 4. Change in age-adjusted AUC for breast cancer by different risk models among postmenopausal women not currently using menopausal hormone replacement therapy.

	Gail 5-year risk[a]				Tyrer–Cuzick 5-year risk[b]				CAD2Y 2-year risk[c]		
Model	*N* cases/controls	AUC (SE)	*P* value[d]	*P* value[e]	*N* cases/controls	AUC (SE)	*P* value[d]	*P* value[e]	*N* cases/controls	AUC (SE)	*P* value[d]
Risk model only	403/842	55.1 (1.8)	—		403/842	60.4 (1.7)	—		250/829	68.8 (1.9)	—
Risk model + DHEA	285/606	57.1 (2.1)	0.091		285/606	60.7 (2.1)	0.092		174/595	67.4 (2.2)	0.355
Risk model + DHEAS	380/788	57.2 (1.8)	0.008		380/788	61.7 (1.8)	0.007		236/776	67.8 (2.0)	0.023
Risk model + mammographic density	397/831	57.2 (1.8)	0.014		397/831	61.5 (1.7)	0.006				
Risk model + DHEA and mammographic density	281/598	57.6 (2.1)	0.031	0.086	281/598	61.3 (2.1)	0.018	0.083			
Risk model + DHEAS and mammographic density	374/777	58.4 (1.8)	0.002	0.006	374/777	61.9 (1.8)	0.001	0.007			

[a]Gail model included risk factors of age, age at menarche, age at first live birth, number of previous breast biopsies, atypical hyperplasia, and first-degree family history of breast cancer.
[b]Tyrer–Cuzick model included risk factors of age, age at menarche, age at first child, menopause, height, weight, MHT, hyperplasia, atypical hyperplasia, lobular cancer *in situ*, and first-/second-degree family history of breast cancer.
[c]CAD2Y risk model included age, menopausal status, BMI, current use of MHT, breast cancer in family, percent mammographic breast density, mammographic density difference (absolute difference between right and left breasts), microcalcification (absolute difference between right and left breasts), and interaction between mammographic density and masses.
[d]*P* value indicates difference in prediction by model with only risk score on the basis of log-likelihood ratio test.
[e]*P* value indicates difference in prediction by model with risk score and mammographic density compared with prediction by risk score together with mammographic density and DHEA or DHEAS, on the basis of log-likelihood ratio test.

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Table 5. Change in age-adjusted AUC for breast cancer by different risk models and tumor characteristics among postmenopausal women not currently using menopausal hormone replacement therapy.

	Gail 5-year risk[a]			Tyrer–Cuzick 5-year risk[b]			CAD2Y 2-year risk[c]		
Model	*N* cases/ controls	AUC (SE)	*P* value[d]	*N* cases/ controls	AUC (SE)	*P* value[d]	*N* cases/ controls	AUC (SE)	*P* value[d]
Early detection (<2 years)									
Risk model only	251/842	56.2 (2.1)	—	251/852	60.6 (2.1)	—	144/829	71.3 (2.3)	—
Risk model + DHEAS	236/788	59.3 (2.1)	0.006	236/788	62.6 (2.1)	0.005	136/776	70.0 (2.5)	0.011
Risk model + mammographic density	246/831	60.3 (2.1)	0.001	246/831	63.2 (2.0)	<0.001			
Risk model + DHEAS and mammographic density	231/777	61.6 (2.1)	<0.001	231/777	64.0 (2.1)	<0.001			
Late detection (≥2 years)									
Risk model only	152/842	55.4 (2.5)	—	152/842	59.9 (2.6)	—	106/829	64.6 (2.7)	—
Risk model + DHEAS	144/788	55.4 (2.6)	0.216	144/788	60.1 (2.6)	0.190	100/776	64.5 (2.8)	0.330
Risk model + mammographic density	151/831	54.8 (2.5)	0.863	151/831	59.6 (2.6)	0.943			
Risk model + DHEAS and mammographic density	143/777	54.9 (2.6)	0.426	143/777	59.8 (2.6)	0.397			
ER-positive									
Risk model only	308/842	54.9 (2.0)	—	308/842	60.5 (1.9)	—	175/829	67.0 (2.2)	—
Risk model + DHEAS	291/788	56.5 (2.0)	0.019	291/788	61.0 (1.9)	0.025	166/776	65.9 (2.3)	0.121
Risk model + mammographic density	304/831	56.6 (2.0)	0.264	304/831	60.5 (1.9)	0.204			
Risk model + DHEAS and mammographic density	287/777	57.0 (2.0)	0.037	287/777	60.8 (2.0)	0.041			
ER-negative									
Risk model only	41/842	60.1 (5.1)	—	41/842	67.4 (4.4)	—	29/829	69.7 (5.3)	—
Risk model + DHEAS	38/788	62.6 (5.2)	0.284	38/788	69.4 (4.2)	0.177	26/776	69.3 (5.6)	0.125
Risk model + mammographic density	39/831	66.0 (4.8)	0.014	39/831	71.6 (4.2)	0.006			
Risk model + DHEAS and mammographic density	36/777	68.3 (4.7)	0.030	36/777	72.5 (3.9)	0.010			
Grades 1–2									
Risk model only	244/842	54.0 (2.0)	—	244/842	58.9 (2.0)	—	150/829	68.0 (2.3)	—
Risk model + DHEAS	232/788	57.2 (2.1)	0.009	232/788	60.1 (2.1)	0.012	143/776	67.1 (2.4)	0.103
Risk model + mammographic density	240/831	54.7 (2.0)	0.423	240/831	58.6 (2.1)	0.370			
Risk model + DHEAS and mammographic density	228/777	57.7 (2.2)	0.021	228/777	59.9 (2.1)	0.026			
Grade 3									
Risk model only	146/842	61.7 (2.6)	—	146/842	66.8 (2.5)	—	91/829	71.9 (2.8)	—
Risk model + DHEAS	136/788	61.1 (2.7)	0.185	136/788	67.1 (2.5)	0.102	84/776	70.5 (3.0)	0.056
Risk model + mammographic density	144/831	64.3 (2.5)	0.002	144/831	68.9 (2.4)	<0.001			
Risk model + DHEAS and mammographic density	134/777	64.0 (2.7)	0.006	134/777	68.5 (2.5)	0.001			

[a]Gail model included risk factors of age, age at menarche, age at first live birth, number of previous breast biopsies, atypical hyperplasia, and first-degree family history of breast cancer.
[b]Tyrer–Cuzick model included risk factors of age, age at menarche, age at first child, menopause, height, weight, MHT, hyperplasia, atypical hyperplasia, lobular cancer *in situ*, and first-/second-degree family history of breast cancer.
[c]CAD2Y risk model included age, menopausal status, BMI, current use of MHT, breast cancer in family, percent mammographic breast density, mammographic density difference (absolute difference between right and left breasts), microcalcification (absolute difference between right and left breasts), and interaction between mammographic density and masses.
[d]*P* value indicates difference in prediction by model with only risk score on the basis of log-likelihood ratio test.

mediating effects though testosterone on the risk of breast cancer by DHEAS, we furthermore adjusted for levels of circulating testosterone in the logistic regression analyses. We did not observe any notable effect of testosterone, thus further supporting that DHEAS independently influences the risk of breast cancer.

In accordance with previous studies, circulating DHEAS was inversely associated with mammographic density among premenopausal women (32, 33), whereas we found no associations among postmenopausal women (34, 35). Breast cancer risk associated with mammographic density was not influenced by addition of either hormone to the model. The association between mammographic density and breast cancer risk has been extensively reported elsewhere (36), and the risk of breast cancer associated with mammographic density was similar to previous finding (12, 35). Others and we have shown that endogenous hormones act independently of mammographic density as risk factors of breast cancer in postmenopausal

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women (10, 12, 35). Collectively, the increasing body of literature suggests that mammographic density is influencing breast cancer risk independently of endogenous hormone levels among women not currently using MHT (10–12, 35).

Inclusion of endogenous DHEAS, but not DHEA, or mammographic density to established risk models improved risk discrimination by the Gail and Tyrer–Cuzick 5-year risk prediction models and the CAD2Y 2-year risk model for postmenopausal women, in a manner comparable with previous findings from ourselves and from others (1–3, 6, 10, 11, 37, 38). Among premenopausal women, we did not detect any significant gain in discriminatory power by adding either hormone to the prediction models. Only one previous study included DHEAS in the final model and found that addition of DHEAS to the Gail 5-year risk score somewhat improved the discriminatory power in postmenopausal women (2). Although addition of DHEAS improved the predictive power of the CAD2Y risk model, there was no gain in AUC. This likely reflects that the logistic regression optimizes the prediction model on the log odds scale, whereas AUC measures the area on the risk scale. Stratification by time to diagnosis and the gain of adding DHEAS to the CAD2Y model indicates that DHEAS alone or in combination with mammographic density is likely better suited for early detected tumors. This suggests that for implementation in clinic, combining endogenous DHEAS and mammographic density might be of most value for short-term risk prediction of women attending mammography screening.

Given the largely independent nature of DHEAS and density, we found that combining biomarkers improved prediction beyond the addition of a single biomarker among postmenopausal women. Simultaneous inclusion of both DHEAS and density provided the greatest improvement in AUC for the Gail (+3.3 compared with baseline model) and Tyrer–Cuzick (+1.5) models. The overall improvement in AUC when adding all biomarkers was less pronounced for the Tyrer–Cuzick compared with the Gail model, possibly because density, and to some extend the androgens, is associated with BMI which is included in the former model.

Collectively, our results are consistent with prior studies, including our own (10), and furthermore suggest independent and potentially additive associations of mammographic density and DHEAS with breast cancer risk. For clinical implementation of individualized breast cancer screening and prevention, a straightforward approach likely identifies high-risk individuals through mammography-based risk prediction. For additional risk stratification, DHEAS may be a suitable candidate marker to add to a selected high-risk population based on mammographic screening.

There are some weaknesses in this study. We used data from a single biomarker measurement collected at study entry up to 5 years prior to breast cancer diagnosis. However, the within-person stability of endogenous hormones including DHEAS over time, and up to 10 years prior to diagnosis, has been demonstrated for both pre- and postmenopausal women (39–41). Although the KARMA cohort is comprehensive and that this study is among the largest to evaluate independence of endogenous hormones and mammographic density as risk factors for breast cancer and risk prediction, hormone data were missing for some participants. The missing data on DHEA may somewhat decrease the specificity of the analyses and may dilute the associations. There were some variations in the number of women included for model comparisons, which could be the main source for the differences seen in the estimates. Also, the matched study design requires adjustment to matching factors and may influence the generalizability of the finding. The CAD2Y model was developed partly using the same cohort data, which may lead to higher discriminatory power and some overestimation. Finally, exposure data are self-reported, which could result in measurement bias. However, all exposure data, mammograms, and blood samples were collected at the same time at study entry, and it is not likely that the participants knew about their mammographic density, hormone levels, or breast cancer risk at time of answering the questionnaire. Furthermore, a nondifferential misclassification of exposures would dilute, not strengthen, the reported associations.

Strengths of our study are the large number of samples and sampling before disease onset, the fast, sensitive, and reliable UPSFC-MS/MS method for simultaneous quantification of endogenous steroids (22), three independently validated risk scores, and possibility to match study participants to the national breast cancer registers. Some hormones, including DHEA(S), display a circadian rhythm; we thus included time of day of blood draw in our models. In addition, the KARMA cohort provides centralized collection and handling of mammograms, blood samples and background information of all study participants, and quantitative assessment of mammographic density by STRATUS (20).

In conclusion, DHEAS was associated with postmenopausal risk of breast cancer independently of mammographic density. We furthermore confirm the improvement in the discriminatory capacity of standardized clinical breast cancer risk prediction models as well as the CAD2Y prediction model with the addition of plasma DHEAS concentrations, among postmenopausal women not using MHT at blood collection. The influence of hormones and density on predicting the risk of breast cancer needs to be validated in larger cohorts for its clinical utility. Our study suggests that information on density and DHEAS combined might contribute additional predictive power to risk models for postmenopausal breast cancer. If our results are confirmed, inclusion of DHEAS in risk prediction may improve risk stratification particularly for short-term risk of breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Bergquist, P. Hall
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Inclusion of Endogenous Plasma Dehydroepiandrosterone Sulfate and Mammographic Density in Risk Prediction Models for Breast Cancer

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