Title

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The association of predicted resting energy expenditure with risk of breast cancer among postmenopausal women in the Women's Health Initiative cohort

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Abstract

Obesity and obesity-related metabolic disorders, such as obesity and chronic inflammation have been positively associated both with postmenopausal breast cancer and with resting energy expenditure (REE). However, there is limited epidemiological evidence on the associations between REE and risk of postmenopausal breast cancer. We used multivariable Cox proportional hazards models to examine the association between predicted REE (calculated using the Ikeda, Livingston and Mifflin equations) and risk of postmenopausal breast cancer overall and by subtypes, and by level of body fat) among 137,305 postmenopausal women in the Women's Health Initiative (WHI). All predicted REEs were positively associated with risk of invasive breast cancer ($HR_{q5\ vs\ q1}$: 1.69; 95% CI: 1.57–1.81, HR: 1.69; 95% CI: 1.57–1.82 and HR: 1.68; 95% CI: 1.56–1.80 for Ikeda, Livingston and Mifflin, respectively). These positive associations were observed irrespective of the hormone receptor subtype, grade and stage of the tumors, but were most pronounced for estrogen receptor positive/progesterone receptor positive tumors. After additional adjustment for BMI, the associations were mostly attenuated and remained statistically significant for most of the outcomes. We also observed an interaction between the predicted REEs and BMI, with the associations being somewhat stronger among normal weight and overweight women than among obese women ($p_{interactions}$ <0.05). Our findings indicate that relatively high REE is associated with increased risk of invasive breast cancer among postmenopausal women

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(particularly for the obesity-related tumor subtypes), irrespective of the equation used. Further studies using more objective measures of REE are, however, needed to confirm our findings.

Keywords

resting energy expenditure; BMI; waist circumference; waist to hip ratio; breast cancer

Introduction

Obesity is one of the key risk factors for postmenopausal breast cancer among women (1,2). This metabolic disorder is thought to result partly from energy intake exceeding energy expenditure (3). Total energy expenditure (TEE)) comprises three components, namely resting energy expenditure (REE), diet-induced thermogenesis, and activity-related energy expenditure (AREE) (4). In a previous Women's Health Initiative (WHI) study, which investigated the association between the AREE component and postmenopausal breast cancer, higher AREE was inversely associated with risk (5).

REE, defined as the rate of energy production necessary for the body to perform important physiological functions at rest (3,6), is the primary component of total energy expenditure (accounting for approximately 60–70% of TEE) (7), but little is known about its association with risk of postmenopausal breast cancer. In a recent study conducted within The European Prospective Investigation into Cancer and Nutrition cohort, there was a 17% increase in the risk of postmenopausal breast cancer per one standard deviation increase in predicted REE (8), and in an earlier study from the National Health and Nutrition Examination Survey (9), relative to women in the second quintile, predicted REE was associated with a twofold increased risk of postmenopausal breast cancer among women in the highest quintile.

Higher REE is a compensatory physiologic change that typically occurs to meet the higher energy demand of obesity (10) and obesity-related metabolic dysfunctions including diabetes, impaired fasting glucose, reduced insulin sensitivity and chronic inflammation (11–13). Obesity and the aforementioned metabolic dysfunctions have all been shown to enhance carcinogenic processes including cell growth, proliferation and migration (14,15) that can lead to breast cancer (16,17). Given the role of energy expenditure in supporting cancer-associated metabolic aberrations, it is important to understand the association between REE and risk of postmenopausal breast cancer.

Indirect calorimetry (IC), performed using a metabolic cart, is regarded as the gold standard for determining REE (18). However, given the high cost of the metabolic cart, the need for highly trained staff, and the limited availability of equipment, its implementation in large-scale epidemiological studies is currently impractical (19). Therefore, most epidemiological studies have utilized various equations to predict REE, as this approach is less expensive and easier to incorporate in such studies than IC (19,20). Previously, in a WHI ancillary study, which aimed to determine which equations that predicted REE yielded results that closely agreed with measured REE, the Ikeda, Livingston and Mifflin equations, were found to perform the best (21). Hence, in the present study, we utilized these three equations to assess the association of predicted REE with risk of postmenopausal invasive breast cancer overall,

by tumor characteristics, and by anthropometric measures which are known to influence REE (3,22).

Methods

Study population and design

A detailed description of the WHI design and study population have been previously published (23). The WHI is a prospective multicenter study comprising 161,808 postmenopausal women from diverse racial and ethnic groups aged 50 to 79 at enrollment who were recruited from 40 US clinical centers throughout the United States between 1993 and 1998. Women participated in one of four clinical trials (hormone therapy (2 trials), low-fat diet modification, and calcium-vitamin D supplementation; n = 68,132) or an Observational Study (OS) group (n = 93,676) (23). The study protocol was reviewed by ethics committees at all 40 clinical centers, by the coordinating center, and by a data and safety monitoring board. The WHI project was reviewed and approved by the Fred Hutchinson Cancer Research Center (Fred Hutch) IRB in accordance with the U.S. Department of Health and Human Services regulations at 45 CFR 46 (approval number: IR# 3467-EXT). All participants provided written informed consent.

At recruitment, a self-administered questionnaire was used to collect information on sociodemographic characteristics, reproductive history, family history of breast cancer, medical history, medication use, and diet and lifestyle factors. Anthropometric measurements (weight, height, waist circumference (WC), hip circumference) were taken by trained clinic staff using a standardized protocol. Body mass index (BMI) was calculated by dividing weight (kg) by the square of standing height (m^2). Waist circumference was measured to the nearest 0.1 centimeter at the narrowest part of the waist by trained staff using tape measures. Waist-to-hip-ratio (WHR) was calculated by dividing waist circumference by the corresponding hip circumference. Among a subgroup of participants (n=11, 393), dual-energy x-ray absorptiometry (DXA)-derived whole body fat and lean body mass were measured by whole body DXA scans performed in fan-beam mode and obtained from Hologic QDR scanners (QDR 2000, 2000+, or 4500) (Hologic, Inc., Waltham, MA) (24). For these participants, fat to lean body mass was calculated by dividing whole body fat mass by the corresponding lean body fat mass.

Analytic cohort

From the total cohort, we excluded women with missing information on all three predicted REEs (n=532), those with a history of breast cancer or missing follow-up time (n=670), and women with implausible dietary energy intake levels (<600kcal or >5000kcal; n=4,239). We also excluded women with a history of thyroid disorders at baseline (n= 16,576) and those with follow-up time of three years or less (n= 23), to minimize the impact of preclinical disease and reverse causation. For each of the predicted equations, we excluded women with predicted REE values considered outliers (i.e., women with values less than the value at the first percentile or greater than the value at the 99th percentile (n= 2,988 for Ikeda and Livingston and 2,732 for Mifflin (there were also 842 women with missing values for

Mifflin)). After exclusion, the final analytical cohort comprised 136,780 women for the Ikeda and Livingston equations and 136,194 women for the Mifflin equation.

Resting energy expenditure

For the main analyses, we utilized three predicted equations for resting energy expenditure, namely the Ikeda, Livingston and Mifflin equations (21). Further information regarding the predicted REE equations is provided in Table 1. Among a subgroup of women from the WHI Nutrition and Physical Activity Assessment Study (N= 450), REE was measured by a trained technician using a VMAX 2900 indirect calorimeter (25). 348 of these women were included in the current analytic cohort.

Outcome ascertainment

Incident invasive breast cancer was the primary outcome in this study. During follow-up, outcome information was collected semi-annually in the CT group and annually in the OS using in-person, mailed, or telephone questionnaires. Incident breast cancer was confirmed via central review of medical records and pathology reports by trained physician adjudicators. Tumor hormone receptor status was coded using the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) coding system (26).

Statistical methods

Predicted REE measures were analyzed after categorization by quintiles (for subgroup analyses by levels of the anthropometric measures, the predicted REE measures were categorized as tertiles). To summarize the population characteristics, we used the median and interquartile ranges for continuous variables and frequencies and percentages for categorical variables. We also examined the distribution of the predicted REEs by the measured REE (n= 348).

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for the associations between the predicted REE measures and risk of breast cancer (overall, and by hormone receptor status, stage and grade). Time to event was the underlying timescale. Participants were censored if they had not developed breast cancer by the end of the follow-up period (August 31st, 2020) or if they died or withdrew from the study before the end of follow-up. Cases contributed person-time to the study from their date of enrollment until the date of breast cancer diagnosis, and non-cases (participants who were censored) contributed person-time from their date of enrollment until the end of follow-up, date of death, or date of withdrawal from the study, whichever came first. The multivariable models were adjusted for age at enrollment (yrs; continuous), race and ethnicity (African-American, Asian, American Indian and Alaskan native, Native Hawaiian and other Pacific Islander, Spanish and Latina, White (not of Hispanic origin), missing), education (high school or less than post-secondary/some college, graduate school /some graduate school, missing), recreational physical activity (Met-hours/week; continuous), smoking status (never, former, current, missing), alcohol consumption (continuous; serving/week), randomization group/study arm ((hormone therapy arm, low-fat diet modification arm, and calcium-vitamin D supplementation arm), ever use of unopposed estrogen therapy (yes/no), ever use of combined estrogen and progesterone therapy (yes/

no), age at menopause (yrs; <45, 45–54, ≥55, missing), ever use of oral contraceptives (yes/no), age at menarche (yrs; <12, 12–13, ≥14, missing), age at first full-term pregnancy (nulliparous, <20, 20–29, 30+, missing), parity (never been pregnant/no term pregnancy, 1, 2, 3, 4+, missing), ever breastfed (yes/no), family history of breast cancer in a 1st degree relative (yes/no), mammogram ever (yes/no), and the healthy eating index 2015 (continuous). Further, given that fat mass and lean body mass influence REE (27,28), in sensitivity analyses, we further adjusted for BMI and fat to lean body mass. Tests for trend were performed by modeling the ordinal variables as continuous variables.

We also assessed the association between the per standard deviation (SD) increase in the predicted REEs and risk of invasive breast cancer by levels of the anthropometric measures. P-values for heterogeneity were estimated by including an interaction term in the Cox regression models and using the Wald test to test its coefficient.

Finally, we performed sensitivity analyses by excluding persons with a history of cardiometabolic diseases (i.e., cardiovascular disease (CVD)/stroke, hypertension and diabetes) at baseline, which can influence REE..

All analyses were conducted using Stata 17.0 (StataCorp, College Station, TX, USA). All *P*-values were two-sided.

Data availability statement

This study was conducted using data from the UK Biobank study. Information on data availability can be obtained at http://www.ukbiobank.ac.uk.

Results

After a median follow-up of 19 years (interquartile range: 9.0–22.8 years), a total of 9,376 incident invasive breast cancer cases had been ascertained. Cases had lower educational level, but were more likely to have a family history of breast cancer in a first degree relative, to have an early age at menarche (<12years), to be nulliparous, to have a higher BMI, to have a higher WC, and to have higher predicted REEs (Table 2).

When we cross-classified the predicted REE measures by measured REE, 63.8%, 69.0% and 60.3% of those in the highest tertile of measured REE were in the highest tertile for Ikeda, Livingston and Mifflin predicted REE, respectively (Supplementary Table 1).

For the 3 predicted REEs, in multivariable models, we observed that those in the highest quintile had increased risk of invasive breast cancer (Tables 3–5). The HRs for the highest versus the lowest quintile were 1.69 (95% CI: 1.57–1.81), 1.69 (95% CI: 1.57–1.82) and 1.68 (95% CI: 1.56–1.80) for Ikeda, Livingston and Mifflin, respectively. Generally, the positive associations were observed irrespective of hormone receptor subtype, stage and grade of the tumors (Tables 3–5). The positive associations between the predicted REEs and risk of postmenopausal breast cancer were strongest for the hormone receptor positive (ER+/PR+: HR: 1.58, 95% CI: 1.36–1.84; HR: 1.48, 95% CI: 1.27–1.73; and HR: 1.46, 95% CI: 1.09–1.96 for Ikeda, Livingston and Mifflin-derived REE, respectively) and high grade

tumors (HR: 1.54, 95% CI: 1.19–1.99; HR: 1.84, 95% CI: 1.58–2.14; and HR: 1.43, 95% CI: 1.16–1.77 for Ikeda, Livingston and Mifflin-derived REE, respectively). In analyses with additional adjustment for BMI, the associations between the predicted REEs were attenuated but still mostly statistically significant (HR: 1.39, 95% CI: 1.23–1.57, HR: 1.37, 95% CI: 1.21–1.55 and HR: 1.34, 95% CI: 1.21–1.48 for the associations between Ikeda, Livingston and Mifflin derived-REE, respectively, and overall breast cancer risk; Tables 3–5). However, for ER+/PR- breast cancer and advanced breast cancers, these associations became null or borderline significant. In sensitivity analyses among the subgroup of women with available DXA measures, the associations between the predicted REEs and risk of invasive breast cancer were similar to those observed in the entire cohort, and were virtually unchanged after additional adjustment for the fat to lean body mass ratio (Supplementary Table 2).

In analyses stratified by BMI category, we observed heterogeneity in the association between the predicted REEs and risk of invasive breast cancer ($p<0.05$; Table 6). Specifically, all predicted REEs were positively associated with risk of invasive breast cancer in all BMI categories but the associations were stronger among overweight (BMI: 25.0–29.9 kg/m^2) and in particular, normal weight women (BMI: 18.5–24.9 kg/m^2) than among obese women (BMI: ≥30 kg/m^2) (Table 6). There was, however, no heterogeneity in the associations by WC or WHR categories (Table 6).

In sensitivity analyses, the associations between the predicted REEs and risk of invasive breast cancer were mostly unchanged after excluding women with a history of chronic diseases at baseline (Supplementary Table 3)

Discussion

In this large prospective study, regardless of which formula was used, the predicted REEs showed similar positive associations with risk of invasive breast cancer among postmenopausal women, overall, and irrespective of hormone receptor status, stage and grade of the tumors. Most of these associations remained after additional adjustment for BMI or for the ratio of fat mass to lean body mass. Further, except for heterogeneity in the association between the predicted REEs and risk of invasive breast cancer by BMI category, there was no evidence of heterogeneity by levels of central adiposity.

Physical activity is inversely associated with cancer-related metabolic disorders such as overweight/obesity, insulin resistance, diabetes, and chronic inflammation (16,17). Therefore, it is not surprising that previously in this cohort, AREE was shown to be inversely associated with risk of breast cancer among postmenopausal women (5). In contrast to the activity-related component of TEE, in the current study and in previous studies (8,9), predicted REE was positively associated with risk of postmenopausal invasive breast cancer.

In this study, the first to assess the association between REE and risk of postmenopausal breast cancer by hormone-receptor subtype, stage and grade, predicted REEs were positively associated with risk irrespective of these tumor characteristics. REE tends to be higher in overweight or obese individuals because a large body mass requires more kilocalories for

movement and to perform other basic energy utilizing functions (10). Moreover, excess adiposity is more strongly associated with the hormone receptor positive breast tumors (1,29) and higher grade breast tumors (1,30,31). In keeping with this, in the current study, we observed that among postmenopausal women, the positive associations between the predicted REEs and risk of breast cancer were most pronounced for the hormone receptor positive and higher grade tumors. Further, in analyses in which we adjusted for BMI, the associations between the predicted REEs and risk of invasive breast cancer(i.e. overall and by subtype) were attenuated, suggesting that body fat level partly explains the association between the predicted REEs and risk of invasive breast cancer.

We also showed positive associations between the predicted REEs and risk of postmenopausal invasive breast cancer irrespective of the categories of anthropometric measures. In this study, the positive associations between the predicted REEs and risk of breast cancer were more prominent among normal weight and overweight women than among obese women. Similar findings were observed in the study by Kliemann et al (8), which utilized the World Health Organization/The Food and Agriculture Organization of the United Nations (WHO/FAO) predicted REE equation (8). When we examined the associations between the predicted REEs and risk of postmenopausal invasive breast cancer by level of central adiposity (i.e., based on WC and WHR categories), we did not find any evidence of heterogeneity in the associations. These findings suggest that higher REE may be associated with higher risk of invasive breast cancer even among postmenopausal women with low to moderate levels of general or central adiposity.

Mechanisms underlying the association between REE and breast cancer are unclear. Nonetheless, our findings are consistent with the notion that various metabolic dysfunctions including impaired fasting glucose, reduced insulin sensitivity, and chronic inflammation (11–13) are energy-demanding and result in increased energy expenditure (10–13). Chronic inflammation, for example, increases energy expenditure by 10% (13). The aforementioned metabolic dysfunctions can contribute to breast carcinogenesis by triggering oxidative stress and DNA damage, and by enhancing tumor cell growth, proliferation, survival, and migration (14,15). Further experimental studies are needed to determine whether REE indirectly induces breast carcinogenesis by providing energy for dysregulated metabolic pathways and their associated carcinogenic processes (32,33).

In this large prospective study, with long-term follow-up and information on a wide range of potential confounding variables, we were able to investigate the associations between the predicted REEs and risk of postmenopausal invasive breast cancer by selected tumor characteristics. Due to the relatively high number of invasive breast cancer cases, we were also able to perform analyses stratified by various anthropometric measures. However, this study has several limitations. Firstly, we used equations to predict REE and therefore it is likely that there was some misclassification of the exposure of interest. The gold standard for measuring REE is indirect calorimetry (18) but there were too few women with available measured REE values to allow examination of the association between measured REE and risk. Nevertheless, in cross-classified analyses among a subgroup of women with measured REE, 60% or more of the participants with measured REEs in the highest tertile were also

in the highest tertile of the predicted REEs. As this study was restricted to postmenopausal women, our findings may not be generalizable to premenopausal women.

Our findings suggest that relatively high REE is positively associated with risk of invasive breast cancer among postmenopausal women, independent of BMI or fat to lean body mass and other confounders. Moreover, the association between the predicted REEs and risk appeared to be most pronounced for tumor subtypes which are more strongly associated with excess adiposity, namely hormone receptor positive subtypes and intermediate and high-grade breast tumors. Given the role of energy expenditure in supporting cancer-associated metabolic processes, further studies should be conducted to improve our understanding of the role of REE in the pathogenesis of breast cancer among postmenopausal women. If our findings are confirmed in future studies, predicted REE may provide a cheap, non-invasive means for predicting risk of breast cancer, and in particular, risk of the obesity-related subtypes, among postmenopausal women within a clinical setting and may be valuable in the development of nutritional interventions aimed at reducing risk of breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Prevention relevance

This study showed that higher resting energy expenditure (REE) was associated with higher postmenopausal breast cancer risk. REE provides energy to support cancer-associated disorders such as obesity and inflammation. Thus, studies on its association with breast cancer can help to improve our understanding of the pathophysiology of breast cancer.

Table 1.

Resting energy expenditure (REE) equations

	REE equation (Kcal/day)
Ikeda	10 × (body weight [kg] − 3 × age [y]) + 750
Livingston and Kohlstadt	$48 \times \text{Weight}^{0.4356} - (5.09 \times \text{Age})$
Mifflin St Jeor	(10 * weight) + (6.25 * height) × (5 * age) × 161

Table 2:

Baseline characteristics of women from the Women's Health Initiative study

Characteristic	Breast cancer	
	Yes (N=9,396)	No (N=127,887)
Age at entry (yrs.)		
Median (IQR)	62 (57–68)	63 (57–69)
Race and ethnicity: N (%)		
African-American	607 (6.3)	11,282 (8.8)
Asian	180 (1.9)	2,721 (2.1)
American Indian and Alaskan native	66 (0.7)	1,007 (0.8)
Native Hawaiian and other Pacific Islander	82 (0.9)	1,400 (1.1)
Spanish and Latina	174 (1.9)	3,953 (3.1)
White (not of Hispanic origin)	8,156 (86.8)	104,174 (81.5)
Missing	147 (1.6)	3,350 (2.6)
Education: N (%)		
Graduate School /Some graduate school	1,679 (17.9)	28,874 (22.6)
Age at first live birth (yrs.): N (%); <12)	1,009 (10.7)	16,383 (12.8)
Family history: N (%)	2,180 (23.2)	21,872 (17.1)
Age at menarche (yrs.): N (%); <12)	2,162 (23.0)	27,413 (21.4)
Parity: (N (%); nulliparous)	1,246 (13.3)	14,851 (11.6)
Breastfed: N (%)	4,813 (51.2)	65,226 (51.0)
Age at menopause (yrs.): (N (%); ≥55)	1,307 (17.8)	16,405 (12.8)
Ever had mammogram: N (%)	9,156 (97.5)	122,551 (95.8)
Unopposed estrogen: N (%)	3.126 (33.3)	44,966 (35.2)
Estrogen/progesterone combined therapy: N (%)	3,110 (33.1)	32,968 (25.8)
Oral contraceptive: N (%)	4,175 (44.4)	53,352 (41.7)
Alcohol serving/week)		
Median (IQR)	0.4 (0.0–3.4)	0.4 (0.0–2.7)
Health eating index		
Median (IQR)	65.8 (58.3–72.9)	65.6 (57.9–72.7)
Physical activity (Met-hours/week)		
Median (IQR)	7.5 (1.5–17.3)	7.5 (1.5–17.5)
BMI (kg/m^2)		
Median (IQR)	27.0 (23.9–31.1)	26.8 (23.7–30.8)

Characteristic	Breast cancer	
	Yes (N=9,396)	No (N=127,887)
WC (cm.)		
Median (IQR)	85.0 (76.5–95.0)	84.0 (76.0–94.2)
WHR		
Median (IQR)	0.80 (0.76–0.85)	0.80 (0.76–0.86)
Smoking status: (N (%); current	594 (6.3)	8,968 (7.0)
Ikeda predicted REE		
Median (IQR)	1,278 (1,191–1,387)	1,263 (1,177–1,374)
Livingston predicted REE		
Median (IQR)	1,276.5 (1,184.5–1,378.8)	1,260.3 (1,169.8–1,366.8)
Mifflin predicted REE		
Median (IQR)	1,262.5 (1,160.3–1,381.6)	1,241.5(1,138.6–1,363.0)

Abbreviations: BMI = body mass index, WC= waist circumference, WHR= waist to hip; Met=metabolic equivalent, IQR= interquartile range

Table 3:

Hazard ratios for the association of predicted REE (Ikeda) with risk of incident, invasive breast cancer in postmenopausal women, overall and by breast cancer subtype

	Quintiles					
	1	**2**	**3**	**4**	**5**	**P-trend**
Invasive breast cancer						
Cases (N)	1,887	1,865	1,896	1,870	1,858	
Age-adjusted HR (95% CI)	1.00	1.05 (0.99–1.12)	1.13 (1.06–1.20)	1.26 (1.18–1.35)	1.44 (1.35–1.54)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.11 (1.04–1.18)	1.23 (1.15–1.31)	1.43 (1.33–1.53)	1.69 (1.57–1.81)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.06 (0.99–1.14)	1.14 (1.06–1.23)	1.28 (1.17–1.39)	1.39 (1.23–1.57)	<0.001
ER+/PR+ breast cancer						
Cases (N)	1,164	1,191	1,258	1,229	1,249	
Age-adjusted HR (95% CI)	1.00	1.12 (1.03–1.22)	1.27 (1.17–1.37)	1.42 (1.31–1.54)	1.70 (1.57–1.85)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.16 (1.07–1.47)	1.58 (1.46–1.72)	1.96 (1.46–1.72)	1.96 (1.80–2.14)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.11 (1.02–1.21)	1.25 (1.14–1.37)	1.40 (1.25–1.56)	1.58 (1.36–1.84)	0.017
ER+/PR− breast cancer						
Cases (N)	269	280	226	207	197	
Age-adjusted HR (95% CI)	1.00	1.15 (0.98–1.37)	0.99 (0.83–1.19)	1.04 (0.87–1.26)	1.17 (0.97–1.41)	0.376
Multivariable-adjusted * HR (95% CI)	1.00	1.17 (0.99–1.39)	1.03 (0.86–1.23)	1.10 (0.91–1.33)	1.24 (1.02–1.52)	0.128
Multivariable-adjusted ** HR (95% CI)	1.00	1.17 (0.98–1.40)	1.03 (0.83–1.27)	1.11 (0.86–1.43)	1.24 (0.87–1.78)	0.557
ER−/PR− breast cancer						
Cases (N)	231	229	218	235	202	
Age-adjusted HR (95% CI)	1.00	1.05 (0.88–1.26)	1.05 (0.87–1.26)	1.28 (1.06–1.53)	1.24 (1.02–1.50)	0.004
Multivariable-adjusted * HR (95% CI)	1.00	1.05 (0.88–1.27)	1.04 (0.86–1.26)	1.25 (1.04–1.52)	1.17 (0.95–1.44)	0.035
Multivariable-adjusted ** HR (95% CI)	1.00	1.01 (0.83–1.23)	0.97 (0.78–1.20)	1.11 (0.86–1.43)	0.95 (0.66–1.36)	0.746
Localised						
Cases (N)	1,434	1,423	1,452	1,378	1,355	
Age-adjusted HR (95% CI)	1.00	1.09 (1.01–1.17)	1.18 (1.10–1.27)	1.29 (1.20–1.39)	1.49 (1.38–1.85)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.12 (1.04–1.21)	1.26 (1.17–1.35)	1.42 (1.32–1.54)	1.69 (1.56–1.84)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.09 (1.01–1.18)	1.19 (1.10–1.30)	1.31 (1.18–1.46)	1.47 (1.28–1.70)	<0.001
Advanced						
Cases (N)	394	407	404	441	435	
Age-adjusted HR (95% CI)	1.00	1.11 (0.96–1.27)	1.16 (1.01–1.33)	1.43 (1.25–1.64)	1.61 (1.40–1.87)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.12 (0.98–1.29)	1.19 (1.03–1.37)	1.48 (1.29–1.71)	1.68 (1.44–1.71)	<0.001

	Quintiles					
	1	2	3	4	5	P-trend
Multivariable-adjusted ** HR (95% CI)	1.00	1.06 (0.91–1.22)	1.06 (0.90–1.25)	1.25 (1.03–1.50)	1.23 (0.95–1.59)	0.038
Low grade						
Cases (N)	528	500	499	468	434	
Age-adjusted HR (95% CI)	1.00	1.02 (0.90–1.16)	1.09 (0.96–1.23)	1.17 (1.03–1.32)	1.27 (1.11–1.44)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.06 (0.94–1.20)	1.17 (1.03–1.33)	1.32 (1.16–1.51)	1.52 (1.32–1.74)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.03 (0.90–1.17)	1.10 (0.95–1.28)	1.20 (1.01–1.43)	1.28 (1.00–1.64)	0.024
Intermediate grade						
Cases (N)	811	775	807	778	796	
Age-adjusted HR (95% CI)	1.00	1.04 (0.94–1.15)	1.16 (1.05–1.28)	1.28 (1.16–1.41)	1.53 (1.38–1.69)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.07 (0.97–1.19)	1.23 (1.11–1.36)	1.42 (1.28–1.57)	1.76 (1.58–1.95)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.04 (0.94–1.15)	1.16 (1.03–1.30)	1.29 (1.13–1.48)	1.49 (1.23–1.80)	<0.001
High grade						
Cases (N)	375	415	398	440	448	
Age-adjusted HR (95% CI)	1.00	1.20 (1.04–1.38)	1.22 (1.06–1.40)	1.53 (1.33–1.76)	1.79 (1.56–2.06)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.21 (1.05–1.40)	1.24 (1.07–1.43)	1.57 (1.36–1.81)	1.81 (1.56–2.10)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.17 1.01–1.37)	1.16 (0.99–1.37)	1.43 (1.18–1.72)	1.54 (1.19–1.99)	<0.001

Abbreviations: REE= resting energy expenditure, HR= hazard ratio; CI= confidence interval; ER = estrogen receptor, PR= progesterone receptor

* Also adjusted for education, physical activity, smoking status, alcohol consumption, randomization group/study arm, unopposed estrogen therapy ever use, combined estrogen and progesterone therapy use ever, breastfed ever, age at menopause, oral contraceptive, healthy eating index 2015, age at menarche and age at first full-term pregnancy, race and ethnicity

** Also adjusted for BMI

Table 4:

Hazard ratios for the association of predicted REE (Livingston) with risk of incident, invasive breast cancer in postmenopausal women, overall and by breast cancer subtype

	Quintiles					
	1	**2**	**3**	**4**	**5**	**P-trend**
Invasive breast cancer						
Cases (N)	1,875	1,878	1,876	1,871	1,876	
Age-adjusted HR (95% CI)	1.00	1.06 (0.99–1.14)	1.17 (1.10–1.25)	1.31 (1.22–1.40)	1.52 (1.42–1.63)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.10 (1.03–1.17)	1.23 (1.15–1.31)	1.41 (1.32–1.51)	1.69 (1.57–1.82)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.05 (0.98–1.13)	1.14 (1.05–1.23)	1.25 (1.14–1.37)	1.37 (1.21–1.55)	<0.001
ER+/PR+ breast cancer						
Cases (N)	1,173	1,186	1,237	1,250	1,247	
Age-adjusted HR (95% CI)	1.00	1.08 (0.99–1.18)	1.25 (1.15–1.36)	1.42 (1.31–1.55)	1.66 (1.53–1.81)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.13 (1.04–1.22)	1.34 (1.23–1.45)	1.58 (1.46–1.73)	1.93 (1.77–2.12)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.07 (0.98–1.16)	1.21 (1.10–1.33)	1.36 (1.21–1.52)	1.48 (1.27–1.73)	<0.001
ER+/PR− breast cancer						
Cases (N)	268	274	233	200	201	
Age-adjusted HR (95% CI)	1.00	1.11 (0.93–1.31)	1.04 (0.87–1.25)	1.01 (0.83–1.11)	1.18 (0.97–1.43)	0.325
Multivariable-adjusted * HR (95% CI)	1.00	1.14 (0.95–1.35)	1.08 (0.90–1.29)	1.06 (0.88–1.29)	1.27 (1.03–1.56)	0.101
Multivariable-adjusted ** HR (95% CI)	1.00	1.16 (0.97–1.40)	1.12 (0.90–1.39)	1.13 (0.86–1.47)	1.40 (0.97–2.02)	0.277
ER−/PR− breast cancer						
Cases (N)	219	240	218	223	216	
Age-adjusted HR (95% CI)	1.00	1.12 (0.93–1.35)	1.09 (0.90–1.32)	1.23 (1.01–1.49)	1.33 (1.10–1.63)	0.003
Multivariable-adjusted * HR (95% CI)	1.00	1.12 (0.93–1.35)	1.09 (0.89–1.32)	1.21 (0.99–1.47)	1.26 (1.02–1.56)	0.027
Multivariable-adjusted ** HR (95% CI)	1.00	1.09 (0.90–1.33)	1.03 (0.82–1.29)	1.11 (0.85–1.44)	1.09 (0.75–1.57)	0.629
Localised						
Cases (N)	1,435	1,427	1,428	1,388	1,366	
Age-adjusted HR (95% CI)	1.00	1.06 (0.99–1.14)	1.17 (1.09–1.26)	1.28 (1.19–1.38)	1.48 (1.36–1.60)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.10 (1.02–1.19)	1.25 (1.15–1.34)	1.41 (1.31–1.53)	1.69 (1.55–1.83)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.07 (0.99–1.15)	1.18 (1.08–1.28)	1.29 (1.16–1.43)	1.45 (1.25–1.67)	<0.001
Advanced						
Cases (N)	384	411	405	434	446	
Age-adjusted HR (95% CI)	1.00	1.11 (0.96–1.28)	1.19 (1.02–1.37)	1.40 (1.22–1.62)	1.64 (1.42–1.90)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.13 (0.98–1.30)	1.21 (1.05–1.40)	1.46 (1.26–1.69)	1.71 (1.47–1.99)	<0.001

	Quintiles					
	1	**2**	**3**	**4**	**5**	**P-trend**
Multivariable-adjusted ** HR (95% CI)	1.00	1.06 (0.91–1.23)	1.08 (0.92–1.27)	1.22 (1.01–1.47)	1.25 (0.96–1.62)	0.049
Low grade						
Cases (N)	510	507	488	484	438	
Age-adjusted HR (95% CI)	1.00	1.04 (0.92–1.18)	1.10 (0.97–1.25)	1.22 (1.07–1.39)	1.28 (1.12–1.47)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.08 (0.96–1.23)	1.19 (1.04–1.35)	1.39 (1.22–1.59)	1.55 (1.35–1.79)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.05 (0.92–1.20)	1.13 (0.97–1.31)	1.28 (1.07–1.53)	1.35 (1.05–1.74)	0.005
Intermediate grade						
Cases (N)	819	765	801	791	792	
Age-adjusted HR (95% CI)	1.00	0.99 (0.90–1.09)	1.14 (1.03–1.26)	1.27 (1.14–1.40)	1.48 (1.33–1.64)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.03 (0.93–1.14)	1.22 (1.10–1.35)	1.40 (1.26–1.55)	1.70 (1.52–1.90)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	0.98 (0.88–1.09)	1.12 (0.99–1.25)	1.23 (1.07–1.41)	1.35 (1.12–1.64)	<0.001
High grade						
Cases (N)	370	427	393	429	457	
Age-adjusted HR (95% CI)	1.00	1.22 (1.06–1.40)	1.22 (1.06–1.41)	1.49 (1.29–1.71)	1.82 (1.57–2.10)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.23 (1.07–1.42)	1.23 (1.06–1.43)	1.50 (1.29–1.75)	1.81 (1.54–2.11)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.24 (1.07–1.43)	1.24 (1.07–1.44)	1.52 (1.31–1.76)	1.84 (1.58–2.14)	<0.001

Abbreviations: REE= resting energy expenditure, HR= hazard ratio; CI= confidence interval; ER = estrogen receptor, PR= progesterone receptor

* Also adjusted for education, physical activity, smoking status, alcohol consumption, randomization group/study arm, unopposed estrogen therapy ever use, combined estrogen and progesterone therapy use ever, breastfed ever, age at menopause, oral contraceptive, healthy eating index 2015, age at menarche and age at first full-term pregnancy, race and ethnicity

** Also adjusted for BMI

Table 5:

Hazard ratios for the association of predicted REE (Mifflin) with risk of incident, invasive breast cancer in postmenopausal women, overall and by breast cancer subtype

	Quintiles					
	1	**2**	**3**	**4**	**5**	**P-trend**
Invasive breast cancer						
Cases (N)	1,497	1,753	1,940	2,043	2,093	
Age-adjusted HR (95% CI)	1.00	1.08 (1.00–1.15)	1.21 (1.13–1.29)	1.34 (1.25–1.43)	1.54 (1.43–1.65)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.11 (1.03–1.19)	1.26 (1.17–1.35)	1.42 (1.32–1.53)	1.68 (1.56–1.80)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.16 (0.99–1.14)	1.16 (1.08–1.25)	1.26 (1.16–1.36)	1.34 (1.21–1.48)	<0.001
ER+/PR+ breast cancer						
Cases (N)	930	1,127	1,257	1,354	1,384	
Age-adjusted HR (95% CI)	1.00	1.12 (1.03–1.22)	1.28 (1.17–1.39)	1.45 (1.33–1.58)	1.69 (1.55–1.84)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.16 (1.06–1.27)	1.35 (1.24–1.47)	1.58 (1.44–1.72)	1.90 (1.73–2.08)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.10 (1.01–1.21)	1.22 (1.11–1.34)	1.34 (1.21–1.48)	1.41 (1.24–1.60)	<0.001
ER+/PR- breast cancer						
Cases (N)	195	269	255	225	226	
Age-adjusted HR (95% CI)	1.00	1.30 (1.08–1.56)	1.26 (1.04–1.52)	1.17 (0.96–1.43)	1.34 (1.09–1.63)	0.053
Multivariable-adjusted * HR (95% CI)	1.00	1.32 (1.10–1.60)	1.28 (1.06–1.56)	1.22 (0.99–1.49)	1.40 (1.14–1.73)	0.023
Multivariable-adjusted ** HR (95% CI)	1.00	1.34 (1.10–1.62)	1.30 (1.06–1.60)	1.25 (0.99–1.57)	1.46 (1.09–1.96)	<0.001
ER−/PR− breast cancer						
Cases (N)	193	197	241	236	246	
Age-adjusted HR (95% CI)	1.00	0.90 (0.74–1.10)	1.09 (0.89–1.32)	1.09 (0.90–1.33)	1.24 (1.02–1.52)	0.004
Multivariable-adjusted * HR (95% CI)	1.00	0.91 (0.74–1.11)	1.08 (0.89–1.32)	1.09 (0.89–1.33)	1.19 (0.96–1.46)	0.025
Multivariable-adjusted ** HR (95% CI)	1.00	0.89 (0.72–1.09)	1.04 (0.84–1.28)	1.02 (0.81–1.28)	1.05 (0.78–1.40)	0.476
Localised						
Cases (N)	1,127	1,349	1,451	1,563	1,520	
Age-adjusted HR (95% CI)	1.00	1.10 (1.02–1.20)	1.21 (1.12–1.31)	1.38 (1.27–1.49)	1.52 (1.40–1.65)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.14 (1.06–1.24)	1.27 (1.17–1.38)	1.48 (1.37–1.61)	1.69 (1.55–1.84)	<0.001

	Quintiles					
	1	2	3	4	5	P-trend
Multivariable-adjusted ** HR (95% CI)	1.00	1.11 (1.02–1.20)	1.19 (1.10–1.30)	1.34 (1.22–1.47)	1.40 (1.24–1.57)	<0.001
Advanced						
Cases (N)	322	363	436	439	504	
Age-adjusted HR (95% CI)	1.00	1.01 (0.90–1.18)	1.21 (1.04–1.40)	1.26 (1.09–1.46)	1.60 (1.38–1.85)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.03 (0.88–1.19)	1.23 (1.06–1.43)	1.30 (1.12–1.51)	1.64 (1.41–1.92)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	0.97 (0.84–1.14)	1.12 (0.96–1.31)	1.11 (0.94–1.32)	1.24 (1.001–1.53)	0.027
Low grade						
Cases (N)	405	477	505	532	493	
Age-adjusted HR (95% CI)	1.00	1.07 (0.93–1.22)	1.14 (0.99–1.30)	1.26 (1.10–1.44)	1.32 (1.15–1.52)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.11 (0.97–1.27)	1.21 (1.06–1.39)	1.39 (1.21–1.60)	1.54 (1.33–1.78)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.08 (0.94–1.24)	1.14 (0.99–1.32)	1.27 (1.08–1.48)	1.30 (1.06–1.59)	0.002
Intermediate grade						
Cases (N)	647	732	813	867	884	
Age-adjusted HR (95% CI)	1.00	1.04 (0.93–1.15)	1.17 (1.05–1.30)	1.31 (1.18–1.46)	1.51 (1.36–1.68)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.07 (0.96–1.19)	1.23 (1.11–1.37)	1.42 (1.27–1.58)	1.69 (1.51–1.89)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.03 (0.92–1.15)	1.14 (1.02–1.27)	1.25 (1.11–1.41)	1.35 (1.15–1.57)	<0.001
High grade						
Cases (N)	305	366	427	460	510	
Age-adjusted HR (95% CI)	1.00	1.09 (0.94–1.28)	1.28 (1.11–1.49)	1.44 (1.24–1.68)	1.78 (1.53–2.07)	<0.001
Multivariable-adjusted * HR (95% CI)	1.00	1.11 (0.95–1.30)	1.30 (1.12–1.51)	1.47 (1.26–1.71)	1.78 (1.53–2.09)	<0.001
Multivariable-adjusted ** HR (95% CI)	1.00	1.07 (0.91–1.25	1.21 (1.03–1.32)	1.30 (1.10–1.55)	1.43 (1.16–1.77)	<0.001

Abbreviations: REE= resting energy expenditure, HR= hazard ratio; CI= confidence interval; ER = estrogen receptor, PR= progesterone receptor

*Also adjusted for education, physical activity, smoking status, alcohol consumption, randomization group/study arm, unopposed estrogen therapy ever use, combined estrogen and progesterone therapy use ever, breastfed ever, age at menopause, oral contraceptive, healthy eating index 2015, age at menarche and age at first full-term pregnancy, race and ethnicity

**Also adjusted for BMI

Table 6:

Hazard ratios for the association of predicted REE with risk of incident, invasive breast cancer in postmenopausal women stratified by anthropometric measures

	Ikeda	Livingston	Mifflin
	Per SD increase		
BMI			
18.5–24.9kg/m^2	1.28 (1.17–1.40)	1.24 (1.14–1.35)	1.22 (1.14–1.30)
25.0–29.9kg/m^2	1.26 (1.16–1.36)	1.26 (1.16–1.37)	1.18 (1.11–1.26)
≥30kg/m^2	1.16 (1.10–1.22)	1.18 (1.11–1.25)	1.13 (1.08–1.19)
P-interaction	0.001	0.012	0.002
WC			
<80cm.	1.15 (1.06–1.24)	1.14 (1.06–1.22)	1.15 (1.08–1.23)
80–<88cm.	1.25 (1.14–1.37)	1.25 (1.14–1.37)	1.22 (1.13–1.32)
≥88cm.	1.18 (1.13–1.22)	1.20 (1.15–1.25)	1.16 (1.12–1.21)
P-interaction	0.735	0.893	0.269
WHR: <0.80			
<0.80	1.22 (1.18–1.27)	1.22 (1.18–1.27)	1.23 (1.18–1.27)
0.80–0.85	1.17 (1.11–1.22)	1.17 (1.12–1.23)	1.15 (1.09–1.20)
>0.85	1.20 (1.15–1.25)	1.22 (1.16–1.28)	1.20 (1.15–1.25)
P-interaction	0.975	0.766	0.469

Abbreviations: REE= resting energy expenditure, SD= standard deviation; BMI = body mass index, WC= waist circumference, WHR= waist to hip

Adjusted for education, physical activity, smoking status, alcohol consumption, randomization group/study arm, unopposed estrogen therapy ever use, combined estrogen and progesterone therapy use ever, breastfed ever, age at menopause, oral contraceptive, healthy eating index 2015, age at menarche and age