Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2011 March ; 20(3): 454–463. doi:10.1158/1055-9965.EPI-10-0974.

Body Size, Physical Activity, and Risk of Triple-Negative and Estrogen Receptor-Positive Breast Cancer

Amanda I. Phipps[1], **Rowan T. Chlebowski**[2], **Ross Prentice**[1], **Anne McTiernan**[1], **Marcia L. Stefanick**[3], **Jean Wactawski-Wende**[4], **Lewis H. Kuller**[5], **Lucile L. Adams-Campbell**[6], **Dorothy Lane**[7], **Mara Vitolins**[8], **Geoffrey C. Kabat**[9], **Thomas E. Rohan**[9], and **Christopher I. Li**[1]

[1]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA

[2]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Los Angeles, CA

[3]Stanford Prevention Research Center, School of Medicine, Stanford University, Palo Alto, CA

[4]Department of Social and Preventive Medicine, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY

[5]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA

[6]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

[7]Department of Preventive Medicine, State University of New York at Stony Brook, Stony Brook, NY

[8]Department of Epidemiology and Prevention, Division of Public Health Sciences, Wake Forest University, Winston-Salem, NC

[9]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY

Abstract

Background—Triple-negative breast cancer, characterized by a lack of hormone receptor and HER2 expression, is associated with a particularly poor prognosis. Focusing on potentially modifiable breast cancer risk factors, we examined the relationship between body size, physical activity, and triple-negative disease risk.

Methods—Using data from 155,723 women enrolled in the Women's Health Initiative (median follow-up 7.9 years), we assessed associations between baseline body mass index (BMI), BMI in earlier adulthood, waist and hip circumference, waist-hip ratio (WHR), recreational physical activity, and risk of triple-negative (N=307) and estrogen receptor-positive (ER+, N=2,610) breast cancers.

Results—Women in the highest versus lowest BMI quartile had 1.35-fold [95% confidence interval (CI): 0.92–1.99] and 1.39-fold (95% CI: 1.22–1.58) increased risks of triple-negative and ER+ breast cancers, respectively. Waist and hip circumferences were positively associated with risk of ER+ breast cancer (p for trend=0.01 for both measures) but were not associated with triple-negative breast cancer. Compared to women who reported no recreational physical activity, women in the highest activity tertile had similarly lower risks of triple-negative and ER+ breast

Corresponding author: Amanda I. Phipps, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., M4-B402, P.O. Box 19024, Seattle, WA 98109-1024, aphipps@fhcrc.org.

cancers [hazard ratio (HR)=0.77, 95% CI: 0.51–1.13 and HR=0.85, 95% CI: 0.74–0.98, respectively].

Conclusions—Despite biological and clinical differences, triple-negative and ER+ breast cancers are similarly associated with BMI and recreational physical activity in postmenopausal women. The biological mechanisms underlying these similarities are uncertain and these modest associations require further investigation.

Impact—If confirmed, these results suggest potential ways postmenopausal women might modify their risk of both ER+ and triple-negative breast cancers.

Keywords

triple-negative; breast cancer; physical activity; body mass index

INTRODUCTION

Defined by a lack of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, triple-negative breast cancer is associated with an aggressive pathology (1–4). Compared to women with ER-positive (ER+) tumors, women with triple-negative breast cancer experience poorer survival (1–4), and are more likely to exhibit high tumor grade (1–4) and elevated Ki-67 (3) and p53 (1,3) expression. The limited epidemiologic literature on triple-negative breast cancer indicates that these tumors occur disproportionately in African-American women (1–3,5) and *BRCA1* mutation carriers (6,7), and tend to be diagnosed at younger ages (2–4) than ER+ breast cancers. It has also been suggested that certain hormone-related factors play a lesser role in relation to risk of triple-negative breast cancer than ER+ disease (8,9). Whereas factors related to reproductive history and triple-negative breast cancer risk have been studied, relatively little attention has been paid to the role of potentially modifiable factors like obesity (5,8–11) and physical activity (5).

Endogenous estrogen levels in postmenopausal women are positively associated with obesity and inversely associated with physical activity (12,13); therefore, it is plausible that these factors would have a stronger relationship to ER+ tumor risk than triple-negative tumors. However, obesity and physical activity may also influence breast cancer risk through mechanisms not directly involving steroid hormones, including effects on levels of insulin and insulin-like growth factors, cytokines, and inflammation (14,15). One study reported a positive association between BMI and risk of postmenopausal triple-negative breast cancer, but only in women who were not hormone therapy (HT) users (10). Other studies have found no association between BMI and postmenopausal triple-negative breast cancer (8,9). One study reported that waist-hip-ratio (WHR) was positively associated with risk of basal-like breast cancer (i.e., triple-negative and positive for cytokeratin 5/6 and/or EGFR expression) (9); however, this finding has not been replicated. An inverse association between physical activity level and triple-negative breast cancer risk in younger women (ages 20–54) who met or exceeded the median activity level of the study population has been reported by one study (5); however, to our knowledge, no studies have assessed this relationship in older women.

Using data from the Women's Health Initiative (WHI), we explored associations between aspects of body size, recreational physical activity, and risk of triple-negative, as well as ER + breast cancer in postmenopausal women.

MATERIALS AND METHODS

Study Population

The WHI is a longitudinal study of postmenopausal women, encompassing multiple concurrent randomized clinical trials and an observational study. WHI recruitment protocols and procedures are described in detail elsewhere (16,17). Briefly, between October 1, 1993, and December 31, 1998, postmenopausal women aged 50 to 79 years were recruited from 40 clinical centers across the United States. Women with a medical condition with a predicted survival less than three years or who were unlikely to stay in the same geographic area for this period were excluded. Additional eligibility criteria related to competing risks and likely adherence were imposed for clinical trial (CT) participation, including a baseline mammogram and/or clinical breast examination suspicious for breast cancer, or a history of breast cancer. Women not meeting CT eligibility criteria or not interested CT participation were given the opportunity to enroll in the WHI Observational Study (OS). At the time of enrollment, all women provided written informed consent for participation. Human Subjects Review Committees at all participating institutions approved the WHI study protocol.

In total, 161,808 women enrolled in the WHI (N=93,676 in the OS; N=68,132 in the CT). For this analysis, we excluded women with a history of breast cancer or mastectomy at baseline (N=5,239) and women without follow-up information for breast cancer diagnoses (N=846), leaving a study population of 155,723 women.

Exposure Assessment

All women completed a series of self-administered questionnaires at the baseline screening visit from which detailed information on demographic factors, reproductive history, medical history, breast cancer family history, and physical activity were collected. Information on lifetime use of postmenopausal HT was collected through a structured in-person interview. Women were classified as current HT users if they reported using estrogen-containing pills or patches at baseline (CT or OS) or were randomly assigned to the active HT arms of one of the HT trials within the CT. Height, weight, and waist and hip circumferences were measured at baseline clinic visits. BMI was calculated as weight (kg) divided by squared height (m^2). OS participants were asked to self-report their weight at ages 18, 35, and 50 years; BMI calculations for those ages were based on self-reported weight at that age and height at baseline. WHR was calculated as waist circumference (measured to the nearest 0.1 cm at the narrowest part of the torso) divided by hip circumference (measured to the nearest 0.1 cm at the maximal circumference).

At baseline, women were asked how often they currently exercised (never, 1, 2, 3, 4, ≥5 days per week) and how long they typically exercised per session (<20, 20–39, 40–59, ≥60 minutes). Questions were structured to inquire separately about strenuous-, moderate-, and low-intensity recreational exercise. Strenuous exercise was defined as exercise that led to sweating and increased heart rate (e.g., aerobics, swimming laps, jogging). Provided examples of moderate-intensity activity included biking outdoors, using an exercise machine, and calisthenics; provided examples of low-intensity activity included bowling and golf. Metabolic equivalent (MET) values, defined as the ratio of metabolic rate during a specific activity relative to metabolic rate at rest, were assigned for strenuous-, moderate-, and low-intensity activities (7, 4, and 3, respectively) and multiplied by the hours exercised at that intensity level per week to obtain composite recreational physical activity variables (MET-hours/week) for each intensity level and for all intensity levels combined (18).

Follow-Up and Outcome Ascertainment

Medical history, including diagnosis of breast cancer, was updated annually (OS) or semiannually (CT) via mailed or telephone-administered questionnaires. Breast cancer diagnoses reported by participants were verified locally by WHI physician adjudicators. Medical records and pathology reports for locally confirmed breast cancers were sent to the WHI Clinical Coordinating Center for central adjudication and coding of ER, PR, and HER2 status.

Over follow-up (median 7.9 years), invasive breast cancer was identified in 5,194 women. Information on ER, PR, and HER2 status was available for 4,677 (90%), 4,600 (89%), and 3,139 (60%) cases, respectively. In light of variability in HER2 testing practices over the study period and across institutions, ER+ cases with unknown HER2 status (N=1,334) were excluded from the ER+ case group to enable greater comparability to the triple-negative group. Cases with missing HER2 data were diagnosed, on average, earlier during the study period than cases with known HER2 status (mean duration of follow-up = 2.9 versus 5.0 years in cases with unknown versus known HER2 status) and were more likely to have been enrolled in the OS (59.0% versus 55.7%). The distribution of exposure variables, however, was similar in cases with unknown versus known HER2 status (26.5% versus 27.2% in the uppermost quartile of baseline BMI; 25.7% versus 23.0% in the uppermost quartile of total recreational physical activity). Of the 3,116 cases with complete tumor marker data, 307 (10%) were triple-negative and 2,610 (84%) were ER+. Remaining cases were ER−/PR−/HER2+ (N=154), ER−/PR+/HER2− (N=31), or ER−/PR+/HER2+ (N=14).

Statistical Analyses

We used Cox regression to assess associations between WHR, waist and hip circumferences, BMI at different ages (baseline and ages 50, 35, and 18), baseline recreational physical activity level (total, strenuous, moderate-/low-intensity), and subtype-specific breast cancer risk. We constructed separate models for triple-negative and ER+ subtypes, with the time axis defined as the time (in days) since randomization (CT) or study enrollment (OS). Women diagnosed with *in situ* breast cancer or an invasive breast cancer other than the model-specific outcome were censored at the time of diagnosis. Proportional hazards assumptions were verified by testing for a non-zero slope of the scaled Schoenfeld residuals on ranked failure times and on the log of analysis time (19).

Analyses were adjusted for a common set of confounders selected *a priori*, including study arm, race, education level, household income, family history of breast cancer in first-degree relatives, receipt of mammography during follow-up, and history of mammography within the two years prior to baseline. Analyses were adjusted for age both explicitly, through inclusion of a linear adjustment term, and implicitly, via stratification of the baseline hazards (10-year categories). Analyses of baseline recreational physical activity were further adjusted for baseline BMI; analyses of baseline body size characteristics were further adjusted for total recreational physical activity at baseline. We also assessed confounding by parity, ages at first birth and menopause, alcohol consumption, and smoking; however, since adjustment for these factors altered effect estimates for both subtypes by less than 10%, none were included in final multivariate models. We evaluated interaction by current HT use with respect to physical activity and baseline body size characteristics; where interaction was found to be statistically significant, we replicated analyses among current non-users of HT.

Anthropometric variables were categorized into quartiles based on distributions in the overall study population. We also conducted analyses of BMI at baseline using categories based on the National Heart Blood and Lung Institute definitions for normal weight (BMI

<25.0 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), and obese (BMI ≥30 kg/m^2) (20). For analyses of total recreational physical activity, we grouped women reporting any activity into three categories based on the tertile distribution of MET-hours/week among active women, with a separate (referent) category for women reporting no activity. For analyses of strenuous-, and moderate-/low-intensity activity, we dichotomized women reporting any activity according to MET-hours/week and, again, used a referent category of women reporting no activity of the intensity level of interest; we mutually-adjusted analyses for activity at these intensity levels. For all exposures, we compared subtype-specific HR estimates using competing risks partial likelihood methods (21). All analyses were performed using STATA SE version 11 (College Station, Texas).

Missing exposure, covariate, and tumor marker data were handled using a complete-case approach, excluding observations with missing exposure or covariate data and censoring case observations with missing tumor marker data at the time of diagnosis. We conducted sensitivity analyses using multiple-imputation (22) to assess the impact of missing tumor marker, exposure, and covariate data. Subtype-specific hazard ratios (HRs) obtained in our multiple-imputation analyses (not shown) were almost identical to those in the primary analysis. Thus, only the results from complete-case analyses are presented here.

RESULTS

Key characteristics of the study population are provided in Table 1. Women diagnosed with triple-negative breast cancer were younger, more likely to be African-American, and more likely to have a breast cancer family history than non-cases or ER+ cases.

There were several similarities in associations between aspects of baseline body size and risks of ER+ and triple-negative breast cancers (Table 2). For ER+ breast cancer, women in the highest baseline BMI quartile had a 1.39-fold [95% confidence interval (CI): 1.22–1.58] increased risk compared to women in the lowest quartile. The association between BMI and triple-negative breast cancer was of similar magnitude (highest versus lowest BMI quartile: HR=1.35, 95% CI: 0.92–1.99), although not statistically significant. Similar associations across subtypes were noted in analyses of BMI categorized by NHLBI standard cut-points. WHR was not associated with risk of either subtype, but waist and hip circumference were modestly positively associated with risk of ER+ breast cancer (highest versus lowest circumference quartile: HR_{waist}=1.34, 95% CI: 1.09–1.64; HR_{hip}=1.28, 95% CI: 1.03–1.58). In contrast, non-significant inverse associations were noted between these measures and triple-negative breast cancer (HR_{waist}=0.66, 95% CI: 0.37 –1.20; HR_{hip}=0.88, 95% CI: 0.41–1.50). However, differences between subtypes were not statistically significant (p=0.07 and 0.31 for waist and hip circumference, respectively).

Patterns of association with self-reported BMI at younger ages differed slightly, but not significantly for ER+ versus triple-negative breast cancer (Table 3). Specifically, ER+ breast cancer risk was inversely associated with BMI at ages 35 (p_{trend}=0.01) and 18 (p_{trend}<0.01) but not BMI at age 50 years (p_{trend}=0.48). In contrast, there was no association between BMI at ages 35 (p_{trend}=0.77) or 18 (p_{trend}=0.59) and triple-negative breast cancer, but there was a suggestive positive association with BMI at age 50 (highest versus lowest quartile: HR=1.93, 95% CI: 0.91–4.08, p_{trend}=0.10). Weight change between these successive ages, and overall since age 18, was associated with an increased risk of ER+ breast cancer (Supplementary Table 1); only weight change between ages 35 to 50 years was significantly associated with triple-negative breast cancer risk (HR=1.69, 95% CI: 1.06–2.71 for a weight gain >6.0 kg versus <2.5 kg, p_{trend}=0.03).

Total weekly energy expenditure from recreational physical activity was modestly inversely associated with ER+ breast cancer risk (Table 4; p_{trend}<0.01). The inverse association between physical activity and triple-negative risk was not significant (highest tertile versus no activity: HR=0.77, 95% CI: 0.51–1.13; p_{trend}=0.47). For both subtypes, there was some suggestion that these modest associations were limited to moderate-/low-intensity activity. There was no significant difference between subtype-specific HR estimates, regardless of intensity level.

There was evidence of interaction by current HT use in associations with baseline BMI, waist circumference, and hip circumference for ER+ ($p_{interaction}$=0.01, 0.03, and 0.04, respectively) but not triple-negative breast cancer ($p_{interaction}$=0.98, 0.36, and 0.83). Positive associations with BMI were more pronounced for ER+ and triple-negative subtypes when restricted to non-users of HT at baseline (Table 5). The previously-noted non-significant inverse association between waist circumference and risk of triple-negative breast cancer was not evident among non-users of HT. There was no evidence of heterogeneity in subtype-specific associations among non-users of HT. Interaction by HT was not significant in analyses of WHR ($p_{interaction}$=0.51 and 0.65 for ER+ and triple-negative subtypes, respectively) or recreational physical activity ($p_{interaction}$=0.85 and 0.34) (results not shown).

DISCUSSION

Despite substantial molecular and clinical differences between triple-negative and ER+ breast cancers, these subtypes of disease appear similar in their associations with baseline BMI and recreational physical activity. In this prospective cohort of postmenopausal women, we found a 1.39-fold increased risk of ER+ and 1.35-fold increased risk of triple-negative breast cancer among women in the highest versus lowest BMI quartile, as well as a 15% lower risk of ER+ and a non-significant 23% lower risk of triple-negative breast cancer among women in the highest versus lowest physical activity level. These associations were all modest in magnitude, and not statistically significant for the triple-negative subtype. However, given the potentially modifiable nature of these exposures, these results suggest that there may be ways postmenopausal women can impact their risks of both ER+ and triple-negative breast cancer.

Few studies have explored the association between body size and triple-negative breast cancer risk, and the results of studies to date have been largely inconsistent. Two of three prior studies in postmenopausal women found no association between BMI and basal-like breast cancer and did not evaluate associations among non-users of HT (8,9); the remaining study reported a 2.7-fold (95% CI: 1.0–7.5) increased risk of postmenopausal triple-negative breast cancer among women in the highest versus lowest BMI quartile, but noted that this association was limited to non-users of HT (10). Consistent with this latter study, our results suggest a positive association between BMI and postmenopausal triple-negative breast cancer; although we noted no interaction in this association by HT use, we also found the association with BMI to be slightly stronger when restricted to non-users of HT. In contrast to a previous study that reported a positive association between WHR and basal-like breast cancer risk (9), we found no association with WHR for either subtype. Inconsistencies across studies may reflect differences in study cohort characteristics, but may also reflect limitations of small sample sizes: previous analyses have included only 56 to 101 postmenopausal triple-negative or basal-like cases (8–10).

Evidence of a positive association between body size and ER+ breast cancer is more substantial and consistent (23–27). In agreement with prior studies, we found that BMI was positively associated with risk of postmenopausal ER+ breast cancer, particularly among non-users of HT. It has been suggested that this association is largely attributable to the positive relationship between BMI and endogenous estrogen levels, since adipose tissue is the primary source of androgen conversion to estrogen in postmenopausal women not using HT (28,29). Similarly, our finding of a modest positive association between waist circumference and ER+ breast cancer risk is consistent with previous studies, and with hypotheses that excess abdominal adiposity contributes to increased breast cancer risk through an influence on sex hormone levels (30). Triple-negative breast cancers, on the other hand are hormone receptor-negative by definition, yet we observed a similar positive association between BMI and breast cancer risk for both subtypes, suggesting that non-hormonal factors may also play a role in mediating associations with this aspect of body size. Although this is inconsistent with prior studies indicating no association between BMI and postmenopausal ER−/PR− breast cancer (23–27), there is some biological plausibility to support such a hypothesis; in particular, obesity is associated with increased inflammation (15,31) and with increased levels of insulin and insulin-like growth factors (14), which may impact breast cancer risk.

Some (5,8,11), but not all (9) previous studies have reported a modest positive association between BMI and triple-negative breast cancer risk in younger women. Consistent with such reports, we observed a positive association between BMI at age 50, weight gain between ages 35 to 50, and triple-negative risk, although we found no association with BMI in earlier adulthood and weight change over other intervals. Our findings regarding the association between these exposures and ER+ breast cancer risk are consistent with previous studies indicating that disease risk is inversely associated with BMI in early adulthood and positively associated with lifetime weight gain (32–34).

Most prior studies, including a study conducted within the WHI OS (35), have suggested a protective role of physical activity against breast cancer in postmenopausal women (36,37). Numerous mechanisms have been proposed for this association (15,35). In particular, physical activity may contribute to reduced risk through reduction of adipose tissue, or by lowering levels of bioavailable sex hormones, insulin, and insulin-like growth factors (12,15). While hormonal mechanisms are plausible, most studies that have stratified associations with physical activity by hormone receptor status report similar associations across case groups defined by ER/PR (23,37–40). The only prior study to assess the association between physical activity and triple-negative breast cancer reported a 27% lower risk of triple-negative breast cancer among women aged 20–54 who met or exceeded the median level of physical activity within the study population (5). Our results support these findings and suggest a modest but not significantly lower risk of triple-negative breast cancer in women who are physically active. Also consistent with this prior report and others that stratified cases by ER/PR status, our results indicate little difference in associations with recreational physical activity for triple-negative versus ER+ subtypes.

Certain limitations should be considered in interpreting these results. Most importantly, HER2 status was unknown for 40% of cases. These cases, and cases with unknown ER/PR status, were censored at the time of diagnosis and, therefore, did not contribute to case groups. However, the distribution of exposure was similar among cases with and without tumor marker data. We also observed little change to our results when using multiple-imputation to account for these missing data. Misclassification of exposure is also a consideration. Physical activity and past BMI variables were based on self-report. Accurate recall of past weight may be problematic; however, because all exposure data were collected prior to breast cancer diagnosis, errors in recall are likely unrelated to outcome. Additionally, physical activity levels presented here reflect energy expenditure from recreational exercise only; thus, we cannot rule out the possibility that non-recreational physical activity is differentially associated with risk of ER+ and triple-negative breast cancers. Misclassification of physical activity levels could also have resulted if women performed activities not referenced in the questionnaire. The use of category mid-points in calculating values for MET-hours/week activity variables could also have contributed to misclassification although, again, misclassification would have been non-differential with respect to outcome. Lastly, we acknowledge that heterogeneity within the triple-negative and ER+ case groups may have obscured differences in associations with body size and physical activity across more finely classified tumor subtypes. Specifically, we did not distinguish ER+ cases according to PR or HER2 status, nor were we able to distinguish triple-negative cases according to the expression of basal markers (e.g., cytokeratin 5/6, EGFR). Although risk factor associations may vary across subsets of ER+ and triple-negative breast cancers, we assume here that heterogeneity within these groups is less pronounced than heterogeneity between groups.

The results of this analysis suggest the existence of modest but modifiable risk factors for postmenopausal triple-negative breast cancer. Risk of triple-negative breast cancer was reduced, albeit not to the extent of statistical significance, among women who were physically active and among women with lower BMI. These factors were similarly associated with lower risk of ER+ breast cancer, suggesting that the protective effects of these exposures are not breast cancer subtype-specific and that there may be lifestyle modifications that postmenopausal women can make to reduce their risk of triple-negative and ER+ breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding information: The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221. This publication was also supported by grant numbers T32 CA09168 and R25-CA-94880 from the National Cancer Institute, National Institutes of Health.

REFERENCES

1. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006; 295:2492–2502. [PubMed: 16757721]
2. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007; 109:1721–1728. [PubMed: 17387718]
3. Lund MJ, Trivers KF, Porter PL, Coates RJ, Leyland-Jones B, Brawley OW, et al. Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA. Breast Cancer Res Treat. 2009; 113:357–370. [PubMed: 18324472]
4. Onitilo AA, Engel JM, Greenlee RT, Mukesh BN. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival. Clin Med Res. 2009; 7:4–13. [PubMed: 19574486]
5. Trivers KF, Lund MJ, Porter PL, Liff JM, Flagg EW, Coates RJ, et al. The epidemiology of triple-negative breast cancer, including race. Cancer Causes Control. 2009; 20:1071–1082. [PubMed: 19343511]
6. Foulkes WD, Stefansson IM, Chappuis PO, Begin LR, Goffin JR, Wong N, et al. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. J Natl Cancer Inst. 2003; 95:1482–1485. [PubMed: 14519755]

7. Atchley DP, Albarracin CT, Lopez A, Valero V, Amos CI, Gonzalez-Angulo AM, et al. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J Clin Oncol. 2008; 26:4282–4288. [PubMed: 18779615]

8. Yang XR, Sherman ME, Rimm DL, Lissowska J, Brinton LA, Peplonska B, et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. Cancer Epidemiol Biomarkers Prev. 2007; 16:439–443. [PubMed: 17372238]

9. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, Smith LV, et al. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat. 2008; 109:123–139. [PubMed: 17578664]

10. Phipps AI, Malone KE, Porter PL, Daling JR, Li CI. Body size and risk of luminal, HER2-overexpressing, and triple-negative breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2008; 17:2078–2086. [PubMed: 18664548]

11. Dolle JM, Daling JR, White E, Brinton LA, Doody DR, Porter PL, et al. Risk factors for triple-negative breast cancer in women under the age of 45 years. Cancer Epidemiol Biomarkers Prev. 2009; 18:1157–1166. [PubMed: 19336554]

12. McTiernan A, Wu L, Chen C, Chlebowski R, Mossavar-Rahmani Y, Modugno F, et al. Relation of BMI and physical activity to sex hormones in postmenopausal women. Obesity (Silver Spring). 2006; 14:1662–1677. [PubMed: 17030978]

13. Chan MF, Dowsett M, Folkerd E, Bingham S, Wareham N, Luben R, et al. Usual physical activity and endogenous sex hormones in postmenopausal women: the European prospective investigation into cancer-norfolk population study. Cancer Epidemiol Biomarkers Prev. 2007; 16:900–905. [PubMed: 17507613]

14. Stoll BA. Upper abdominal obesity, insulin resistance and breast cancer risk. Int J Obes Relat Metab Disord. 2002; 26:747–753. [PubMed: 12037643]

15. McTiernan A. Mechanisms linking physical activity with cancer. Nat Rev Cancer. 2008; 8:205–211. [PubMed: 18235448]

16. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials. 1998; 19:61–109. [PubMed: 9492970]

17. Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, et al. The Women's Health Initiative recruitment methods and results. Ann Epidemiol. 2003; 13:S18–S77. [PubMed: 14575939]

18. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr. Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc. 1993; 25:71–80. [PubMed: 8292105]

19. Therneau, TM.; Grambsch, PM. Modeling survival data: Extending the Cox model. New York: Springer; 2000.

20. Institute NHBaL. , editor. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: The evidence report. Bethesda, MD: 1998.

21. Kalbfleisch, JD.; Prentice, RL. The Statistical Analysis of Failure Time Data. 2nd edition. New York, NY: John Wiley & Sons, Inc.; 2002. ed.

22. Raghunathan TE, Lepkowski JM, Van Hoewyk J, Solenberger P. A multivariate technique for multiply imputing missing values using a sequence of regression models. Surv Method. 2001; 27:85–95.

23. Enger SM, Ross RK, Paganini-Hill A, Carpenter CL, Bernstein L. Body size, physical activity, and breast cancer hormone receptor status: results from two case-control studies. Cancer Epidemiol Biomarkers Prev. 2000; 9:681–687. [PubMed: 10919738]

24. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. J Natl Cancer Inst. 2004; 96:218–228. [PubMed: 14759989]

25. Li CI, Malone KE, Daling JR. Interactions between body mass index and hormone therapy and postmenopausal breast cancer risk (United States). Cancer Causes Control. 2006; 17:695–703. [PubMed: 16633917]

26. Suzuki R, Rylander-Rudqvist T, Ye W, Saji S, Wolk A. Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: A prospective cohort study. Int J Cancer. 2006; 119:1683–1689. [PubMed: 16646051]

27. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status--a meta-analysis. Int J Cancer. 2009; 124:698–712. [PubMed: 18988226]
28. Verkasalo PK, Thomas HV, Appleby PN, Davey GK, Key TJ. Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). Cancer Causes Control. 2001; 12:47–59. [PubMed: 11227925]
29. Key TJ, Appleby PN, Reeves GK, Roddam A, Dorgan JF, Longcope C, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. J Natl Cancer Inst. 2003; 95:1218–1226. [PubMed: 12928347]
30. Ballard-Barbash R. Anthropometry and breast cancer. Body size--a moving target. Cancer. 1994; 74:1090–1100. [PubMed: 8039144]
31. Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab. 2001; 280:E745–E751. [PubMed: 11287357]
32. Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, et al. Dual effects of weight and weight gain on breast cancer risk. JAMA. 1997; 278:1407–1411. [PubMed: 9355998]
33. Feigelson HS, Patel AV, Teras LR, Gansler T, Thun MJ, Calle EE. Adult weight gain and histopathologic characteristics of breast cancer among postmenopausal women. Cancer. 2006; 107:12–21. [PubMed: 16718671]
34. Vrieling A, Buck K, Kaaks R, Chang-Claude J. Adult weight gain in relation to breast cancer risk by estrogen and progesterone receptor status: a meta-analysis. Breast Cancer Res Treat. 2010; 123:641–649. [PubMed: 20711809]
35. McTiernan A, Kooperberg C, White E, Wilcox S, Coates R, Adams-Campbell LL, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. JAMA. 2003; 290:1331–1336. [PubMed: 12966124]
36. Monninkhof EM, Elias SG, Vlems FA, van der Tweel I, Schuit AJ, Voskuil DW, et al. Physical activity and breast cancer: a systematic review. Epidemiology. 2007; 18:137–157. [PubMed: 17130685]
37. Schmidt ME, Steindorf K, Mutschelknauss E, Slanger T, Kropp S, Obi N, et al. Physical activity and postmenopausal breast cancer: effect modification by breast cancer subtypes and effective periods in life. Cancer Epidemiol Biomarkers Prev. 2008; 17:3402–3410. [PubMed: 19029400]
38. Adams SA, Matthews CE, Hebert JR, Moore CG, Cunningham JE, Shu XO, et al. Association of physical activity with hormone receptor status: the Shanghai Breast Cancer Study. Cancer Epidemiol Biomarkers Prev. 2006; 15:1170–1178. [PubMed: 16775177]
39. Peplonska B, Lissowska J, Hartman TJ, Szeszenia-Dabrowska N, Blair A, Zatonski W, et al. Adulthood lifetime physical activity and breast cancer. Epidemiology. 2008; 19:226–236. [PubMed: 18277160]
40. Bardia A, Hartmann LC, Vachon CM, Vierkant RA, Wang AH, Olson JE, et al. Recreational physical activity and risk of postmenopausal breast cancer based on hormone receptor status. Arch Intern Med. 2006; 166:2478–2483. [PubMed: 17159013]

Table 1

Distribution of baseline demographic characteristics, breast cancer case groups and non-cases

	Non-cases	Cases*	
		ER+	Triple-negative
	n (%)	n (%)	n (%)
Age at randomization / enrollment			
50–59	50,445 (33)	746 (29)	122 (40)
60–69	67,606 (45)	1,250 (48)	125 (41)
70–79	32,654 (22)	614 (24)	60 (20)
Race / ethnicity			
White, not of Hispanic origin	124,164 (83)	2,317 (89)	241 (79)
Hispanic/ Latina	6,089 (4)	53 (2)	8 (3)
African-American	13,681 (9)	149 (6)	50 (16)
Other	6,391 (4)	85 (3)	7 (2)
Missing	380	6	1
Education			
≤High school diploma / GED	33,967 (23)	483 (19)	75 (25)
Vocational / training school	15,370 (10)	232 (9)	30 (10)
Some college / associates degree	41,558 (28)	696 (27)	78 (26)
≥College graduate	58,684 (39)	1,177 (45)	118 (39)
Missing	1,126	22	6
Household income level			
<$35,000	57,879 (41)	910 (37)	108 (38)
$35,000 – $74,999	56,720 (40)	1,023 (42)	126 (44)
≥$75,000	26,004 (18)	507 (21)	50 (18)
Missing	10,102	170	23
History of breast cancer in female relatives			
No	116,762 (82)	1,901 (77)	207 (72)
Yes	25,713 (18)	574 (23)	81 (28)
Missing	8,230	135	19
Hormone therapy (HT) use at baseline			
No	64,636 (43)	975 (37)	138 (45)
Yes	85,775 (57)	1,633 (63)	169 (55)
Missing	118	2	0
History of mammography in past 2 years			
No	24,242 (17)	327 (13)	43 (15)
Yes	121,520 (83)	2,212 (87)	253 (85)
Missing	4,767	71	11
Parity			
Nulliparous	17,509 (12)	380 (15)	23 (8)
1	13,151 (9)	248 (10)	20 (7)
2	37,355 (25)	683 (26)	90 (29)

	Non-cases	Cases*	
		ER+	Triple-negative
	n (%)	n (%)	n (%)
≥3	81,558 (55)	1,279 (49)	173 (57)
Missing	956	20	1
Age at first birth (parous women only)			
<20	19,365 (16)	258 (13)	43 (18)
20–29	87,961 (74)	1,481 (74)	184 (76)
≥30	10,861 (9)	255 (13)	16 (7)
Missing	13,877	216	40

*ER+ = estrogen receptor-positive cases with known HER2 expression status; triple-negative = ER−/PR−/HER2−

Table 2

Relationship between measures of body size at baseline and risk of ER+ and triple-negative breast cancer

	Non-cases	Cases*				
		ER+		Triple-negative		
	n (%)	n (%)	HR (95% CI)†	n (%)	HR (95% CI)†	p-value‡
BMI(kg/m^2)						
Quartiles						
<23.75	37,377 (25)	596 (23)	1.0 (ref)	66 (22)	1.0 (ref)	0.28
23.75 – 26.89	37,318 (25)	650 (25)	1.19 (1.05–1.35)	71 (23)	0.99 (0.67–1.46)	
26.90 – 31.04	37,326 (25)	648 (25)	1.17 (1.03–1.33)	80 (26)	1.21 (0.83–1.77)	
>31.05	37,207 (25)	698 (27)	1.39 (1.22–1.58)	89 (29)	1.35 (0.92–1.99)	
Missing	1,301	18		1		
p_{trend}			<0.01		0.07	
Standard Cutpoints						
<25.0	53,107 (35)	845 (33)	1.0 (ref)	96 (31)	1.0 (ref)	0.36
25.0 – 29.9	52,676 (35)	889 (34)	1.14 (1.02–1.26)	103 (34)	1.16 (0.84–1.61)	
≥30.0	45,700 (30)	858 (33)	1.35 (1.20–1.51)	107 (35)	1.37 (0.98–1.93)	
Missing	1,301	18		1		
p_{trend}			<0.01		0.06	
Waist-to-hip ratio (WHR)§						
<0.758	37,507 (25)	633 (24)	1.0 (ref)	75 (24)	1.0 (ref)	0.36
0.758 – 0.804	37,472 (25)	621 (24)	0.93 (0.82–1.05)	84 (27)	1.13 (0.79–1.62)	
0.805 – 0.856	37,629 (25)	663 (25)	1.04 (0.91–1.18)	73 (24)	0.99 (0.68–1.46)	
≥0.857	37,220 (25)	689 (26)	1.06 (0.93–1.21)	75 (24)	0.99 (0.66–1.49)	
Missing	701	4		0		
p_{trend}			0.21		0.82	
Waist circumference (cm)§						
<76	37,786 (25)	574 (22)	1.0 (ref)	82 (27)	1.0 (ref)	0.07
76 – 84.4	37,537 (25)	663 (25)	1.14 (0.99–1.31)	58 (19)	0.61 (0.40–1.95)	
84.5 – 94.5	38,596 (26)	671 (26)	1.14 (0.96–1.35)	83 (27)	0.66 (0.40–1.08)	
≥95	36,061 (24)	699 (27)	1.34 (1.09–1.64)	84 (27)	0.66 (0.37–1.20)	

	Non-cases	Cases*				
		ER+		Triple-negative		
	n (%)	n (%)	HR (95% CI)†	n (%)	HR (95% CI)†	p-value‡
Missing	549	3		0		
p_{trend}			0.01		0.23	
Hip circumference (cm)§						
<98	38,707 (26)	574 (22)	1.0 (ref)	71 (23)	1.0 (ref)	0.31
98 – 104.4	37,141 (25)	646 (25)	1.19 (1.03–1.37)	68 (22)	0.87 (0.56–1.33)	
104.5 – 112.9	38,611 (26)	712 (27)	1.27 (1.08–1.51)	85 (28)	0.87 (0.52–1.43)	
≥113	35,442 (24)	675 (26)	1.28 (1.03–1.58)	83 (27)	0.81 (0.44–1.50)	
Missing	628	3		0		
p_{trend}			0.01		0.54	

*ER+ = estrogen receptor-positive cases with known HER2 expression status; triple-negative = ER−/PR−/HER2−

†Adjusted for age, education, income, family history of breast cancer, race, and recreational physical activity level, history of mammography (at baseline), and mammography during follow-up.

‡Analysis of the partial likelihoods for equality between subtype-specific estimates.

§Additionally adjusted for BMI at baseline.

Table 3

Relationship between self-reported BMI (kg/m^2) in earlier adulthood and risk of ER+ and triple-negative breast cancer*

	Non-cases	Cases*				
		ER+		Triple-negative		
	n (%)	n (%)	HR (95% CI)†	n (%)	HR (95% CI)†	p-value‡
BMI at age 50						
<22.07	20,841 (25)	349 (24)	1.0 (ref)	37 (21)	1.0 (ref)	0.28
22.07 – 24.08	20,829 (25)	402 (28)	1.10 (0.92–1.31)	40 (23)	1.37 (0.78–2.41)	
24.08 – 26.84	20,777 (25)	353 (25)	0.95 (0.77–1.18)	43 (24)	1.42 (0.73–2.77)	
≥26.85	20,870 (25)	325 (23)	0.95 (0.74–1.22)	57 (32)	1.93 (0.91–4.08)	
Missing	1,591	20		0		
p_{trend}			0.48		0.10	
BMI at age 35						
<20.83	20,926 (25)	360 (25)	1.0 (ref)	37 (21)	1.0 (ref)	0.39
20.83 – 22.30	20,632 (25)	402 (28)	1.08 (0.92–1.28)	40 (23)	1.01 (0.60–1.70)	
22.31 – 24.14	20,760 (25)	376 (26)	0.95 (0.79–1.13)	53 (30)	1.21 (0.72–2.06)	
≥24.15	20,893 (25)	289 (20)	0.79 (0.64–0.97)	47 (27)	1.03 (0.57–1.87)	
Missing	1,697	22		0		
p_{trend}			0.01		0.77	
BMI at age 18						
<19.33	20,793 (25)	368 (26)	1.0 (ref)	47 (27)	1.0 (ref)	0.53
19.33 – 20.76	20,739 (25)	413 (29)	1.12 (0.95–1.30)	46 (26)	1.14 (0.72–1.83)	
20.77 – 22.41	20,848 (25)	321 (23)	0.81 (0.68–0.96)	38 (21)	0.90 (0.55–1.49)	
≥22.42	20,856 (25)	324 (23)	0.83 (0.69–0.98)	46 (26)	0.94 (0.56–1.56)	
Missing	1,672	23		0		
p_{trend}			<0.01		0.59	

*Observational Study only. ER+ = estrogen receptor-positive with known HER2 status; triple-negative =ER−/PR−/HER2−

†Adjusted for age, education, income, family history of breast cancer, race, and recreational physical activity level, history of mammography (at baseline), BMI at baseline, and mammography during follow-up.

‡Analysis of the partial likelihoods for equality between subtype-specific estimates..

Table 4

Relationship between recreational physical activity (MET-hours per week) at baseline and risk of ER+ and triple-negative breast cancer

	Non-cases	Cases[*]				
		ER+		TN		
	n (%)	n (%)	HR (95% CI)[†]	n (%)	HR (95% CI)[†]	p-value[‡]
Total recreational physical activity						
No activity	22,807 (16)	386 (16)	1.0 (ref)	54 (18)	1.0 (ref)	0.30
0.01 – 6.50	39,080 (27)	693 (28)	1.00 (0.87–1.15)	75 (25)	0.67 (0.46–0.99)	
6.51 – 16.50	39,799 (28)	726 (29)	0.95 (0.83–1.09)	86 (29)	0.81 (0.55–1.18)	
≥16.50	41,721 (29)	686 (28)	0.85 (0.74–0.98)	81 (27)	0.77 (0.51–1.13)	
Missing	7,121	119		11		
p_{trend}			<0.01		0.47	
Strenuous recreational physical activity[§]						
No activity	107,778 (75)	1,906 (73)	1.0 (ref)	215 (70)	1.0 (ref)	0.53
0.01 – 10.49	14,098 (10)	209 (8)	0.89 (0.76–1.05)	36 (12)	1.17 (0.77–1.78)	
≥10.50	21,531 (15)	376 (14)	0.95 (0.84–1.07)	45 (15)	0.98 (0.68–1.44)	
Missing	7,122	119		11		
p_{trend}			0.25		0.91	
Moderate and low-intensity recreational physical activity[§]						
No activity	61,822 (43)	1,096 (44)	1.0 (ref)	137 (46)	1.0 (ref)	0.53
0.01 – 5.74	40,642 (28)	680 (27)	0.90 (0.81–1.00)	88 (30)	0.83 (0.61–1.12)	
≥5.75	40,943 (29)	715 (29)	0.88 (0.79–0.98)	71 (24)	0.75 (0.54–1.04)	
Missing	7,122	119		11		
p_{trend}			0.01		0.07	

[*] ER+ = estrogen receptor-positive cases with known HER2 expression status; triple-negative = ER−/PR−/HER2−

[†] Adjusted for age, education, income, family history of breast cancer, race, history of mammography (at baseline), mammography during follow-up, and BMI at baseline.

[‡] Analysis of the partial likelihoods for equality between subtype-specific estimates.

[§] Mutually-adjusted for strenuous-intensity and moderate/low-intensity activity.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 5

Relationship between measures of body size at baseline and risk of ER+ and triple-negative breast cancer among non-users of hormone therapy at baseline

	Non-cases	Cases*				
		ER+		Triple-negative		
	n (%)	n (%)	HR (95% CI)†	n (%)	HR (95% CI)†	p-value‡
BMI(kg/m^2)						
Quartiles						
<23.75	17,070 (23)	209 (19)	1.0 (ref)	28 (18)	1.0 (ref)	0.71
23.75 – 26.89	18,038 (24)	247 (22)	1.27 (1.03–1.56)	37 (24)	1.18 (0.66–2.12)	
26.90 – 31.04	19,439 (26)	291 (26)	1.37 (1.11–1.68)	46 (30)	1.59 (0.91–2.76)	
≥31.05	21,256 (28)	369 (33)	1.71 (1.39–2.10)	44 (28)	1.50 (0.85–2.67)	
Missing	722	9		0		
p_{trend}			<0.01		0.11	
$p_{interaction}$			0.01		0.98	
Standard Cutpoints						
<25.0	24,154 (32)	303 (27)	1.0 (ref)	45 (29)	1.0 (ref)	0.74
25.0 – 29.9	26,220 (35)	372 (33)	1.21 (1.02–1.44)	54 (35)	1.22 (0.76–1.96)	
≥30.0	25,429 (34)	441 (39)	1.59 (1.33–1.89)	56 (36)	1.47 (0.91–2.38)	
Missing	772	9		0		
p_{trend}			<0.01		0.12	
$p_{interaction}$			0.04		0.97	
Waist circumference (cm)§						
<76	16,861 (22)	188 (17)	1.0 (ref)	35 (23)	1.0 (ref)	0.68
76 – 84.4	18,224 (24)	254 (23)	1.20 (0.94–1.52)	27 (17)	0.63 (0.32–1.21)	
84.5 – 94.5	20,335 (27)	317 (28)	1.32 (1.00–1.74)	46 (30)	0.85 (0.42–1.75)	
≥95	20,834 (27)	366 (33)	1.46 (1.06–2.00)	47 (30)	1.07 (0.47–2.45)	
Missing	321	0		0		
p_{trend}			0.02		0.63	
$p_{interaction}$			0.03		0.36	

	Non-cases	Cases*				
		ER+		Triple-negative		
	n (%)	n (%)	HR (95% CI)†	n (%)	HR (95% CI)†	p-value‡
Hip circumference (cm)§						
<98	18,757 (25)	213 (19)	1.0 (ref)	38 (25)	1.0 (ref)	0.63
98 – 104.4	18,138 (24)	247 (22)	1.13 (0.90–1.43)	34 (22)	0.72 (0.39–1.32)	
104.5 – 112.9	19,447 (26)	323 (29)	1.33 (1.02–1.74)	38 (25)	0.61 (0.30–1.23)	
≥113	19,867 (26)	341 (30)	1.28 (0.93–1.76)	45 (29)	0.77 (0.34–1.77)	
Missing	366	1		0		
p_{trend}			0.10		0.50	
$p_{interaction}$			0.04		0.83	

*ER+ = estrogen receptor-positive cases with known HER2 expression status; triple-negative = ER−/PR−/HER2−

†Adjusted for age, education, income, family history of breast cancer, race, and recreational physical activity level, history of mammography (at baseline), and mammography during follow-up.

‡Analysis of the partial likelihoods for equality between subtype-specific estimates.

§Additionally adjusted for BMI at baseline.