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Adult body size and physical activity in relation to risk of breast cancer according to tumor androgen receptor status

Xuehong Zhang[1], **A. Heather Eliassen**[1,2], **Rulla M. Tamimi**[1,2], **Aditi Hazra**[1,2], **Andrew H. Beck**[3], **Myles Brown**[4], **Laura C. Collins**[3], **Bernard Rosner**[1,2], and **Susan E. Hankinson**[1,2,5]

[1]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

[2]Department of Epidemiology, Harvard School of Public Health, Boston, MA

[3]Department of Pathology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

[4]Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

[5]Division of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts, MA

Abstract

Background—Obesity and physical activity have been hypothesized to affect breast cancer risk partly via the androgen signaling pathway. We conducted the first study to evaluate these associations by tumor androgen receptor (AR) status.

Methods—Height, weight, and physical activity were assessed using questionnaires in the Nurses' Health Study. AR, estrogen receptor (ER) and progesterone receptor (PR) status were determined using immunohistochemistry on tumor tissue and medical/pathology reports.

Results—1,701 AR+ and 497 AR- cases were documented during 26 years of follow-up of 103,577 women. After adjusting for ER/PR status and other risk factors, the relative risks (RRs) and 95% confidence intervals (95%CIs) for every 5 kg/m^2 increase in body mass index (BMI) were 1.07(1.01–1.13) for AR+ and 1.16(1.05–1.29) for AR- tumors (*p*-heterogeneity=0.17). The RRs(95%CIs) per 5 hours of brisk walking/week were 0.87(0.73–1.04) for AR+ and 0.67(0.45–0.99) for AR- tumors (*p*-heterogeneity=0.22). Further, BMI, but not physical activity, associations differed significantly across ER/PR/AR subtypes (*p*-heterogeneity=0.04 and 0.63, respectively). The RRs(95%CIs) for 5 kg/m^2 increase in BMI were 1.23(1.04–1.45) for ER+PR+AR−, 1.19(1.01–1.39) for ER−PR−AR−, 1.15(1.08–1.23) for ER+PR+AR+, 0.88(0.75–1.03) for ER+PR−AR+ tumors.

Corresponding author: Xuehong Zhang, MD, ScD, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Room #355, Boston, MA 02115, Tel: 617-525-0342, Fax: 617-525-2008, poxue@channing.harvard.edu.

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Conclusions—Higher BMI was associated with an increased risk of both AR+ and AR− breast tumors in postmenopausal women, while physical activity, including brisk walking, was associated with a reduced risk of both subtypes. Additionally, a significant positive association was observed between higher BMI and ER−PR−AR− tumors.

Impact—The similar associations observed by AR status suggest that mechanisms other than androgen signaling underlie these two breast cancer risk factors.

Introduction

Considerable evidence supports an important role of estrogen signaling, through binding to the nuclear estrogen receptor (ER), in breast carcinogenesis.(1–10) The FDA has approved tamoxifen and raloxifene, drugs that block ER activity, for breast cancer chemoprevention among high-risk women.(11–12) In contrast, the role of androgen signaling in breast cancer, through the nuclear androgen receptor(AR), remains less clear although some recent studies support an independent beneficial role of AR in breast cancer prognosis.(13–16)

AR is expressed in normal breast epithelium and 60–70% of breast tumors.(17–20) Depending on the experimental system, laboratory studies indicate either a beneficial or deleterious effect of androgens on breast carcinogenesis. However, cohort studies are highly consistent in showing that elevated levels of pre-diagnostic circulating androgens (e.g., testosterone, DHEAS) are associated with an increased risk of postmenopausal breast cancer.(2–6,10,21–22) Further, several confirmed breast cancer risk factors, such as obesity, weight gain, and physical activity, have been hypothesized to influence breast cancer risk, at least in part, through the androgen signaling pathway.(23–24) To date, no study has specifically examined whether the associations with these risk factors differ by tumor AR status. Observing differential associations by AR status would suggest a role of androgen signaling in these associations, thus improving our understanding of underlying etiologic mechanisms in breast carcinogenesis.

We hypothesized that the positive associations between obesity, weight gain, and postmenopausal breast cancer risk, as well as the inverse association of physical activity with risk, would be stronger among women with AR+ tumors compared to AR− tumors. We tested this hypothesis in women in the Nurses' Health Study (NHS). We further evaluated whether these associations were independent of or varied by breast tumor ER/PR status.

Materials and Methods

Study population

The NHS has been described in detail elsewhere.(25–26) In brief, the NHS was established in 1976, when 121,700 female registered nurses aged 30–55 years in the U.S. completed and returned a self-administered questionnaire. Questionnaires have been mailed to women every 2 years since 1976 to collect information on demographics, lifestyle, medical history, and disease outcomes. The follow-up rate has been greater than 90%. The institutional review board at the Brigham and Women's Hospital approved this study, and return of the questionnaires was considered to imply informed consent.

Assessment of adult body size and weight change

Information on adult body weight was first assessed in 1976 and updated every 2 years thereafter. Self-reported weight in this cohort was validated with a correlation of 0.97 between reported and measured weight.(27) In 1980, we also asked about body weight at age 18 years. The correlation for recalled weight with college or nursing school records was 0.87 for weight at the age of 18 in a similar cohort of women, the Nurses' Health Study II.(28) In 1986, we asked women to measure their waist circumference and their hip circumference. The Pearson correlation coefficients between self-reported and technician measurements were 0.89 for waist circumferences and 0.84 for hip circumferences.(27)

Assessment of physical activity

Physical activity assessment has been described in detail elsewhere.(29) Briefly, beginning in 1986 and almost every 2 years thereafter, participants reported their average time per week during the past year spent doing any of the following activities: walking/hiking outdoors, jogging, running, bicycling, lap swimming, tennis, calisthenics/aerobics/aerobic, dance/rowing machine, and squash or racquet ball. Additionally, women reported their usual walking pace and the number of flights of stairs climbed daily. We calculated metabolic equivalent task hours (MET-h) per week for each activity by multiplying the MET score and reported hours per week. In the validation study of 151 participants in the NHSII,(30) the correlation between the questionnaire and four 7-day activity diaries was 0.62 for moderate/vigorous activity and 0.70 for walking, the primary activity among the participants in this study.

Assessment of other breast cancer risk factors

Information on age at menarche, height, and age at first birth was obtained in 1976. We also inquired information on parity and history of breast cancer in the participants' mothers and sisters. Alcohol consumption was first assessed in 1980 using a validated semiquantitative food frequency questionnaire, and every 2–4 years thereafter.(31–32) Data on diagnosis of benign breast disease, menopausal status, age at menopause, and postmenopausal hormone use(PMH) were collected biennially.

Identification of breast cancer cases and assessment of tumor AR status

Using biennial questionnaires, we identified cases of incident invasive breast cancer and contacted the participants (or next of kin) to confirm the diagnosis and obtained permission to collect relevant medical/pathology reports. Study investigators, blinded to exposure status, reviewed these records and abstracted information on tumor characteristics. Over 99% of self-reported breast cancers were confirmed by review of medical records. To identify cases of cancer in non-respondents who died, we obtained death certificates for all deceased participants and medical records.

We requested paraffin-embedded breast tumor blocks for all cases diagnosed in the NHS through 2006. We received 4,655 tumor blocks out of 7,666 eligible cases (61%).(33) Breast cancer cases with tumor blocks were similar to all eligible cases on age and menopausal status at diagnosis, as well as tumor characteristics(e.g., ER+: 87% received vs. 87% eligible, PR+: 47% received vs. 51% eligible).(33) The construction of tumor tissue

microarrays (TMAs) among these cases has been described in detail previously.(33–34) Briefly, AR status was determined using immunohistochemistry on sections from these TMAs. Nuclear staining of AR for each of the three cores was scored as negative, low positive (1–10% of tumor cell nuclei staining), or positive(>10% tumor cell nuclei staining).(14) Consistent with our previous work,(14) breast tumors scored as either low positive or positive were considered to be positive for AR. There was excellent concordance of AR status between any 2 of 3 cores per women included in TMAs with a *k* statistic ranging from 0.86 to 0.88.(14) Given that AR status was determined using TMAs, we used TMAs as a primary resources to determine the ER/PR status for this analyses. We further used medical/pathology reports to determine the missing values for ER/PR among women with TMAs (4.6%). We have observed high concordance of 92.3% of ER status between TMAs and medical/pathology reports.(34)

Statistical analyses

We used different baselines for our analyses of adult body size, weight change, and physical activity depending on the availability of information collected on each variable (Supplementary Table 1). We treated 1980 as the baseline for analyses of adult body size and weight change because less than 50 AR+ cases were diagnosed before 1980 and dietary factors including alcohol consumption were first assessed in 1980. We treated 1986 as the baseline for analysis of physical activity because physical activity was first assessed in detail that year. Because obesity is associated with a lower risk of premenopausal breast cancer and there were less than 200 premenopausal breast cancer cases with AR status in this study, we restricted our analyses to postmenopausal women for the adult body size and weight change. Physical activity is associated with a lower risk of both premenopausal and postmenopausal breast cancer and we therefore conducted the analyses of physical activity among all women.

We calculated person-time for each woman from the date of baseline questionnaire return (Supplementary Table 1) to the date of death, loss to follow-up, breast cancer diagnosis, or end of follow-up(June 1, 2006), whichever came first. We excluded participants with a history of cancer (except for non-melanoma skin cancer) before baseline. Women who died or reported cancer during follow-up were censored and excluded from subsequent follow-up.

First, we used Cox proportional hazards models to calculate multivariable relative risks (RRs) and 95% confidence intervals (CIs) of adult body size, weight change, and physical activity in relation to overall invasive breast cancer risk. Breast cancer cases for which AR status was not available were censored in the statistical analysis of AR+ and AR− tumors. We stratified simultaneously for age (in months) and year of questionnaire return, and adjusted for other established breast cancer risk factors. For these factors, we used the most updated information for all covariates, if available, before each follow-up cycle. Secondly, because approximately 60–80% of AR+ tumors are also ER+/PR+ tumors in this study, without considering ER/PR status, the observed association might have simply mirrored the well-established associations between these factors and ER+/PR+ tumors. Hence, we further employed a constrained competing risk survival model (35) to account for ER/PR status and

adjust for other risk factors when evaluating the associations with AR+ and AR− tumors. Lastly, we used Cox models to evaluate the associations with each combination of the ER/PR/AR status to consider the potential interactive effects. We conducted a global test for heterogeneity among these subtypes.

We modeled BMI both categorically (<23, 23–<25, 25–<27.5, 27.5–<30, ≥30 kg/m^2) and continuously (per 5 kg/m^2 increase). Consistent with our previous publication in the same cohort (36), weight change since age 18 years was calculated as the difference between current weight and weight at age 18 years. Current weight was queried biennially and we used updated weight change for each questionnaire cycle. We used similar categories as in previous analyses in the NHS(36)(loss ≥5.0, 2.0–<5, maintaining[Loss or gain<2.0, reference], gain weight[2.0–<10, 10–<20, ≥20 kg]). In addition, we estimated the RRs per 5 kg change in weight. Using same approach as BMI analysis, we calculated the cumulative average of physical activity using the mean MET-h per week from all previous physical activity assessments as a measure of long-term physical activity. We then modeled categorically (<3, 3–<9, 9–<18, 18–<27, and ≥27 MET-h/wk) and continuously (per 20 MET-h/wk increase, equivalent to 5 hours of brisk walking/wk).(29) Furthermore, we used the same categories as our previous analyses(37) on waist circumference and waist:hip ratio. We used these continuous variables to perform a Wald test for trend.

We conducted all analyses using the SAS software (SAS Institute, Inc., Version 9.2, Cary, NC). All statistical analyses were two-sided with a *p*-value<0.05 indicating statistical significance.

Results

In this study, we documented a total of 1,701 AR+ and 497 AR− tumors during 26 years of follow-up. AR positivity (AR+) was observed more frequently in ER+ tumors (85%) than in ER- tumors (50%). Similarly, AR+ was observed in 86% of PR+ tumors and in 62% of PR− tumors (Supplementary Table 2). The mean age for women in this study was 62 years. As shown in Table 1, obese women were more likely to have higher body weight at age 18 and gain more weight during adulthood but were less likely to be nulliparous, drink alcohol, have benign breast disease, and use PMH. In addition, women engaged in more physical activity were less likely to gain weight but more likely to use PMH, drink alcohol and have benign breast diseases. Other baseline characteristics were comparable.

Compared to women with normal weight, those who were obese were at approximately 50% higher risk (95%CI:1.35–1.59) of developing breast cancer in the entire cohort (Table 2). Further, obesity (BMI ≥ 30 vs < 23 kg/m^2) was associated with an increased risk for both AR+ tumors (RR=1.20, 1.03–1.40) and AR- tumors (RR=1.54, 1.15–2.06, *p*-value for heterogeneity by AR subtypes=0.14). We further accounted for ER/PR status and results were essentially unchanged. The corresponding RRs (95%CIs) were 1.17(1.00–1.37) for AR + and 1.64(1.21–2.24) for AR- tumors (*p*-value for heterogeneity by AR subtypes=0.05).

Compared to women who maintained their weight during adulthood, those who gained more than 20 kilograms were at approximately 50% higher risk (95%CI: 1.31–1.66) of overall

invasive breast cancer (Table 2). Similarly, we observed significant positive associations of weight gain with breast cancer among both AR+ and AR− tumors. Results were essentially unchanged after accounting for ER/PR status (Table 2).

Women engaged in higher amounts of total physical activity including brisk walking were at a lower risk of developing any invasive breast cancer (Table 3). The RRs (95% CIs) per approximately 5 hours of brisk walking/week were 0.87(0.73–1.04) for AR+ and 0.67(0.45–0.99) for AR− tumors (*p*-value for heterogeneity=0.22). Results were essentially the same when further adjusting for adult BMI (data not shown).

We also examined these associations by joint ER/PR/AR status and found that only BMI associations differed significantly across these subtypes (*p*-value for heterogeneity=0.04, Table 4). Specifically, the associations were only statistically significantly different between ER+PR−AR+ and each of ER+PR+AR+ (*p*-value=0.003), ER+PR+AR−(*p*-value=0.004), and ER−PR−AR− (*p*-value=0.02). Although tests for heterogeneity were not statistically significant, we observed a similar pattern for both weight change and brisk walking. Increased waist circumference was positively associated with breast cancer risk after accounting for ER/PR status, while waist:hip ratio was not significantly associated with risk. No significant heterogeneity by AR status was noted (supplementary Table 3).

Discussion

In this study of 103,577 women with 26 years of follow-up, obesity and weight gain were associated with an increased risk of both AR+ and AR− tumors among postmenopausal women, while physical activity, including brisk walking, was associated with a reduced risk of both subtypes. These associations were independent of tumor ER/PR status and established breast cancer risk factors. Notably, these associations seem slightly stronger for AR− tumors than for AR+ tumors although the difference was not statistically significant. When evaluating these associations by joint ER/PR/AR status, the strongest associations tended to be seen for the ER+PR+AR− and ER+PR+AR+ tumors. Interestingly, a significant positive association also was observed between obesity and ER−PR−AR− tumors.

Consistent with previous work, including our own,(29,37–38) we observed significant positive associations with obesity and weight gain during adulthood for overall postmenopausal breast cancer in this study. Several mechanisms related to estrogen signaling have been proposed to explain these well-established associations. For example, obesity increases circulating levels of estrogen, which influence breast carcinogenesis via increasing proliferation and decreasing apoptosis.(1) Epidemiological data are highly consistent in showing strong positive associations between elevated circulating levels of estrogens and breast cancer risk among postmenopausal women not taking PMH,(1–9) even for these hormones measured 16–20 years before breast cancer diagnosis.(10) Regarding physical activity, most epidemiological studies have observed significantly inverse associations with overall breast cancer risk.(39) However, whether physical activity influences breast cancer risk via the estrogen signaling pathway is not clear and epidemiological studies have been inconsistent with regard to this association by ER/PR status.(29,40–43)

In contrast to the well-established effect of estrogens on breast cancer risk, tjamahe role of androgens in breast carcinogenesis is unclear although androgen excess was first postulated to increase breast cancer risk over four decades ago.(44–45) Several lines of evidence suggest that androgen could also play a role in the associations between obesity and physical activity and breast cancer risk. For example, in postmenopausal women, obese women tend to have a lower level of sex-hormone binding globulin (SHBG), develop hyperandrogenism, and have increased conversion of androgen to estrogen in adipose tissue, thereby increasing breast cancer risk.(23–24) While results are not entirely consistent, current epidemiologic studies in aggregate suggest an inverse association between higher physical activity and androgen levels. For instance, in two randomized trials,(46–47) women who lost ≥1% of body fat and exercised had significantly lower levels of androgens compared to women who lost body fat but did not exercise.

We are not aware of any prior study that has examined obesity or physical activity in relation to risk of breast cancer by tumor AR status. Our data suggest that obesity and weight gain were associated with an increased risk, while physical activity was related to a lower risk of both AR+ and AR− breast tumors. Although the associations of BMI and waist circumference with AR− tumors appeared slightly stronger than those for AR+ tumors, we did not detect any statistically significant heterogeneity by AR status. Thus, overall, the similar associations observed for both AR+ and AR− breast tumors suggest that androgen signaling is not important in mediating the effects of obesity or physical activity on risk. Interestingly, among the molecular subtypes characterized by the combined ER/PR/AR status, we observed the strongest associations for ER+PR+AR− and ER+PR+AR+ tumors. Laboratory evidence suggests that androgens are estrogen antagonists in a high estrogen environment but estrogen agonists in a low estrogen environment.(48–49) In this context, ER+PR+AR− and ER+PR+AR+ tumors represent the most active estrogen signaling pathway as PR is an important marker of ER activation.(35) Thus, overall our results support the hypothesis that estrogen signaling, but not androgen signaling, plays an important role in the postmenopausal BMI/breast cancer relationship. Furthermore, the positive association observed between BMI and ER−PR−AR− tumors suggests that pathways other than sex steroids(e.g., the insulin pathway) might play an etiologic role in breast cancer carcinogenesis. The statistically significant difference in BMI association between ER+PR−AR+ tumor with the aforementioned three subtypes was unexpected. It might be due to chance or potentially reflect unknown biology, which requires further investigation. It also is worthwhile noting that although the current study does not support a strong role of androgen in mediating the effect of obesity and physical activity on breast cancer risk, mounting evidence supports the beneficial role of androgens in breast cancer survival.(13–16) Clearly, more research is desired to better elucidate the role of androgens in both breast cancer risk and survival.

Several potential limitations of this study warrant consideration. First, we did not have tissue on all cases and used 3 just cores to represent the tumor. However, cases with tumor blocks were similar to cases without blocks and 3 cores appear to reflect adequately the entire tumor.(33–34) Second, although misclassifications of obesity and physical activity were possible as with any epidemiological studies, we had repeated assessments and the information was collected before cancer diagnosis therefore minimizing differential

misclassifications. These factors have also shown strong associations with breast cancer risk in our previous work.(29,37–38) Thirdly, our results may not be generalizable to other racial/ethnic groups as our participants are primarily Caucasians. However, it is unlikely that the underlying biology among these women would differ from women in general. Fourthly, our study is large overall but we had limited power to detect potential differences in certain associations by joint ER/PR/AR status and the analysis of waist circumferences for AR- tumors. Lastly, unmeasured confounding possibly exists. Nonetheless, the age-adjusted results were essentially the same as multivariable adjusted results, arguing against missing strong associations due to residual confounding.

Despite these potential limitations, our study has some important strengths including its prospective design and overall large sample size. Additionally, this study is the first, to our knowledge that has assessed the associations between obesity, weight gain and physical activity and risk of breast cancer by tumor AR status. Importantly, we evaluated the independent and joint associations by tumor ER/PR/AR status to decipher a potential role of androgen in breast carcinogenesis.

In summary, we observed that higher adult body size and weight gain were associated with an increased risk of developing both AR+ and AR− tumors in postmenopausal women, while physical activity, including brisk walking, was associated with a reduced risk of both subtypes. More studies are warranted to confirm and extend these findings and clarify other potential pathways that may play an etiologic role in breast carcinogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Age and Age-Standardized Characteristics of 103,577 Women by Body Mass Index and Physical Activity in the Nurses' Health Study.*

	BMI (kg/m^2)					Total physical activity, MET-hours/week				
	< 23	23–<25	25–27.5	27.5–<30	≥ 30	< 3	3–<9	9–18	18–27	≥ 27
Age, y†	62.2(8.2)	62.4(7.7)	62.8(7.6)	63.0(7.4)	62.8(7.2)	61.2(9.4)	60.7(8.9)	61.0(8.8)	61.1(8.6)	61.4(8.4)
Age at menarche, y	12.8(1.4)	12.7(1.4)	12.6(1.4)	12.5(1.4)	12.3(1.4)	12.5(1.4)	12.6(1.4)	12.6(1.4)	12.6(1.4)	12.6(1.5)
Body mass index at age 18y, kg/m^2‡	20.2(2.2)	20.8(2.4)	21.3(2.6)	21.9(2.8)	23.1(3.5)	21.5(3.1)	21.3(2.9)	21.3(2.8)	21.2(2.7)	21.2(2.7)
Nulliparous, %	7	6	6	5	5	5	5	5	5	6
Parity, number of children§	3.2(1.5)	3.3(1.6)	3.3(1.6)	3.3(1.6)	3.3(1.6)	3.2(1.6)	3.2(1.5)	3.2(1.5)	3.1(1.5)	3.1(1.5)
Age at first birth,y	25.5(3.5)	25.4(3.4)	25.3(3.4)	25.2(3.4)	25.1(3.4)	25.2(3.4)	25.1(3.3)	25.1(3.3)	25.0(3.2)	25.0(3.2)
Age at menopause,y//	48.5(5.6)	48.7(5.5)	48.5(5.8)	48.5(5.9)	48.5(6.2)	48.4(5.7)	48.7(5.6)	48.8(5.6)	48.9(5.6)	48.8(5.7)
Current PMH use, %	37	36	34	32	28	30	33	35	36	36
Mammography within past 2 y, %	67	69	68	67	65	72	77	80	81	81
Family history of breast cancer, %	12	12	13	12	12	12	13	13	13	13
History of benign breast disease, %	43	43	41	40	39	43	44	46	47	47
Weight gain since age 18 y, kg	2.4(6.8)	8.5(6.6)	13.2(7.4)	18.1(8.0)	27.9(11.4)	15.4(13.4)	13.8(12.0)	12.3(11.4)	11.4(11.0)	10.0(10.8)
Height, m	1.6(0.1)	1.6(0.1)	1.6(0.1)	1.6(0.1)	1.6(0.1)	1.6(0.1)	1.6(0.1)	1.6(0.1)	1.6(0.01)	1.6(0.1)
Alcohol, g/day	7.1(11.3)	6.4(10.5)	5.6(10.1)	4.7(9.3)	3.4(8.0)	5.0(10.4)	5.1(9.5)	5.4(9.5)	5.8(9.6)	6.3(10.0)
Total physical activity, MET-h/week	19.3(20.6)	17.5 (19.2)	16.4(18.2)	14.6(16.9)	11.9(15.3)	1.3(0.9)	5.7(1.8)	13.0(2.7)	22.1(2.5)	47.2(19.3)
Brisk walking, MET-h/wk	5.0(10.0)	4.3(9.1)	3.5(8.2)	2.6(7.1)	1.4(5.4)	0.1(0.9)	2.5(4.3)	2.5(4.3)	5.9(8.2)	10.4(14.2)

*The analysis of body mass index was restricted to postmenopausal women and characteristics of the aforementioned factors used data from the 1980 questionnaire except for the physical activity data from 1986. The analysis for physical activity included a total of 97,803 premenopausal and postmenopausal women and characteristics of the aforementioned factors used data from the 1986 questionnaire.

Values are means (SD) or percentages and were standardized to the age distribution of the study population.

†Value is not age adjusted

‡Body mass index was calculated as weight in kilograms divided by the square of height in meters.

§Among parous women only.

//Among women with natural menopause or bilateral oophorectomy.

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Table 2

Multivariable* Relative Risks of Postmenopausal Breast Cancer by AR Status According to Body Mass Index and Weight Change in the Nurses' Health Study (1980–2006).

	Overall invasive breast cancer (n=5,953)	NOT accounting for ER/PR status			Accounting for ER/PR status		
		AR+ (n=1,701)	AR− (n=497)	*P*-het†	AR+ (n=1,701)	AR− (n=497)	*P*-het†
BMI (kg/m^2)							
<23	1 (ref.)	1 (ref.)	1 (ref.)		1 (ref.)	1 (ref.)	
23–<25	1.09 (1.01, 1.18)	0.96 (0.83, 1.10)	1.34 (1.03,1.75)		0.98 (0.85, 1.14)	1.39 (1.02,1.88)	
25–<27.5	1.18 (1.09, 1.27)	1.10 (0.95, 1.26)	1.20 (0.91,1.58)		1.09 (0.95, 1.26)	1.29 (0.95,1.75)	
27.5–<30	1.34 (1.23, 1.46)	1.15 (0.98, 1.35)	1.68 (1.26,2.26)		1.13 (0.96, 1.33)	1.55 (1.11,2.17)	
≥ 30	1.47 (1.35, 1.59)	1.20 (1.03, 1.40)	1.54 (1.15, 2.06)	0.14	1.17 (1.00, 1.37)	1.64 (1.21,2.24)	0.05
p-trend	<0.0001	0.003	0.01		0.12	0.09	
Per 5 kg/m^{2}increment	1.16 (1.13,1.20)	1.09 (1.03,1.15)	1.14 (1.03,1.27)	0.47	1.07 (1.01, 1.13)	1.16 (1.05, 1.29)	0.17
Weight change since age 18 y, kg							
Loss							
≥ 5.0	0.80 (0.66, 0.97)	0.98 (0.70, 1.36)	1.40 (0.74, 2.64)		0.96 (0.68, 1.34)	0.99 (0.47, 2.09)	
2.0–<5	1.05 (0.87, 1.26)	0.95 (0.68, 1.34)	1.88 (1.04, 3.38)		0.87 (0.60, 1.25)	1.59 (0.81, 3.11)	
Loss or gain <2.0	1 (ref.)	1 (ref.)	1 (ref.)		1 (ref.)	1 (ref.)	
Gain							
2.0–<10	1.19 (1.05, 1.34)	1.10 (0.89, 1.35)	1.50 (0.97, 2.33)		1.10 (0.89, 1.38)	1.29 (0.79, 2.11)	
10–<20	1.23 (1.10, 1.39)	1.14 (0.93, 1.41)	1.57 (1.01, 2.42)		1.12 (0.90, 1.40)	1.44 (0.89, 2.33)	
≥ 20	1.48 (1.31, 1.66)	1.24 (1.00, 1.54)	1.76 (1.12, 2.75)	0.17	1.23 (0.98, 1.53)	1.59 (0.98, 2.60)	0.34
Per 5 kg change	1.06 (1.05, 1.08)	1.04 (1.02,1.06)	1.04 (1.00,1.08)	>0.99	1.04 (1.01,1.06)	1.05 (1.01,1.10)	0.52

*MV-Adjusted for age at menarche, body mass index at age 18 years, height, parity and age at first birth, alcohol intake, postmenopausal hormone use, age at menopause, family history of breast cancer, and history of benign breast disease. There were 5,191 overall invasive breast tumors, 1,520 AR+, and 446 AR− tumors for weight change analyses.

†*p*-values for heterogeneity between AR+ and AR− tumors.

Table 3

Multivariable* Relative Risks of Breast Cancer by AR Status According to Physical Activity in the Nurses' Health Study (1986–2006).

Physical activity (MET-hrs/wk)	Overall invasive breast cancer (n=5,410)	Not accounting for ER/PR status			Accounting for ER/PR status		
		AR+ (n=1,661)	AR− (n=467)	*P*-het†	AR+ (n=1,661)	AR− (n=467)	*P*-het†
<3	1.0 (ref.)	1 (ref.)	1 (ref.)		1 (ref.)	1 (ref.)	
3–<9	0.99 (0.91, 1.08)	0.95 (0.82, 1.11)	0.99 (0.74, 1.32)		0.95 (0.81, 1.11)	0.99 (0.71, 1.38)	
9–<18	0.93 (0.85, 1.02)	0.88 (0.75, 1.03)	1.10 (0.83, 1.47)		0.84 (0.72, 0.99)	1.16 (0.83, 1.60)	
18–<27	0.94 (0.85, 1.03)	0.91 (0.76, 1.09)	0.97 (0.70, 1.36)		0.90 (0.75, 1.08)	1.04 (0.71, 1.51)	
≥ 27	0.86 (0.78, 0.95)	0.89 (0.75, 1.06)	0.74 (0.52, 1.04)	0.34	0.85 (0.71, 1.01)	0.73 (0.49, 1.07)	0.47
p-trend	<0.001	0.21	0.08		0.12	0.05	
Per 20 MET-hrs/wk (equivalent to 5 hours of brisk walking per week)	0.89 (0.81, 0.98)	0.83 (0.70, 0.98)	0.67 (0.47, 0.95)	0.28	0.87 (0.73, 1.04)	0.67 (0.45, 0.99)	0.22

*MV-Adjusted for age at menarche, body mass index at age 18 years, height, parity and age at first birth, alcohol intake, postmenopausal hormone use, age at menopause, family history of breast cancer, and history of benign breast disease.

†*p*-value for heterogeneity between AR+ and AR− tumors.

Table 4

Multivariable* Relative Risks of Breast Cancer by ER/PR/AR Status According to adult body size and physical activity in the Nurses' Health Study

	ER+PR+AR+ (n=1,163)	ER+PR+AR− (n=181)	ER+PR−AR+ (n=260)	ER+PR−AR− (n=75)	ER−PR−AR+ (n=197)	ER−PR−AR− (n=205)
BMI (kg/m^2)† per 5 increment	1.15 (1.08, 1.23)	1.23 (1.04, 1.45)	0.88 (0.75, 1.03)	0.92 (0.70, 1.22)	1.08 (0.92, 1.28)	1.19 (1.01, 1.39)
Weight change: per 5 kg change	1.06 (1.03, 1.08)	1.07 (1.00, 1.14)	0.95 (0.89, 1.01)	1.00 (0.90, 1.11)	1.05 (0.99, 1.12)	1.07 (1.01, 1.14)
5 hours of brisk walking per week	0.81 (0.66, 0.99)	0.73 (0.42, 1.26)	1.01 (0.67, 1.51)	0.43 (0.15, 1.27)	0.78 (0.47, 1.31)	0.72 (0.42, 1.23)

*MV-Adjusted for age at menarche, body mass index at age 18 years, height, parity and age at first birth, alcohol intake, postmenopausal hormone use, age at menopause, family history of breast cancer, and history of benign breast disease. For the weight change analysis, the cases numbers were 1,045 ER+PR+AR+, 160 ER+PR+AR−, 228 ER+PR−AR+, 179 ER−PR−AR+, 184 ER−PR−AR−, and 70 ER+PR−AR− tumors. The corresponding case numbers for the physical activity analysis were 1,162, 177, 233, 180,186, and 68.

†For the pair-wise comparisons, the associations were only statistically significantly different between ER+PR−AR+ and each of ER+PR+AR+ (p-value=0.003), ER+PR+AR− (p-value=0.004), and ER−PR−AR− (p-value=0.02).