Leisure-Time Physical Activity is Associated with reduced Risk of Breast Cancer and Triple Negative Breast Cancer in Nigerian Women

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Abstract

Background: Physical activity (PA) is associated with reduced risk of breast cancer and its various subtypes but this association is less well described in African women, particularly in women with triple-negative breast cancer that is more common in Sub-Saharan Africa. In this study, we examined the associations between leisure-time physical activity (LTPA) and breast cancer in total and by subtypes in Nigerian women.

Methods: We studied 472 newly diagnosed primary invasive breast cancer patients age-matched (±5years) with 472 controls from the Nigerian Integrative Epidemiology of Breast Cancer (NIBBLE) Study enrolled from January 2014 to July 2016. We derived the average amount of time spent on LTPA per week over the past year using a modified Nurses' Health Study-II physical activity questionnaire. We calculated the total metabolic equivalents (METs) for each reported LTPA per hour/week (i.e. walking, cycling, and dancing) and compared odds of breast cancer among participants who attained the World Health Organization (WHO) physical activity(PA) recommendations of at least 150 minutes of moderate-intensity or/and 75 minutes of vigorous-intensity aerobic activity/week with those who did not. In addition, we evaluated these by categories of LTPA in quartiles of METs. We used conditional and unconditional logistic regression models to estimate the adjusted Odds Ratio (OR) of LTPA for overall breast cancer and by molecular subtypes.

Results: The mean age (SD) of cases, 44.4 (10.0) years, was similar to that of controls, 43.5 (9.5) after matching. The OR for breast cancer among women who attained the WHO PA recommendations compared with those who did not was 0.64 (95% CI: 0.45-0.90). LTPA was associated with 51% reduced odds of hormone receptor-positive and 65% reduced odds of triple-negative breast cancer. We observed a significant dose-response relationship where women with high levels of LTPA had lower odds of overall breast cancer, triple-negative and hormone receptor-positive breast cancer.

Conclusions: Increasing LTPA in African women may play a significant role in reducing the incidence of breast cancer, particularly of the more aggressive subtype as triple-negative, which is more prevalent in Sub-Saharan Africa.

Background

The incidence of breast cancer in Sub-Saharan Africa is rising, and it is now the commonest cancer in women in most countries in this area (1). In Nigeria, which constitutes nearly 52% of the population of West Africa, breast cancer incidence increased by approximately 25% per decade from estimated age-standardized incidence rate (ASR) of 13.7 per 100,000 in 1960-1969 to ASR of 41.7 per 100,000 in 2018 (2). In 2018, the amount of newly diagnosed breast cancers in Nigeria was estimated to be 26,310 which is 37.0% of all new cancers in Nigerian women and 15.6% of all new breast cancer cases in Africa (1).

Several factors are responsible for the rising rates of breast cancer in Sub-Saharan Africa. These include increased life expectancy thereby increasing the number of women growing into cancer-bearing old age, reduced risk of death from competing causes such as infections, social-economic development (3), lifestyle changes including delays in commencement of childbearing, reduced parity, and reduced duration of breastfeeding, obesity, and physical inactivity. (1, 4-8).

The prevalence of physical inactivity in Sub-Saharan Africa has risen in recent times as the population transition from predominantly rural and agrarian to more developed urban, socio-economic systems (4). In Nigeria, more than 80% of urbanized adult women are physically inactive and do not meet the World Health Organization's (WHO) criteria for minimum levels of physical activity needed to maintain a healthy lifestyle and reduce the risks of chronic diseases including breast cancer (5)(9-12).

Physical inactivity may be associated with an increased risk of breast cancer through several biological mechanisms. Women with high levels of leisure-time physical activity (LTPA) have lower serum estradiol and higher sex hormone-binding globulin levels after adjusting for obesity and this association is more pronounced in post-menopausal compared to pre-menopausal breast cancer (13, 14). Exercise may influence breast cancer risk by inducing systemic anti-inflammatory effect and other effects that may be mediated through reduction in visceral fat mass. (14-16).

Whereas acute physical activity is associated with oxidative stress, human adaptation to repeated exercise leads to the development of protective anti-oxidant effect associated with reduced cancer progression and metastasis (14, 17). In addition, physical activity reduces insulin resistance and circulating leptin and insulin levels, while increasing adiponectin, IGFBP-1 and IGFBP-3 levels (18-20). These influence the associations between the insulin pathway and breast cancer development and progression (10, 15, 16, 21-24).

Recent studies show that physical inactivity is associated with breast cancer and its various molecular subtypes (25-27). However, there has been no previous study of the associations between breast cancer and its molecular subtypes, particularly triple-negative breast cancer (TNBC) in African women (28-30). Since physical inactivity is one of the potentially modifiable risk factors for breast cancer, studies of its prevalence and association with breast cancer are likely to be informative and contributory to public policy (31). In this study, we examined associations between LTPA and breast cancer and its molecular subtypes in Nigerian women. Furthermore, we examined whether Nigerian women who followed the WHO LTPA recommendations had significantly lower risk for overall, hormone receptor-positive and triple-negative breast cancer.

Methods

Study design and setting

We studied women enrolled in the Nigerian Integrative Epidemiology of Breast Cancer (NIBBLE) Study, a case-control study of female breast cancer that recruited participants at six government hospitals in Nigeria, five of whom are located in Abuja (National Hospital, University of Abuja Teaching Hospital Gwagwalada, Asokoro District Hospital, Garki Hospital and Wuse General Hospital) and the sixth hospital, the University of Nigeria Teaching Hospital, in Enugu, between January 2014 and July 2016. The details of the study design and setting have been previously published (2).

Participants

Overall, 508 newly diagnosed patients with primary invasive breast cancer aged 18 years and above were identified at their first visit to the clinical sites. Research nurses informed potential participants about the study and obtained their informed consent. Age-matched hospital-based controls (892) were women who did not have cancer or endocrine diseases and were within ±2.5 year of the age of specific breast cancer patients enrolled within one month in the same hospital. Most (94.0%) of the women approached consented to participate. Research nurses conducted face-to-face interviews in the English language (70.6%) or local Nigerian language (29.4%) according to the patient's preference.

Primary exposure

For the LTPA assessment, we used a modification of the U.S. Nurses' Health Study (NHS) II physical activity questionnaire (4). The questionnaire measures the average amount of time spent per week on moderate and vigorous leisure-time activities. Participants reported the average time per week spent on each of the following moderate or vigorous activities, in the past year: walking, hiking, jogging, running, bicycling, dancing, playing tennis, soccer, squash; golf, swimming, aerobics, weightlifting or resistance exercise. We calculated participants' metabolic equivalents (METs) - hour/week of total LTPA by multiplying the number of hours per week of each activity with its corresponding MET values and then summarized all the MET values (32). We excluded one participant with an extreme MET value. The final MET score was used to create two categories of participants: *'Leisure-time physical active'* - participants who met the WHO PA recommendations of at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic LTPA, or an equivalent combination, and *'Leisure-time physical inactive'* - for those who did not meet the WHO PA recommendations (33). In addition, we created categories of LTPA in quartiles of METs (< 3.00, 3.00-5.49, 5.50-11.49, 11.50 ≤) based on the distribution of the study sample.

Breast cancer and breast cancer subtypes

Needle core biopsies were performed using Bard Magnum Biopsy Gun®. Breast specimens were fixed in 10% neutral buffered formalin and processed within 48 hours of fixation with a minimum fixation time of 8 hours in Leica® automatic tissue processors at the African Collaborative Center for Microbiome and Genomics Research (ACCME) Laboratory at the Institute of Human Virology, Nigeria.

Histology

Sections of Paraffin-embedded blocks were cut at 3-4 μm and stained with hematoxylin and eosin stains. Histological features were classified according to the 2003 WHO classification of breast diseases and graded using the Nottingham modification of the Bloom-Richardson grading (34). Only participants with final histologic confirmation of breast cancer were included in the analysis.

Immunohistochemistry (IHC)

Histologically confirmed invasive breast tumors were stained by immunohistochemical techniques using the Thermo Scientific Lab Vision primary antibodies (clones ER-SP1; PR-SP2; Her2-SP3) and Thermo Scientific™ Ultra Vision™ Quanto HRP DAB detection kit according to manufacturer's recommended protocol. In brief, formalin-fixed paraffin-embedded (FFPE) tissues were sectioned serially into 4 μm, placed in histogrip coated microscope slides, incubated overnight at 60 C, deparaffinized in series of xylene (three changes), graded alcohol (2 changes 100%, 90%, and 70% ethanol) and rehydrated in distilled water. Antigen retrieval was performed, sections were washed with Phosphate Buffered Saline (PBS) and blocked with hydrogen peroxide for 10 minutes. Then Ultra V was applied to block nonspecific background staining for 5 minutes. Sections were washed with PBS and primary antibodies (ER-SP1; PR-SP2; Her2-SP3) were applied on the sections and incubated at room temperature for 1 hour followed by application of primary antibody enhancer and HRP polymer. Staining was visualized using Diaminobenzidine (DAB) and counterstained with haematoxylin. Sections were dehydrated and cover slipped. We planned to perform immunohistochemistry (IHC) for all participants recruited into the NIBBLE study but in a few cases the core tissue biopsies were too small so IHC was not feasible.

IHC interpretation

We considered ER and PR were positive if ≥ 1% nuclei of the tumor cells were stained per the American Society College Oncology/College American Pathology (ASCO/CAP) guidelines (35). HER2 staining was scored as 0, 1+, 2+, or 3+ and we considered a staining of 3+ (uniform, intense membrane staining of > 30% of invasive tumor cells) a positive HER2 result (36).

Breast cancer subtypes

Overall, 57% of the cases (292/508) had estrogen, progesterone and human epidermal growth factor 2 test results. Some 32.2% (n=94/292) were classified as HP, and 42.1% (n=123/292) as TNBC. We classified breast cancer subtypes using combinations of the IHC markers as follows (a) hormone receptor positive (HP) were tumors that had positive estrogen and progesterone tests but negative HER2 test and (b) triple-negative breast cancer (TNBC) were tumors that lacked all 3 markers (37).

Covariates

We collected information on age in years, levels of education completed (elementary, completed high school, post-high school with no university degree, completed university), marital status (married, single, separated/divorced/widowed), smoking experience (yes vs. no), alcohol use (yes vs. no), age at menarche, number of pregnancies (0, 1-2, 3-5, 6≤), ever use of oral contraceptive (yes vs. no), menopausal status (premenopausal vs. postmenopausal), and breastfeeding experience of more than one month (yes vs. no). Research nurses measured participants' height, weight, waist, and hip circumferences and we derived body mass index (BMI kg/m^2) and waist-hip ratio (WHR) from these measurements. Participants with extreme values of WHR of less than 0.7 or higher than 1.6 or with a BMI less than 10 kg/m^2 or greater than 50 kg/m^2 were excluded from the analyses (38). BMI was categorized into < 25, 25 - 29.9, ³30) and WHR was categorized to ≤0.85, and > 0.85. To compute socio-economic status, we calculated the 'wealth index' using the following variables - house ownership and type of house owned (e.g. home, apartment, house or duplex); source of drinking water (e.g. from outside, well, borehole, piped or bottled); type of cooking fuel; use of separate room for cooking; type of toilet; and ownership of household goods including car and refrigerator. We used Principal Component Analysis (PCA) with varimax rotation to compute factor scores based on the sum of responses to these variables weighted by their factor loading. We used the first component in the PCA that explained (35%) of the variations in the data, to generate a wealth index (39). The wealth index variable was used to classify participants to low socio-economic status (lowest 40% of the score distribution), middle (middle 30%) and high (highest 30%) socio-economic class.

Statistical Analysis

Overall breast cancer

From the initial study sample (n=1,400), we matched 472 cases with 472 controls based on age (±5 year) using propensity score with the optimal matching procedure making a final sample of 944 participants. To examine bivariate associations between independent variables, primary exposure (LTPA) by cases and controls, we implemented conditional logistic regressions for each independent variable separately. To construct our multivariable models, we selected independent variables with *p*-value < 0.20 in the bivariate analysis for inclusion. Multiple imputations technique was performed to impute missing values of the independent variables after conducting missing completely at random test (MCAT) (p-value=0.63). For multivariable analyses, we conducted conditional logistic regression models and used Wald tests to identify covariates with significant associations (*p*-value < 0.05) with risk of overall and molecular subtypes of breast cancer.

Breast cancer subtypes

To examine associations between LTPA and breast cancer subtypes, we used two subsamples – cases classified as HP on immunohistochemistry, and those classified as TNBC. We used unconditional logistic regression models to identify age-adjusted variables with p-value < 0.20 in bivariate analyses. These were included in multivariable unconditional logistic regression models for each breast cancer subtype, separately.

We present the adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) of LTPA variables with breast cancer overall and by subtypes. All analyses were performed using Stata SE version 15.1 (College Station, Texas) and R-Studio Version 1.1.447.

Results

The characteristics of cases and controls are shown in Table 1. Women with breast cancer were older, more likely to be post-menopausal, have lower educational attainment and more likely to have non-professional jobs compared to women in the control group. However, the two groups were similar with regards to socio-economic status, marital status, number of pregnancies, and breastfeeding experience. Women in the control group were more likely to be physically active and to be in the categories with the highest levels of LTPA compared to cases.

Table 2 shows the results of the multivariable conditional logistic regression models. We found a significant association between LTPA and overall breast cancer risk. Specifically, women who met the WHO recommendation for LTPA had significantly lower odds of breast cancer compared to women who did not (OR = 0.64, 95% CI: 0.45-0.90; *p*-value=0.01) after controlling for significant covariates. Furthermore, women who performed 11.5 METs and more of physical activity per week had lower odds of breast cancer compared to women who had less than 3.00 METs of physical activity per week (OR = 0.49, 95% CI: 0.32 - 0.74; *p*-value< 0.001).

In Table 3, we show the results of the analyses of LTPA and molecular subtypes of breast cancer. We compared women in extreme quartiles of LTPA and found significantly lower odds of hormone receptor-positive breast cancer (OR = 0.49, 95% CI: 0.24 - 0.97; *p*-value=0.04) and triple-negative breast cancer (OR = 0.35 95% CI: 0.18 - 0.67; *p*-value<0.001). Women who met the WHO recommendation for LTPA showed only a significant reduction in the odds of having triple-negative breast cancer (OR = 0.52, 95% CI: 0.33 - 0.92; *p*-value=0.03).

Discussion

In this study, we found that LTPA is associated with a reduction in the odds of overall, triple-negative and hormone receptor-positive breast cancer among Nigerian women. Our result on association between LTPA and overall breast cancer is consistent with findings from other breast cancer studies in African women (9, 11). For example, a multi-country case-control study of women from Nigeria, Cameroon, and Uganda who completed culturally tailored physical activity questionnaires showed a significant reduction in breast cancer risk and a dose-response relationship (10).

Our finding of association between LTPA and hormone receptor-positive and triple-negative breast cancer is the first in African women and similar to findings in other populations (12, 16, 25-27, 40, 41). For example, a multi-center population-based case-control study of young women in the United States showed a 27% reduction in risk of triple-negative breast cancer (42). Another study utilizing data from the Women's Health Initiative examined the baseline recreational physical activity and the risk of breast cancer subtypes, eight years later. Women in the highest recreational physical activity category had significantly reduced risk of triple-negative and estrogen receptor-positive breast cancer compared to women who reported no recreational physical activity (17).

In this study, majority of the participants did not meet the WHO recommendation for minimum levels of physical activity and this is similar to the findings from our previous study of LTPA among urbanized Nigerians (5). Compared with the global average, where only 1 in 4 adults do not meet the WHO recommendation, the prevalence of physical inactivity in urbanized Nigerian women is significantly high (43). Furthermore, the median activity level in our study sample was 5.5 MET-hours/week overall, which is lower than the median activity level of 8.0 MET-hours/week found in studies done in the US and Europe (12).

In this study, the commonest physical activities were dancing, walking and hiking (data not shown). This is similar to the findings of other studies in Nigeria (4) which showed that dancing contributed the highest MET-hours/week for LTPA among adult Nigerian women, followed by walking, hiking and jogging. In Nigeria, dancing most frequently occurred during religious observances, therefore intervention programs to encourage uptake of physical activity should consider approaches that enhances and promotes current, culturally relevant practices (4).

Numerous case-control and cohort studies suggest there is an overall average of 20 to 25% reduction in risk of breast cancer associated directly with increased physical activity (6, 7, 44, 45). Although our findings are similar to these previous studies, the potential risk reduction in our population is much higher after controlling for BMI, WHR, alcohol use, fertility covariates, and sociodemographic factors. This is because of the currently high levels of physical inactivity in Nigerian women. Although the incidence of breast cancer in Nigeria is lower than in high-income countries, some reduction in incidence may be attained by increasing uptake of LTPA in this population.

The limitations of our study include recall bias, the potential impact of breast cancer on levels of LTPA and the use of a self-reported questionnaire (46). Previous studies of LTPA in Nigerian women without breast cancer, however, showed similar results to our study (5). We did not adjust for family history of breast cancer, but previous studies showed a low prevalence of this risk factor in Nigerian breast cancer patients. We also did not adjust for foods and nutrients intakes, but we adjusted for BMI, WHR and for alcohol intakes, the dietary factors most consistently associated with breast cancer risk. The study used a modification of the U.S. Nurses' Health Study (NHS) II physical activity questionnaire, which has not been extensively validated in African populations.

Despite these limitations, the strengths of our study include histological and immunohistochemical confirmation of breast cancer and its molecular subtypes, a large sample size with sufficient power to detect significant results, inclusion of a broad range of well-established covariates and confounders such as BMI, menopausal status, demographic variables, types of occupation, as well as relative homogeneity of the study population (9, 26, 47).

Conclusions

In low- and middle-income countries where the incidence of breast cancer is rising, increased uptake of LTPA can significantly reduce the incidence of breast cancer, particularly of the more aggressive subtype as triple-negative breast cancer, which is more prevalent in women in Sub-Saharan Africa.

Declarations

Ethical approval and consent to participate

Ethical approval was obtained from the National Health Research Ethics Committee of Nigeria, Health Research Ethics Committees in each participating hospital and the institutional ethics committees at the University of Maryland School of Medicine, Baltimore (US). All participants gave written informed consent in accordance with the Declaration of Helsinki and the Nigerian National Code for Health Research Ethics.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

CAA had the idea for the NIBBLE study, designed it, obtained funding, supervised implementation, data management and analysis. GB conducted the data analysis, and drafted the manuscript; TY, MY, OO, OB, EE, IS, EM, IA, EJ and BA contributed to participants' recruitment, data collection and data quality; AF led the laboratory diagnosis; SA contributed to the study design, data management, data analysis. All authors contributed to drafting the manuscript, provided critical revisions and approved the final draft.

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Abbreviations

ASR, Age-Standardized incidence Rate

WHO, World Health Organization

PA, Physical Activity

LTPA, Leisure-Time Physical Activity

METs, Metabolic Equivalents

OR, Odds Ratio

NIBBLE, Nigerian Integrative Epidemiology of Breast Cancer

NHS, Nurses' Health Study

IHC, Immunohistochemistry

TNBC, Triple-Negative Breast Cancer

HP, Hormone Receptor Positive Breast Cancer

HER2, Human Epidermal Growth Factor 2

ER, Estrogen Receptor

PR, Progesterone Receptor

BMI, Body Mass Index

WHR, Waist-Hip Ratio

CI, Confidence Interval

PCA, Principal Component Analysis

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Tables

Table 1

Descriptive characteristics of the study population, the Nigerian Integrative Epidemiology of Breast Cancer Study (NIBBLE), year 2014-2016.

N=944		Cases [a] N=472 N(%) / Mean±SD	Control [a] N=472 N(%) / Mean±SD	*p-value* [a]
Age, years		44.4 ± 10.0	43.5 ± 9.5	0.18[+]
Age at first menstrual period, years		14.4 ± 1.7	14.5 ± 1.9	0.23
BMI kg/m^2				0.013
	<25	147 (31.1)	116 (24.6)	
	25-29.99	162 (34.3)	161 (34.1)	
	≥30	147 (31.2)	185 (39.2)	
	Missing	16 (3.4)	10 (2.1)	
WHR				0.07
	High, >0.85	330 (69.9)	306 (64.8)	
	Missing	16 (3.4)	14 (3.0)	
Education				0.004
	Elementary≤	135 (28.6)	94 (19.9)	
	Complete HS	101 (21.4)	120 (25.4)	
	Post HS no university	118 (25.0)	111 (23.6)	
	Completed University	112 (23.7)	145 (30.7)	
	Missing	6 (1.3)	2 (0.4)	
Marital status				0.93
	Married	341 (72.3)	344 (72.9)	
	Single	53 (11.2)	54 (11.4)	
	Separated/Divorced/Widowed	72 (15.3)	73 (15.5)	
	Missing	6 (1.3)	1 (0.2)	
Occupation				<0.001
	Self-employed	124 (26.3)	49 (10.4)	
	Unskilled manual	197 (41.7)	258 (54.7)	
	Skilled manual	112 (23.7)	76 (16.1)	
	Professional/executive	22 (4.7)	71 (15.0)	
	Missing	17 (3.6)	18 (3.8)	
Wealth index				0.43
	Low	183 (38.8)	188 (39.8)	
	Middle	152 (32.2)	123 (26.1)	
	High	126 (26.7)	154 (32.6)	
	Missing	11 (2.3)	7 (1.5)	
Ever used oral contraceptives				0.25
	Yes	141 (29.9)	160 (33.9)	
	Missing	11 (2.3)	6 (1.3)	
Number of pregnancies				0.97
	0	49 (10.4)	45 (9.5)	
	1-2	86 (18.2)	95 (20.1)	
	3-5	227 (48.1)	231 (48.9)	
	≥6	99 (21.0)	98 (20.9)	
	Missing	11 (2.3)	3 (0.6)	
Menopausal status				0.05
	Postmenopausal	167 (35.4)	146 (30.9)	
	Missing	6 (1.3)	2 (0.4)	
Ever breastfed more than one month				0.21
	Yes	364 (77.1)	377 (79.9)	

	Missing	14 (3.0)	14 (3.0)	
Smoke				NA
	Yes	2 (0.4)	3 (0.6)	
	Missing	7 (1.5)	2 (0.4)	
Alcohol use				0.06
	Yes	100 (21.2)	79 (16.7)	
	Missing	9 (1.9)	4 (0.9)	
Leisure-time physical activity (meet the WHO recommendations)				<0.001
	Physical active	83 (17.6)	135 (28.6)	
	Physical inactive	356 (75.4)	322 (68.2)	
	Missing	33 (7.0)	15 (3.2)	
Leisure-time physical activity by MET h/w				<0.001
	<3.00	140 (29.7)	86 (18.2)	
	3.00-5.49	117 (24.8)	107 (22.7)	
	5.50-11.49	95 (20.1)	123 (26.0)	
	11.50 ≤	87 (18.4)	141 (29.9)	
	Missing	33 (7.0)	15 (3.2)	

Cases and controls are matched by age (±5 years)

+t-test

BMI, Body Mass Index; WHR, Waist-Hip Ratio; MET, Metabolic Equivalent; SD, standard deviation; N, number of subjects; HS, High School; WHO, World Health Organization

Table 2

Age-adjusted and multivariable models of leisure-time physical activity and risk of total breast cancer in the Nigerian Integrative Epidemiology of Breast Cancer Study (NIBBLE), the year 2014-2016, N=944

	Age-adjusted model [a] OR (95% CI)	Multivariable model [a] [b] [b] OR (95% CI)
Leisure-time physical activity [c] (meet the WHO recommendations)	0.57 (0.42-0.77)	0.64 (0.45-0.90)
P-value	<0.001	0.01
Leisure-time physical activity by MET h/w [d]		
3.00-5.49	073 (0.50-1.05)	0.91 (0.60-1.41)
5.50-11.49	0.51 (0.34-0.76)	0.52 (0.34-0.79)
11.50 ≤	0.41 (0.28-0.60)	0.49 (0.32-0.74)
P-trend	<0.001	<0.001

[a] Cases and controls were matched by age (±5 years) analyses were done using a conditional logistic regression model.

[b] The models were WHR, BMI, education, occupation, menopause status, alcohol use.

[c] Reference category- leisure-time physical inactive, those who did not meet the WHO recommendations for physical activity

[d] Reference category- leisure-time physical activity of less than 3.00 MET h/w

BMI, Body Mass Index; WHR, Waist-Hip Ratio; MET, Metabolic Equivalent, OR, Odds Ratio; CI, Confidence Interval; h, hour; w, week

Table 3

Age-adjusted and multivariable models of leisure-time physical activity and risk of breast cancer subtypes (HP, TNBC) in the Nigerian Integrative Epidemiology of Breast Cancer Study (NIBBLE), the year 2014-2016.

	HP (ER+/PR+)/HER2- , n=94		TNBC, n=123	
	Age-Adjusted model [a] OR(95% CI)	Multivariable Model [a b] OR(95% CI)	Age-Adjusted model [a] OR(95% CI)	Multivariable Model [a b] OR(95% CI)
Leisure-time physical activity [c] (meet the WHO recommendations)	0.66 (0.38-1.13)	0.72 (0.41-1.27)	0.49 (0.29-0.83)	0.52 (0.33-0.92)
P-value	0.13	0.26	0.01	0.03
Leisure-time physical activity by MET h/w [d]				
3.00-5.49	0.54 (0.29-1.00)	0.59 (0.31-1.15)	0.50 (0.29-0.86)	0.64 (0.35-1.14)
5.50-11.49	0.47 (0.26-0.88)	0.50 (0.26-0.97)	0.39 (0.23-0.68)	0.47 (0.26-0.85)
11.50 ≤	0.40 (0.21-0.75)	0.49 (0.24-0.97)	0.28 (0.16-0.51)	0.35 (0.18-0.67)
P-trend	0.007	0.04	<0.001	0.001

[a] Unconditional logistic regression models with complete control sample of n=892

[b] The models were adjusted for WHR, BMI, education, occupation, menopause status, alcohol use.

[c] Reference category-leisure-time physical inactivity, did not meet the WHO recommendations for physical activity

[d] Reference category-leisure-time physical activity of less than 3.00 MET h/w

HP, Hormone Receptor Positive; ER, Estrogen Receptor; PR, Progesterone Receptor; HER2, Human Epidermal Growth Factor-2; TNBC, Triple-Negative; BMI, Body Mass Index; WHR, Waist-Hip Ratio; MET, Metabolic Equivalent, OR, Odds Ratio; CI, Confidence Interval; h, hour; w, week