Leisure-Time Physical Activity is Associated with reduced Risk of Breast Cancer and Triple Negative Breast Cancer in Nigerian Women: a matched case-control study

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Abstract

Background Physical activity is associated with reduced risk of breast cancer and its various subtypes but this association is less known in African women, particularly with triple-negative breast cancer that occurs more frequently in Sub-Saharan Africa compared to developed countries. In this study, we examined the association between leisure-time physical activity (LTPA) and breast cancer in total and by its subtypes in Nigerian women. **Methods** Overall, 630 newly diagnosed patients with primary invasive breast cancer were age-matched (± 5 years) with 630 controls from the Nigerian Integrative Epidemiology of Breast Cancer (NIBBLE) Study from 01/2014-07/2016. 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 this 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 with overall breast cancer and by hormone receptor-positive and triple-negative breast cancer. **Results** The mean ages of cases and controls were similar after matching, 42.5 ± 10.1 and 41.5 ± 9.2 years (mean $\pm$ SD), respectively. Women who attained the WHO PA recommendations had a 42% reduction in the odds of having breast cancer (OR = 0.58 95% CI: 0.43-0.78) compared with those who did not. LTPA was associated with reduced odds of having hormone receptor-positive by 41% and significantly associated with reduced odds of having triple-negative breast cancer by 45%. In addition, a significant dose-response relationship was observed, women with higher levels of LTPA had lower odds of having overall breast cancer as well as having triple-negative and hormone receptor-positive breast cancer. **Conclusions** Increasing LTPA in African women can 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 (2-4). 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 (4).

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, lifestyle changes including delays in commencement of childbearing, reduced parity, and reduced duration of breastfeeding, obesity, and physical inactivity. (1, 5-9).

The prevalence of physical inactivity in Sub-Saharan Africa has risen in recent times as the population's transition from predominantly rural and agrarian to more developed urban, socio-economic systems (5). In Nigeria, more than 80% of urbanized adult women are physically inactive and do not meet the World Health Organization (WHO) criteria for minimum levels for physical activity to maintain a healthy lifestyle and reduce the risks of chronic diseases (Akarolo-Anthony & Adebamowo, 2014). Physical inactivity lifestyle may place African women at a higher risk of breast cancer (10-13).

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 (14, 15). Exercise may influence breast cancer risk by inducing systemic anti-inflammatory effect and other effects that may be mediated through the reduced visceral fat mass. (15-17).

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 (15, 18). In addition, physical activity reduces circulating leptin and insulin levels, and insulin resistance while increasing adiponectin, IGFBP-1 and IGFBP-3 levels (19-21). These influence the associations between the insulin pathway and breast cancer development and progression (11, 16, 17, 22-25).

Recent studies show that physical inactivity is associated with breast cancer and its various subtypes based on the hormone receptor and human epidermal growth factor-2 status (26-28). However, there has been no previous study of these relations in African women, particularly with triple-negative breast cancer that occurs more frequently in Sub-Saharan Africa compared to developed countries (29-31). Since physical inactivity is one of the potentially modifiable breast cancer risk factors, studies of its prevalence and association with breast cancer are likely to be informative and contribute to public policy on breast cancer prevention. Therefore, to fill this need, we examined associations between LTPA and total as well as molecular subtypes of breast cancer of hormone receptor-positive and triple-negative in Nigerian women. In addition, we examined whether Nigerian women who follow the LTPA recommendations of the WHO bore a significantly lower risk for overall and molecular subtypes of 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 about the study design and setting have been previously published (2).

Participants

Overall, 831 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 (996) were women who did not have cancer or endocrine diseases and were within ± 2.5 year of the age of specific patients enrolled within one month in the same hospital. Predominantly, >94.0% of 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. 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, weight lifting 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 value of MET. The final MET score was used to create two categories of participants: '*Leisure-time physical activity*'-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 inactivity*' – for those who did not meet the WHO PA recommendations (33). In addition, we created categories of LTPA in quartiles of METs (< 2.99, 2.99 - 5.80, 5.81 - 11.25, > 11.25) 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.

Histology

Sections of Paraffin-embedded blocks were cut at 3-4 μm and stained routinely with hematoxylin and eosin stains. Histological features were classified adopting 2003 WHO classification of breast diseases and graded using the Nottingham modification of the Bloom-Richardson grading (34).

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 (Petrosyan et al., 2002). In brief, formalin-fixed paraffin-embedded (FFPE) tissues were sectioned serially into 4 μm and were placed in histogrip coated microscope slides and 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 using a microwave at a level in 10 mM citrate buffer (pH 6.0) at 95 °C for 45 min. Sections were then washed with Phosphate Buffered Saline (PBS) and blocked with hydrogen peroxide for 10 minutes. Then Ultra V was applied to block nonspecific backgrounds staining for 5 minutes. At this stage, 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.

IHC interpretation

We obtained results of estrogen (ER), progesterone (PR) and human epidermal growth factor-2 (HER2) status in about 40% of participants. ER and PR were considered positive if $\geq 1\%$ nuclei of the tumor cells were stained as per the American Society College Oncology/College American Pathology (ASCO/CAP) guidelines (35). HER2 staining was scored as 0, 1+, 2+, or 3+ a positive HER2 result is IHC staining of 3+ (uniform, intense membrane staining of > 30% of invasive tumor cells, (36).

Breast cancer subtypes

Overall, 36% of the cases (301/831) had immunohistochemistry tests that included results of estrogen, progesterone and human epidermal growth factor 2. We classified breast cancer subtypes using combinations of the IHC markers as follows (a) hormone receptor positive (estrogen and progesterone) /HER2 negative (HP), and triple-negative tumors which lacked all 3 markers (TNBC) (37). Therefore, among those cases: 34.0% (n=103/301) were classified as HP, and 47.8% (n=144/301) as TNBC to further analysis subtypes of breast cancer.

Covariates

We collected information on age in years, levels of education (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 - 3, 4 - 6, ≥ 7), ever use of oral contraceptive (yes vs. no), menopausal status (premenopausal vs. postmenopausal), age at menopause in years and breastfeeding experience of more than one month (yes vs. no). Research nurses measured participant's 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 and with a BMI less than 10 kg/m^2 or greater than 50 kg/m^2 were excluded from the analyses (38). 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 most of the variations in the data, to generate a wealth index (39). The wealth index variable was used to classify participants to inferior socio-economic status (lowest 40% of the score distribution), middle (middle 40%) and high (highest 20%) socio-economic class.

Statistical Analysis

From the initial study sample (1,827), the following variables included missing values: marital status (1.8%), education (2.0%), menopausal status (2.5%), pregnancy (2.8%) wealth index (2.9%), LTPA (7.8%), BMI (4.1%), WHR (4.2%), smoking (2.5%), alcohol (2.5%) and occupation (4.8%), age at the first menstrual period (6.9%), use of contraceptives (2.7%) and breastfeeding experience (4.1%). We excluded women with missing values, which reduced the sample size to 1,444. Subsequently, of those, 630 cases were matched with 630 controls based on age (± 5 year) using propensity score with the optimal matching procedure.

Overall breast cancer

To examine bivariate associations between independent variables, primary exposure (LTPA) by cases and control, we implemented conditional logistic regressions. Then, for the multivariable models, we selected the independent variables that examined differences between cases and controls p -value < 0.20 in the bivariate analysis. Significantly, alcohol use that has been associated with breast cancer in previous publications was included in our multivariable models as well. In the multivariable odds ratios, we conducted conditional logistic regression models employing Wald tests to identify covariates with the significant association (p -value < 0.05) with overall breast cancer risk and to examine our main study hypothesis.

Breast cancer subtypes

To examine associations between LTPA and breast cancer subtypes, we used from the initial sample, subsamples of HP cases ($n=103$), and of TNBC ($n=144$) vs. controls ($n=996$) and applied unconditional logistic regression models to assess age-adjusted and multivariable odds ratios for each subtype separately.

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 described in Table 1. Women with breast cancer were older, attained menopause at an older age, retained lower levels of education, and held more non-professional jobs compared to women in the control group. However, the two groups were similar with regards to socio-economic status, marital status, and number of pregnancies, breastfeeding experience, and alcohol use. The mean BMI and WHR were moderately higher among controls than cases. Women in the control groups (30.0%) were more likely to be physically active compared to those in the case group (18.1%). A similar trend was found in the highest levels of LTPA where a higher proportion of women in the control group performed more than 5.8 METs of LTPA per week than the case group.

Table 2 shows the results of the multivariable conditional logistic regression models. Based on the final models, there was a significant association between LTPA and overall breast cancer risk. Specifically, women who met the WHO recommendation for LTPA demonstrated a significant reduction of 42% in the odds of having breast cancer compared to women who did not ($OR = 0.58$, 95% CI: 0.43 - 0.78; p -value < 0.001) after controlling for significant covariates. Furthermore, women who had more than 11.25 METs hour per week of LTPA had 55% reduction in odds of having breast cancer compared to women who had less than 2.99 METs per week ($OR_{1\text{ vs }4} = 0.45$, 95% CI: 0.31 - 0.65; 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 having hormone receptor-positive breast cancer ($OR_{1\text{ vs }4} = 0.42$, 95% CI: 0.21 - 0.83) and triple-negative breast cancer ($OR_{1\text{ vs }4} = 0.34$ 95% CI: 0.19 - 0.63). Ultimately, women who met the WHO recommendation for LTPA showed a 41% reduction in the odds of having hormone receptor-positive and 45% reduction in the odds of having triple-negative breast cancer.

Discussion

In this study, we showed that LTPA is associated with a reduction in the odds of having overall breast cancer and having triple-negative and hormone receptor-positive breast cancer among Nigerian women. Our results are consistent with findings from other breast cancer studies in African women (10, 12). For example, a multi-country case-control study of women from Nigeria, Cameroon, and Uganda who completed a culturally tailored physical activity, questionnaires showed a significant reduction in breast cancer risk of up to 60%, with a dose-response relationship (Hou et al., 2014).

Our finding of association between LTPA and molecular subtypes of hormone receptor-positive and triple-negative breast cancer is the first in African women and similar to findings in other populations (13, 17, 26-28, 40, 41). For example, a multi-center population-based case-control study of young women in the United States experienced 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 activity category demonstrated 23% more reduced risk of triple-negative and 15% lower risk of estrogen receptor-positive breast cancer compared with women who reported no recreational physical activity (Phipps et al., 2011.).

In the current study, majority of the breast cancer cases and controls did not meet the WHO recommendation for minimum levels of physical activity, and this is similar to the findings from another study of LTPA among urbanized Nigerians (Akarolo-Anthony & Adebamowo, 2014). 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 5.8 MET-hours/week overall, which is lower than the median activity level of 8.0 MET-hours/week found in cancer cohort studies in the US and Europe (13).

In this study, among the approximately 20% of participants who were physically active, the most frequent physical activities were dancing, walking and hiking (data not shown). This is similar to the findings of other studies in Nigeria (5) 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 (5).

Numerous case-control and cohort studies suggest there is an overall average of 20-25% risk reduction for breast cancer-associated directly with increased physical activity (7, 8, 44, 45). Although our study findings replicate these previous studies, the potential risk reduction in our population is higher up to 55% after controlling for BMI, WHR, alcohol use, fertility covariates, and sociodemographic factors, possibly because of the current extreme levels of physical inactivity in Nigerian women. Although the incidence of breast cancer in Nigeria is currently lower than in high-income countries, 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 (Akarolo-Anthony & Adebamowo, 2014). 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 factor most consistently associated with breast cancer risk.

Despite these limitations, the strengths of our study include histological and immunohistochemical confirmation of 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 (10, 27, 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.

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

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) and the London School of Hygiene and Tropical Medicine (UK). The study was carried out in compliance with the Nigerian National Code for Health Research Ethics. 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

GB had the idea for the study, conducted the data analysis, and drafted the manuscript and made subsequent revisions to the manuscript; TY, MY, OO, OB, EE, IS, EM, IA, and BA contributed to data collection, data quality and approved the final draft; AF contributed to the description of the materials and methods; EA contributed to manuscript revision; SA contributed to the study design, data quality, data analysis, and manuscript revision; CA had the idea for the study design, obtained funding, supervised data analyses and provided critical revisions to the manuscript. All authors read and approved the final draft.

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Tables

Table 1

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

		Cases ^a	Control ^a	<i>p-value</i> ^a
		Mean±SD /N(%)	Mean±SD /N(%)	
		N=630	N=630	
Age, years		42.5 ± 10.1	41.5 ± 9.2	0.096 ⁺
Age at first menstrual period, years		14.3 ± 1.7	14.4 ± 1.9	0.179
BMI kg/m ²		28.1 (5.8)	28.8 (5.8)	0.025
WHR		1.14 (0.1)	1.16 (0.1)	<0.001
Education				0.378
	Elementary<=	131 (20.8)	112 (17.8)	
	Complete HS	141 (22.4)	165 (26.2)	
	Post HS no university	174 (27.6)	149 (23.7)	
	Completed University	184 (29.2)	204 (33.3)	
Marital status				0.863
	Married	453 (71.9)	450 (71.4)	
	Single	97 (15.4)	99 (15.7)	
	Separated/Divorced/Widowed	80 (12.7)	81 (12.9)	
Occupation				<0.001
	Self-employed	169 (26.8)	73 (11.6)	
	Unskilled manual	263 (41.8)	351 (55.7)	
	Skilled manual	158 (25.1)	109 (17.3)	
	Professional/executive	40 (6.3)	97 (15.4)	
Wealth index				0.155
	Low	223 (35.4)	257 (40.8)	
	Middle	296 (47.0)	265 (42.1)	
	High	111 (17.6)	108 (17.1)	
Ever used oral contraceptives				0.065
	No	453 (72.0)	419 (66.8)	
	Yes	177 (28.0)	211 (33.2)	
Number of pregnancies				0.080
	0	90 (14.3)	81 (12.9)	
	1-3	138 (21.9)	118 (18.7)	
	4-6	288 (45.7)	305 (48.4)	
	≥7	114 (18.1)	126 (20.0)	
Menopausal status				0.022
	Premenopausal	449 (71.3)	475 (75.4)	
	Postmenopausal	181 (28.7)	155 (24.6)	
Ever breastfed more than one month				0.060
	No	154 (24.4)	129 (20.5)	
	Yes	476 (75.6)	501 (79.5)	
Smoke				0.178
	No	627 (99.7)	624 (99.0)	
	Yes	3 (0.3)	6 (1.0)	
Alcohol use				0.558
	No	499 (79.3)	508 (80.7)	
	Yes	131 (20.7)	122 (19.3)	
Leisure-time physical activity (meet the WHO recommendations)				<0.001
	Physical active	114 (18.1)	189 (30.0)	
	Physical inactive	516 (81.9)	441 (70.0)	
Leisure-time physical activity by MET h/w				<0.001
	<2.99	197 (31.3)	107 (17.0)	
	2.99-5.80	164 (26.0)	156 (24.8)	
	5.81-11.25	150 (23.8)	181 (28.7)	
	11.25<	119 (18.9)	186 (29.5)	

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

	Age-adjusted model ^a		Multivariable model ^{a b}	
	OR (95% CI)	P-value	^b OR (95% CI)	P-value
Leisure-time physical activity ^d (meet the WHO recommendations)	0.52 (0.39-0.68)	<0.001	0.58 (0.43-0.78)	<0.001
Leisure-time physical activity by MET h/w ^e		<0.001 ^c		<0.001 ^c
2.99-5.80	0.57 (0.41-0.79)	0.001	0.69 (0.47-0.99)	0.044
5.81-11.25	0.44 (0.32-0.62)	<0.001	0.50 (0.35-0.73)	<0.001
11.25<	0.35 (0.25-0.49)	<0.001	0.45 (0.31-0.65)	<0.001

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

^b The models were adjusted for age at first menstrual period, WHR, BMI, education, occupation, menopause status, oral contraceptive use, alcohol use, smoking, breastfeeding experience, Wealth index.

^c P-trend

^d Reference category- leisure-time physical inactive, did not meet the WHO recommendations for physical activity

^e Reference category- leisure-time physical activity of less than 2.99 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-		TNBC	
	Age-Adjusted model ^a	Multivariable Model ^{a b}	Age-Adjusted model ^a	Multivariable Model ^{a b}
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Leisure-time physical activity ^d (meet the WHO recommendations)	0.60 (0.35-1.02)	0.59 (0.33-1.06)	0.53 (0.33-0.86)	0.55 (0.33-0.91)
P-value	0.061	0.081	0.009	0.021
Leisure-time physical activity by MET h/w ^e				
2.99-5.80	0.62 (0.34-1.11)	0.65 (0.34-1.22)	0.50 (0.30-0.83)	0.59 (0.34-1.03)
5.81-11.25	0.55 (0.30-0.99)	0.60 (0.32-1.11)	0.45 (0.27-0.74)	0.53 (0.31-0.90)
11.25<	0.40 (0.21-0.74)	0.42 (0.21-0.83)	0.30 (0.17-0.52)	0.34 (0.19-0.63)
P-trend ^c	0.004	0.015	<0.001	0.001

^a Unconditional logistic regression models with complete study sample

^b The models were adjusted for age at first menstrual period, WHR, BMI, education, occupation, menopause status, oral contraceptive use, alcohol use, smoking, breastfeeding experience, Wealth index.

^c P-trend

^d Reference category-leisure-time physical inactivity, did not meet the WHO recommendations for physical activity

^e Reference category-leisure-time physical activity of less than 2.99 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