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Systematic Review

Role of physical activity and metabolic syndrome in determining the risk of postmenopausal breast cancer: a systematic review

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ABSTRACT

Physical activity (PA) and metabolic syndrome (MetS) have emerged as crucial factors in facilitating the incidence of postmenopausal (PM) breast cancer (BC). The association of PA, MetS and its components with PM BC was explored in this study. PRISMA guideline was followed and online databases were searched comprehensively to find relevant cohort and case-control studies until 18 February 2021 using keywords such as "physical activity", "metabolic syndrome" and "breast cancer". Eligible studies evaluating BC in postmenopausal women with a clear definition and measure of PA, MetS and its individual components were selected. A total of twenty-three articles related to PA and fifteen articles for MetS met the eligibility criteria and were assessed thoroughly. PA and MetS were significantly associated with PM BC. There was evidence of dose-response effect of PA and Mets on PM BC. Obesity, diabetes and dyslipidaemia were independently associated with PM BC and posed an increased risk on PM BC whereas the association of HPTN with PM BC was not prominent. Consistent and sustained long term PA throughout one's lifetime was observed to decrease PM BC risk whereas increasing number of MetS components increased the risk of PM BC. Routine screening for PM women with ≥2 MetS components and obese or overweight women with any of the MetS components may be beneficial in early BC detection. Lifestyle modifications with emphasis on long term PA would be beneficial to public health in preventing and improving MetS outcomes as well as a primary prevention of sporadic PM BC.

Keywords: Physical activity, Metabolic syndrome, Obesity, Hypertension, Diabetes, Dyslipidaemia, Postmenopausal breast cancer

INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed malignancy in females worldwide, surpassing lung cancer incidence in 2020. It represents 11.7% of all cancer cases, ranks fifth in cancer mortality and represents 1 in 4 cancers diagnosed among women globally.[1] As of now, the incidence of BC in Asian women is still lower compared to western countries. However, the rate of BC incidence is expected to increase in many less developed countries due to the increased life expectancy and westernisation of their lifestyle. The rate of premenopausal breast cancers is rising in higher-income countries, whereas the trend of postmenopausal (PM) BC is on the rise in developing, but lower-income countries.[2]

The pathogenesis of BC involves genetic, environmental and hormonal factors. Although BCs are typically associated with non-modifiable risk factors such as family history, age, early menarche and menstrual history, most BCs are sporadic.

Physical activity

PA is defined as bodily movement via skeletal movement which generates expenditure of energy above the resting metabolic rate. It is represented by modality, frequency, intensity, duration, and context of practice.[3] A study done in 2007 stated that, decreased hormone replacement therapy (HRT) usage and the substantially increased obesity rate may be attributable to physical inactivity emerging as the major modifiable risk factor for BC.[4] Besides, a systematic review study found exercise to decrease PM BC risk by approximately 15%-20%.[5] Several studies showed a dose-response relationship between PA and BC risk where increased frequency and duration of activity provides greater benefit.[4-6]

Metabolic syndrome (MetS)

MetS is characterised by a combination of biological abnormalities and clinical conditions such as altered glucose and metabolism leading to hyperglycaemia and hyperinsulinaemia, obesity, dyslipidaemia characterised by low high-density lipoprotein (HDL) cholesterol and high triglyceride level and hypertension (HPTN). Each component plays a unique role in influencing the evolution of BC. Although MetS often meets various definitions, it is often defined as having 3 or more components including: Fasting glucose ≥100 mg/dL or receiving drug therapy for hyperglycaemia, blood pressure(BP) ≥130/85 mm Hg or receiving drug therapy for HPTN, triglycerides ≥150 mg/dL or receiving drug therapy for hypertriglyceridemia, HDL-C < 40 mg/dL in men or < 50 mg/dL in women or receiving drug therapy for reduced HDL-C, waist circumference ≥102 cm (40 in) in men or ≥88 cm (35 in) in women; if Asian American, ≥90 cm (35 in) in men or ≥80 cm (32 in) in women.[7]

MetS is a known risk factor for cardiovascular diseases. However, recently, MetS has been linked with the pathogenesis and prognosis of various cancers. Age was also observed to impact the occurrence of MetS and BC, thus menopausal status could be the causal relationship between these conditions.[8]

According to the Million Women Study, the majority of cancers, 81% occurred in postmenopausal women and obesity was found to be the most attributable cause in approximately half of them.[9] Many epidemiological studies have proven obesity and diabetes to be independently associated with PM BC however, the association of dyslipidaemia and HPTN especially on PM BC are still controversial.

Objective

This systematic review has explored the association of physical activity, metabolic syndrome as well as its individual components with postmenopausal breast cancer respectively.

METHODS

This study has been approved by the Perdana University Institutional Review Board (PU-IRB). This study was conducted in accordance with the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) guidelines.[11] Online databases such as PubMed, Google scholar and Embase and Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (EBCOHost) were searched comprehensively to find relevant articles until 18 February 2020. Keywords such as “physical inactivity” or “physically inactive” or “obese” or “obesity” and “metabolic syndrome” or “metabolic disorders” and “breast cancer” or “breast neoplasm” and “postmenopausal women” or “menopause” were used to form the search strategy. Manual searches were also performed to look for more eligible articles in the reference lists of the retrieved and review articles. The study title along their abstracts were imported into EndNote to remove duplicates and to screen literature.

Eligibility criteria

Inclusion criteria: The studies were considered eligible if they met the following criteria: the study design was a cohort or case-control; PA measure was clearly defined (type of activity, duration, intensity); MetS was clearly defined; BC in PM women was evaluated; only studies published in English language were included; relative risk (RR) or odds ratio (OR) or Hazard ratio (HR) with 95% confidence intervals (CIs) on the association between PA, MetS and PM BC respectively was reported.

Exclusion criteria were: non-human experiments; no clear definition of MetS; no clear definition and measure of PA; did not distinguish the menopausal status; prior diagnosis of other cancers except non-melanoma skin cancer; no recurring BC patients; if physical inactivity was measured by sedentary behaviour (lack of exercise).

Quality assessment

The quality of studies was assessed according to the Newcastle Ottawa quality assessment scale which is a validated scale for nonrandomized studies.[11] Good quality was defined as a score ≥7, fair was defined as a score of 5–6 and poor quality being score of <5.

Literature screening and data extraction

The titles and abstracts were screened based on the eligibility criteria. After removing duplicates and unrelated articles, 24 articles related to PA and 15 articles for MetS were evaluated. Then, relevant data was comprehensively extracted and tabulated in a word document which included study characteristics and summary of results of all studies assessed. The article screening process is depicted in Figure 1.

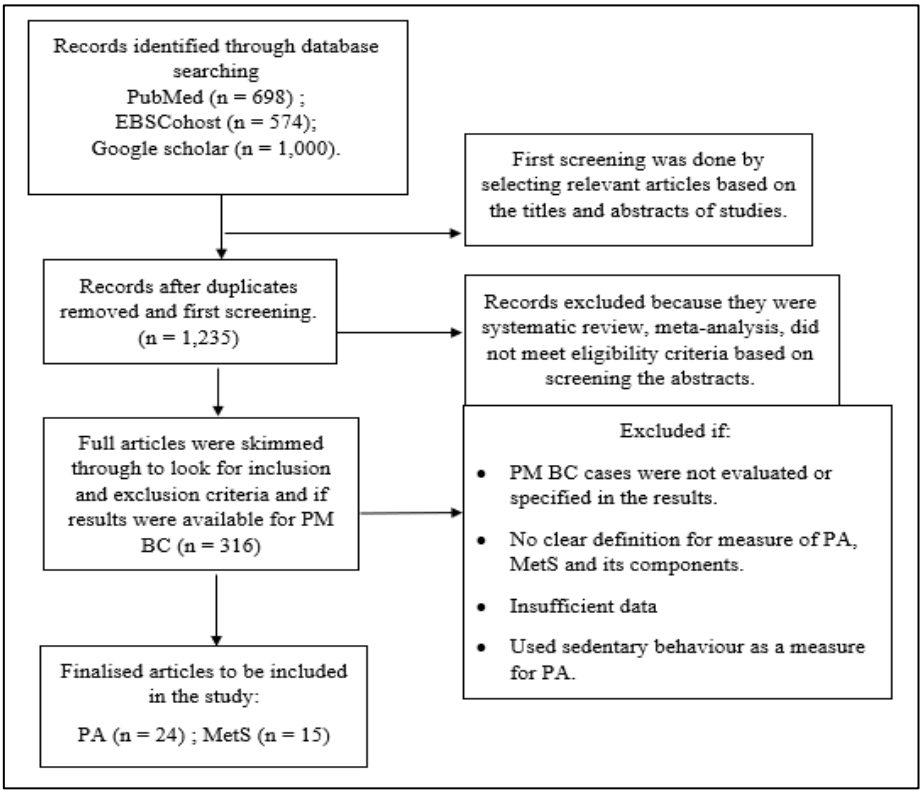

Figure 1: Screening process for studies to be included in this systematic review.

RESULTS

The characteristics of the cohort studies included are summarised in Table 1. Out of 17 cohort studies included, 14 studies had a follow-up of more than 5 years, with the longest follow-up being 27 years 26 and the shortest being 4.7 years.[14] The quality of all studies included assessed based on the NOS scale ranged from a minimum of 6 stars to 9 stars and for cohort studies, 15 out of 17 studies obtained 7 or more stars, indicating good quality. The characteristics of 18 case-control and 3 case-cohort studies are summarised in Table 2. Of the 20 studies, 17 were of good quality, with ≥7 stars. Most included studies considered women to have attained menopause if period had stopped ≥12 months prior to selection or diagnosis or if the cessation of menses is caused by bilateral oophorectomy or hysterectomy with removal of <2 ovaries or of older age which varied across studies. The crucial factors included and adjusted for in most studies are, age at menarche, parity, family history of BC, BMI, dietary pattern, history of breastfeeding history, use of HRT, smoking history, alcohol consumption, use of birth control, age at first pregnancy.

For studies determining the association between PA and PM BC, the measures of PA, results, summary and adjusted variables are outlined in Table 3. Data on PA was self-reported and collected via questionnaires, telephone or face-to-face interviews. Different parameters were investigated in each study such as the domain of PA and the dose of PA (frequency, duration and intensity). A total of eleven studies investigated recreational PA, ten studies investigated total PA done throughout participants' life until selection/diagnosis and only 7 studies investigated occupational PA(OPA) alone in PM women, out of which 5 studies yielded significant association between OPA and PM BC.[13,18,23,29,33] Of the 23 studies that presented results for the association between PA and PM BC, statistically significant PM BC risk reduction was evident in 22 studies and one study produced non-statistically significant risk reduction while another did not observe strong association as only baseline PA and PM BC was significantly associated.[12,28] Certain studies exhibited dose-response relationship where with increasing frequency and intensity of PA, the risk of PM BC incidence decreased.[14,15,23,31,36,37,38]

Some included studies found that the association between PA and PM BC is affected by HRT while some did not find any effect modification by HRT.[14,16-20,28,30,32] However, some studies have shown promising results as PA reduces risk among HRT users who are particularly a high-risk group for developing PM BC.[14] Besides, several included studies observed a more pronounced impact of exercise among lean women or from lower tertiles of BMI whereas some studies found greatest risk reduction among women in the higher BMI category.[14,16,23,30,34,38,39] Some studies did not find any effect modification by BMI on PA.[18,22,31,37] Table 4 describes the measures, results, summary and adjusted variables of all studies investigating MetS and PM BC.

Table 1: Characteristics of cohort studies included.

Author	Country	Baseline year	Cohort Size	Postmenopausal Cases	Age (years) at recruitment	Mean follow-up years	Outcome measured	Quality Score (good, fair, poor)
Physical activity and postmenopausal breast cancer								
Rosenberg et al[12]	USA	1995	Total: 44,708 PM: 12,639	661	≥ 30	16	Incident invasive BC	Good
Ekenga et al[13]	USA and Puerto Rico	2004-2009	Total: 47,649 PM: 21,820	1,363	30-74	4.7 ± 1.6	Incident BC	Good
McTiernan et al[14]	USA	1993-1998	PM only: 74,171	1,780	50-79	4.7	Incident invasive and in situ BC	Good
Bardia et al[15]	USA	1986	PM only: 41,836	2,548	55-69	18	Incident BC	Good
Chang et al[16]	USA	1993-2001	PM only: 38,660	764	55-74	9.3	Incident BC	Good
Patel et al[17]	USA	1992	PM only: 72,608	1,520	50-74	5	Incident BC	Good
George et al[18]	USA	1995-1996	PM only: 97,039	Invasive: 2,866 In situ: 570	50-71	7	Incident invasive and in situ BC	Good
Eliassen et al[19]	USA	1986	PM only: 95,396	Invasive: 4,782	30-55	20	Incident invasive BC	Fair
Howard et al[20]	USA	1994-1998	Total: 45,631 PM only: Not stated	Total: 864 PM only: Not stated	Mean age: 47.2	8.9	Incident invasive BC	Fair
Suzuki et al[21]	Japan	1988-1990	Total: 30,157 PM only: 23,004	Total: 207 Pm only: Not stated	40-69	12.4	Incident BC	Good
Pronk et al[22]	China	1996-2000	Total: 73 049 Not stated	Total: 717 PM only: Not stated	40-70	9	Incident BC	Good
	Metabolic syndrome and postmenopausal breast cancer							
Kabat et al[8]	USA	1993-1998	PM only: 4,888	165	50-79	Median: 8	In situ and invasive BC	Good
Osaki et al[23]	Japan	1992-2000	Total: 15,386	42	≥ 55	Mean: 9.1	Incident BC	Good
Bosco et al[24]	USA	1995 -2007	Total: 59,000	362	21-69	Mean: 10.5	Incident BC	Good
Kabat et al[25]	USA	1993-1998	PM only: 21,000	1,176	50-79	15	Invasive BC	Good
Lindgren et al[26]	Finland	1972-1988	9,112	251	≥ 51	27	Incident BC	Good
Reeves et al[27]	USA	1986-1988	8,956	551	≥65	14.4	Incident BC	Good

Table 2: Characteristics of Case-control studies included.

Author	Country Population	Year of Activity assessment	Number of cases	Number of controls	Study base Case/control	Age Group	Outcome measured	Quality Score (good, fair, poor)
Physical activity and postmenopausal breast cancer								
Catsburg et al[28] (Case-cohort)	Canada	1992-1998	PM only: 541 Follow up years (mean)= 6.7	Subcohort: 2,210 Follow up years (mean)= 12.2	Population/ population	Mean age: Cases: 63.7 Subcohort: 67.9	Incident, incident BC	Good
Friedenreich et al[29]	Canada	1995-1997	Total : 1,237 PM only: 771	Total: 1,241 Post: 762	Population/ population	≤ 80 Mean= 56	Incident in situ or invasive BC	Good
Shoff et al[30]	USA	1988-1991	PM only : 4,614	Post : 5,817	Population/ population	20-74	Incident invasive BC	Good
John et al[31]	USA	1995-1998	PM only : 847	Post: 1,065	Population/ population	35-79	Primary Invasive BC	Good
Carpenter et al[32]	USA	1980-1990	PM only : 1,883	Post: 1,628	Population/ population	55-72	Incident BC	Good
Dorn et al[33]	USA	1986-1991	PM only : 439	Post: 494	Hospital/ population	40-85	Incident Primary BC	Good
Hirose et al[34]	Japan	1988-2000	Total: 2,376 PM only : 1,024	Total: 18,977 Post: 6,989	Hospital/ Hospital	≥ 30	Incident BC	Fair
Awatef et al[35]	Tunisia	2006-2009	Total: 400 PM only : 309	Total: 400 Post: 266	Hospital/ Hospital	25-75	BC	Good
Gilliland et al[36]	Mexico	1992-1994	PM Hispanic: 171 PM Non-Hispanic: 228	PM Hispanic: 210 PM Non-Hispanic: 224	Population/ population	35-74	New diagnosis of invasive or in situ breast carcinoma	Good
Si et al[37]	Australia	2009-2011	Total: 1,205 PM only : 336	Total: 1,789 Post: 421	Population/ population	18-80	Primary Invasive BC	Good
Yang et al[38]	USA	1995-1997	Total: 501 PM only : 278	Total: 594 Post: 302	Population/ population	25-74	Primary Incident BC	Good
Dirx et al[39]	Netherlands	1986	PM only : 1,208	SUBCOHORT : 1,716	- Follow up= 7.3 years	55-69	Incident BC	Good
Metabolic syndrome and postmenopausal breast cancer								
Rosato et al[40]	Italy and Switzerland	1983-2007	Post: 3,869	Post: 4,082	Hospital/ Hospital	33-86	Incident BC	Good
Capasso et al[41]	Italy	2008-2009	Post: 210	Post: 289	Not stated	35–75	Operated for breast cancer	Poor

Continued.

Author	Country Population	Year of Activity assessment	Number of cases	Number of controls	Study base Case/control	Age Group	Outcome measured	Quality Score (good, fair, poor)
Wu et al[42]	USA (Asian)	1995-2001 2003-2006	Total: 2,167	Total: 2,035	Population/ population	25-74	Incident BC including in situ BC	Good
Wang et al[43]	China	2011-2013	Post: 43	Post: 86	Population/ population	Mean age of Cases : 53.33 Controls: 53.67	PM BC (self-reported)	Fair
Noh et al[44]	Korea	1995-2011	Total: 270	Total: 540	Hospital/ Hospital	Mean age of Cases : 59.43 Controls: 59.34	Incident BC	Good
Agnoli et al[45]	Italy	1993-1998	Total: 593	Subcohort: 555	Population/ population	Not stated	Incident BC (in situ and invasive)	Good
Agnoli et al[46]	Italy	1987-1992	PM only : 176 (After a follow up of 13.5 years)	PM: 702	Population/ population	35-69	Incident BC (in situ and invasive)	Good
Ronco et al[47]	Uruguay	2004-2009	PM only : 367	PM: 545	Hospital/ Hospital	23-69	Incident BC	Good
Carpenter et al[32]	USA	1980-1990	Post: 1,883	Post: 1,628	Population/ population	55-72	Incident BC	Good

Table 3: Measure, definition, results, summary and adjusted variables of studies investigating relationship PA and PM BC.

Author	Measure and Life period of Exposure; Domain of PA Definition	Contrast	Risk Estimate (95% CI) Test for Trend	Summary	Adjusted variables
Rosenberg et al[12]	hours/week ; Lifetime; Recreational PA (vigorous activity) Average number of hours per week spent in vigorous physical activity e.g. basketball, swimming, running, aerobics which was measured at 4 time points: Baseline, 30 years, 21 years and high school Hours per week of walking for exercise was also reported at baseline.	≥7 hrs/wk vs <1 hr/wk	IRR= 0.94 (0.66–1.36) P for Trend = 0.55	No strong association between PM BC and vigorous activity. Vigorous exercise at baseline was inversely associated with overall breast cancer incidence. High levels of recent vigorous exercise or brisk walking may be associated with a reduction in incidence of BC in African-American women.	Age, time period (questionnaire cycle), BMI, parity, years of education, dietary pattern.
McTiernan et al[14]	MET-hours/week ; Lifetime ; Recreational PA	>40 MET hrs/wk versus none. Total PA by BMI tertiles	RR = 0.78 (0.62-1.00) ; P for Trend = 0.03 ≤24.13 BMI tertile	Increased PA is associated with reduced risk for BC in PM women, longer duration provides most benefit, and that such activity need not be strenuous. The effect	Age, BMI, use of hormone therapy, race, geographic region, income, education, ever breastfed,

Continued.

Author	Measure and Life period of Exposure; Domain of PA Definition	Contrast	Risk Estimate (95% CI) Test for Trend	Summary	Adjusted variables
	Strenuous or very hard exercises (long enough to work up a sweat and make their heart beat fast) at least 3 times per week at ages 18, 35, 50 years and currently.	>40 MET hrs/wk versus none.	0.63 (0.43-0.93) 35 P for Trend = 0.03	of exercise was most pronounced in women in the lowest tertile of BMI (<24.1), but also was observed for women in the middle tertile of BMI (24.1-28.4). Women engaged in strenuous PA at least 3 times per week at age 35 years had a statistically significant decreased risk of BC of 14%.	hysterectomy status, first-degree relative with BC, smoking status, parity, age at first birth, number of mammograms in 5 years before study enrolment, and use of alcohol, age at menarche and age at menopause.
Ekenga et al[13]	Total work years and proportion in active jobs; Lifetime ; Occupational PA (OPA) PA at each job was self-reported and categorized as mostly sitting, sitting and standing equally, mostly standing, and active. Active defined as continuous walking or heavy manual labour	Proportion of work years in active jobs >75 % vs Never Total work years in active jobs >10 years vs never	HR= 0.67 (0.45–0.98) P for Trend = 0.73 HR= 0.85 (0.68, 1.05) P for Trend = 0.34	OPA was associated with a reduced risk of BC. Women who reported a history of at least one active job had a borderline reduced risk of PM BC (HR 0.86; 95 % CI 0.74, 1.00) compared with women who never reported an active job. No significant trends were observed for the duration of employment or the proportion of work years in active jobs. Women who reported three-quarters or more of work years in active jobs had a decreased risk of PM BC.	Race/ethnicity, education level, income, parity, age at first term pregnancy, menopause status, age at menopause, BMI, work at night, and recreational PA in quartiles, hormonal birth control use, hormone therapy use, marital status, Alcohol consumption, smoking status, and chronic disease history.
Bardia et al[15]	MET-hours/week ; Lifetime; Recreational PA High PA: participation in vigorous activity 2 or more times per week or moderate activity more than 4 times per week. Medium PA: participation in vigorous activity once per week or moderate activity 1 to 4 times per week. Low PA composed the rest of the cohort.	High PA vs Low PA	RR= 0.86 (0.78-0.96) P for trend = 0.01	Compared with low PA, high PA levels were inversely associated with risk of BC (14% decreased risk). Higher recreational PA might reduce the risk of PM BC overall. Risk reduction varies by ER/PR status of the tumour, being most marked for ER⩽/PR− tumours, (33% lower risk) which have been associated with a clinically more aggressive tumour phenotype generally.	Age, educational level, family history of breast cancer, age at menarche, number of live births, age at first live birth, oral contraceptive use, age at menopause, use of hormone therapy, alcohol use, and smoking
Chang et al[16]	Hours/week ; lifetime Recreational PA ; Vigorous activities, such as swimming, brisk walking.	≥ 4 hours vs None	RR= 0.78 (0.61-0.99) P for trend = 0.153	Women with >4 hrs/wk of vigorous recreational PA had a significantly reduced risk of BC compared with those who reported no recreational PA.	Age, study centre, race, height (continuous), family history of breast cancer, history of benign breast disease, age at menarche, age at first birth, parity,

Continued.

Author	Measure and Life period of Exposure; Domain of PA Definition	Contrast	Risk Estimate (95% CI) Test for Trend	Summary	Adjusted variables
					age at menopause, menopausal hormone therapy, and education.
Patel et al[17]	MET-hours/week ; past year Recreational PA Walking, jogging/running, lap swimming, tennis or racquetball, bicycling or stationary biking, aerobics/calisthenics, and dancing	> 42 MET hrs/wk vs none	RR= 0.71 (0.49–1.02) P for trend = 0.03	Women who were most physically active (>42.0 MET-h/week) at baseline had 29% lower incidence rates than active women with the least activity.	Age, race, BMI, weight change from age 18 to 1992, family history of breast cancer, personal history of breast cysts, duration of OC use, HRT use, parity, age at menarche, age at menopause, smoking, alcohol intake, caloric intake, education, and mammography histor
George et al[18]	Routine; Past 10 years; Occupational and Household PA (Non-recreational PA) 5 options: sitting all day; sitting and a little walking; standing or walking, but no lifting; lifting or carrying light loads, or climbing stairs often; and heavy lifting or carrying. Transportation activity Total number of years walked or biked to work for most days of the week.	Heavy lifting or carrying versus sitting all day ≥ 10 years vs <1year	Invasive BC : RR= 0.62 (0.42-0.91) P for trend= 0.024 In situ BC : RR= 1.21 (0.56-2.61) P for trend= 0.644 Invasive BC : RR= 0.86 (0.67-1.11) P for trend = 0.081 In situ BC : RR= 0.92 (0.53-1.60) P for trend= 0.57	Independent of recreational moderate–vigorous PA level, increase in routine activity during the day at work or home and, possibly, active commuting may be protective against invasive but not in situ BC. Women who reported engaging in heavy lifting or carrying as routine activity during the day at work or home had a 38% risk reduction for invasive BC compared with those who reported sitting all day.	Age, energy, recreational moderate–vigorous PA, parity or age at first live birth, menopausal hormone therapy use, number of breast biopsies, smoking, alcohol intake in grams per day, race, education.
Eliassen et al[19]	MET-hours/week ; Follow-up period Total PA Walking or hiking outdoors, jogging, running, bicycling, lap swimming, tennis, calisthenics/aerobics/aerobic dance/ rowing machine, and squash or racquet ball. In addition,	≥27 MET hrs/wk vs <3 MET hrs/wk	HR= 0.88 (0.79-0.98) P for trend= 0.03 HR= 0.85 (0.69-1.05) P for trend= 0.09	No association was observed between baseline total activity and BC risk. Significantly, lower BC risks were associated with higher activity using both the simple update and cumulative average assessments. Higher levels of both recent and long-term total and moderate/vigorous	Age at menarche, BMI at age 18, height, parity and age at first birth, alcohol intake, postmenopausal hormone use, age at menopause, missing age at menopause, family history of breast cancer, and

Continued.

Author	Measure and Life period of Exposure; Domain of PA Definition	Contrast	Risk Estimate (95% CI) Test for Trend	Summary	Adjusted variables
	participants reported their usual walking pace and the number of flights of stairs climbed daily. Moderate/vigorous PA brisk or very brisk walking, jogging, or running.			PA were associated with lower BC risk among PM women.	history of benign breast disease.
Howard et al[20]	MET-hours/week ; previous year to baseline. Recreational PA Hours spent per week during the previous year engaging in each of the following activities: exercising strenuously (e.g., aerobics, jogging, swimming)	>10 hrs/wk vs <1 hr/week	Ever used MHT: HR= 1.12 (0.41–3.03) P for trend = 0.929 Never used MHT: HR= 0.57 (0.23–1.42) P for trend= 0.07	Women who never used menopausal hormone therapy (MHT) had reduced risks of BC associated with PA whereas no relation was observed among ever users of MHT.	Entry age, BMI, age at menarche, parity, age at first birth, family history of BC, personal history of BC, Oral contraceptive use, race, smoking, and alcohol consumption, age at menopause.
Suzuki et al[21]	Total Lifetime PA Recreational PA and commuting to work Amount of time spent walking, amount of time spent exercising, and PA at the work place.	Most physically active group compared with the rest of the women by	HR= 0.53 (0.29 – 0.96) P for trend = 0.528	Walking for 1 hour per day and undertaking additional weekly exercise both seemed to be protective against breast cancer, regardless of menopausal status or BMI.	Age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of BC in a first-degree relative, menopausal status, and menopausal age for PM women.
Pronk et al[22]	MET- week/year; Lifetime Non-occupational PA Exercise during adolescence (13–19 years), In adulthood, up to three exercise activities were reported for the 5-year period before the interview, household activities (h per day) and active transportation kJ/min ; kJ/hour Occupational PA Defined according to a Job exposure matrix, which assigned occupation codes into categories of low,	>17.6 MET /wk/yr vs None	HR= 0.73 (0.57, 0.92) P for trend = 0.05	Adult exercise at or above the recommended level (8 MET hr/wk/yr) was associated with lower risk of breast cancer in PM women. Compared with women who were both occupationally inactive and had inadequate exercise, BC risk was 30% lower among women who had either active jobs or Adequate exercise, but having both an active job and adequate exercise did not confer further reduction in risk. No statistically significant interaction was observed.	Age, education, family history of breast cancer, age at first birth, and number of pregnancies.

Continued.

Author	Measure and Life period of Exposure; Domain of PA Definition	Contrast	Risk Estimate (95% CI) Test for Trend	Summary	Adjusted variables
	medium, and high sitting time and low, medium, and high energy expenditure.				
Catsburg et al[28]	MET hours/week ; Lifetime Recreational PA amount of time per week spent walking, hiking, jogging, running, bicycling, in calisthenics or aerobics, playing tennis or squash, lap swimming, and in other aerobic recreation.	>30.9 MET hrs/wk vs <3 MET hrs/wk	HR= 0.96 (0.69–1.32) P for trend= 0.42	Exercising 30.9 MET hours per week was associated with a non-significant 4 % decreased risk of PM BC.	Age at menarche, use of oral contraceptives, use of hormone therapy, number of live births, age at first live birth, family history of BC, menopausal status at baseline, alcohol intake in grams per day, stratified by BMI.
Friedenreich et al[28]	MET-hours/week/year reported ; lifetime Total PA occupational (including means of transportation to and from work if by bicycle or walk) household, and recreational activity separately	≥ 160.9 MET hrs/wk/yr vs 0– <104.8 hrs/wk/yr	OR= O.70 (0.52-0.94) P for trend= unknown	BC risks were particularly reduced for PM women in the highest category of activity during their childhood and adolescence (0–17 years). Sustained, moderate-intensity total PA confers an approximate 30% reduction in PM BC risk and that occupational and household activities are particularly relevant to achieve this decreased risk.	Age, waist-hip ratio, educational level, ever-use of hormone replacement therapy, ever-diagnosis with benign breast disease, first-degree family history of breast cancer, ever-alcohol consumption, and current smoking.
Shoff et al[30]	Frequency of activity (times/year); Total early life PA Sum of Frequency of participation in strenuous PA/ team sports participation (MET3 6) such as basketball, soccer, and swimming as well as labour at 14-18 and 18-22 Weight change; Four levels of weight change (difference between recent weight and weight at age 18) were defined: (a) weight loss (weight change < 0); and (b) tertiles of weight gain (weight change ≥ 0) based on the distribution of controls.	≥361 times/year vs 0 times/year > 15 kg vs < 0 kg	OR= 0.55 (0.39–0.78) P for trend = 0.002 OR= 1.40 (1.26–1.56) P for trend = < 0.001	Reduced risk of PM BC associated with frequent, early-life PA may be greatest in women who, over the adult years, either lost weight or gained only modest amounts. Reductions in PM BC risk associated with strenuous PA were greatest for women in the fourth quartile of body mass index at age 18	BMI at age 18, age at first full-term pregnancy, parity, age at menarche, family history of breast cancer, education, and age at menopause.
John et al[31]	MET ; Lifetime Total PA (regular PA)	≥ 21.7 hrs/wk vs <9.6 hrs/wk	OR= 0.81 (0.64–1.02)	Summing activities from all sources over an individual's lifetime, reduced BC risk in both pre- and PM women with the highest	Age, race/ethnicity, country of birth, education, family history of breast

Continued.

Author	Measure and Life period of Exposure; Domain of PA Definition	Contrast	Risk Estimate (95% CI) Test for Trend	Summary	Adjusted variables
	Moderate and vigorous PA, including recreational activity, walking, bicycling, household and outdoor chores, and occupation.		P for trend= unknown	versus lowest tertile of average lifetime activity was found.	cancer, age at menarche, parity, breastfeeding, age at menopause, and other components of total activity.
Carpenter et al[32]	MET-hours/week ; Lifetime; Total PA; Lifetime histories on exercise activity where duration of activity was at least 2 hr/week for 1 year. Type of activity, ages started and stopped, and number of hr/week spent exercising was recorded. For each year of life, we computed total hr/week spent on all exercise activities.	≥ 17.6 average MET-hrs/wk vs 0 MET-hrs/wk	OR= 0.66 (0.48–0.90) P for trend= 0.07	PM BC risk was reduced among women who maintained, on average, 17.6 metabolic equivalent of energy expenditure (MET)-hr of activity/week from menarche onward.	Age at first full-term pregnancy, age at menarche and menopause, family history of breast cancer, interviewer and body-mass index at reference date.
Dorn et al[33]	Hours/year ; Lifetime Adult Lifetime Total PA (Sum of total in strenuous physical activity 2, 10, and 20 years ago) Exercise or sports strenuous enough to sweat and miles walked per week for time periods 2, 10, and 20 yr before the interview and at age 16. Lifetime occupational history was obtained. Jobs were coded according to the National Cancer Institute's PA job matrix.	>546 hrs/yr vs 0 hr/yr Occupational PA	OR= 0.78 (0.47–1.29) P for trend= 0.19	Among women categorized as active at all four periods, a strong, significant protective effect was observed in PM women. A strong protective effect was observed for activity performed 20 years prior, in PM women, although CIs overlapped for different time periods. There was some indication of increased risk for the upper category of occupational PA for PM women, perhaps related to other industrial occupational exposure	Adjusted for age, education, age of menarche, relative with breast cancer, benign breast disease, BMI and age first pregnancy.
Hirose et al[34]	Number of times exercise was done ; Lifetime Recreational PA	≥2 times/week vs None	OR= 0.85 (0.69–1.04) P for trend = 0.131	PA, especially exercise for health twice a week or more, reduces the risk of BC among PM women.	Age, visit year, age at menarche, family history, parity, age at first full-term pregnancy, drinking, intake of fruit, dietary restriction, history of stomach cancer screening, body mass index and occupation.

Continued.

Author	Measure and Life period of Exposure; Domain of PA Definition	Contrast	Risk Estimate (95% CI) Test for Trend	Summary	Adjusted variables
Awatef et al[35]	MET/hours/week/year ; Lifetime Total PA Work activities (time spent sitting, standing, and walking); sports and conditioning activities (school sports, teams); individual activities (walking, cycling); activities performed at home (major cleaning, light daily housework, quiet inactivity) (type, duration, frequency, and intensity)	>150 MET/hrs/wk/yr vs <100 MET/hrs/wk/yr	OR= 0.32 (0.22–0.71) P for trend= 0.002	A significant 56% reduction BC risk was found in PM women adjusted on five-year age-groups. The risk was further reduced to 68% after multivariate adjustment. BMI and parity were mainly responsible for that reduction.	BMI, breast-feeding, parity.
Gilliland et al[36]	MET/hours/week ; Lifetime Total PA Activity type and weekly duration of usual non-occupational PA (walking/hiking, running/ jogging, exercise class, biking, dancing, lap swimming, tennis, squash/racquetball, calisthenics/rowing, bowling, golf, softball/baseball, basketball, volleyball, housework, and heavy outside work)Vigorous PA: (≥5 METs).	≥80 MET/hrs/wk vs 0-<25 MET/hrs/wk	Hispanic women : OR= 0.38 (0.18–0.77) P for trend= 0.002 Non-Hispanic women: OR= 0.45 (0.24–0.85) P for trend= 0.0019	Both pre- and postmenopausal Hispanic women showed decreasing risk with increasing level of activity. PA was protective only among PM non-Hispanic White women	Age within strata, age at first full-term birth, months of lactation, parity, years of oral contraceptive use, and years of hormone replacement therapy use.
Si et al[37]	MET/hours/week/year ; Lifetime Total PA Recreational, household, occupational and transport physical activities. Occupational PA	≥131.3 MET/hrs/wk/yr vs 0–68.5 MET/hrs/wk/yr ≥ 52.8 MET/hours/week VS <0.1 MET/hours/week	OR= 1.23 (0.97-1.58) P for trend= 0.03 OR= 1.18 (0.90, 1.56) P for trend= 0.42	Recreational PA and PM BC risk was significantly associated. The effects total Lifetime PA were stronger among PM women with the lowest BC risk. PA was associated with a reduced risk of BC among PM women, but not in a linear fashion. Increasing moderate-intensity recreational PA up to 16 METs hour/week seemed to be associated with lower risk of BC. OPA was not significantly associated with PM BC.	Age, menopausal status, family history of breast cancer, education levels, type of HRT, age at menarche and age at first birth

Continued.

Author	Measure and Life period of Exposure; Domain of PA Definition	Contrast	Risk Estimate (95% CI) Test for Trend	Summary	Adjusted variables
Yang et al[38]	Average MET hours/week; Lifetime Recreational PA Recreational PA in which they had participated regularly (at least 1 hour per week or 52 hours per year) from age 10 years to the reference age (1 year before diagnosis for cases and 1 year before interview for control participants). Participation in physical education classes during school years was included.	> 12 average MET hrs/wk vs 0-3 average MET hrs/wk	OR= 0.55 (0.33–0.92) P for trend = 0.003	A significant trend of decreasing risk with increasing level of recreational PA was evident. The pattern of risk reduction in premenopausal and postmenopausal women remained unchanged after further adjustment for BMI.	Age, three ethnic groups (Chinese, Japanese, and Filipino), education, Migration, parity, menopausal status, years with active jobs and job activity category, soy intake during adolescence and adult life.
Dirx et al[39]	MET (min/day); Lifetime Recreational PA ; Total recreational PA : Number of minutes spent per day biking/walking, shopping, and walking the dog and the number of hours spent per week on gardening/doing odd jobs, cycling/walking, and sport/gymnastics Energy expenditure (kJ/min); Lifetime Occupational PA Assessment of PA at work was based on job title and the longest job held. The total energy expenditure was based on a rating system.	Recreational PA: >90 mins/day vs <30 mins/day Occupational PA for longest held job: >12 kJ/min vs < 8 kJ/min	RR= 0.76 (0.58–0.99) P for trend = 0.003 RR= 0.83 (0.51–1.34) P for trend = 0.69	This study shows that PA protects against BC in PM women. Baseline recreational PA showed an inverse association with breast carcinoma risk, especially daily walking and biking >1 hour a day, which demonstrated a protective effect (RR=0.81). No relation was found between OPA and BC risk.	Age, age at menarche, age at menopause, benign breast disease, parity, age at first birth, maternal breast carcinoma, breast carcinoma in sister(s), education, height, and baseline alcohol and energy intake

Table 4: Measure, definition, results, summary and adjusted variable of Studies investigating relationship MetS and PM BC.

Author	Exposure measurement	Contrast	Risk Estimate (95% CI) Test for Trend	Summary	Adjusted variables
Rosato et al[40]	BMI was calculated (kg/m^2). Waist circumference: 2 cm above the umbilicus. Diabetes, drug-treated HPTN, drug-treated hyperlipidaemia, and clinical obesity was self-reported and included age at first diagnosis. Diseases whose onset was <1 year before hospital admission, were not considered.	≥ 3 No of MetS components vs None	OR= 1.75 (1.37–2.22) *P* for trend = <0.0001	The risk of PM BC was significantly increased for women with MetS, for three or more MetS components, P for trend for increasing number of components < 0.0001) and the risk was higher at older age. This study supports a direct association between MetS and PM BC risk.	Age, study center, study period, education, alcohol consumption, age at menarche, age at first birth, age at menopause, hormone replacement therapy use, and family history of breast cancer.
Capasso et al[41]	Anthropometric features were measured, including weight in kilograms, height in meters, waist and hip circumference. Arterial BP was taken and venous blood was collected. BMI (kg/m²) was calculated from weight and height values according to WHO. Waist and hip circumference obtained by measuring the smallest circumference of both to discriminate between android and gynoid fat distribution	High grade MetS (≥ 3 No of MetS components) vs Low Grade MetS (<3 MetS components)	OR= 1.69 (0.94-3.05) *P* for trend= Unknown	Higher prevalence of MetS (30%) in PM BC patients compared to healthy women (19%). None of the individual MetS features was strong enough to be considered responsible for breast carcinogenesis alone. This study supports the hypothesis that MS may be an indicator of BC risk in PM women.	Not stated
Wu et al[42]	Waist circumference was measured at the narrowest torso circumference and hip circumference was measured at the widest hip circumference. Relative body weight was evaluated by BMI, calculated as the weight in kilograms divided by the square of height in meters (kg/m2). BMI was categorised according to WHO. Subjects were asked about history of specific conditions, including HBP, diabetes and high cholesterol that were diagnosed by a physician at least 1 year before diagnosis (for cases) and interview (for controls)	3 MetS conditions vs None BMI > 24.9 and diabetes	OR= 1.87 (1.11-3.15) *P* for trend= 0.001 OR= 0.89 (0.56-1.40) *P* for trend= 0.097	History of high cholesterol and long history (>10 years) of diabetes were significantly associated with risk in PM Asian American women; risks increased with increasing duration of these conditions.	Asian ethnicity, age, education, income, years of residence in the US among non-US born, interviewer, family history of breast cancer, benign breast diseases, parity, age at menarche, education and BMI, age at menopause and type of menopause.
Wang et al[43]	Anthropometric characteristics, including weight, height, BMI and BP, were measured. Blood samples were drawn after the participants had fasted overnight. HDL cholesterol, triglyceride, and glucose levels were measured	4 MetS factors vs None	OR= 12.211 (1.562-95.446) *P* for trend= 0.01	MetS was strongly associated with BC risk. Patients with MetS were more than three times more likely to have BC. There was no significant association between	Education, breastfeeding, family history of BC, age at menarche, age at menopause, number of

Continued.

Author	Exposure measurement	Contrast	Risk Estimate (95% CI) Test for Trend	Summary	Adjusted variables
				PM BC and HPTN as well as diabetes. Dyslipidaemia and overweight (BMI≥ 25 kg/m^2) showed most significant interaction on BC. With BMI≥ 25 kg/m^2, the interaction of dyslipidaemia and other metabolic factors on PM BC was higher.	full-term pregnancies, and age at first birth.
Noh et al[44]	Blood samples were drawn after overnight fasting (>12 h). HDL-C, triglyceride, glucose levels and Haemoglobin A1c was measured. BP was measured using an automatic sphygmomanometer, with the participants in a sitting position. If the automatically measured BP was beyond normal range, a trained nurse measured BP again manually using a mercury sphygmomanometer used for analysis. Body weight (kg) and height (cm) were measured to the nearest 0.1 kg and 0.1 cm, respectively, in light clothing and no shoes. BMI was calculated as weight divided by height squared (kg/m^2).	3–5 MetS factors vs 0 factor (Includes obesity BMI ≥ 25 as an essential element)	OR= 2.36 (1.10–5.10) *P* for trend= Not stated	Only obesity was associated with an increased risk of PM BC among individual metabolic factors. Women with aggregation of three or more metabolic factors showed greater risk for PM BC risk compared with women without any factor. Although obesity was the only metabolic factor associated with PM BC, the presence of other metabolic factors may further increase the risk of PM BC when combined with obesity.	Number of live births, family history of BC, age at menarche, smoking, alcohol drinking, PA and use of HRT
Agnoli et al[45] (Case-cohort)	At baseline, weight, height, and BP were measured and a 30 ml fasting blood sample was taken, all according to standardized procedures. Triglycerides, HDL cholesterol and glucose were measured in plasma samples For all analyses, laboratory staff were blind to the case-control status ofsample	Presence of MetS (≥ 3 components) Vs absence of MetS (<3 components) Number of MetS components ≥3 vs 0 MetS component	HR= 1.80 (1.22–2.65) *P* for trend= Not stated HR= 3.12 (1.43–6.79) *P* for trend= 0.001	MetS was significantly associated with PM BC. Of metabolic syndrome components, only high blood glucose was significantly associated with increased PM BC risk.	number of full-term pregnancies, age at menarche, smoking status, education, physical activity, and alcohol intake; stratified by age (5-year classes) and centre

Continued.

Author	Exposure measurement	Contrast	Risk Estimate (95% CI) Test for Trend	Summary	Adjusted variables
Agnoli et al[46]	Anthropometric measurements were made with women in light clothes and without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m2); Waist-to-hip ratio (WHR) was calculated dividing waist circumference (measured at the narrowest point between the iliac crest and the lower rib, as observed from the front) by hip circumference (measured at the pubic symphysis). BP was measured three times with the subject in the sitting position, using a standard mercury sphygmomanometer. We considered the mean of the second and third measurements. The first and fifth phases of the Korotkoff sounds were recorded. Observers had been trained and standardized [27,28] in the measurement of the blood pressure. We measured triglycerides, HDL-cholesterol and glucose in serum samples stored for up to 15 years.	Presence of MetS Yes vs No Number of MetS components 3-5 vs 0 component	HR= 1.58 (1.07-2.33) HR= 2.60 (1.47-4.61) *P* for trend= 0.001	MetS was significantly associated with PM BC risk with a significant risk increase for increasing number of components. Among individual MetS components, only low serum HDL-cholesterol and high triglycerides were significantly associated with increased risk.	Age, age at menarche, years from menopause, number of full-term pregnancies, age at first birth, oral contraceptive use, hormone therapy use in the past, years of education, family history of BC, breastfeeding, smoking (pack-years) and alcohol consumption
Ronco et al[47]	Height and weight were measured Waist circumferences (in cm of waist, hip, flexed and tensed arm, calf, Skinfolds (in mm) of tricipital, subscapular, supraspinal, calf was measured. Diameters (in mm): bicondyleal (femur) and bicondyleal (humerus) measured. Queries on personal history of components of MetS and others: diabetes, HPTN, dyslipidaemia were asked in the questionnaire.	Diabetes and risk of PM BC	OR=1.64 (1.00-2.69)	A personal history of diabetes was positively associated to BC risk and was higher among PM women. A personal history of diabetes and overweight was strongly associated to BC The risks of BC for diabetes in PM women with overweight combined with dyslipidaemia and high fat/muscle ratio were significantly high.	age, residence, family history of BC 1ºdegree, age at menarche, number of live births, age at first delivery and number of breastfeeding months.
Catsburg et al[28]	Adult weight gain; High BMI Anthropometric measurements were taken. Participants were provided at baseline with tape measures and instructions on how to measure their waist and hip circumferences, current weight and weight at age 20.	Adult weight gain >15.9 kg vs < 4.6 kg	HR= 1.39 (0.98–1.98) *P* for trend= 0.01	No evidence was found for an increased risk of PM BC with increasing BMI or waist circumference. Adult weight gain was strongly associated with PM BC risk. This study estimated a 6 % increase in PM BC risk with every 5 kg gained since age 20. The associations of BMI and weight gain with PM BC risk were not modified by use of HRT.	Age at menarche, use of oral contraceptives, use of hormone therapy, number of live birth, age at first live birth, family history of breast cancer, menopausal status at baseline, alcohol intake (gpd), and physical activity in MET hours per week.

Continued.

Author	Exposure measurement	Contrast	Risk Estimate (95% CI) Test for Trend	Summary	Adjusted variables
Carpenter et al[32]	BMI & Adult weight change only Self-reported height and weight at age 18 years and at the reference date was recorded. BMI was estimated as weight in kilograms divided by the square of height in meters. Percent change in weight between age 18 and the reference date was calculated.	Change in weight from age 18 to reference date (%) ≥ 29.2 % vs Negative change to no change	OR= 1.36 (1.08–1.73) *P* for trend= 0.01	Women who experienced the greatest percent weight gain between age 18 and the reference age were at increased PM BC risk.	Age at first full-term pregnancy, ages at menarche and menopause, family history of BC, interviewer, average MET hours per week of lifetime exercise activity

Table 5: Results of the association between individual components of MetS and PM BC.

Author	Dyslipidaemia	High blood pressure/ hypertension	High fasting blood glucose or diabetes	High waist circumference	High BMI
Rosato et al[40]	OR= 1.08 95% CI = 0.95–1.22 (No Significant Association)	OR= 1.19 95% CI = 1.07–1.33 *	OR = 1.33 95% CI = 1.09–1.62 *	OR = 1.22 95% CI = 1.09–1.36 * (For Waist Circumference ≥ 88 Cm)	OR = 1.26 95% CI = 1.11–1.44 * (For BMI ≥ 30 kg/m^2)
Capasso et al[41]	OR = 1.29 95% CI = 1.06 - 1.56 *	OR = 1.54 95% CI = 1.05-1.37 *	OR = 1.29 95% CI = 1.06-1.56 * (Hyperinsulinaemia)	OR = 2.66 95% CI = 2.06 - 3.49 *	(No Significant Association)
Lindgren et al[26]	OR = 1.35 95% CI = 1.11-1.63 * (Hyperlipidaemia)	OR = 1.11 95% CI = 0.92-1.35 *	OR = 1.30 95% CI = 0.97-1.73*		
Wang et al[43]	OR = 3.191 95% CI = 1.253–8.125 * (High Triglyceride)	OR = 1.463 95% CI= 0.608–3.517 (No Significant Association)	OR = 1.993 95% CI= 0.769–5.164 (No Significant Association)		OR = 3.016 95% CI = 1.044–8.715 * (BMI ≥ 25 kg/m^2)
Noh et al[44]	OR = 0.64 95% CI= 0.35–1.17 (Triglycerides ≥ 1.69 Mmol/L) OR = 1.03 95% CI = 0.56–1.86 (Hdl < 1.29 Mmol/L)	OR= 1.01 95% CI = 0.58–1.78 (BP ≥ 130/Or 85 mm hg, Or Antihypertensive Medication) (No Significant Association)	OR = 1.08 95% CI = 0.59–1.98 (Fasting Serum Glucose ≥ 5.55 mmol/L Or Hypoglycaemic Medication) (No Significant Association)		OR= 2.24 95% CI = 1.22–4.10*

Continued.

Author	Dyslipidaemia	High blood pressure/ hypertension	High fasting blood glucose or diabetes	High waist circumference	High BMI
	(No Significant Association)				
Kabat et al[8]	HR = 1.44 95% CI = 0.95-2.20 * *P* For Trend= 0.049 (Triglycerides ≥ 150 G/Dl) HR = 0.70 95% CI = 0.47-1.05 *P* For Trend= 0.34 (HDL 50-<63 mg/dL) (No Significant Association)	HR = 1.16 95% CI = 0.77-1.76 *P* For Trend= 0.45 (Systolic BP ≥ 130 mm Hg) (No Significant Association) HR = 2.40 95% CI = 1.49-3.87 * *P* For Trend= 0.002 (Diastolic BP ≥ 85 mm Hg)	HR = 1.57 95% CI = 1.01-2.46 * *P* For Trend= 0.04 (Glucose Average ≥ 100 mg/dL)	HR = 0.40-1.18 95% CI = 0.69 *P* For Trend= 0.17 (Waist Circumference ≥ 88 Cm) (No Significant Association)	
Bosco et al[24]	IRR = 1.13 95% CI = 0.92–1.38 (High Cholesterol) (No Significant Association)	IRR = 1.10 95% CI= 0.91–1.34 (No Significant Association)	IRR = 0.93 95% CI = 0.73–1.19 (No Significant Association)	IRR = 1.09 95% CI = 0.91–1.31 (Abdominal Obesity) (No Significant Association)	
Kabat et al[25]					HR = 1.12 95% CI = 0.95-1.33 * (BMI >25 < 30 kg/m^2) HR = 1.51 95% CI = 1.28-1.78 * (BMI ≥ 30 kg/m^2) *P* For Trend= <0.0001
Agnoli et al[45]	HR = 1.21 95% CI = 0.80–1.83 (High Triglycerides) HR = 1.11 95% CI = 0.64–1.93 (Low HDL)	HR = 1.51 95% CI = 0.96–2.39 (High BP)	HR = 1.89 95% CI = 1.29–2.77 * (High Fasting Glucose)	HR = 1.04 95% CI = 0.69–1.57	
Agnoli et al[46]	HR = 1.59 95% CI = 1.10-2.29 * (Triglycerides >126 mg/dL) HR = 1.60	HR = 1.29 95% CI = 0.87-1.93 (Mean BP ≥ 106.5 mm Hg Or Antihypertensive Drug Assumption)	HR = 1.29 95% CI = 0.87-1.93 (Glucose >88 mg/dL Or Self-Reported Diabetes)	RR = 1.23 95% CI = 0.83-1.81 (Waist Circumference >86 cm) (No Significant Association)	

Continued.

Author	Dyslipidaemia	High blood pressure/ hypertension	High fasting blood glucose or diabetes	High waist circumference	High BMI
	95% CI = 1.10-2.33 * (HDL ≤ 55 mg/dL)	(No Significant Association)	(No Significant Association)		
Ronco et al[47]	OR = 0.59 95% CI = 0.38-0.94 (No Significant Association)	OR = 1.49 95% CI = 0.95-2.33 (No Significant Association)	OR = 1.92 95% CI = 1.04-3.52 *		OR = 0.77 95% CI = 0.48-1.25 (No Significant Association)
Catsburg et al[28]				HR = 1.30 95% CI = 0.92–1.82 (Wait Circumference >92.7 cm) *P* For Trend= 0.09 (No Significant Association)	HR = 1.24 95% CI = 0.90–1.71 (Obese) HR = 1.22 95% CI = 0.99–1.52 (Overweight) *P* For Trend= 0.08 (No Significant Association)
Chang et al[16]					RR = 1.35 95% CI = 1.06-1.70 * *P* For Trend= 0.014
Carpenter et al[32]					OR = 1.34 95% CI = 1.09–1.66 * *P* For Trend= 0.005
Shoff et al[30]					OR= 1.33 95% CI = 1.18–1.49 * *P* for trend = < 0.001 (Recent BMI > 26.5 kg/m^2) OR= 0.92 95% CI = 0.82–1.03 * *P* for trend = 0.05 (BMI at age 18 > 21.8 kg/m^2)

Most studies had trained personnel measure the anthropometric characteristics such as weight, height, waist circumference and draw blood to analyse the serum glucose, triglyceride, HDL levels and measure BP during clinic visits and the method used was standardised for all participants accordingly in every study.

Some studies obtained self-reported history of medication used for the metabolic conditions and self-reported body weight and height. All studies included demonstrated a significant association between MetS and PM BC risk. 15 studies evaluated the role of MetS and all studies found MetS to be a significant predictor of PM BC. A dose-response relationship was evident, where increasing number of MetS components further increased the PM BC incidence. There were some studies observed effect modification by HRT on BMI or weight gain.[16,25,24,44]

MetS is an aggregation of multiple factors which are also standalone risk factors of BC. To overcome this limitation, we also looked into the influence of individual components of MetS. Table 5 shows the results of studies depicting the association between individual factors of MetS and PM BC. In relation to PM BC, seven out of ten studies produced significant association for BMI, 2 out of 7 studies showed significant association for high waist circumference, 6 out of 10 studies showed significant association for diabetes, 5 out of 11 studies demonstrated significant association for dyslipidaemia and 4 out of 10 studies showed significant association for hypertension. Obesity and diabetes posed the highest risk of PM BC of all the other individual MetS components. There were few studies which showed significant association between high BP and PM BC, however the results were inconsistent.

DISCUSSION

In this systematic review, the key observational epidemiologic studies examining the impact of PA and MetS and its components, obesity, HPTN, T2DM and dyslipidaemia on PM BC independently have been qualitatively studied and the results outlined. This study has demonstrated a very strong inverse association between PA and PM BC. Similarly, an inverse association between PA and PM BC was evident in a 2007 systematic review which produced PM BC risk reductions ranging from 20-80%.[5] This hypothesis is also in line with many epidemiological studies further strengthening this association.[4,6] A possible linear dose-response relationship was observed in this study and of note, one study demonstrated a non-linear dose response relation where significant PM BC risk reduction was observed when moderate-intensity recreational PA increased up to 16 METs-hour/week but higher intensity of PA exceeding 16 METs-hr/wk was not associated with decreased risk.[37]

The impact of PA varies depending on its domains, duration and intensity. In particular, recreational PA domain was the most prominent in PM BC risk reduction. A study that investigated occupational and household PA showed a significant association with 38% risk reduction for invasive BC in women who were engaged in heavy lifting or carrying routinely at home or work.[18]

Future researches should explore more on OPA and transport related PA domains as there are not many studies available on this currently although the in this era, PA related to occupation and transportation may not be as effective in contributing to PM BC risk reduction as people are mostly chairbound in their workplace and commute using public transport or motor vehicles. The exact period in life which was most important to be physically active could not be distinguished from this study. One of the studies included demonstrated PM BC risk reduction among women who maintained an average of 17.6 MET-hour of activity per week starting from their menarche.[32] Another study stated that greatest reduction in risk of PM BC was associated with frequent early life PA in those who either lost weight or gained modest amount of weight over their adult life.[30] From the existing evidence, the key to having the greatest risk reduction of PM BC may be engaging in sustained, moderate-intensity PA from menarche onwards throughout one's lifetime. Exercising during childhood and adolescence may be beneficial as exercise is proven to reduce fat storage and exposure to sex hormones, delaying menarche and increased anovulation while exercising after menopause may be helpful in reducing weight gain which in turn decreases the risk of PM BC.[29] Another study observed BC risk reduction in those who exercise at or above the recommended level (8 MET hr/wk/yr).[23] Also, just walking for an hour per day and engaging in weekly exercises seemed to be efficacious against PM BC.[22]

BMI was observed to attenuate the effect of PA on PM BC in several studies however the results did not consistently show a differential effect of PA on high or low BMI groups. On the contrary, another systematic review stated that BMI does not modify the effect of PA on PM BC risk.[5] Hence, it is unclear if the lack of association in among high or low BMI women is due to lesser number of women with the required PA level or if the independent impact of PA is overshadowed by excessive adiposity. One of the studies included observed a significant PM BC risk reduction of 56% being further reduced to 68% after multivariate adjustment, in which BMI and parity were mainly responsible.[35] The accumulating evidence that PM BC risk is increased by higher body fat distribution is insufficient in confirming this hypothesis as the relation between PA and body fat distribution is scarcely studied. Future researches on the associations between PA, (including recreational, occupational, household, transport related sources), BMI and distribution of body fat may be enlightening in terms of the mechanisms underlying the impact of PA on PM BC risk.

The PM BC risk could be lowered by long term PA via the pathways of estrone, BMI, insulin resistance, and C-reactive protein, with estrone and BMI most convincingly associated with PA and PM BC risk. PA in general is said

to reduce the higher circulating level of oestrogen and androgen in PM women and enhance immune surveillance by modulating immune responses in circulation as well as alter the immune landscape within the tumour microenvironment leading to better infiltration of effector cells and reduced immunosuppression.48 Importantly, PA after menopause is specifically associated with suppressed level of sex hormones or increased insulin sensitivity. Studies have proven that decreased BMI further decreases insulin and insulin resistance after engaging in physical exercises.[21] The consensus is, women who were engaged in at least recommended or moderate level of PA regularly or had an active lifestyle overall and maintained a normal adult body weight had the greatest PM BC risk reduction. A major limitation in the included studies is, the information on minimal dose of PA necessary to cause an impact on the risk of PM BC was lacking. Also, different intensities of recreational PA may have different dose-response effect with PM BC risk. In that case, it is safe to conclude that recommended level or consistent moderate intensity PA is sufficient to induce PM BC risk reduction. These results are promising as engaging in the most strenuous activities are not necessarily required to reduce the risk of PM BC.

The jury is still out on the debate whether MetS is a real syndrome or a cluster of unrelated phenotypes. Nonetheless, MetS fulfils the criteria of a syndrome which means aggregation of factors which occur together more often than by chance alone and for which the reason is uncertain.[7] In this study, MetS was significantly associated with PM BC and a linear association was observed suggesting that multiple molecular pathways underlying MetS are activated which may contribute to breast tumorigenesis. The results produced by this study is supported by another meta-analysis which showed a two-fold increase in BC risk among PM MetS and a few other studies which reported a significant association between MetS and PM BC with increasing number of MetS components, the risk of PM BC was markedly increased.[7,8,49]

A few mechanisms namely, increased visceral adiposity, android fat distribution, hyperinsulinemia, chronic inflammation and free androgen are the suggested pathogenesis by which MetS per se leads to breast carcinogenesis.41 Importantly, the presence of other metabolic factors together with obesity posed a higher risk of PM BC.[25,43,44,47] Obesity, represented by high BMI and diabetes emerged as the most significant effect modifier followed by dyslipidaemia and HPTN. This study proves that obesity when combined with diabetes and dyslipidaemia posed the greatest risk of PM BC, emerging as the most lethal combination of biological abnormality. This gives rise to a new perspective to consider in regards to prevention of PM BC incidence. A large prospective cohort study demonstrated obese women who are metabolically unhealthy had the highest PM BC risk and despite metabolic health, obesity increased the risk of PM BC.[25] High BMI, dyslipidaemia and diabetes demonstrated an independent association with PM BC. On the contrary to this result, several studies stated that none of the individual MetS components were strong enough to be considered responsible for breast carcinogenesis alone.[41,44]

Besides BMI, other indicators of adiposity, such as waist circumference, waist-to-hip ratio and adult weight gain have been also deemed as probable risk factors of PM BC risk because accumulation of visceral adipose tissue in PM women is related to the alteration of the concentration and availability of sex hormones after menopause.[6,28,32,40] In contrast, a study done in the Canadian study of diet, lifestyle and health cohort showed no evidence between PM BC with increasing BMI, but adult weight gain was found to be strongly associated with PM BC risk which estimated a 6% increase in PM BC risk with every 5 kg gained since age 20 independent of the use of HRT.[28]

The most plausible mechanism linking MetS to PM BC is hormone-related, particularly insulin, which is why MetS is also called as the insulin resistance syndrome. The molecular mechanism underlying all MetS components are somehow interlinked. The main contributing factor to the progression of insulin resistance is the excessive amount of circulation fatty acid released from adipose tissue. The insulin resistance provides a conceptual framework which relates a number of otherwise unrelated pathophysiological pathways as it acts as a chain reaction which leads to the occurrence of consequent biological mechanisms. Insulin is the main hormone involved in stimulating cell proliferation hence it directly promotes the growth of breast tissue and tumour cells, leading to BC incidence. Insulin upregulates insulin-like growth factor (IGF) levels acting as mitogens.[48] Another vital factor, the adiponectin (adipocyte-associated protein) aids with the metabolism of fatty acid and glucose metabolism as well as insulin sensitivity and resistance. In obese patients, adiponectin level is substantially reduced, which gives a suitable medium for tumour angiogenesis.[49]

The oestrogen levels in adipose tissue of obese PM women are generally high after menopause as the ovarian oestrogen production decreases and adipose tissue becomes the major source of oestrogen due to androgen aromatization in peripheral adipose tissue into estradiol. Obesity facilitates this process, increasing estradiol which decreases production of adiponectin and thereby weakening the antitumour effect of adiponectin. On the other hand, there is sex hormone binding globulin (SHBG) which is a glycoprotein synthesised by liver which binds and transports active forms of oestrogens and androgens in blood.[49] In cases of hyperinsulinemia, increased IGF and obesity, SHBG synthesis is decreased which results in increased circulating bioavailable oestrogens, subsequently prompting a vicious cycle. This mediating role of oestrogen is supported from observations that the association between BMI and PM BC was essentially eliminated after adjustment for bioavailable oestrogen concentration.[48] Besides, the substantially weakened association with BMI in HRT users also indicates that this

exogenous hormone source overrides the effect of endogenous oestrogen production from peripheral fat tissue. This study also corroborates this finding where HRT was found to exert some modification on the association of BMI with PM BC. More exploration is needed to identify how HRT comes into play in regards to its effect on the association between, PA, BMI and weight gain with PM BC.

In this review, the studies included showed a significant association between T2DM and PM BC. However, there might be possible residual confounding by overweight/obesity as the insulin resistance caused by obesity may give rise to diabetes due to their common pathophysiological pathway. A meta-analysis has demonstrated a 20% increase in BC risk compared to women without diabetes.[50] The effect of insulin resistance seemed more marked in PM women. To strengthen this observation, PM women with T2DM were 17% more likely to get BC than women without diabetes in the Nurses' Health Study even after controlling for all the confounding variables.

The association between HPTN and PM BC has been long investigated, yet with inconsistent results. A cohort study which investigated HPTN only concluded that PM BC incidence in general, does not vary from that of the general population however, elevated DBP levels may be associated with an increased BC risk among non-pharmacologically treated women. Besides the common pathophysiological pathway, it shares with other MetS factors, another possible explanation is that HPTN may increase BC risk by blocking and subsequently modifying apoptosis, thereby affecting the regulation of cell turnover.[26]

Age is an integral factor in pathogenesis of BC as the transition from premenopausal to postmenopausal constitutes a window where there is hormonal imbalance which favour the initiation of breast tumorigenesis.[6] Thus far, BMI and sex hormones are the most commonly cited biomarkers associating PA and reduced risk of PM BC, however emerging studies propose insulin resistance and chronic inflammation could be pivotal too as several mechanisms act simultaneously in increasing the incidence of PM BC.

There were a few limitations in this review. Firstly, the heterogeneity among studies was unavoidable although subgroup analysis was conducted because the measures of the MetS factors and PA varied across studies making interpretation challenging. Only observational studies can be conducted to evaluate the association between PA, MetS and its factors with PM BC respectively. Thus, only cohort and cross-sectional studies were included. Moreover, recall bias was possible because the data from recalling PA done in early adulthood and their body weight might have been inaccurate. The strengths of this review are, a wide range of studies with a large scale of participants and long follow up years were included. Most of the studies included were of high quality.

CONCLUSION

In summary, it is evident that PA and MetS are significantly associated with postmenopausal breast cancer. Regular PA of moderate intensity or recommended level of PA while maintaining a normal BMI from menarche onwards may be helpful in lowering PM BC risk whereas having ≥3 factors of MetS increases the risk of PM BC. This systematic review has shown obesity, diabetes and dyslipidaemia to pose an increased risk on PM BC whereas the association of HPTN and PM BC was weak. Routine BC screening could help detect BC in its early stages for PM women with MetS or overweight or obese women with other MetS components. As opposed to menopausal status, age or genetic background, obesity is a preventable and reversible modifiable risk factor hence, specific interventions to reduce obesity and adult weight gain as well as promoting sustained PA would be beneficial in curbing MetS and decreasing the risk of PM BC. Mechanistic insight underpinning the definite molecular and biological pathways by which long-term PA contribute to the risk of PM BC to highlight the existing epidemiologic gaps are needed to confirm the causal relationship between these factors. This would also create awareness among public about the health benefits of PA in reducing the risk of BC in a postmenopausal woman and for medical practitioners to prescribe PA as a critically crucial regimen extending beyond improving outcomes of MetS and also in reducing the risk of PM BC.

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