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. 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. Besides, a systematic review study found exercise to decrease PM BC risk by approximately 15%-20%. Several studies showed a dose-response relationship between PA and BC risk where increased frequency and duration of activity provides greater benefit.

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 hypertriglyceridaemia, 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.

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.

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. 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. 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 neoplasms” 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. 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.
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 and the shortest being 4.7 years. 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. 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.

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. 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. 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. Some studies did not find any effect modification by BMI on PA. Table 4 describes the measures, results, summary and adjusted variables of all studies investigating MetS and PM BC.
| 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: 17,004 | 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 | Age Group | Outcome measured                | Quality Score |
|----------------------|--------------------|------------------------------|-----------------|--------------------|------------|-----------|---------------------------------|---------------|
| **Physical activity and postmenopausal breast cancer**                                  |                    |                              |                  |                    |            |                       |                |
| Catsburg et al²⁸     | Canada             | 1992-1998                   | PM only: 541    | Subcohort: 2,210  | Population/ Case/control | Mean age: Case: 63.7 Subcohort: 67.9 | Incident, incident BC | Good          |
| (Case-cohort)        |                    |                              | Follow up years (mean)= 6.7 | Follow up years (mean)= 12.2 |            |           |                                 |               |
| Friedenreich et al²⁹ | Canada             | 1995-1997                   | Total : 1,237    | Total: 1,241       | Population/ population | ≤ 80 Mean= 56           | Incident in situ or invasive BC | Good          |
|                      |                    |                              | PM only: 771    | Post: 762          |            |           |                                 |               |
| Shoff et al³⁰        | USA                | 1988-1991                   | PM only : 4,614  | Post : 5,817       | Population/ population | 20-74     | Incident invasive BC            | Good          |
|                      |                    |                              |                  |                    |            |           |                                 |               |
| John et al³¹         | USA                | 1995-1998                   | PM only : 847    | Post: 1,065        | Population/ population | 35-79     | Primary Invasive BC             | Good          |
|                      |                    |                              |                  |                    |            |           |                                 |               |
| Carpenter et al³²    | USA                | 1980-1990                   | PM only : 1,883  | Post : 1,628       | Population/ population | 55-72     | Incident BC                     | Good          |
|                      |                    |                              |                  |                    |            |           |                                 |               |
| Dorn et al³³         | USA                | 1986-1991                   | PM only : 439    | Post: 494          | Hospital/ population | 40-85     | Incident Primary BC            | Good          |
|                      |                    |                              |                  |                    |            |           |                                 |               |
| Hirose et al³⁴       | Japan              | 1988-2000                   | Total: 2,376     | Total: 18,977      | Hospital/ Hospital | ≥ 30      | Incident BC | Fair                         |               |
|                      |                    |                              | PM only: 1,024   | Post: 6,989        |            |           |                                 |               |
| Awatef et al³⁵       | Tunisia            | 2006-2009                   | Total: 400       | Total: 400         | Hospital/ Hospital | 25-75     | BC                           | Good          |
|                      |                    |                              | PM only: 309    | Post: 266          |            |           |                                 |               |
| Gilliland et al³⁶    | Mexico             | 1992-1994                   | PM Hispanic: 171 | PM Hispanic: 210   | Population/ population | 35-74     | New diagnosis of invasive or in situ breast carcinoma | Good          |
|                      |                    |                              | PM Non-Hispanic: 228 | PM Non-Hispanic: 224 |            |           |                                 |               |
| Si et al³⁷           | Australia          | 2009-2011                   | Total: 1,205     | Total: 1,789       | Population/ population | 18-80     | Primary Invasive BC            | Good          |
|                      |                    |                              | PM only : 336   | Post: 421          |            |           |                                 |               |
| Yang et al³⁸         | USA                | 1995-1997                   | Total: 501       | Total: 594         | Population/ population | 25-74     | Primary Incident BC            | Good          |
|                      |                    |                              | PM only : 278   | Post: 302          |            |           |                                 |               |
| Dirx et al³⁹         | 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 al⁴⁰       | Italy and Switzerland | 1983-2007               | Post: 3,869      | Post: 4,082        | Hospital/ Hospital | 33-86     | Incident BC                     | Good          |
| Capasso et al⁴¹      | 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 | Outcome measured | Quality Score | Outcome measured |
|-----------------|---------|------------|------------------------------|-----------------|-------------------|-------------------------|-----------|-----------------|------------------|---------------|------------------|
| Wu et al⁴²       | USA     | (Asian)    | 1995-2001 2003-2006          | Total: 2,167    | Total: 2,035       | Population/population   | 25-74    | Incident BC     | Incident BC     | Good          | Incident BC     |
| Wang et al⁴³     | 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 al⁴⁴      | Korea   |            | 1995-2011 Total: 270 Total: 540 | Hospital/Hospital | Mean age of Cases : 59.43 Controls: 59.34 | Incident BC | Good          |                  |
| Agnoli et al⁴⁵   | Italy   |            | 1993-1998 Total: 593 Subcohort: 555 | Population/population | Not stated | Incident BC (in situ and invasive) | Good |
| Agnoli et al⁴⁶   | 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 al⁴⁷    | Uruguay |            | 2004-2009 PM only : 367 PM: 545 | Hospital/Hospital | 23-69 | Incident BC | Good |
| Carpenter et al⁴²| 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 al⁴²| hours/week ; Lifetime; Recreational PA (vigorous activity)  | ≥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 al⁴⁴ | 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                                                                 |
|-----------------|-------------------------------------------------------------|----------|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Thamilmanni et al. | Int J Community Med Public Health. 2021 Jul;8(7):3561-3584  |          |                                        | 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 al13   | 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 al15   | 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 al16    | 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                                                                                       |
|------------|-------------------------------------------------------------|----------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Patel et al17 | 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-hr/week) at baseline had 29% lower incidence rates than active women with the least activity. | age at menopause, menopausal hormone therapy, and education. |
| George et al18 | 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 <1 year | 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 | 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, 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 history. |
| Eliassen et al19 | 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 activity were associated with decreased BC risk. | 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 mammography history. |

Continued.
| Author          | Measure and Life period of Exposure; Domain of PA Definition | Contrast | Risk Estimate (95% CI) Test for Trend | Summary                                                                 | Adjusted variables                       |
|-----------------|--------------------------------------------------------------|----------|----------------------------------------|------------------------------------------------------------------------|-------------------------------------------|
| Howard et al20   | 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. | >10 hrs/wk vs <1 hr/week | Ever used MHT: HR= 1.12 (0.41–3.03) P for trend = 0.929 | PA were associated with lower BC risk among PM women.                    | history of benign breast disease.        |
| Suzuki et al21   | 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 | 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. |
| Pronk et al22    | 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. |
| Author          | Measure and Life period of Exposure; Domain of PA Definition | Contrast | Risk Estimate (95% CI) Test for Trend | Summary                                                                                                                                                                                                                                                                                                                                 | Adjusted variables                                                                                                                                                                                                                                                                                                                                                     |
|-----------------|-------------------------------------------------------------|----------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Catsburg et al²⁸ | 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 al²⁸ | 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= 0.70 (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 al³⁰    | 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 | OR= 0.55 (0.39–0.78) P for trend = 0.002 | 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 al³¹     | 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.                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                           |
| Author          | Measure and Life period of Exposure; Domain of PA Definition                                                                 | Contrast                              | Risk Estimate (95% CI) Test for Trend | Summary                                                                                                                                                                                                                                                                                                                                 | Adjusted variables                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Carpenter et al | Moderate and vigorous PA, including recreational activity, walking, bicycling, household and outdoor chores, and occupation. | ≥ 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.                                                                                                                                                                                                 | cancer, age at menarche, parity, breastfeeding, age at menopause, and other components of total activity.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Dorn et al      | Hours/year ; Lifetime Adult Lifetime Total PA (Sum of total in strenuous physical activity 2, 10, and 20 years ago)            | >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. | Age at first full-term pregnancy, age at menarche and menopause, family history of breast cancer, interviewer and body-mass index at reference date.                                                                                                                                                                                                                                                                                                                                                     |
| Hirose et al    | 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                                                                 |
|---------------|------------------------------------------------------------|----------|----------------------------------------|------------------------------------------------------------------------|
| Awatet al      | MET/hours/week/year ; Lifetime Total PA                    | ≥150     | 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| 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      | OR= 0.38 (0.18–0.77) P for trend= 0.002| 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       | MET/hours/week/year ; Lifetime Total PA Recreational, household, occupational and transport physical activities. | ≥131.3   | OR= 1.23 (0.97–1.58) P for trend= 0.03 | 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 |
|               | Occupational PA                                            | ≥ 52.8   | OR= 1.18 (0.90, 1.56) P for trend= 0.42|                                                                       |                          |

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 | Average MET hours/week; Lifetime | Recreational PA | > 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 | MET (min/day); Lifetime | Recreational PA ; Total recreational PA ; Number of minutes spent per day | Recreational PA: >90 mins/day vs <30 mins/day | RR= 0.76 (0.58–0.99) | P for trend = 0.003 | 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 |

- **Yang et al**: Participated regularly in recreational PA 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.

- **Dirx et al**: 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.
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 al40  | BMI was calculated (kg/m²). 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 al41 | 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 al42      | 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                                                   | OR= 1.87 (1.11-3.15) P for trend= 0.001 | 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 al43     | 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 |
| Author          | Exposure measurement                                                                 | Contrast                                                                 | Risk Estimate (95% CI) Test for Trend | Summary                                                                                                                                                                                                 | Adjusted variables                                                                 |
|-----------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 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/m²). 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 of sample. Presence of MetS (≥ 3 components) Vs absence of MetS (<3 components) | HR= 1.80 (1.22–2.65) P for trend= Not stated | 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    | 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                | HR= 1.58 (1.07-2.33)                  | 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     | Height and weight were measured. Waist circumferences (in cm of waist, hip, flexed and tensed arm, calf, Skinfolds (in mm) of tricipital, subcapular, 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  | 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. |
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 al⁴⁰    | OR = 1.08     | OR = 1.19                          | OR = 1.33                              | OR = 1.22                | OR = 1.26 |
|                   | 95% CI = 0.95–1.22 | 95% CI = 1.07–1.33 * | 95% CI = 1.09–1.62 * | 95% CI = 1.09–1.36 * | 95% CI = 1.11–1.44 * |
|                   | (No Significant Association) |                           | (For Waist Circumference ≥ 88 Cm)      | (For BMI ≥ 30 kg/m²)     |          |
| Capasso et al⁴¹   | OR = 1.29     | OR = 1.54                          | OR = 1.29                              | OR = 2.66                |          |
|                   | 95% CI = 1.06 - 1.56 * | 95% CI = 1.05-1.37 * | 95% CI = 1.06–1.56 * | 95% CI = 2.06 - 3.49 * |          |
|                   | (Hyperlipidaemia) |                                 | (Hyperinsulinaemia)                     |                          |          |
| Lindgren et al⁴²  | OR = 1.35     | OR = 1.11                          | OR = 1.30                              |                          |          |
|                   | 95% CI = 1.11-1.63 * | 95% CI = 0.92-1.35 * | 95% CI = 0.97-1.73* |                          |          |
|                   | (Hyperlipidaemia) |                                 |                                         |                          |          |
| Wang et al⁴³      | OR = 3.191    | OR = 1.463                         | OR = 1.993                             |                          |          |
|                   | 95% CI = 1.253–8.125 * | 95% CI = 0.608–3.517 * | 95% CI = 0.769–5.164 |                          |          |
|                   | (High Triglyceride) |                                 | (No Significant Association)           |                          |          |
| Noh et al⁴⁴       | OR = 0.64     | OR = 1.01                          | OR = 1.08                              |                          |          |
|                   | 95% CI= 0.35–1.17 | 95% CI = 0.58–1.78  | 95% CI = 0.59–1.98 |                          |          |
|                   | (Triglycerides ≥ 1.69 Mmol/L) |         | (Fasting Serum Glucose ≥ 5.55 mmol/L Or Hypoglycaemic Medication) |                          |          |
|                   | OR = 1.03     | 95% CI = 0.56–1.86                 | OR = 1.08                              |                          |          |
|                   | 95% CI < 1.29 Mmol/L |         | 95% CI = 0.59–1.98 |                          |          |

Continued.
| Author         | Dyslipidaemia | High blood pressure/hypertension | High fasting blood glucose or diabetes | High waist circumference | High BMI                                                                 |
|---------------|---------------|---------------------------------|--------------------------------------|-------------------------|--------------------------------------------------------------------------|
|               | (No Significant Association) |                                |                                      |                         |                                                                          |
| Kabat et al   | HR = 1.44     | HR = 1.16                        | HR = 1.57                            | HR = 0.40-1.18          |                                                                          |
|               | 95% CI = 0.95-2.20 * | 95% CI = 0.77-1.76                  | 95% CI = 1.01-2.46 *                  | 95% CI = 0.69          |
|               | P For Trend= 0.049 | P For Trend= 0.45                    | P For Trend= 0.04                     | P For Trend= 0.17       |                                                                          |
|               | (Triglycerides ≥ 150 G/Dl) |                                | (Systolic BP ≥ 130 mm Hg)            | (Waist Circumference ≥ 88 cm) |                                                                          |
|               | HR = 0.70     | HR = 2.40                        | HR = 1.57                            | HR = 1.51              |                                                                          |
|               | 95% CI = 0.47-1.05 | 95% CI = 1.49-3.87 *               | 95% CI = 1.01-2.46 *                  | 95% CI = 1.28-1.78 *    |                                                                          |
|               | P For Trend= 0.34 | P For Trend= 0.002                  | P For Trend= 0.04                     | P For Trend= <0.0001    |                                                                          |
|               | (HDL 50-<63 mg/dL) |                                |                                      |                         |                                                                          |
|               | (No Significant Association) |                                |                                      |                         |                                                                          |
| Bosco et al24 | IRR = 1.13    | IRR = 1.10                        | IRR = 0.93                           | IRR = 1.09              |                                                                           |
|               | 95% CI = 0.92–1.38 | IRR = 0.91–1.34                  | 95% CI = 0.73–1.19                   | 95% CI = 0.91–1.31     |                                                                           |
|               | (High Cholesterol) |                                | (No Significant Association)         | (Abdominal Obesity)    |                                                                           |
|               | (No Significant Association) |                                |                                      | (No Significant Association) |                                                                           |
| Kabat et al25 | HR = 1.12     |                                 |                                      |                         |                                                                          |
|               | 95% CI = 0.95-1.33 * |                                |                                      |                         |                                                                          |
|               | (BMI >25 < 30 kg/m²) |                                |                                      |                         |                                                                          |
|               | HR = 1.51     |                                 |                                      |                         |                                                                          |
|               | 95% CI = 1.28-1.78 * |                                |                                      |                         |                                                                          |
|               | (BMI ≥ 30 kg/m²) |                                |                                      |                         |                                                                          |
|               | HR = 1.51     |                                 |                                      |                         |                                                                          |
|               | 95% CI = 1.28-1.78 * |                                |                                      |                         |                                                                          |
|               | (BMI ≥ 31 kg/m²) |                                |                                      |                         |                                                                          |
| Agnoli et al45| HR = 1.59     | HR = 1.29                        | HR = 1.89                            | HR = 1.04              |                                                                          |
|               | 95% CI = 1.10-2.29 * | HR = 0.96-2.39                  | 95% CI = 1.29-2.77 *                  | 95% CI = 0.69-1.57     |                                                                          |
|               | (Triglycerides >126 mg/dL) |                                | (High BP)                            |                         |                                                                          |
|               | HR = 1.60     | HR = 1.29                        | HR = 1.89                            | HR = 1.04              |                                                                          |
|               | 95% CI = 1.10-2.29 * | HR = 0.87-1.93                  | 95% CI = 1.29-2.77 *                  | 95% CI = 0.69-1.57     |                                                                          |
|               | (Mean BP ≥ 106.5 mm Hg Or Antihypertensive Drug Assumption) |                                | (High Fasting Glucose)              |                         |                                                                          |
|               | HR = 1.59     | HR = 1.29                        | RR = 1.23                            |                         |                                                                          |
|               | 95% CI = 1.10-2.29 * | HR = 0.87-1.93                  | 95% CI = 0.83-1.81                   |                         |                                                                          |
|               | (Triglycerides >126 mg/dL) |                                | (Glucose >88 mg/dl Or Self-Reported Diabetes) |                         |                                                                          |
|               | HR = 1.60     | HR = 1.29                        | RR = 1.23                            |                         |                                                                          |
|               | 95% CI = 1.10-2.29 * | HR = 0.87-1.93                  | 95% CI = 1.29-2.77 *                  |                         |                                                                          |
|               | (Mean BP ≥ 106.5 mm Hg Or Antihypertensive Drug Assumption) |                                | (Glucose >88 mg/dl Or Self-Reported Diabetes) |                         |                                                                          |
| Author          | Dyslipidaemia | High blood pressure/hypertension | High fasting blood glucose or diabetes | High waist circumference | High BMI |
|----------------|---------------|----------------------------------|----------------------------------------|--------------------------|----------|
| Ronco et al⁴⁷  | 95% CI = 1.10-2.33 * (HDL ≤ 55 mg/dL) | (No Significant Association) | (No Significant Association) | OR = 0.77 | 95% CI = 0.48-1.25 (No Significant Association) |
| Catsburg et al³⁸ | 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 * | 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 al¹⁶  | RR = 1.35 95% CI = 1.06-1.70 * P For Trend= 0.014 | | | | |
| Carpenter et al³² | OR = 1.34 95% CI = 1.09–1.66 * P For Trend= 0.005 | | | | |
| Shoff et al³⁰  | OR = 1.33 95% CI = 1.18–1.49 * P for trend = < 0.001 (Recent BMI > 26.5 kg/m²) OR = 0.92 95% CI = 0.82–1.03 * P for trend = 0.05 (BMI at age 18 > 21.8 kg/m²) | | | | |
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.10,25,34,44

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 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%. This hypothesis is also in line with many epidemiological studies further strengthening this association. 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 increased risk. 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 hyperinsulinaemia, 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.\(^5\) 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.\(^2\)\(^6\)

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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