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CHAPTER

# 5

# AGE AND THE EFFECT OF PHYSICAL ACTIVITY ON BREAST CANCER SURVIVAL: A SYSTEMATIC REVIEW

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## ABSTRACT

The effect of physical activity (PA) on cancer survival is still the topic of debate in oncology research focusing on survivorship, and has been investigated retrospectively in several large clinical trials. PA has been shown to improve quality of life, fitness and strength, and to reduce depression and fatigue. At present, there is a growing body of evidence on the effects of PA interventions for cancer survivors on health outcomes. PA and functional limitations are interrelated in the elderly. However, the relationship between breast cancer survival and PA in older breast cancer patients has not yet been fully investigated. Our systematic review of the existing literature on this topic yielded seventeen studies. Most reports demonstrated an improved overall survival (OS) and breast cancer-specific survival (BCSS). Furthermore, in studies that compared younger women with older or postmenopausal women, it was suggested that the beneficial effect of PA may be even greater in older women. Understanding the interaction between physical functioning and cancer survival in older breast cancer patients is key, and may contribute to successful treatment and survival. In this population of cancer survivors it is therefore imperative to embark on research focused on improving physical functioning in the context of comorbidities and functional limitations.

## INTRODUCTION

There is a growing body of evidence on the effects of physical activity (PA) interventions for cancer survivors on health outcomes. PA in breast cancer has shown to improve quality of life, fitness and strength and to reduce depression and fatigue.[1] Also, PA has shown to have an inverse association with postmenopausal breast cancer risk.[2] Previous randomized controlled trials have demonstrated better quality of life and other health outcomes in patients who undertake regular PA.[3] The effect of PA on cancer survival after breast cancer diagnosis, however, is still the topic of debate in oncology research.[4]

Breast cancer is increasingly becoming a disease of the elderly and, simultaneously, the number of breast cancer survivors is steadily rising.[5] For example, in the United Kingdom, 45% of breast cancer patients are older than 65 years at diagnosis.[6] In elderly patients, cancer occurs in a background of normal aging and comorbidity, thereby making this specific population heterogeneous in nature. Although older patients are known to have a higher disease-specific mortality, more than 65% of breast cancer patients older than 75 years die of other causes than breast cancer.[7] In contrast to younger patients, survival in the elderly breast cancer population has not improved in the last decade.[8] While breast cancer has a profound effect on psychological functioning and quality of life in younger females, elderly patients are affected by the disease physically more than psychologically.[9] At an older age, the decline in physical functioning may be induced or amplified as a result of local and/or systemic treatments. Regardless of age, decline in physical functioning is associated with higher mortality.[10] Therefore, new strategies to decrease the effect of breast cancer on physical decline and to improve overall and disease-specific survival are needed. The purpose of this study was to review the current literature in relation to the effect of PA on survival in breast cancer patients, with a focus on the elderly breast cancer patient in particular.

## MATERIALS AND METHODS

### Search strategy

Studies were identified through systematic review of the available literature in the PubMed database, EMBASe, Cochrane and Web of Science up to November 9th, 2012. PubMed, EMBASE, Cochrane and Web of Science were all searched using the following set of search terms which described breast cancer, physical activity, survival and elderly patients according to the following algorithm: ("Breast Neoplasms"[majr] OR "breast cancer"[ti] OR "Breast Neoplasm"[ti] OR "Breast Tumors"[ti] OR "Breast Tumor"[ti] OR "Breast Tumours"[ti] OR "Breast Tumour"[ti] OR "Breast Carcinoma"[ti] OR "Breast Carcinomas"[ti] OR "Cancer of the Breast"[ti] OR "Cancer of Breast"[ti]) AND ("physical activity" OR "Motor activity"[mesh] OR "Sports"[mesh] OR "Exercise"[mesh] OR Exercise[ti] OR Exercises[ti] OR "Resistance Training"[ti] OR Running[ti] OR Jogging[ti] OR Swimming[ti] OR Walking[ti] OR "Sports"[mesh] OR "Physical Exertion"[Mesh] OR exertion[ti]) AND (survival OR surviv* OR "Survival"[Mesh] OR "Mortality"[Mesh] OR "mortality"[Subheading] OR "Survival Rate"[Mesh] OR "Survival Analysis"[Mesh]) AND ("Aged"[mesh] OR Elderly OR aged OR Adult OR Adults OR

"Adult"[mesh] OR woman[tiab] OR women[tiab]) AND (eng[la]) AND ("Cohort Studies"[mesh] OR prognosis).

**Selection criteria**

Two independent reviewers (D.F., N.G.) selected studies for inclusion in the review. Only reports written in English were eligible. Articles included original studies in which the effect of PA on survival outcomes was investigated in breast cancer patients only. Studies were included if the primary or secondary outcome was related to the influence of PA on OS, BCSS or breast cancer recurrence after breast cancer diagnosis. PA was defined as any physical activity relating to aerobic, endurance, or strength training for the purposes of recreation, household, commuting, or work. Where evident, activities including yoga, Pilates, Tai Chi, or stretching were not included in the analyses. There were no restrictions with regard to patient characteristics, breast cancer subtype, treatment, age, condition, comorbidities, and other features. Only studies investigating leisure or total activity (occupational and/or non-occupational) were selected. Studies measuring PA using biological parameters (i.e. cardiorespiratory fitness, energy expenditure (in KJ or Kcal), oxygen use (in $vO_2$ /$vCO_2$), etc.) were not included in our selected abstracts. In case of an update of previously published data, the most recent publication was included. Reports on pilot data or descriptions of a study design were excluded from this review. Studies were also excluded if the PA intervention was combined with another intervention.  To ensure that no other studies were missed for inclusion in the current review, additional articles were identified by a manual search of the reference list of the selected manuscripts.

**Data extraction**

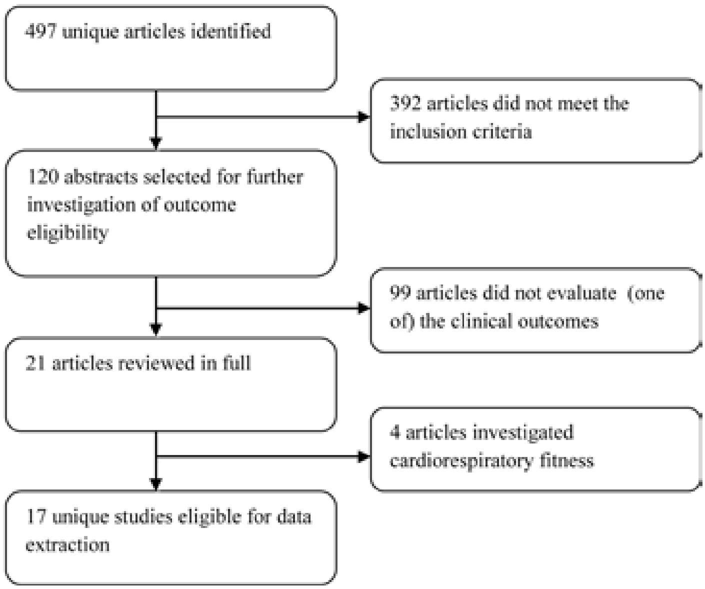
Data extraction was performed by 3 reviewers (D.F., N.G. and M.D.). Relevant data was determined prior to reading the selected articles. For all included studies, we documented the type of study, inclusion period, year of publication, primary and (where possible) secondary endpoints. Results from each study was documented and independently reviewed and verified by two independent reviewers (D.F. and N.G.). Aspects of PA were the type of activity, PA measurement unit (including frequency, duration and intensity, which were frequently converted into Metabolic Equivalent Task (MET) hours), time and timeframe of measurement(s), method of data collection, number of patients, mean and median age and age range, in- and exclusion criteria, as well as tumor- and patient-related characteristics. Results for specific population subgroups, including age (and/or menopausal status) and Body-Mass Index (BMI) were documented where available. Due to the fact that ages varied greatly between studies, we defined 'elderly' as 65 years or older. Primary and/or secondary endpoints included all-cause mortality, breast cancer-specific mortality, and breast cancer recurrence.

## RESULTS

### Patients

A total of 497 unique articles were identified in the PubMed, EMBASe, Cochrane and Web of Science searches, of which seventeen studies were deemed eligible after applying in- and exclusion criteria to the titles and abstracts (Table 1 and Figure 1). A total of 35,026 breast cancer patients were included in our review. Only one study investigated solely postmenopausal patients.11 In most studies, PA was measured in the first year after primary diagnosis. Two studies only included patients who were diagnosed with early-stage breast cancer. Fourteen studies also included patients with a more advanced breast cancer stage.

*Figure 1.* **Flow chart**




### Studies

The majority of the studies assessed were prospective observational cohort studies.[11-23] Two studies were part of the same side study of a randomized controlled trial investigating dietary change.[24, 25] A final study was a retrospective analysis of PA in patients participating in a multicenter case-control study.[26]

### Questionnaires

In all studies, data collection was through self-administered and/or interviewer-administered questionnaires, performed either in person or by telephone. Questionnaires were completed either once [12-15, 18, 19, 21-23, 25, 26]

*Table 1.* **Physical activity outcomes in all studies**

| Study | Patients | Age | Type of study | Measurement of PA |
| --- | --- | --- | --- | --- |
| Bertram et al.[24] | 2361 BC survivors stage I-III, 1 year post-treatment | 18-70, median age 54.3 | Side study of randomized controlled trial of dietary change (WHEL-study) | 9-item physical activity measure adapted from the WHI. Conversion to MET-hrs |
| Cleveland et al.[13] | 1508 early-stage BC patients | Mean age 58.6 | Population-based longitudinal study (Long Island Breast Cancer Study Project) | MET-hrs/week |
| Dal Maso et al.[28] | 1453 BC patients | 23-74, median age 55 | Multicentre case-control study | Retrospective questionnaire on PA at various ages |
| Emaus et al.[12] | 1364 BC patients | 17-79, mean age 57.5 | Population-based survival study (Norwegian Counties Study) | Questionnaire on pre-diagnostic PA |
| Friedenreich et al.[14] | 1183 BC patients | Mean age 56 | Population-based sample of breast cancer survivors | Assessment of lifetime PA. Conversion to MET-hrs |
| Hellman et al.[15] | 528 primary BC patients | 33-95, median age 66.9 | Prospective population-based study (Copenhagen City Heart Study) | Self-administered questionnaire on PA |
| Holick et al.[27] | 4482 BC patients, 91% postmenopausal. | 20-79, mean age 58.5 | Prospective population-based study (Collaborative Women's Longevity Study (CWLS)) | CWLS questionnaire. Conversion to MET-hrs |
| Holmes et al.[16] | 2987 nurses with stage I/II/III BC | 30-55 on enrolment in NHS | Prospective observational study (Nurses' Health Study) | Questionnaire on PA, calculated in MET-hrs/wk (<3/3-8/9-14/15-23/>24) |
| Irwin et al.[17] | 933 BC patients with local or regional breast cancer | Mean age 55.5 (6 months post-diagnosis) | Population based multicentre prospective cohort study (Health, Eating, Activity and Lifestyle (HEAL) Study) | Modifiable Activity Questionnaire in MET-hrs/wk (all types of PA) light (<3) moderate (3-6), vigorous (>6) |
| Irwin et al.[11] | 4643 post-menopausal BC patients | 50-79 | Prospective longitudinal study (Women's Health Initiative (WHI)) | Questionnaire on PA. Conversion to MET-hrs |
| Pierce et al.[25] | 1490 early-stage BC patients | <70, mean age 50 | Side study of randomized controlled trial of dietary change (WHEL-study) | 9-item PA measure adapted from the WHI. Conversion to MET-hrs |
| Rohan et al.[19] | 451 BC patients | 20-74 | Population-based cohort | Questionnaire on recreational PA. Conversion to total kcal expended per week |
| Sternfeld et al.[20] | 1970 early-stage BC patients | 18-79, mean 60.6 | Prospective, observational study (Life After Cancer Epidemiology (LACE) Study) | Questionnaire based on the Arizona Activity Frequency Questionnaire. Conversion to MET-hrs |
| Keegan et al.[18] | 4153 BC patients (320 patients excluded from Australian cases) | 18-69 | Population-based cancer registries (Breast Cancer Family Registry) | Questionnaires administered post-diagnosis. Conversion to MET-hrs. |
| West-Wright et al.[21] | 3,539 BC patients with invasive BC | 26-94, mean age 58.9 | Prospective Cohort Study (California Teacher's Study) | PA questionnaire on recreational PA. hrs/week and months per year recorded. |
| Enger et al.[22] | 717 BC patients with in situ or invasive BC | 21-40 | Population-based case-control study | Lifetime PA measured in hrs/week of recreational exercises. |
| Abrahamson et al.[23] | 1264 BC patients with invasive BC | 20-54, median 42 | Population-based cohort study (parent study) | Relative MET scores for vigorous (9 METs) and moderate (5 METs) activities. Scores weighted by frequency of the activity per week. |

BC, breast cancer; HR, Hazard Ratio; PA, physical activity; hrs, hours; MET-hrs, Metabolic Equivalent Task hours

| Details of study | Primary outcome | Overall results |
|---|---|---|
| Questionnaire at baseline and 12-months. Post-treatment and change in PA | Invasive breast-cancer events and all-cause mortality | High baseline (post-treatment) PA (conform guidelines) lead to 35% reduction in all-cause mortality (HR 0.39 (0.21-0.72) for highest quintile total PA vs no PA). Change in PA had no effect on outcomes |
| Baseline interview post-diagnosis on pre-diagnosis recreational PA | 5-year all-cause mortality and BC-specific mortality | Significant lower risk for BC-specific mortality (HR 0.63 (043-0.92)) (any total lifetime RPA vs no RPA), significantly lower risk for all-cause mortality (HR 0.58 (0.43-0.78)) |
| Questionnaire completed once max 1 year post-diagnosis | All-cause mortality and BC-specific mortality | Leisure time PA was not associated with BC mortality: HR=0.85(0.68-1.07) for PA <2hr/wk vs. >2/wk Leisure time PA was not associated with all-cause mortality: HR=0.92 (0.67-1.01) for PA<2hr/wk. vs. >2/wk Occupational PA was not associated with BC mortality or all-cause mortality |
| Questionnaire on pre-diagnosis PA (for the year preceding each survey) | All-cause mortality and BC-specific mortality | Overall mortality was not significantly better in active patients (HR 0.74 (0.51-1.08)) (highest category vs lowest category of PA) or with BC-specific mortality (HR 0.75 (0.49-1.15)) |
| Questionnaire on lifetime recreational, household and occupational PA, recorded at baseline only | All-cause mortality, BC-specific mortality, recurrence, progression, new primary | Vigorous intensity was not related to recurrence, BC-specific mortality and all-cause mortality. However, moderate intensity recreational physical activity was beneficial for all the outcomes (HR BC-specific mortality 0.66 (0.48-0.91), HR all-cause mortality 0.76 (0.58-1.06 with p=0.05), HR recurrence 0.48-0.91) |
| Self-reported pre-diagnosis PA | All-cause mortality | High PA (>4h/wk) vs moderate PA (2-4h/wk) vs no PA was not associated with reduced all-cause mortality after BC diagnosis (Moderate: HR=1.07, 0.77-1.49; High: HR=1.00, 0.69-1.45). High vs moderate vs no PA was not associated with reduced BC-specific mortality (Moderate: HR=0.73, 0.50-1.08; High: HR=0.70, 0.46-1.09). |
| Telephone interview within 2 years of diagnosis. Survivors completed a questionnaire for recent post-diagnosis PA. | All-cause mortality and BC-specific mortality | Compared with low recent post-diagnosis recreational PA (<2.8MET-hr/wk), higher PA was associated with a decreased risk of BC death. Overall mortality was also improved with increasing levels of PA. When stratified, moderate-intensity recreational PA had a significant beneficial effect on both outcomes, but vigorous-intensity PA did not |
| Questionnaires every 2 years from 1976-2004 for current PA. | BC-specific mortality | The HR for BC mortality was 0.80 (0.60-1.06) for 3- 8.9 MET-hrs/wk; 0.50 (0.31-0.82) for 9 to 14.9 MET-hr/wk; 0.56 (0.38- 0.84) for 15 to 23.9 MET-hr/wk; and 0.60 (0.40-0.89) for 24 or more MET-hr/wk |
| In-person baseline interview (4-8 months) post-diagnosis. Follow-up interview 3 years post-diagnosis | BC-specific mortality and all-cause mortality | Compared with inactive women (0 MET-hr/wk) BC mortality in pre-diagnostic PA: >9MET-hr was not significantly better (HR 0.69 (0.45-1.06)), but post-diagnosis PA was beneficial (HR 0.33 (0.15-0.73)). Increase in PA lead to non-significant 45% lower risk of all-cause mortality (HR 0.55,(0.22-1.38)); decrease in PA: HR=3.95 (1.45-10.5) |
| Questionnaire on recreational and household PA at baseline, year 3 and year 6 post-diagnosis | All-cause mortality and BC-specific mortality | Moderate- to vigorous-intensity post-diagnosis PA lead to a lower risk for all-cause mortality (HR 0.54 (0.38-0.79)) and a lower risk for BC-specific mortality (HR 0.61 (0.35-0.99)). Increase of PA after diagnosis of 9 MET-hr/wk or more lead to 33% less risk of all-cause mortality (HR 0.67 (0.46-0.96)) |
| Baseline PA questionnaire | All-cause mortality | Compared with low PA (0-225 MET-min/wk), high PA was associated with lower all-cause mortality 225-636 MET-min/wk: HR=0.86, 636-1320 MET-min/wk: HR=0.76, 1320-6420 MET-min/wk: HR 0.58 (p=0.02, no 95%-CI reported) |
| Reported pre-diagnosis recreational PA (divided into winter and summer PA) | BC-specific mortality | There was no association between PA and BC-specific mortality in the whole study group (ref 0 kcal/wk). There was also no association between PA and BC-specific mortality when stratified by PA level (light, moderate, and vigorous PA). |
| Semi-annual questionnaire about primary outcomes (self-reported) | All-cause mortality, BC-specific mortality, BC recurrence | There was no association between total PA and all-cause mortality, BC-specific mortality and recurrence, but there was a significantly beneficial effect of moderate activity on all-cause mortality (HR 0.66 (0.42-1.03, p for trend=0.04)), but not on BC-specific mortality and recurrence. |
| Lifetime history of recreational PA and 3 years pre-diagnosis | All-cause mortality | Any recent moderate/vigorous PA versus no activity showed a significantly lower all-cause mortality (HR=0.73, (95%CI 0.60-0.89). Stratified by Estrogen Receptor (ER) status, only ER positive patients had a benefit of PA (HR=0.67 (95%CI 0.4-0.94)) for active vs non-active patients, ER-negative patients: HR=1.05 (95%CI 0.66-1.68) |
| PA questionnaire for long-term and recent pre-diagnosis recreational PA | BC-specific mortality, all-cause mortality | BC-specific mortality was significantly better for long-term intermediate PA HR 0.65 (95%CI 0.45-0.93) and high PA HR 0.53 (0.35-0.80) vs low PA, (p=0.003). For recent PA there was no beneficial effect for BC-specific mortality intermediate PA HR 1.17 (0.84-1.65), high PA HR 1.08 (0.73-1.58), p=0.69. Overall survival was better in long-term PA: intermediate PA HR 0.83 (0.65-1.07) and high PA (0.73 (0.55-0.96) vs low PA (p=0.03). Recent PA was borderline significantly beneficial for overall survival: intermediate PA HR 0.89 (0.71-1.11), high PA HR 0.78 (0.60-1.02) vs low PA (p=0.06) |
| In-person interview on lifetime PA (from first menses) up to 12 months pre-diagnosis | BC-specific mortality | There was no significant benefit of PA: 0.1-0.7hrs: HR 0.86 (0.56-1.32); 0.8-1.6 hrs: HR 0.59 (0.35-1.01); 1.7-3.7hrs: HR 0.87 (0.57-1.33); 3.8+hrs: HR 1.30 (0.81-2.09); p(trend)=0.88 |
| In-person interview for average PA at 12-13 years, 20 years, and the year before diagnosis. | All-cause mortality | There was no significantly beneficial effect of PA in year before diagnosis for: Q2 HR 0.86 (0.63-1.18); Q3: HR 0.81 (0.6-1.12); Q4: HR 0.78 (0.56-1.08) vs quartile Q1. (p=0.10) |

or on two or more occasions.[11, 16, 17, 20, 24, 27] Questionnaires included inquiries on occupational, recreational and/or household activities, either combined or separately. Furthermore, data were collected on either current, pre-diagnostic or post-diagnostic PA, or a combination of these. For most studies[11, 14, 16, 17, 20, 23, 23-25, 27] Metabolic Equivalent Task (MET)-hours were used (or calculated) to assess PA in relation to survival outcomes. MET-hours are a validated measurement of PA, and are frequently used to define intensity and duration of PA. One MET-hour is defined as the equivalent of sitting quietly, or 3.5ml oxygen*kg-1 body weight*minute-1 (1 kcal*kg-1 body weight*hour-1).[28] The remaining studies used either the absolute number of hours of PA[12, 15, 21, 22, 26] or the total kcal expended per week.[19] A majority of studies used validated questionnaires, including the Modifiable Activity Questionnaire [17] and the Collaborative Women's Longevity Study (CWLS) questionnaire.[27] In most studies, tumor and treatment characteristics, socio-demographic characteristics, lifestyle habits (education, occupation, smoking, alcohol use), menstrual and reproductive history, exogenous hormone use, and comorbidities were also documented.

**Primary endpoints**

Fourteen studies assessed all-cause mortality[11-15, 17, 18, 20, 21, 23-27], 12 studies assessed breast cancer-specific mortality[11-14, 16, 17, 19-22, 26, 27], and three studies investigated breast cancer recurrence as primary endpoint(s).[14, 20, 24] All hazard ratios (HR) reported in this review concern the highest amount of PA versus the lowest amount of PA, the lowest level of PA being the reference value. All reported HRs are multivariable adjusted.

**Effects of physical activity on breast cancer-specific and all-cause mortality**

Eight out of 12 studies that investigated the effect of PA on BCSS found a significant advantage of PA on survival, ranging from a 36-67% reduction in risk of death for the highest amount of PA versus no PA (HR ranging from 0.53 (95%CI 0.35-0.80) to 0.80 (no 95%CI reported)[11-14, 16-18, 27]. Three of the remaining four studies found a non-significant benefit (HR 0.85 (95%CI 0.68-1.07), HR 0.72 (95%CI 0.29-1.81), HR 0.90 (95%CI 0.51-1.58))[19, 20, 26] while the fourth study found a non-significant worse BCSS (HR 1.30 (95%CI 0.81-2.09)).
Fourteen studies described the effect of PA on all-cause mortality, of which ten studies found a significant improvement in all-cause mortality with increasing PA.[13, 14, 17, 18, 20, 21, 24, 25, 27] This effect ranged from 14% to 56% (HR ranged from 0.39 (95%CI 0.21-0.72) to 0.73 (95%CI 0.60-0.89). The remaining studies reported a non-significant protective effect of PA on all-cause mortality.

**Physical activity outcomes in elderly patients**

There were no studies that investigated elderly patients (defined as older than 65 years) separately. However, eight studies stratified their analyses by menopausal status or age[12, 13, 15-19, 27], and one study included postmenopausal patients only (Table 2).[11] Five studies grouped their patients by pre- and postmenopausal status[11, 13, 15-17, 19], while the remaining studies stratified their analyses by age.[12, 17, 18, 27] Three studies found a significantly lower risk of either breast cancer-specific mortality[16] (HR 0.80 (95%CI 0.60-1.06)) or overall mortality[17] (HR 0.29 (95%CI 0.14-0.60)) in the older or postmenopausal active group (highest versus lowest amount of PA) (data from Keegan et al.[18] not shown). The study in which exclusively postmenopausal patients were included demonstrated a significantly lower risk of all-cause mortality (HR 0.67 (95%CI 0.46-

0.96)) and breast cancer-specific mortality (HR 0.61 (95%CI 0.35-0.99)) in patients who were moderate- to vigorously active after diagnosis.[11] The remaining five studies all reported a non-significant benefit of PA on outcomes.[12, 13, 15, 19, 27]

**Differences in outcomes between pre- and post-diagnostic physical activity**

Out of all studies, eleven investigated the effect of pre-diagnostic PA on overall mortality, breast cancer-specific mortality and/or disease-free survival.[12-15, 18, 19, 21-23, 25, 26] Three studies assessed the effect of post-diagnostic PA[16, 20, 27], one study investigated the effect of post-diagnostic PA at different time points[24], and the remaining two studies examined both pre- and post-diagnostic PA.[11, 17] These two studies looked at the effect of pre-diagnostic PA as well as the effect of change in PA after diagnosis on at least one of the outcomes.

*Table 2.* **Physical activity outcomes in older breast cancer patients**

| Study | n | Age | Primary outcome | Age-specific results |
|---|---|---|---|---|
| Cleveland et al.[13] | 1508 | mean 58.6 | 5-year all-cause mortality and BC-specific mortality | Postmenopausal active women had a non-significant decreased risk of BC-specific mortality (HR 0.79 (0.45-1.39)), and a borderline significant decreased risk of all-cause mortality (HR 0.65 (0.42-1.00)) |
| Emaus et al.[12] | 1364 | 17-79, mean 57.5 | All-cause mortality and BC-specific mortality | Non-significant decreased overall mortality in patients >55 (HR 0.60 (0.36-0.99) and non-significant risk of BC death (HR 0.57 (0.31-1.04)) |
| Hellman et al.[15] | 528 | 33-95, median 66.9 | All-cause mortality | In active postmenopausal patients, HR for overall death was 1.71 (1.16-2.54) in highest amount of PA vs no PA |
| Holick et al.[27] | 4482 | 20-79, mean 58.5 | All-cause mortality and BC-specific mortality | The most active patients >59 years had a non-significantly lower risk of BC-mortality (HR 0.85 (0.47-1.54)) |
| Holmes et al.[16] | 2987 | 30-55 | BC-specific mortality | Active postmenopausal women had a significantly lower risk of BC-death (HR 0.73 (0.54-0.98)) |
| Irwin et al.[17] | 933 | mean 55.5 | All-cause mortality and BC-specific mortality | Active women >55years had a significantly lower risk of all-cause mortality (HR 0.29 (0.14-0.60)) |
| Irwin et al.[11] | 4643 | 50-79 | All-cause mortality and BC-specific mortality | Moderate- to vigorous-intensity post-diagnosis PA lead to a lower risk for all-cause mortality (HR 0.54 (0.38-0.79)) and a lower risk of BC-specific mortality (HR 0.61 (0.35-0.99)). Increase in PA after diagnosis of 9 MET-h/week or more lead to 33% decreased risk of all-cause mortality (HR 0.67 (0.46-0.96)) |
| Rohan et al.[19] | 451 | 20-74 | BC-specific mortality | Postmenopausal active women did not have a decreased risk of BC mortality (HR 0.72 (0.29-1.81)) |
| Keegan et al.[18] | 4153 | 18-69 | All-cause mortality | No difference between different ages at diagnosis of menopausal stage (no HRs reported) |

BC, breast cancer; HR, hazard ratio; PA, physical activity; MET, Metabolic Equivalent Task.

Pre-diagnostic PA lead to a significantly better OS in five out of 11 studies[13, 14, 18, 21, 25], of which three studies also ascertained a significantly better BCSS.[13, 14, 21] The remaining studies found beneficial effects, although they did not reach statistical significance. All studies investigating post-diagnostic PA found a beneficial effect on OS.[11, 16, 17, 20, 24, 27] BCSS was significantly lower in three out of five studies that had this endpoint.[16, 17, 27]

An increase in PA was beneficial in one out of two studies, with a HR of 0.67 (95%CI 0.46-0.99) (for the greatest increase in physical activity).[11] Although the second study investigating change in physical activity found a non-significant benefit of increased physical activity (HR 0.55 (95%CI 0.22-1.38)), a much higher risk of all-cause mortality was established in patients with a reduction in PA (HR 3.95 (95%CI 1.45-10.5)) (Table 3).[17]

*Table 3.* **Effect of physical activity on outcomes**

| Study | n | Age | Breast cancer specific mortality | All-cause mortality | Breast cancer recurrence |
|---|---|---|---|---|---|
| Bertram et al.[24] | 2361 BC survivors stage I-III, 1 year post-treatment | 18-70 Median age 54.3 | - | ↓ | - |
| Cleveland et al.[13] | 1508 early-stage BC patients | Mean age 58.6 | ↓ | - | - |
| Dal Maso et al.[26] | 1453 BC patients | 23-74 Median age 55 | No difference | No difference | - |
| Emaus et al.[12] | 1364 BC patients | 17-79 Mean age 57.5 | No difference | No difference | - |
| Friedenreich et al.[14] | 1183 BC patients | Mean age 56 | ↓ | ↓ | ↓ |
| Hellman et al.[15] | 528 primary BC patients | 33-95 Median age 66.9 | No difference | No difference | - |
| Holick et al.[27] | 4482 BC patients, 91% postmenopausal. | 20-79 Mean age 58.5 | ↓ | ↓ | - |
| Holmes et al.[16] | 2987 nurses with stage I/II/III BC | 30-55 | ↓ | - | - |
| Irwin et al.[17] | 933 BC patients with local or regional breast cancer | Mean age 55.5 (6 months post-diagnosis) | ↓ | - | - |
| Irwin et al.[11] | 4643 post-menopausal BC patients | 50-79 | ↓ | ↓ | - |
| Pierce et al.[25] | 1490 early-stage BC patients | <70 Mean age 50 | - | ↓ | - |
| Rohan et al.[19] | 451 BC patients | 20-74 | No difference | - | - |
| Sternfeld et al.[20] | 1970 early-stage BC patients | 18-79 Mean age 60.6 | No difference | ↓ | No difference |
| Keegan et al.[18] | 4153 BC patients (320 patients excluded from Australian cases) | 18-69 | - | ↓ | - |
| West-Wright et al.[21] | 3,539 BC patients with invasive BC | 26-94 Mean age 58.9 | ↓ | ↓ | - |
| Enger et al.[22] | 717 BC patients with in situ or invasive BC | 21-40 | No difference | - | - |
| Abrahamson et al.[23] | 1264 BC patients with invasive BC | 20-54 Median age 42 | No difference | - | - |

BC, breast cancer.

## Physical activity in different BMI-groups

Nine studies stratified their analyses by different BMI-groups.[11-13, 17, 18, 20, 21, 23, 27] Two studies reported on breast cancer-specific mortality as well as all-cause mortality for the stratified groups, while one study reported on breast cancer-specific mortality only. The remaining six studies reported all-cause mortality only for the different groups. The study by Cleveland et al.[13] showed a non-significant lower risk of breast cancer-specific mortality in active patients with a BMI under 25 (HR 0.57 (95%CI 0.30-1.09)) and a significantly lower risk in active patients with a BMI over 25 (HR 0.63 (95%CI 0.40-0.99)).[13] Similarly, the study by Holick et al.[27] found a better BCSS for active patients with a BMI below 25 (although not statistically significant), and a borderline significant effect in patients with a BMI above 25 (HR 0.63 (95%CI 0.39-1.02)).[27] West-wright et al.[21] did not find a significant benefit for active patients with a BMI under 25 (HR 1.15 (95%CI 0.32-0.86)), but a significantly better BCSS in patients with a BMI above 25 (HR 0.41 (95%CI 0.23-0.74) for high PA versus low PA). In patients with a BMI below 25, all-cause mortality was significantly lower in four out of eight studies.[12, 13, 20, 27] One study reported a benefit that was even greater in patients who were 55 years or older.[13] Four studies found a lower all-cause mortality in active patients with a BMI over 25.[13, 17, 23, 27]

## DISCUSSION

We present an overview of the available literature on the effect of PA on breast cancer outcomes. Most studies demonstrate that PA has a positive effect on OS and BCSS. Post-diagnostic PA was most beneficial for breast cancer outcomes. Most investigations were observational studies with low median ages, with the exception of one study that investigated only postmenopausal breast cancer patients. Although no study specifically addressed patients who were 65 years or older, we observed that older and/or postmenopausal patients acquired the greatest advantage of PA.

Several explanations have been proposed for the age-related benefit. In addition to concurrent comorbid conditions, aging is associated with declines in physical and cognitive functioning. A large cohort study of breast cancer survivors showed that functional limitations were associated with worse all-cause and competing-cause mortality.[29] Cancer patients are at increased risk of reporting limitations in their activities of daily living compared to non-cancer patients.[9, 30] Several exercise programs demonstrated varying positive effects in older people, including improved muscle strength and gait speed, reduction in falls, improved balance, bone mineral density and increased mental health.[31-37] The Canadian Study of Health and Aging showed that older persons who participated in high levels of PA had a lower risk of death than those who did little or no exercise; the absolute benefits were greatest for those with the highest number of health deficits.[37]

Investigators have speculated on the biological mechanism behind these findings. The effect of PA on breast cancer specific survival was stronger for overweight patients (BMI>25) than normal-weight patients. Although these findings were not paralleled for all-cause mortality, the effect of PA on the reduction in weight and, subsequently, on insulin levels are a likely explanation. It is well-known that postmenopausal patients with obesity and high insulin levels and/or diabetes mellitus have a greater risk of breast cancer.[38-40] Insulin resistance is thought to influence the risk of breast cancer recurrence and mortality[41-43] Pasanisi et al. found that higher insulin levels and insulin resistance syndrome are associated with breast cancer mortality.[41] Importantly, PA can significantly lower insulin levels in women with breast cancer. It has also been suggested that PA reduces breast cancer risk by improving metabolic profiles as well as by decreasing levels of endogenous estrogens and body fat.[44]

Aging is a strong predictor of functional decline and comorbidities, and literature suggests that older cancer patients are more likely to be affected by cancer in terms of physical than cognitive functioning.[9, 45, 46] Physical domains are especially important in elderly patients, as they can make the difference between independent and assisted living. As breast cancer in elderly patients is predominantly estrogen receptor (ER)-positive, systemic endocrine treatment is frequently warranted. Toxicities of endocrine therapy and the larger number of comorbid conditions with increasing age may result in patients being more vulnerable to the clinical consequences of adverse events. Previous reports have demonstrated that PA can improve

comorbid conditions and adverse effects of adjuvant treatment [47, 48], therefore, PA can provide an additional benefit in these patients.
Because of the heterogeneity of the data collected and different definitions of low, moderate and high intensity PA, we could not perform a pooled meta-analysis of the reported HRs. Furthermore, this study is limited to some extent by the lack of evidence that focuses on the effect of PA on breast cancer outcomes in the elderly breast cancer patients specifically. Consequently, the effect of PA on overall and breast cancer-specific mortality in elderly patients may reveal an even greater benefit, given the prevalence of more ER-positive tumors as well as frailer patients who are likely to gain most from PA. To add, it is important to realize that other factors may also influence the possibility for patients to partake in PA at all. One can presume that, generally speaking, patients without functional limitations are more likely to be healthy and capable of exercising, while patients who are restricted due to health deficits are already less physically active, and thus at an increased risk of adverse outcomes. For this reason, further investigations into the cancer-aging interface and the influence of breast cancer on functional decline in elderly patients are indispensable. We have initiated 'Climb Every Mountain', a longitudinal, prospective cohort study that measures physical, cognitive, and social health during and after breast cancer treatment. The purpose of this study is to generate new knowledge on the prevalence and impact of functional, cognitive, and social limitations in elderly breast cancer survivors. A second phase will use those domains most affected by cancer diagnosis and treatment, to develop a patient-tailored physical intervention study aimed specifically at the elderly breast cancer patient.

## CONCLUSION

This review covers a very heterogeneous group of patients, consisting of pre-and postmenopausal breast cancer patients with varying tumor-biological and clinical characteristics. In older breast cancer patients specifically, the majority of studies demonstrated a decrease in both all-cause and breast cancer-specific mortality with increasing levels of PA. To add, the decrease in breast cancer-specific mortality was more prominent in overweight patients than in normal-weight patients. Overall, it can be concluded that some degree of PA leads to improved survival outcomes in breast cancer patients, which provides the prospect of employing a practical intervention that can act as a targeted treatment for breast cancer.

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