Effects of Physical Activity on Cancer Survival: A Systematic Review

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ABSTRACT

Purpose: Physical activity (PA) has been suggested to help increase the survival of individuals with cancer. The objective of this review was to systematically evaluate and summarize the available evidence investigating the effect of PA on the survival of individuals with cancer.
Methods: Electronic databases (CINAHL, EMBASE, and MEDLINE) were systematically searched for randomized controlled trials and cohort studies. Selected studies were assessed by two independent investigators for methodological quality, using the PEDro scale.
Results: Ten prospective cohort studies met the inclusion criteria. Quality-assessment scores averaged 5/10 on the PEDro scale, with two articles obtaining a score of 6/10. The majority of studies found that individuals participating in higher levels of physical activity had a reduced risk of cancer-related mortality. This trend was observed specifically for breast, colon, and colorectal cancers. On average, it appears that engaging in higher levels of metabolic equivalent hours per week may help to improve survival rates among individuals diagnosed with cancer.
Conclusion: Patients diagnosed with cancer demonstrated a trend toward increased survival with greater levels of PA. However, because only prospective cohort studies were included in the study, the conclusions drawn should be regarded with caution.

Key Words: cancer, exercise, physical activity, survival, systematic review

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RÉSUMÉ

Objectif : L'activité physique (AP) a été suggérée comme moyen d'aider à la survie des individus atteints de cancer. L'objectif de cette analyse consistait à évaluer systématiquement et à résumer l'ensemble des preuves disponibles relativement aux effets de l'activité physique sur la survie des personnes atteintes de cancer.
Méthode : Une recherche systématique a été réalisée dans les bases de données électroniques (CINAHL, EMBASE et MEDLINE), afin de répertorier les essais cliniques comparatifs randomisés et les études par cohortes. La qualité méthodologique des études sélectionnées a été évaluée par deux chercheurs indépendants à l'aide de l'échelle PEDro.
Résultats : Dix études prospectives par cohortes satisfaisaient les critères d'inclusion. Les résultats de l'évaluation de la qualité se chiffraient en moyenne à 5/10 sur l'échelle de PEDro ; deux articles ont obtenu une note de 6/10. La majorité des études ont permis de constater que les individus prenant part à de l'activité physique plus soutenue couraient moins de risque de mourir du cancer. Cette tendance a été particulièrement observée pour le cancer du sein, du côlon et pour le cancer colorectal. En moyenne, il semble que le fait de participer à des niveaux plus élevés d'équivalents métaboliques par semaine peut aider à améliorer les taux de survie chez les individus ayant reçu un diagnostic de cancer.
Conclusion : Les patients ayant reçu un diagnostic de cancer ont démontré un plus grand taux de survie avec un niveau plus élevé d'AP. Toutefois, en raison de l'inclusion d'études sur cohortes seulement, les conclusions de cette étude doivent toutefois être considérées avec prudence.

Mots clés : activité physique, cancer, exercice, revue systématique, survie

INTRODUCTION

Some 24.6 million people worldwide are living with a diagnosis of cancer.[1] Cancer is one of the leading causes of death worldwide, accounting for 13% of all deaths, equivalent to 7.4 million people per year.[2] In Canada alone, an estimated 75,300 deaths from cancer were predicted to occur in 2009.[3] Based on current mortality rates, one in every four Canadians will die from cancer.[3]

According to the World Health Organization (WHO), physical activity (PA) is among the nine modifiable risk

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factors for cancer.[2] Low levels of PA, together with obesity, are associated with one-fifth to one-third of all colon, breast, kidney, and digestive cancers.[4]

The effectiveness of PA interventions in patients with various types of cancer has previously been investigated in the literature. According to a recent review by Courneya et al.,[5] PA and its direct relation to cancer prevention remains the most studied. With more than 250 articles examining this topic, it is the general consensus that PA is "convincingly associated with the reduced risk of developing colon and breast cancers"[5(p.245)] and may be associated with a reduced risk of endometrial, prostate, and lung cancers.[5] Several recent systematic reviews have demonstrated the effectiveness of PA in reducing fatigue and improving physical functioning, quality of life, and cardiorespiratory fitness in breast-cancer patients and survivors.[6–8] PA has also been suggested to help increase the survival of individuals with cancer by reducing the risk of recurrence or by slowing the progression of cancer and reducing the risk of secondary life-threatening diseases.[5] Studies have begun to examine the impact of PA beyond cancer incidence and to investigate its effect on survival after diagnosis; to our knowledge, however, no systematic review (SR) has been performed on this topic. The purpose of this SR, therefore, was to systematically evaluate the methodological quality of investigations into the effect of PA on the survival of individuals with cancer and to summarize the available evidence.

METHODS

Inclusion Criteria

A study was eligible for inclusion if it was a randomized controlled trial (RCT) or cohort study that investigated the effect of PA on survival of patients diagnosed with cancer. Studies meeting the following criteria were included: (1) participants with a diagnosis of any type, level, and severity of cancer at any time point throughout the study period; (2) adult subjects (>18 years of age); (3) minimum follow-up period of 3 years post-diagnosis; and (4) assessment of participation in physical activity. No language restrictions were used; any non-English studies retrieved through the literature search would be translated to determine the appropriateness of inclusion. No exclusion criteria were established.

PA is defined as "bodily movement produced by skeletal muscles that results in energy expenditure,"[9(p.126)] including conditioning exercises, sports, occupational activities, and household activities.[9] An attempt will be made here to present levels of PA uniformly in metabolic equivalents, a recognized and commonly used measure of PA. Metabolic equivalent (MET) is defined as "the ratio of work metabolic rate to a standard resting metabolic rate."[10(p.71)] For example, 1 MET is equivalent to the energy expended during quiet sitting.[10] For comparison purposes, 1 MET equals 1 $kcal \cdot kg^{-1} \cdot hr^{-1}$.[10]

The primary outcome of interest was *survival*, assessed by vital status at the end of the study period. Other outcomes include survival probability, disease-free survival, and cancer-specific and overall mortality. These outcomes are primarily expressed as relative risks or hazard ratios. Relative risk (RR) is defined as the risk of an event's occurring relative to exposure.[11] An RR of >1 increases one's risk of an event's occurring (in this case, death), whereas an RR of <1 demonstrates a protective effect, decreasing the chance of the outcome's occurring (in this case, a decreased risk of death). Hazard ratio (HR) is a measure of how often an event occurs in one group compared to how often the same event occurs in another group.[11] An HR >1 indicates that the event (in this case, death) occurs more frequently in the reference group, whereas an HR <1 indicates that the event occurs less frequently in the reference group.

Search Strategy

Eligible studies were identified by searching the following databases: CINAHL (1982–May 2008), EMBASE (1980–2008), and MEDLINE (1950–May 2008). A librarian was consulted prior to initiating the search in order to identify appropriate search terms related to PA and cancer survival. Search terms used were *neoplasm(s)*, *cancer(s)*, *exercise*, *exercise therapy*, *physical activity*, *physical fitness*, *exercise capacity*, *survival*, *survivor(s)*, *survival analysis*, and *survival rate*. Two reviewers (MB, OC) independently screened the titles, abstracts, and key words of the retrieved articles for inclusion. After independently reviewing the articles for inclusion, the reviewers compared selected articles to ensure consensus. Once agreement had been reached, a full-text copy of each article that met the inclusion criteria was obtained.

Quality Assessment

The methodological quality of the studies was assessed independently by two blinded reviewers (EB, LM). Evidence suggests that lower and more consistent quality-assessment scores are obtained when reviewers are blinded to authors, title, journal, and institution.[12] Because of the potential for inclusion of both RCTs and observational cohort studies, a scale that would allow for comparison between study designs was necessary for quality assessment. Therefore, each study was evaluated using the 11-item PEDro scale. Although this scale was developed to assess the quality of RCTs in physiotherapy literature,[13] it has also been used to evaluate a variety of study designs. For example, both PsycBITE[14] and PEDro[15] databases use this scale to analyse all study designs, including observational studies. The total score ranges from 0 to 10, with a higher score signifying higher

Table 1 Quality-Assessment Scores using the PEDro Scale

Article	*PEDro Scores*										
	Overall Score	*Random Allocation*	*Concealed Allocation*	*Groups Similar*	*Subject Blinding*	*Therapist Blinding*	*Assessor Blinding*	*<15% Dropouts*	*Intention to Treat*	*Between-Group Comparison*	*Variability Data*
Breast Cancer											
Abrahamson et al. (2006)[18]	5/10	No	Yes	Yes	No	No	No	Yes	No	Yes	Yes
Borugian et al. (2004)[19]	5/10	No	Yes	Yes	No	No	No	Yes	No	Yes	Yes
Enger & Bernstein (2004)[20]	3/10	No	Yes	No	No	No	No	No	No	Yes	Yes
Holick et al. (2008)[23]	5/10	No	Yes	Yes	No	No	No	Yes	No	Yes	Yes
Holmes et al. (2005)[24]	6/10	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
Pierce et al. (2007)[30]	5/10	No	Yes	Yes	No	No	No	Yes	No	Yes	Yes
Rohan et al. (1995)[31]	5/10	No	Yes	Yes	No	No	No	Yes	No	Yes	Yes
Colon or Colorectal Cancer											
Haydon et al. (2006)[22]	5/10	No	Yes	Yes	No	No	No	Yes	No	Yes	Yes
Meyerhardt et al. (2006a)[28]	6/10	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
Meyerhardt et al. (2006b)[29]	4/10	No	Yes	Yes	No	No	No	No	No	Yes	Yes

quality.[13] It is acknowledged that evaluating non-RCTs with PEDro will yield lower scores because of the lack of randomization—a specific criterion on this scale. Based on the limitations of the PEDro scale in the evaluation of observational studies, the Newcastle-Ottawa Scale (NOS)[16] was selected to further analyse the methodological strengths and weaknesses of the included cohort studies. The NOS is a comprehensive, validated tool used to evaluate the quality of non-RCTs in meta-analysis.[17]

The reviewers pilot-tested the quality assessment on similar articles that were not included in the study, which allowed them to become familiar with the use of the scale and to ensure a common interpretation of the items.

RESULTS

Completion of the literature search outlined above yielded a total of 1,552 articles. Of these articles, 16[18–33] were considered to be potentially relevant. Walsh et al.[33] was later excluded because although the study assessed performance status, after further review this was determined not to be a measure of PA as defined by the authors. Meyer et al.[27] did not report the interaction between PA and cancer mortality and was therefore not included. Sawada et al.[32] did not satisfy the inclusion criteria, as the study measured only physical fitness, with no assessment of PA. Three additional studies[21,25,26] were excluded because no incidence or prevalence of cancer cases was outlined, meaning that the rates of cancer survival, and the subsequent effect of PA post-diagnosis, could not be determined. All articles included in this SR were prospective cohort studies (level 2b in Sackett's levels of evidence).[34]

Quality assessment was completed for the remaining 10 articles[18–20,22–24,28–31] that met the inclusion criteria. The kappa (κ) value for interrater reliability for PEDro scores was 0.96**,** representing excellent agreement between raters.[35] The majority of the studies were found to be of moderate methodological quality (mean PEDro score of 5/10). Table 1 shows quality-assessment scores for the included studies; further details of these studies are provided in Table 2.

Diagnosis

Studies included in this SR investigated the effect of PA on different types of cancer: seven studies investigated participants with breast cancer,[18–20,23,24,30,31] two examined colorectal cancer,[22,28] and one investigated colon cancer.[29]

Physical Activity Assessment

All studies included in this SR categorized participants based on level of PA.[18–20,22–24,28–31] The majority of the studies categorized level of PA based on METs or

Table 2 Characteristics of Included Studies

First Author (Year), Location	*Sample*	*Follow-Up (years)*	*Cancer Type*	*Physical Activity Assessment*	*Main Results*
Abrahamson et al. (2006), USA[18]	$N = 1{,}264$ Sex: Female Age: 20–54 years	8–10	Breast cancer—localized, regional, distant	Frequency per week of participation in vigorous PA (e.g., lap swimming, dance, basketball, gymnastics, running, fast cycling, aerobics, field hockey) and moderate PA (e.g., brisk walking, volleyball, recreational tennis, softball, leisurely cycling, golfing) Frequency of climbing at least two flights of stairs within 1 year	Increasing PA frequency in the year before diagnosis was significantly associated with decreased risk of mortality: HR = 0.86 (95% CI: 0.63–1.18) for 2nd quartile of PA, 0.81 (95% CI: 0.60–1.12) for 3rd quartile of PA, 0.78 (95% CI: 0.56–1.08) for 4th quartile of PA (p trend = 0.10).* Reduced risk was not seen for activity at age 13 years, age 20 years, or overall average ($p = 0.08$, 0.55, and 0.25 respectively).
Borugian et al. (2004), Canada[19]	$N = 603$ Sex: Female Age: 19–75 years	10	Breast cancer—stage I, II, III	Frequency per week, month, or year of participation in physical exercise, active sports, jogging or running, swimming or taking long walks, and gardening or fishing or hunting Number of blocks walked per day Flights of stairs climbed per day	No clear dose–response association was observed for any of the leisure-time physical activity measures and mortality. Women reporting participation in sports only a few times per year versus no sports participation in the last year had an increased risk of mortality (RR = 2.5; 95% CI: 1.0–5.9; p value not reported). Pre-menopausal women who participated in PA >3 times/week had an increased risk of mortality compared with non-exercisers (RR = 2.9; 95% CI: 1.1–7.3; p value not reported).*
Enger & Bernstein (2004), USA[20]	$N = 717$ Sex: Female Age: ≤40 years	10.4	Breast cancer—*in situ*, localized, regional, distant	Average hours/week of participation in vigorous activity such as competitive athletic teams, dance, exercise classes, or jogging/running 1.6 km at least twice weekly	Lifetime vigorous exercise was not found to be significantly associated with survival. Vigorous exercise 1 year prior to diagnosis was weakly associated with longer survival (p trend = 0.31).*
Holick et al. (2008), USA[23]	$N = 4{,}482$ Sex: Female Age: 20–79 years	5.5	Breast cancer—regional, local	Average time per week spent participating in activities such as walking outdoors (usual walking pace reported), running ≥10 min/mile, lap swimming, tennis, squash or racquetball, calisthenics, aerobics or rowing, marching, and other aerobic activities (e.g., lawn mowing) Number of flights of stairs climbed daily	Greater activity levels were associated with a significantly lower risk of dying from breast cancer: HR = 0.65 (95% CI: 0.39–1.08) for 2.8–7.9 MET-hr/wk; HR = 0.59 (95% CI: 0.35–1.01) for 8.0–20.9 MET-hr/wk; and HR = 0.51 (95% CI: 0.29–0.89) for ≥21.0 MET-hr/wk (p trend <0.001).
Holmes et al. (2005), USA[24]	$N = 2{,}987$ Sex: Female Age: 30–55 years	8	Breast cancer—stage I, II, III	Average time spent per week on walking (usual walking pace reported), hiking, jogging, bicycling, swimming, tennis, calisthenics, aerobics, aerobic dance, rowing machine, squash, or racquetball	Increased risk of mortality observed for women who engaged in lower amounts of PA: breast-cancer-related mortality: RR = 0.80 (95% CI: 0.60–1.06) for 3–8.9 MET-hr/wk; RR = 0.50 (95% CI: 0.31–0.82) for 9–14.9 MET-hr/wk; RR = 0.56 (95% CI: 0.38–0.84) for 15–23.9 MET-hr/wk; and RR = 0.60 (95% CI: 0.40–0.89) for ≥24 MET-hr/wk (p trend = 0.004). Overall mortality: RR = 0.71 (95% CI: 0.56–0.89) for 3–8.9 MET-hr/wk; RR = 0.59 (95% CI: 0.41–0.84) for 9–14.9 MET-hr/wk; RR = 0.56 (95% CI: 0.41–0.77) for 15–23.9 MET-hr/wk; and RR = 0.65 (95% CI: 0.48–0.88) ≥24 MET-hr/wk (p trend = 0.003).
Pierce et al. (2007), USA[30]	$N = 1{,}409$ Sex: Female Age: ≤70 years	6.7	Breast cancer—stage I, II, III	Frequency, duration, and speed of walking outside the home and participation in strenuous, moderate-intensity, or mild-intensity exercise	Linear trend with the highest mortality in the lowest PA quartile observed; unadjusted HR = 0.86 for 3.75–10.6 MET-hr/wk, 0.76 for 10.6–22 MET-hr/wk, 0.58 for >22 MET-hr/wk (p trend = 0.02). *Note:* MET-min/wk were converted into MET-hr/wk by dividing MET-min/wk by 60.

Rohan et al. (1995), Australia[31]	$N = 451$ Sex: Female Age: 20–74 years	5.5	Breast cancer	Number of hours/week spent doing light activity (e.g., bowling, walking, golf), moderate activity (e.g., dancing, horseback riding), vigorous activity (e.g., competitive squash, tennis)	Little association between risk of mortality from breast cancer and PA levels: HR = 1.42 (95% CI: 0.78–2.60) for ≤2000 kcal/wk; HR = 0.73 (95% CI: 0.37–1.42) for 2000–4000 kcal/wk; HR = 0.98 for >4000 kcal/wk (p trend = 0.803)*
Haydon et al. (2006), Australia[22]	$N = 526$ Sex: 270 male, 256 female Age: 27–75	5.5	Colorectal cancer—stage I, II, III, IV	Number of times per week vigorous exercise was performed for at least 20 min Number of times per week less vigorous exercise was performed for recreation, sport, health, and fitness purposes	Individuals who performed regular PA demonstrated increased disease-specific survival (HR = 0.73; 95% CI: 0.54–1.00; $p = 0.05$) and overall survival (HR = 0.77; 95% CI: 0.58–1.03; $p = 0.08$).* Decreased mortality risk was largely confined to stage II–III tumours: HR = 0.49 (95% CI: 0.30–0.79, $p = 0.01$).
Meyerhardt et al. (2006a), USA[28]	$N = 573$ Sex: Female Age: Median 65 years	9.6	Colorectal cancer—stage I, II, III	Duration per week of participation in walking, jogging, running, bicycling, swimming laps, racket sports, other aerobic exercises, lower-intensity exercise (yoga, stretching), or other vigorous activities	Increasing levels of exercise after diagnosis of colorectal cancer reduced the risk of cancer-specific and overall mortality. Cancer-related mortality: HR = 0.92 (95% CI: 0.50–1.69) for 3–7.9 MET-hr/wk; HR = 0.57 (95% CI: 0.27–1.20) for 9–17.9 MET hr/wk; HR = 0.39 (95% CI: 0.18–0.82) for ≥18 MET hr/wk (p trend = 0.008). Overall mortality: HR = 0.77 (95% CI: 0.48–1.23) for 3–7.9 MET-hr/wk; HR = 0.50 (95% CI: 0.28–0.90) for 9–17.9 MET hr/wk; HR = 0.43 (95% CI: 0.25–0.74) for 18 MET hr/wk (p trend = 0.003). Pre-diagnosis PA level was not predictive of mortality. Increasing PA levels from pre-diagnosis to post-diagnosis versus no change decreased the risk of cancer-specific and all cause mortality compared to those with no change in activity: Cancer-related mortality HR = 0.48 (95% CI: 0.24 to 0.97, p trend = 0.02); overall mortality HR = 0.51 (95% CI: 0.30 to 0.85, p trend = 0.002).
Meyerhardt et al. (2006b), USA[29]	$N = 832$ Sex: 470 male, 362 female Age: Median 59 years	3.8	Colon cancer—stage III	Duration of participation in walking (usual walking pace reported), jogging, running, bicycling, swimming laps, racket sports, other aerobic exercise, lower-intensity exercises (yoga, toning, stretching) Number of flights of stairs climbed daily	Women participating in greater levels of PA demonstrated significantly increased disease-free survival: HR = 0.87 (95% CI: 0.58–1.29) for 3–8.9 MET-hr/wk, HR = 0.90 (95% CI: 0.57–1.40) for 9–17.9 MET-hr/wk, HR = 0.51 (95% CI: 0.26–0.97) for 18–26.9 MET-hr/wk, HR = 0.55 (95% CI: 0.33–0.91) for ≥27 MET-hr/wk (p trend = 0.01).

PA = physical activity; HR = hazard ratio; RR = relative risk; CI = confidence interval; MET = metabolic equivalent

* Unable to convert results into MET-hr/wk.

kilocalories (kcal) per unit of frequency and duration, such as MET hours per week (see Table 2 for other PA categories). Depending on the study, the participant's level of PA was assessed based on at least one of three time frames: (1) activity level at least 1 year prior to diagnosis; (2) lifetime level of PA; and (3) level of PA post-diagnosis and throughout follow-up.

Physical Activity and Breast-Cancer Survival

Of the seven articles investigating the effect of PA on breast-cancer survival,[18,20,23,24,30,31] five studies based results on baseline levels of PA[19,23,24,30,31] while the remaining two investigated lifetime levels of PA.[18,20] Three of the five measuring baseline PA levels studies provided statistically significant evidence in support of the role of PA in decreasing cancer mortality in patients with breast cancer.[23,24,30]

In a sample of primarily non-Hispanic white participants, Holmes et al.[24] found that the adjusted RR of death from breast cancer decreased with increasing levels of PA.[24] Women who engaged in ≥9 MET-hr/wk of PA demonstrated an RR of 0.63 (95% CI: 0.48–0.81).[24] These results were more pronounced in the population of women with hormone-responsive tumours (RR = 0.50; 95% CI: 0.34–0.74).[24] In women who engaged in >9 MET-hr/wk, the 5-year survival rate was 97%; the 10-year survival rate was 92%.[24] The 5- and 10-year survival rates for women who engaged in <3 MET-hr/wk of PA were 93% and 86%, respectively.[24] Holick et al.[23] found that Caucasian women who participated in >2.8 MET-hr/wk of PA had statistically significant improvements in breast-cancer survival and overall survival (p trend = 0.05).[23] An increment of 5 MET-hr/wk of moderate activity was found to be associated with a 15% lower risk of death from breast cancer (p trend = 0.03).[23] However, 5 MET-hr/wk of vigorous activity was not found to improve breast-cancer survival (p trend = 0.92).[23] Pierce et al.[30] reinforced these findings, reporting a linear trend with the highest mortality rate in the quartile representing the lowest level of PA (<3.75 MET-hr/wk);[30] reduced mortality was observed for women in the highest two quartiles of PA (p trend = 0.02).[30]

In the studies by Rohan et al.[31] and Borugian et al.,[19] there was no significant inverse relationship between PA and cancer mortality. Borugian et al.[19] found no clear relationship between PA levels and breast-cancer-related mortality in an urban Caucasian cohort.[19] In fact, participation in PA was shown to increase the risk of breast-cancer-related mortality in pre- and post-menopausal women.[19] In post-menopausal women, a statistically significant RR of 2.5 (95% CI: 1.0–5.9) was associated with random bouts of sports activity versus reports of no sport-related activity.[19] Pre-menopausal women were found to have increased risk of mortality with participation in PA >3 times per week compared to women who did not exercise at all (RR = 2.9; 95% CI: 1.1–7.3).[19]

The studies by Abrahamson et al.[18] and Enger and Bernstein[20] categorized participants based on level of PA during the year prior to diagnosis, as well as activity level through adolescence and early adulthood. The results in the study by Abrahamson et al.[18] indicated that higher levels of PA in the year preceding the diagnosis of breast cancer decreased rates of cancer mortality; HR = 0.78 (95% CI: 0.56–1.08) for mortality in the highest quartile of PA relative to the lowest quartile (p trend = 0.10).[18] In the study by Enger and Bernstein,[20] the definition of PA was based on participation in high-intensity activities, including competitive sports or running/jogging, during the years following menses. This study concluded that lifetime exercise is not associated with improved breast-cancer survival.[20] However, there was a trend toward improved rates of cancer survival with participation in PA 1 year prior to diagnosis ($p = 0.31$).[20]

Physical Activity and Colon/Colorectal-Cancer Survival

Three studies investigated the effects of exercise on cancer survival in patients diagnosed with colon[29] or colorectal[22,28] cancer. Meyerhardt et al.[29] demonstrated that disease-free colon-cancer survival improved with increasing levels of PA (p trend <0.01). Based on the results of this study, it is suggested that a protective HR is observed with >18 total MET-hr/wk or equivalent; the protective HR does not improve beyond 27 MET-hr/wk.[29]

Two studies investigated the effect of PA on mortality in patients diagnosed with colorectal cancer.[22,28] Haydon et al.[22] demonstrated that persons who exercised at least once a week had improved disease-specific survival (HR = 0.73; 95% CI: 0.54–1.00, $p = 0.05$). The benefit of PA was largely confined to stage II–III tumours (HR = 0.49; 95% CI: 0.30–0.79, $p = 0.01$), while no association was seen in stage I (least severe) or stage IV (most severe) tumours.[22] The results of the study by Meyerhardt et al.[28] supported the role of post-diagnosis PA in decreasing cancer-specific mortality ($p = 0.008$) and overall mortality ($p = 0.003$). Pre-diagnosis level of PA was not found to be predictive of mortality,[28] whereas women who increased their activity level after diagnosis had an HR of 0.48 (95% CI: 0.24–0.97) for colorectal-cancer deaths and an HR of 0.51 (95% CI: 0.30–0.85) for all-cause mortality versus those with no change in activity.[28] In contrast, among women who decreased their activity level there was a modest, though non-significant, increase in both cancer-specific and overall mortality.[28]

DISCUSSION

The results of this SR should be interpreted with caution, for a number of reasons to be discussed below.

With this in mind, there appears to be a trend toward increased survival among patients diagnosed with breast and colon/colorectal cancer who participate in greater levels of PA. The majority of studies,[18,22–24,28–30] including the two studies of highest methodological quality,[24,28] supported this trend.

Participation in PA was found to improve rates of breast-cancer survival in four of the seven studies.[18,23,24,30] Unfortunately, conclusions cannot be drawn with respect to an optimal dose of PA because of differences in the methods used to measure PA and in the time points of PA assessment (i.e., pre- versus post-diagnosis). Although the exact mechanism through which PA may affect breast-cancer survival is unknown, a few possible hypotheses exist. PA may influence prognosis by similar mechanisms to those thought to prevent the incidence of breast cancer, including decreased lifetime estrogen exposure,[36] enhanced immune function,[37] and reduced insulin resistance.[36] Lower blood-estrogen levels,[38] higher insulin growth factor–I (IGF-I) concentration,[39] and lower levels of fatty tissue have all been associated with participation in PA.[39] Reductions in blood-estrogen levels have been associated with decreased proliferative activity in breast tissue.[40]

Similarly, higher PA levels pre- and post-diagnosis of colon cancer and post-diagnosis of colorectal cancer were also associated with a decreased cancer-related mortality risk in this SR.[22,28,29] PA appeared to further improve survival rates in conjunction with other standard cancer treatments.[29] It is of interest that cancer-specific and overall mortality rates were very similarly affected by PA.[28] If the overall mortality rate was further decreased by increasing PA, one would expect that this was due to a decrease in non-cancer-related deaths;[28] the fact that there was no difference in the effect of PA between cancer-specific and overall mortality suggests that improved survival was likely a direct effect of PA on tumour biology.[28] One possible mechanism by which PA may have an effect on tumour biology is by increasing insulin sensitivity, thus decreasing serum insulin concentrations; it has been suggested that insulin promotes carcinogenesis in various organs, including the colon.[40] Another possible mechanism by which PA may decrease mortality from colon/colorectal cancer is by reducing bowel transit time, altering prostaglandin levels and immune-system function.[22,40]

As discussed above, a PA level of >3 MET-hr/wk was shown to have a beneficial effect on breast-cancer survival, whereas the beneficial effects of PA on colon cancer began at >18 MET-hr/wk. Although the exact mechanism for this substantial difference is unknown, it may be explained by the means through which PA affects each type of cancer. For example, the protective effect of PA on breast cancer may be primarily due to its effect on serum estrogen levels.[40] This hormonal effect may play less of a role in improving survival in other types of cancer, such as colon cancer, which may explain the differences in the protective effects associated with the PA levels presented above.

It must be acknowledged that 3 of the 10 studies did not display statistically significant results supporting the positive effect of PA on breast-cancer survival.[19,20,31] One study rejected an inverse relationship between PA level and breast-cancer mortality because of the finding of an increased risk of death among post-menopausal women participating in random bouts of sport-related activity and among pre-menopausal women participating in exercise.[19] The reason for these results is unclear; however, the authors speculate that their results may have been influenced by the inclusion of a fairly sedentary cohort, or may have occurred by chance.[19] Of the two studies that did not find an association between PA and cancer survival, one was of moderate methodological quality,[31] while the other study had significant limitations.[20] For example, the latter study assessed only high-intensity PA and made no mention of controlling for confounding variables.[20]

As mentioned above, results drawn from this SR must be interpreted with caution because of methodological limitations. It is important to note that the NOS was used as a guideline to discuss the methodological strengths and weaknesses of the studies included in this SR. To begin with, the generalizability of the results is affected by the study population. The majority of participants were Caucasian[18,19,23,24,29] women[18–20,23,24,28,30,31] ranging from 20 to 75 years of age. A few studies limited their sample to pre-menopausal women.[18,20,24] Typically, study samples included individuals diagnosed with stage I–III cancer.[18,19,24,28,30] As a result, their results cannot be generalized beyond the populations represented above.

All studies included in this review were limited by the tools used to assess PA levels. The majority of studies presented PA as METs, referencing the *Compendium of Physical Activities*.[10,41] Other studies did not use standardized measures of PA; that is, activities were measured by frequency, with no assessment of duration,[19] making it impossible to convert these results into METs-hrs/wk. The majority of the studies in this SR did not include activity associated with household chores, domestic responsibilities, or occupation in their measure of PA. Participation in household activity has been shown to be an important source of energy expenditure.[26] Consequently, it would be advantageous to include measures of non-exercise activity, such as household chores, as women tend to spend more time performing these tasks.[26,42,43] Although these were not included in the measures of PA, several studies did include validated questionnaires.[23,24,28–31] It is anticipated that had domestic tasks been included, a stronger trend toward improved cancer survival would have been observed.[18,26] Recall bias, as well as exposure misclassification, may have occurred as a result of the use of self-report mea-

sures and the assessment of retrospective levels of PA, which may have led participants to over- or under-report their PA levels.

The time period at which PA was measured also differed across studies. Often PA was based on levels of activity prior to diagnosis.[19,23,24,30,31] As a consequence, the authors of these studies may have falsely assumed that levels of PA remain constant from pre- to post-diagnosis; however, PA levels may in fact have been affected by cancer-related symptoms or by side-effects of medical treatment. Evidence is conflicting regarding the change in PA levels pre- and post-diagnosis. Although the American Cancer Society states that levels of PA decrease following the diagnosis of breast cancer,[44] other studies have demonstrated that PA levels remain constant[45] or increase.[18] Given the conflicting evidence with respect to changes in PA levels pre- and post- diagnosis, caution must be used when interpreting the results of these studies.

It must be considered that there was potential for misclassification of cancer-related deaths as a result of the methods used to determine vital status. Although the majority of studies used medical records and death certificates, one relied on family reports or postal authorities,[24] which may have increased the potential for misdiagnosis of cause of death.[24] A similar concern was not observed in the methods used to identify a diagnosis of cancer; all included studies relied on medical records to verify cancer diagnoses.

A methodological strength across the included studies was that analyses adequately controlled for confounding variables, with the exception of Enger and Bernstein[20] and Pierce et al.[30] As well, a small number of subjects were lost to follow-up in the majority of studies,[20,29] thus reducing related bias. Finally, an adequate follow-up period was observed, with the majority of studies following patients for a minimum of 5 years.[18–20,22–24,28,30,31]

LIMITATIONS

Although this SR is the first to examine the effect of PA on survival in patients diagnosed with cancer, it is important to recognize certain limitations. As in any SR, there was a potential for selection bias. To reduce this bias, two independent researchers performed an extensive literature search and selected articles for inclusion. Further limiting the strength of this SR, no RCTs investigating PA and cancer survival were available; as a result, conclusions drawn from this review are based on the results of prospective cohort studies, in which bias can arise through study design. For example, bias may occur because participants are not randomly allocated to the exposure of interest, and therefore the exposure of PA cannot be controlled for between groups, which limits the researchers' ability to report concrete recommendations on the most effective intensity, frequency, and duration of PA. Comparison of studies was also difficult, as the assessment of PA was inconsistent and therefore meta-analysis of the data was not possible. Where possible, results were converted into METs for clearer interpretation and synthesis. A further limitation was the lack of validation of the PEDro scale for observational studies.[13] Nevertheless, an attempt was made at critical evaluation of the methodological quality of the studies included, using the NOS. Given the extent of limitations identified, the strength of the conclusions presented here may be limited.

CONCLUSION

There appears to be a trend toward increased survival in patients diagnosed with breast or colon/colorectal cancer who participated in greater levels of PA. Although no concrete conclusions can be drawn with respect to the optimal dose and type of PA, some recommendations can be made. It appears that engaging in higher levels of MET hours per week (i.e., >9 MET-hr/wk) may help to increase cancer survival rates.[18,22–24,28–30] This would be equivalent to ≥ 3 hours of walking per week at a pace of 2 to 2.9 mph.[24] More research is required to confirm these findings. There appears to be a need to educate individuals on the role of PA, not only to aid in the prevention of cancer but also to improve survival rates following diagnosis.

This was the first SR investigating the effects of PA on cancer survival. Because of the limited amount of published evidence, only prospective cohort studies were available. More research in this area is needed, including RCTs, to further support conclusions drawn from this SR. Further research is also required to determine the optimal level of PA, including the threshold at which increasing levels of PA may no longer be of benefit. In addition, studies need to be conducted with more ethnically diverse populations and with a greater range of cancer diagnoses. PA measures that have undergone rigorous psychometric testing need to be used in future studies. Ideally, non-exercise activities such as household tasks should also be included in these assessments. Furthermore, PA assessment needs to be conducted at different points following the diagnosis of cancer to help determine the optimal time points at which participation in PA is most beneficial to decrease mortality and other consequences of cancer.

KEY MESSAGES

What Is Already Known on This Subject

The benefits of exercise and increased physical activity on people diagnosed with cancer are many, including improved function, quality of life, strength, and endurance and reduced depression, nausea, and pain.

New evidence has also demonstrated that increased activity levels are associated with reduced cancer recurrence.

What This Study Adds

The current study contributes to the growing evidence that increased physical activity may improve survival for people with some types of cancer.

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