


Physical Activity as a Nonpharmacological Symptom Management Approach in Myeloproliferative Neoplasms: Recommendations for Future Research

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Abstract

Purpose: Essential thrombocythemia, polycythemia vera, and myelofibrosis are rare chronic hematological malignancies known as myeloproliferative neoplasms (MPNs) and are characterized by deregulated myeloid lineage cell production, splenomegaly, and heterogeneous symptom profiles. MPN patients suffer from a significant symptom burden (eg, fatigue, depressive symptoms, early satiety) and an impaired overall quality of life (QoL). Current treatments typically include pharmacological approaches, which may come with additional side effects and may be limited by treatment-associated toxicities (ie, cytopenias). Nonpharmacological approaches such as physical activity may be beneficial for reducing symptom burden and improving QoL. To date, no studies have examined physical activity as a nonpharmacological approach in MPN patients despite preliminary evidence supporting its benefit in other hematological cancers. The purpose of this article is to (1) review the literature related to physical activity and specific hematological cancer subtypes and to (2) make suggestions for future research involving physical activity in MPN patients as a symptom management strategy. **Methods:** A brief review of studies examining physical activity in leukemias, lymphomas, and myelomas (excluding stem-cell transplant patients) was conducted. **Results:** There is preliminary evidence to suggest that physical activity may be an effective approach to improve patient-reported outcomes (fatigue, depression, anxiety, sleep), physical fitness (cardiovascular fitness, balance, body composition), and overall QoL in other hematological cancers. **Conclusions:** Based on encouraging findings in other hematological cancers, future research should examine the feasibility and effectiveness of physical activity in MPN patients.

Keywords

exercise, aerobic, resistance, quality of life, cancer, health promotion

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Introduction

In 2014, there were an estimated 1 665 540 new cancer cases and 585 720 cancer deaths in the United States.^{1,2} Hematological cancers, although less prevalent than some of the more common types of cancers (ie, breast, prostate, lung and bronchus, colorectal), accounted for 9.4% of all cancers diagnosed as well as 3.3% of all cancer deaths in the United States in 2014.³ Hematological cancers represent a heterogeneous group of blood- and lymph-related disorders, including leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, myelodysplastic syndromes, myeloma, and myeloproliferative neoplasms (MPNs).³

The most common forms of hematological cancer are leukemia, lymphoma, and myeloma.⁴ Although there are many

subtypes among each of these hematological cancers, typical symptoms for leukemia may include fatigue, increased susceptibility to infections, and bleeding or bruising easily.⁴ Typical lymphoma symptoms may include night sweats, unintentional weight loss, recurrent fevers, fatigue, and pruritis.⁴ For myeloma, patients often experience bone pain, fatigue, anemia, hypercalcemia, or frequent infections.⁴ In general, hematological cancer treatment may include (but is not limited to)

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chemotherapy or other drug therapies, radiation, immunotherapy, vaccines, blood transfusions, or stem-cell transplantation.⁵ However, choice of treatment may be dependent on a variety of factors, including type of blood cancer, disease stage, phase or category, symptoms presented, blood cell counts, or location of the cancer, to name a few.⁵ Additionally, nonpharmacological (ie, complementary or alternative) approaches, such as yoga, massage, or physical activity, may be used to help patients deal with symptoms or treatment-related side effects.^{5,6}

Compared with other hematological cancers, the recognition of MPNs is relatively new, being first recognized in 1951 by William Dameshek as “myeloproliferative disorders.”⁷ The classic Philadelphia-negative MPNs, as they are now referred to, include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Each is characterized by mutually exclusive Janus kinase 2 (*JAK2*), calreticulin (*CALR*), and myeloproliferative leukemia oncogene virus (*MPL*) mutations. *JAK2* mutation is the most frequently occurring gene mutation, occurring in approximately 98% of PV cases, 50% to 60% of ET cases, and 55% to 65% of PMF cases.⁸ Because of differences in the etiology between MPN subtypes, symptom profiles can vary greatly. Typical symptoms, however, include (but are not limited to) fatigue, pruritus, loss of appetite, night sweats, splenomegaly, abdominal pain, bone pain, weight loss, microvascular complications, and anemia.^{9,10} Fatigue is the most commonly reported symptom among MPN patients. In a survey of 1179 MPN patients, fatigue was reported by 81% of patients.⁹ In separate surveys, fatigue has been reported by as many as 92.7% of patients.¹¹ Other commonly reported symptoms include insomnia (65.4%), sad mood (62.7%), early satiety (61.9%), concentration difficulties (61.7%), numbness (61.3%), inactivity (60.5%), sexual problems (57.9%), dizziness (55.2%), and pruritus (52.6%).¹¹ Some of the symptoms that MPN patients experience are similar to those experienced by other hematological cancer patients, including fatigue, weight loss, pruritus, and anemia, to name a few.

The symptom burden of MPNs often leads to a reduced overall quality of life (QoL), including a reduced ability to participate in physical and social functions as well as a reduced capacity to complete activities of daily living.⁹ As many as 84% of MPN patients report an impaired QoL, which has been defined as a score of >0 (0-10 scale) on the Myeloproliferative Neoplasm Symptom Assessment Form (MPN SAF).⁹ Treatment for MPNs primarily focuses on managing disease progression as well as maintaining or improving QoL and reducing symptom burden. To date, pharmacological approaches have been the mainstay of treatment options for the MPN patient population. Typical treatment options for this population may include, but are not limited to, pharmacotherapy (eg, aspirin, hydroxyurea, interferon, cytoreduction, androgens, corticosteroids, erythropoiesis-stimulating agents, radioactive phosphorus [P-32], and JAK inhibitors), radiation

therapy (eg, splenic irradiation), or surgery (eg, splenectomy, stem-cell transplantation).^{10,12} The treatments used for MPN patients are sometimes similar to those utilized in other hematological cancer patients (eg, cytoreduction, radiation therapy, stem-cell transplantation).

Allogenic stem-cell transplantation is the only curative therapy for MPN patients but is utilized very infrequently and is reserved for those afflicted with intermediate- to high-risk PMF. Given the lack of curative therapies for the treatment of MPNs, patients often live with a significant symptom burden for the rest of their lives. Current pharmacological approaches, specifically JAK-inhibitors, have demonstrated some success in improving symptom burden and overall QoL in MPN patients^{10,13}; however, these treatment modalities often come with side effects (eg, anemia, thrombocytopenia). For example, ruxolitinib (selective JAK-inhibitor) has demonstrated efficacy in clinical trials for improving MPN-related symptoms (fatigue, inactivity, night sweats, muscle/bone pain, pruritus, early satiety, dyspnea, and abdominal discomfort) and QoL as well as reducing splenomegaly¹⁴⁻¹⁹; however, anemia and thrombocytopenia are common side effects of this particular treatment.^{10,13} Thus, there is a need to explore other approaches (without side effects) to manage symptom burden and QoL in MPN patients.

Nonpharmacological treatment such as physical activity may be an effective approach to help MPN patients manage symptoms. In other cancers (eg, breast, colon, some hematological), physical activity has been suggested as a means of improving patient outcomes, including the deleterious physiological (eg, decreases in muscle/bone mass caused by inactivity, decreases in aerobic capacity caused by cardiac toxicity, decreases in body weight caused by cancer cachexia, increased risk of illness as a side effect of treatment), psychosocial (increases in fatigue, increases in anxiety and depressive symptoms, and reduced QoL), and cognitive (eg, impaired cognitive function) side effects associated with typical cancer treatments.²⁰⁻²²

Physical activity during treatment in a variety of cancers has demonstrated success at improving cardiovascular fitness, muscular fitness, a variety of psychosocial outcomes (ie, fatigue, anxiety, self-esteem, mood), and QoL.^{20,23-25} In cancer survivors (ie, those that have completed treatment), recent reviews and meta-analyses have demonstrated that physical activity interventions are effective at reducing insulin-like growth factor-I and improving cardiovascular and muscular fitness, body mass index (BMI) and body weight, psychosocial outcomes (ie, fatigue, anxiety, depression), health-related QoL, emotional well-being, social functioning, and cognitive function.^{21,26,27} The mechanisms underlying improvements in cancer patient outcomes caused by physical activity are not completely understood, but it has been suggested to exert its effects through improvements in inflammatory state (ie, reductions in proinflammatory cytokines and increases in

anti-inflammatory cytokines), decreases in growth-promoting hormones (eg, insulin and insulin-like growth factors), and increases in the expression of neurotrophic/neuroprotective factors and neurotransmitters (eg, dopamine).^{21,26-28}

In MPNs, the mechanisms underlying disease progression and symptom development are not very well understood. Specific genetic mutations (eg, *JAK2*, *CALR*, and *MPL*) have been identified in MPNs and have been associated with disease development and progression.⁸ Recent research has identified alterations in hematopoietic protein homeostasis through increased insulin-like growth factor receptor levels as a potential driver of MPN development.²⁹ As mentioned previously, physical activity has been shown to reduce insulin-like growth factor levels. Therefore, it is possible that this is one mechanism through which MPN patients could experience benefits related to physical activity. Additionally, inflammation has been suggested to be involved in the development of disease-related symptoms.³⁰ Specific proinflammatory cytokines (eg, interleukin [IL]-1, IL-6, IL-8, and tumor necrosis factor- α) have been associated with particular patient-reported symptoms, including fatigue, abdominal complaints, microvascular symptoms, and constitutional symptoms. Paradoxically, the development of MPN-related symptoms may drive patients to reduce activity levels (ie, fatigue-driven sedentary lifestyles), further exacerbating inflammatory state and worsening symptoms,³⁰ thus making physical activity a potentially useful strategy for improving symptom burden in MPN patients through its beneficial effects on inflammatory state. However, to date, there have been no studies that have explored the use of physical activity to manage symptom burden in MPN patients. Therefore, the purpose of this article is to (1) briefly, yet systematically review what is known about physical activity in other hematological cancers, and (2) make suggestions for future research in MPN patients. MPN patients are an understudied population, and the information gained from this study will help inform future interventions in the MPN patient population.

Methods

For the purposes of this brief review, we performed a selective inclusion of studies investigating physical activity (defined as any activity that caused an increase in energy expenditure above resting) in specific hematological cancer subtypes (see Table 1). Studies including current patients (ie, undergoing treatment) or survivors (ie, completed treatment) diagnosed with leukemia, lymphoma, and/or myeloma were included. Studies that examined physical activity as an independent variable or a dependent variable were included as were intervention (eg, randomized controlled trial, quasi-experimental) or epidemiological (eg, longitudinal, cross-sectional) study designs. However, systematic reviews and meta-analyses as well as studies that

Table 1. Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Published study between 1995 and 2015 • Examined any type of physical activity either as an independent variable or a dependent variable • Included leukemia, lymphoma, and/or myeloma patients or survivors as study participants • Intervention or epidemiological study design 	<ul style="list-style-type: none"> • Study participants included patient population receiving stem-cell transplantation • Examines physical activity in relation to hematological cancer risk • Systematic review or meta-analysis study design

examined physical activity in relation to hematological cancer risk were excluded because this review intended to focus on primary research examining physical activity in relation to hematological cancer patient outcomes, particularly symptoms or treatment-related side effects. Additionally, studies including a patient population that underwent stem-cell transplantation were excluded because this patient population may present with complications and issues that are not transferrable to the general MPN patient population. Stem-cell transplantation may result in acute and chronic complications, such as reduced immune function, prolonged neutropenia, infectious complications, veno-occlusive liver disease, and graft-versus-host disease,³¹ that are not typically present in the general MPN patient population because this type of surgery is usually reserved for high-risk PMF patients. A medical librarian developed search strategies for Ovid MEDLINE, Ovid EMBASE, and PubMed to identify articles. The search strategies were peer reviewed by another experienced medical librarian. Limitations included a publication date range of 1995 to 2015. Search strategies included the MeSH terms and keywords above (see Table 2). A total of 12 articles were included for review (see Figure 1 for article selection flow chart) and are summarized in Table 3.

Physical Activity and Hematological Cancer Subtypes

Lymphomas

Many of the included studies examining the effects of physical activity during and after hematological cancer treatment have been in lymphoma patients. In general, physical activity has been shown to be feasible in lymphoma patients as well as efficacious for improving sleep-related outcomes, physical functioning, fatigue, happiness, depression scores, cardiovascular fitness, balance, body composition, and overall QoL.³²⁻³⁸ The exercise prescriptions utilized (ie, frequency,

Table 2. Keyword Search Terms.

MeSH Terms (Ovid MEDLINE, PubMed)	Keywords (Ovid MEDLINE, Ovid EMBASE, PubMed)
Motor activity	Physical activity
Exercise	Exercise
Physical fitness	Fitness
Yoga	Yoga
Tai chi	Tai chi, Qui gong
Resistance training	Resistance training
Muscle stretching exercises	Stretching
Pliability	Flexibility
Running	Running
Walking	Walking
Jogging	Jogging
Swimming	Swimming, aqua aerobics, water aerobics
Bicycling	Bicycling, biking
Tennis	Tennis
Golf	Golfing
Recreation	Recreation, Recreational sports
Dancing	Dancing, Zumba, Salsa dancing Wii, Pilates, Skating
Hematological neoplasms	Blood cancer
Hematological diseases	Hematological diseases
Leukemia	Leukemia
Lymphoma	Lymphoma
Multiple myeloma	Myeloma
Myeloproliferative disorders	Myeloproliferative disorders
Thrombocytopenia, essential	Essential thrombocytopenia
Polycythemia vera	Polycythemia vera
Primary myelofibrosis	Primary myelofibrosis
Lymphoma, non-Hodgkin	Non-Hodgkin lymphoma

intensity, time, type/duration), however, vary significantly between studies. Exercise intervention frequencies ranged from once per week to thrice per week, with thrice per week being the most common. Intensities ranged from light to vigorous, although the method of prescribing intensity varied between studies to include percentage of maximum heart rate or percentage of peak power for aerobic exercise. Aerobic exercise (ie, cycle ergometer or treadmill walking/jogging) was the most commonly utilized type of exercise, with yoga, resistance exercise, and sensorimotor (ie, balance) exercise being much less common. Exercise session durations also varied between studies, ranging from 15 to 60 minutes.

As mentioned previously, aerobic exercise has been the most frequently studied type of activity in lymphoma patients. In particular, Courneya et al³³⁻³⁵ demonstrated the efficacy of a 12-week, 3-times/wk, moderate- to vigorous-intensity (60%-75% of peak power output), progressive aerobic exercise intervention (ie, cycle ergometer) for improving physical functioning, fatigue, happiness, depression scores, cardiovascular fitness, lean body mass, and

overall QoL in lymphoma patients ($n = 60$) when compared with a usual care control group ($n = 62$). In addition to these improvements, the exercise intervention did not interfere with chemotherapy completion rate or treatment response. Overall QoL outcomes, however, were moderated by general health status and BMI. The best QoL response to the aerobic exercise intervention was seen in patients who were in poor/fair health ($P = .012$) and in those with either a normal or an obese BMI ($P = .01$).

Courneya et al³³ demonstrated that an aerobic exercise intervention is feasible in lymphoma patients because the aerobic exercise group attended an average of 78% (28 of 36) of the exercise sessions. This is a slightly higher adherence rate than what has been observed in breast cancer patients participating in supervised exercise interventions (70%-73%).^{39,40} Adherence rates were moderated by patient age and past exercise history. Poorer exercise adherence was significantly associated with age <40 years ($P = .016$) and insufficient activity at baseline (ie, ≤ 150 min/wk of moderate- or vigorous-intensity exercise; $P = .024$).⁴¹

Though Courneya³⁴ found that an aerobic exercise intervention was efficacious in improving QoL (among other outcomes), other studies with similar methodology found otherwise. Elter et al³⁶ conducted a 12-week, 3-times/wk, 15- to 30-min/session, aerobic exercise (ie, cycle ergometer) feasibility study in leukemia/lymphoma patients currently undergoing chemotherapy. No significant improvements in QoL were found; however, participants demonstrated an improvement in relative endurance capacity (ie, W/kg). The nonsignificant findings on QoL may be a result of the small sample size ($n = 12$) because this may limit the statistical power to detect significant improvements in study outcomes. This is a significant limitation when interpreting the findings of the study and warrants future research interventions with larger sample sizes.

Whereas it seems that aerobic exercise is potentially efficacious for improving specific patient-related outcomes in lymphoma patients, other forms of physical activity may also have potential utility for lymphoma patients. Cohen et al³² demonstrated significant improvements in sleep-related outcomes in lymphoma patients ($n = 20$) participating in a yoga intervention when compared with a wait-listed control group ($n = 19$). In this study, lymphoma patients were randomized into an intervention group (ie, yoga group) or a wait-listed control group. The intervention group performed Tibetan yoga (eg, breathing, visualization, mindfulness, and low-impact postures) once per week for 7 weeks (duration of each session was not specified). Although significant improvements in subjective sleep quality, faster sleep latency, longer sleep duration, and less reported use of sleep medications were found, there were no significant differences between groups for state anxiety, depression, or fatigue. However, this may be partly a result of both the adherence rate and the dose of the intervention.

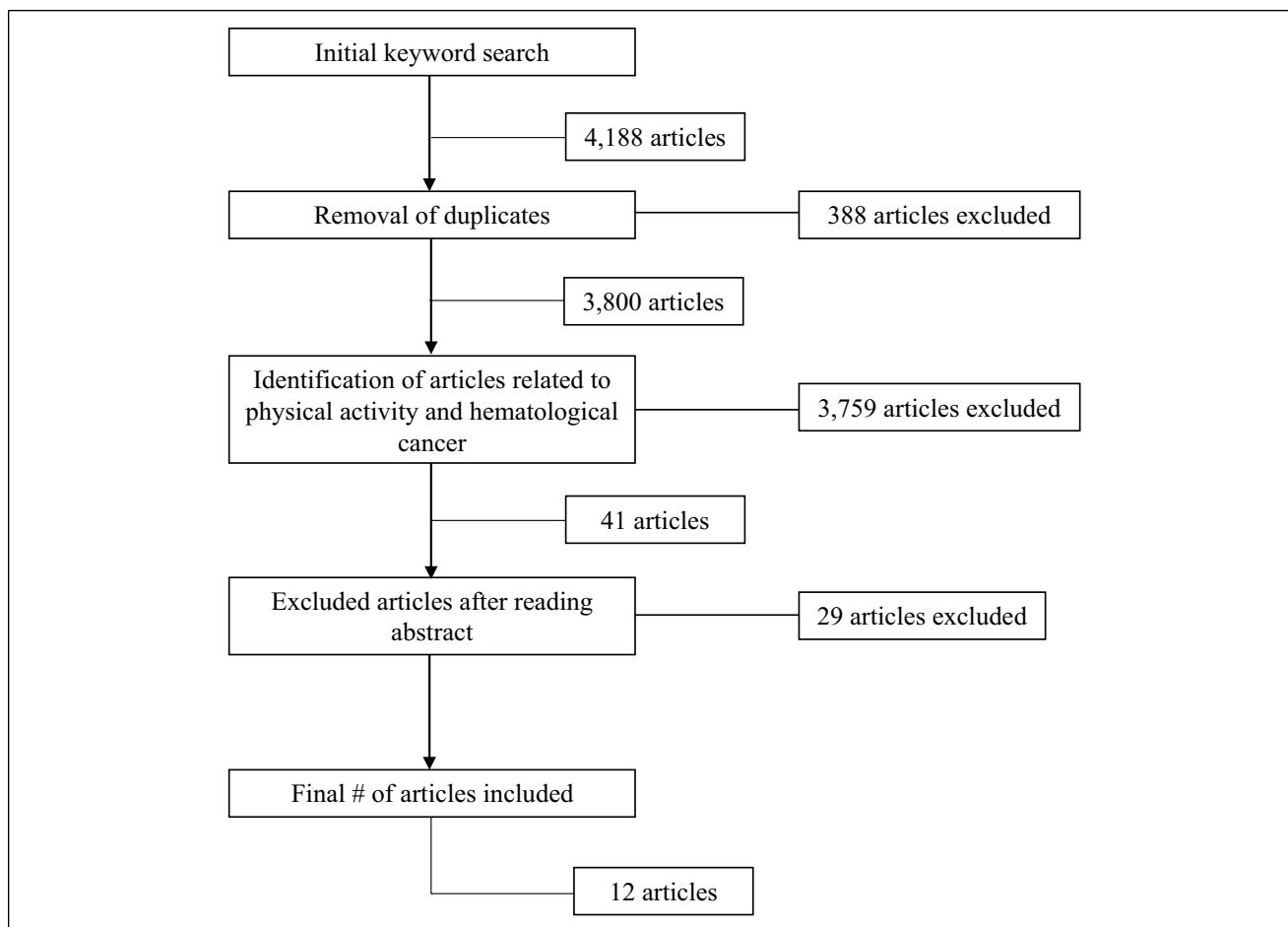


Figure 1. Article selection flowchart.

Only 58% of patients in the intervention group completed at least 5 yoga sessions (out of 7 total sessions). Additionally, 7 total sessions may not have been a potent enough stimulus to improve QoL-related outcomes (ie, anxiety, depression, fatigue) because previous yoga studies demonstrating significant improvements in anxiety, depression, and fatigue in breast cancer patients have used higher doses (ie, 18-24 sessions of 60 minutes).⁴²⁻⁴⁴ Therefore, studies examining the impact of yoga on QoL outcomes in lymphoma patients (ie, anxiety, depression, fatigue) with doses greater than 7 total sessions are needed to draw more definitive conclusions.

Only 1 study has examined a combination of exercise types (ie, aerobic and resistance exercise) on lymphoma patient outcomes. Streckmann et al³⁸ randomized 61 lymphoma patients to an intervention group (n = 30) or a control group (n = 31). The intervention group performed a combination of aerobic exercise (ie, 10 to 30 minutes of treadmill walking/jogging at 60%-80% maximum heart rate), resistance exercises (ie, 4 resistance band exercises performed for 1 minute each), and sensorimotor (ie, balance) exercises (ie, 4 postural stabilization exercises performed for 3 sets of

20 s). Each session lasted for approximately 60 minutes and was performed twice per week for 36 weeks. Overall adherence in the intervention group was 65% (ie, attended all exercise sessions and all measurement time points), and patients significantly improved their overall QoL, balance, and lactate threshold. It is unknown whether or not a particular type of exercise (ie, aerobic, resistance, or sensorimotor exercise) or whether a synergistic effect of combined exercise types was responsible for these significant findings. More research examining combined exercise interventions is needed with larger sample sizes and multiple control groups to differentiate between the independent effects of resistance, sensorimotor, and aerobic exercises.

It has been suggested that one potential biological mechanism underlying the positive effects of physical activity during cancer treatment is its impact on proinflammatory cytokine concentrations.²¹ Zimmer et al⁴⁵ aimed to test this hypothesis and demonstrated that 1 single bout of physical activity significantly reduces specific proinflammatory cytokines in lymphoma patients receiving immunochemotherapy treatment. Specifically, patients were treated with immunochemotherapy

Table 3. Summary of Included Articles.

Reference	Study Design	Study Sample	Exercise Prescription	Significant Findings	Limitations
[51]	Quasi-experimental (no control group)	Acute myeloid leukemia patients recovering from chemotherapy (n = 35)	Unknown study duration; 4-5 times/wk; 50%-75% intensity (aerobic); 1-3 sets of resistance exercises; 30-45 min/session; combination of aerobic, resistance, and flexibility exercise	97% Retention rate; 5.9% adherence rate; ↑VO ₂ peak; ↑functional fitness; ↓upper-body strength; ↓anxiety	Lack of control group; low adherence rate; unspecified study duration
[52]	RCT	Acute myeloid leukemia patients who completed treatment (n = 38; 21 in intervention group)	12 Weeks; 3-5 times/wk; moderate intensity; target of 150 min/wk; combination of aerobic, resistance, and flexibility exercise	91% Retention rate; 28% adherence rate; no significant findings	Low adherence rate in intervention group
[32]	RCT (wait-list control group)	Lymphoma patients (n = 39; 20 in intervention)	7 Weeks; once per week; light intensity; unknown session duration; Tibetan yoga	89% Completed 2-3 sessions; 57% completed ≥5 sessions; ↓sleep disturbance; ↑sleep quality; faster sleep latency; ↓use of sleep medications	Low overall exercise dose; small sample size in intervention group (n = 20); yoga session duration not specified
[33] ^a	RCT (wait-list control group)	Lymphoma patients (n = 122; 60 in the intervention group)	12 Weeks; 3 times/wk; 60%-70% peak power output; 15-45 min/session; aerobic exercise	↑QoL outcomes in participants who were unmarried, in poor/fair health, and with normal or obese BMI; ↑body composition outcomes in participants with advanced disease state and good health status	Limited statistical power to detect interactions
[34] ^a	RCT (wait-list control group)	Lymphoma patients (n = 122; 60 in intervention group)	12 Weeks; 3 times/wk; 60%-70% peak power output; 15-45 min/session; aerobic exercise	↑Physical function; ↑QoL; ↓fatigue; ↑happiness; ↓depression; ↑general health; ↑cardiovascular fitness; ↑lean body mass	Limited statistical power to detect subgroup effects; heterogeneous study sample
[39] ^a	RCT (wait-list control group)	Lymphoma patients (n = 122; 60 in intervention group)	12 Weeks; 3 times/wk; 60%-70% peak power output; 15-45 min/session; aerobic exercise	77.8% adherence rate; age <40 years and insufficient activity (<150 min/wk) at baseline were significantly associated with poorer exercise adherence	Limited focus to supervised exercise in a well-staffed, university-based facility; effects of unsupervised exercise unknown
[35] ^a	RCT (wait-list control group)	Lymphoma patients (n = 122; 60 in intervention group)	12 Weeks; 3 times/wk; 60%-70% peak power output; 15-45 min/session; aerobic exercise	No significant improvements; significant ↑ in global sleep quality only in participants who were poor sleepers at baseline, had an obese BMI status, were <2 years postdiagnosis, and were receiving chemotherapy	No objective sleep measures
[53]	Cross-sectional (questionnaire based)	Multiple myeloma patients (n = 229)	N/A	↓PA since prediagnosis; fatigue, injuries, and pain were strongest barriers to PA participation; 41% indicated intent to attend exercise intervention if one were offered; sufficient PA prediagnosis significantly associated with greater likelihood of being sufficiently active posttreatment	Cross-sectional study design; therefore, causality cannot be established

(continued)

Table 3. (continued)

Reference	Study Design	Study Sample	Exercise Prescription	Significant Findings	Limitations
[36]	Quasi-experimental (no control group)	Lymphoma and leukemia patients (n = 12)	~12 Weeks; 3 times/wk; submaximal intensity; 15-30 min/session; aerobic exercise	↑Relative endurance capacity (W/kg); ↓body weight	Lack of control group; limited exercise intervention description
[37]	Quasi-experimental (no control group)	Lymphoma (n = 12)	20 Weeks; 3 times/wk; 60%-85% maximum HR; 40-60 min/session; aerobic exercise	↓Fatigue; ↑physical functioning; ↑VO ₂ maximum	Lack of control group
[38]	RCT	Lymphoma (n = 6); 30 in intervention group)	36 Weeks; 2 times/wk; 60%-80% maximum HR (aerobic); 3 sets x20 s sensorimotor exercises; 1 set x1 minute resistance exercises; 60 min/session; combination of aerobic, resistance, and sensorimotor exercise	65% Adherence rate; ↑QoL; ↑balance; ↑lactate threshold	Study design does not allow an examination of the independent effects of aerobic, resistance, and sensorimotor exercise
[45]	RCT	Lymphoma (n = 30); healthy controls (n = 10)	Single 30-minute, moderate-intensity exercise bout	↓IL-6 cytokine concentration	Only assessed effects of a single exercise bout; long-term effects unknown

Abbreviations: BMI, body mass index; HR, heart rate; IL-6, interleukin-6; PA, physical activity; QoL, quality of life; RCT, randomized controlled trial.

^aResults from this article were published based on 1 study conducted by Courneya et al.³⁴

for 3 months before having IL-6 and macrophage migration inhibiting factor (MIF) concentrations measured. IL-6 is associated with cancer-related side effects (eg, fatigue and cachexia),⁴⁶⁻⁴⁸ whereas MIF is associated with reduced activity of natural killer cells and increases in metastasis.^{49,50} Compared with healthy controls, both these cytokine levels were significantly elevated after 3 months of treatment. After performing one 30-minute bout of moderate-intensity aerobic activity on a cycle ergometer, significant reductions in IL-6 were observed, whereas MIF levels were not significantly influenced. This study provides preliminary support for identifying a potential mechanism through which physical activity exerts positive effects on hematological cancer-related outcomes. A limitation of this study, however, is that only 1 exercise bout and its effects on cytokine concentrations were examined. Therefore, the chronic effects of repeated exercise bouts on proinflammatory cytokine concentrations are not known. Additionally, patient-reported outcome measures were not assessed, which inhibits the ability to examine associations between the changes in cytokine concentrations and cancer-related symptoms. Future studies should aim to include longer exercise interventions that examine both cytokine concentrations and patient-reported outcomes to determine the long-term impact of aerobic exercise on proinflammatory cytokine levels and their associations with cancer-related outcomes.

Leukemias

Fewer of the included studies have examined the effects of physical activity on outcomes in leukemia patients and cancer-related side effects (however, many studies were excluded with this patient population because patient treatment included stem-cell transplantation). Whereas the majority of studies described above for lymphoma patients focused on aerobic exercise, interventions in leukemia patients have consisted primarily of combined exercise interventions (ie, aerobic, resistance, and flexibility exercise). Overall, exercise interventions in leukemia patients demonstrate significant improvements in cardiovascular fitness, functional fitness, and anxiety.²³ However, very poor adherence rates and study design methodologies act as major limitations when interpreting these findings. In particular, Alibhai⁵¹ demonstrated that a combined aerobic (ie, walking or cycling at 50%-75% of heart rate reserve for 10-40 minutes), resistance (ie, exercises targeting each major muscle group performed for 1-3 sets/10-25 minutes), and flexibility (ie, static stretching targeting each major muscle group performed for 5-10 minutes) exercise intervention significantly improved VO_2 peak, functional fitness (ie, 6-minute walking test), and anxiety in leukemia patients ($n = 35$) recovering from chemotherapy treatment; however, QoL and fatigue did not significantly improve. Although 97% of participants were retained throughout the

duration of the study, only 5.9% adhered to the exercise intervention (ie, ≥ 150 min/wk of moderate- to vigorous-intensity aerobic activity and 2 d/wk of resistance training). An adherence rate this low makes it difficult to draw definitive conclusions when interpreting the results. Higher adherence rates would have led to study participants experiencing a greater dose of exercise, which could affect the outcomes of the study. Additionally, there was no control group with which to compare these outcomes.

In another study conducted by Alibhai et al,⁵² leukemia survivors ($n = 22$) participated in a 12-week, 3- to 5-times/wk, home-based, combined aerobic, resistance, and flexibility exercise intervention. A primary target was to have participants engage in 150 min/wk of moderate- to vigorous-intensity aerobic activity. Adherence was defined as achieving at least 150 min/wk of moderate- to vigorous-intensity aerobic activity for at least 70% of the 12-week intervention. There were no significant findings from the present study, which included QoL and fatigue as primary outcomes and measures of fitness as secondary outcomes. The lack of significant findings could be a result of a low adherence rate (28%) in the intervention group as well as a small sample size (intervention, $n = 22$; control, $n = 18$), which limits the statistical power of the study in detecting significant findings.

Because of study design and study participant adherence limitations, it is difficult to determine whether or not exercise interventions in leukemia patients are efficacious. Additionally, both the studies described above were in patients posttreatment. Future studies should aim to include larger sample sizes and patients both during and after treatment. Finally, moderators of exercise adherence should be explored, so that future interventions can address them in order to improve adherence rates.

Myelomas

We did not include any intervention studies examining the effects of physical activity in myeloma patients (however, there were a few physical activity studies in myeloma patients that were excluded because patient treatment included stem-cell transplantation). It has been demonstrated in a recent cross-sectional survey of 229 myeloma patients that physical activity levels declined significantly from prediagnosis to postdiagnosis, with pain and fatigue being reported as the most common barriers to physical activity participation.⁵³ However, 41% mentioned that they would be interested in participating in an exercise program if one were offered.⁵³ Improving physical activity levels or even maintaining prediagnosis activity levels may have benefits for this hematological cancer subtype population. This demonstrates the need for future studies investigating the effects of physical activity on myeloma patient outcomes.

Table 4. Summary of Future Research Suggestions.

- Explore the feasibility of physical activity (ie, aerobic, resistance, mindfulness-based) for the MPN patient population
- Examine the effects of physical activity (ie, aerobic, resistance, mindfulness-based) on MPN patient symptom burden and QoL
- Identify barriers to physical activity participation within the MPN patient population, with specific emphasis on strategies to overcome fatigue as a major barrier
- Explore MPN patient perceptions regarding the use of physical activity as a symptom management tool

Abbreviations: MPN, myeloproliferative neoplasms; QoL, quality of life.

Implications for Future MPN Research

Based on the aforementioned literature, the following research suggestions should be considered (see Table 4). First, studies should explore the feasibility of exercise interventions in the MPN patient population. The feasibility of exercise interventions (ie, satisfaction, attendance) for other hematological cancer patients is conflicting. For example, Courneya et al³³ demonstrated a 78% adherence rate to an aerobic exercise intervention in lymphoma patients, whereas Alibhai⁵¹ demonstrated adherence rates as low as 5.9% in a combined exercise (ie, aerobic and resistance) intervention. Differences in definitions of adherence and exercise prescriptions may partially explain these discrepancies; however, this demonstrates that there is significant heterogeneity in the feasibility of exercise interventions. Therefore, future research in the MPN patient population should first aim to explore the feasibility of exercise interventions in this unique population.

Second, the effectiveness of physical activity (ie, aerobic, resistance, mindfulness-based) for improving MPN patient symptom burden and QoL should be explored. The efficacy of aerobic exercise has received the most attention in other hematological cancers. Resistance exercise has received less attention and has not been examined independently of other modes of exercise. Interestingly, the only mode of mindfulness-based physical activity that has been examined in hematological cancer subtypes is yoga. In a survey by Scherber et al,⁵⁴ more than 40% (n = 670) of MPN patients (n = 1676) reported that they tried yoga to reduce fatigue, and 63% reported that they were successful in reducing fatigue. This evidence is cross-sectional, however, and requires further experimental investigation to identify yoga as an effective symptom management tool for the MPN patient population.

Because there is still much research to be done supporting the role of physical activity in hematological cancers and this work may not be directly transferrable to the MPN population, it would be reasonable to use physical activity guidelines provided by the American Cancer Society (ACS)

when designing interventions for MPN patients. The ACS recommends that cancer survivors engage in at least 150 min/wk of physical activity (ie, 150 minutes moderate-intensity or 75 minutes vigorous-intensity activity) in addition to at least 2 days of resistance exercise targeting each major muscle group.⁵⁵ There are currently, however, no specific physical activity recommendations for cancer patients undergoing treatment. These recommendations provide a starting point for future interventions, in which the purpose is to examine the effects of physical activity on MPN patient outcomes. Additionally, it may be important to conduct epidemiological research to understand MPN patients' physical activity levels both during and after treatment. This will potentially allow researchers to determine what dose of physical activity is realistic for MPN patients to achieve.

Third, barriers to physical activity participation should be explored in the MPN patient population. Barriers to engaging in and adhering to physical activity have been identified in both lymphoma (age <40 years and history of inactivity)³³ and myeloma patients (fatigue and pain).⁵³ Identifying barriers specific to the MPN population as well as strategies to overcome them may be important for promoting physical activity participation because approximately 60% of MPN patients report being inactive.¹¹ Additionally, those who are inactive more frequently report moderate to severe fatigue as compared with more active patients.⁵⁶ It may be likely that MPN-specific symptoms (eg, fatigue, abdominal pain, splenomegaly, bone pain) and treatment-related side effects act as barriers to physical activity participation; however, this has yet to be explored. Fatigue is the most commonly reported symptom in MPN patients and may be an important barrier to address.

Interventions may need to explore strategies that focus on increasing the likelihood of maintaining physical activity participation, even when fatigued. For example, interventions that are based in the home may be useful for MPN patients suffering from fatigue because these patients often report reduced social activity and activities of daily living.⁵⁷ In a recent feasibility study conducted by Huberty et al⁵⁸ of home-based, online-streamed yoga for MPN patients, 68% were either satisfied or very satisfied with participating in online yoga; 75% felt that online yoga was helpful in dealing with MPN-related symptoms (including fatigue); 39% reported that they would prefer online yoga over studio-based yoga; and 82% said that they would recommend online yoga for other MPN patients. Additionally, because patients reported reduced social activity, including components of social support/interaction within an intervention may be important as well to promote physical activity.⁵⁹ More research in this area is warranted to identify specific barriers as well as strategies to overcome them in the MPN population.

Finally, patient perceptions of physical activity as a symptom management tool should be explored. It has

been demonstrated in a survey of 1788 MPN patients that 73% have attempted to exercise to self-manage fatigue, with 63% of these patients reporting exercise to have been a successful strategy.⁵⁴ Furthermore, MPN patients report fatigue as the symptom that they would like to resolve the most.⁶⁰ Together, the previous data indicate that there is an interest in utilizing exercise as a fatigue-management strategy. However, this area of research needs to be further explored to gain a better understanding of the types of exercise patients are interested in, how patients plan on integrating exercise into their routine, and patient perceptions surrounding the utility of exercise for symptom management.

Limitations

Although we have reviewed the literature in hematological cancer subtypes to inform future research using physical activity as a symptom management strategy in MPN patients, the limitations of this review should be discussed. First, the literature, to date, in hematological cancer suffers from its own limitations, such as small sample sizes, lack of control groups, low adherence rates, lack of resistance training and mindfulness-based exercise interventions, and heterogeneity in the exercise prescriptions utilized. Additionally, because of etiological and treatment differences between MPNs and other hematological cancers, the findings of the studies discussed in this review cannot be used to make predictions as to how MPN patients will respond to physical activity. For example, whereas both MPN and related hematological cancer patients may experience similar treatments (eg, cytoreductive therapy, radiation therapy, stem-cell transplantation), chemotherapy is not typically considered in the MPN patient population. This is an important difference because studies investigating the effects of physical activity on hematological cancer patient outcomes during treatment may include patients receiving chemotherapy. However, because the MPN patient population is severely understudied and there is no literature exploring nonpharmacological approaches (ie, physical activity) to help improve symptom burden and QoL in these patients, it is hoped that this information will provide support for the need to explore nonpharmacological treatment strategies in MPN patients, particularly physical activity. Additionally, this was a brief review, with emphasis on 3 hematological cancer subtypes to inform MPN research, and thus, we may have missed articles that would have contributed to the recommendations presented here. Finally, risk of bias was not assessed within individual studies.

Conclusions

MPN patients are understudied and there are currently no studies that have explored the effects of physical activity

on symptom burden and QoL in these patients. There is some evidence demonstrating the efficacy of physical activity for improving a variety of outcomes in specific hematological cancer subtypes. Because of preliminary evidence suggesting a positive impact of physical activity on other hematological cancer patient outcomes, exploratory research within the MPN patient population should be considered to evaluate the potential impact of physical activity on MPN-associated symptoms and reduced QoL. However, it should be recognized that the etiology and treatment of MPNs is unique when compared with other hematological cancers, and therefore, the findings discussed in this review should not be interpreted to suggest that physical activity will yield similar outcomes in the MPN patient population. Research in this area is highly warranted.

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