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The role of Physical Activity in the Prevention and Management of Various Cancers

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Abstract

Background: Cancers remain a leading cause of mortality in a modern society, and their incidence is growing each year. The disease and its related therapies cause considerable side effects, functional deterioration, and reduce quality of life (QoL), all of which correlate with less favourable outcomes. Physical activity (PA) represents a cost-effective and non-invasive adjunct to the traditional therapy regimes, which can alleviate these negative effects and improve clinical outcomes

Aim: The narrative review summarises current evidence about the role of PA in oncology. It provides a solid background in biochemical mechanisms involved in the modulation of cancer biology and evaluates its clinical significance by assessing psychological, physiological, cognitive, QoL and mortality rates

Methods: We conducted a narrative review of the available literature on the role of physical activity in modulating physiological and functional parameters, as well as mortality, in cancer patients. We considered original studies, reviews, systematic reviews and meta-analyses.

Results: Evidence indicates that PA is an effective tool in both the prevention and management of cancers. Patients who engage in PA have improved metabolic, immune and oxidative stress parameters, which provide clinical outcomes such as improved QoL, cognitive, psychological and physiological performance. This consequently leads to a better prevention of cancers and provides benefits in terms of overall survival

Conclusions: PA is an effective strategy for enhancing clinical outcomes in the cancer population and should be considered as an additional approach integrated into clinical guidelines.
Keywords: cancer, physical activity, exercise, sport

1. Introduction

Cancers are one of the major preoccupations in modern medicine. According to the International Agency for Research on Cancer (IARC) report from 2022, there were 20 million new cancer cases and 9.7 million deaths. About 1 in 5 people develops cancer in their lifetime. It is also predicted that by 2050, there will be a 77% increase from the estimated 20 million cases in 2022 [1]. The same report has stated that only 39% of the participating countries in the survey covered the financial basics for cancer management, and only 28% have covered the palliative care basics [1]. As our population tends to live longer thanks to advances in the medical field and novel therapies, the cancer incidence increases [2]. This causes a substantial burden in economics [3]. Therefore, there is a need to develop new cost-effective and evidence-based strategies that could apply to the entire population to 1) reduce cancer incidence; 2) improve cancer management and survival; 3) increase the quality of life (QoL) of cancer patients.

Physical activity (PA) is an important public health tool which can be used in the treatment and prevention of various physical diseases, including diabetes [4], hypertension [5], dyslipidemias [6], osteoporosis [7] and psychiatric issues [8]. This is especially important in the context of cancer patients since malignancies tend to alter muscle function, which can be further declined using treatment regimens which can cause cardiotoxicity, nephropathies and muscle atrophy [9]. This may consequently lead to a sedentary lifestyle and make patients more prone to cardiovascular diseases (CVDs) [10].

PA has an array of positive functions in our body, including the modulation of the immune system [11], decreasing the glucose and lipid levels [6,12] and managing oxidative stress (OS) [13]. The importance of physical activity is especially highlighted by the fact that various medical associations include it as a first-line intervention in common civilisation diseases [14]. It is stated that moderate physical activity can alleviate symptoms of the disease and should be considered as part of rehabilitation in various diseases, including cancers.

Not only can PA be helpful in patients with already diagnosed cancer, but some studies suggest an inverse association between PA and tumour incidence [15].

Therefore, our goal was to provide the current evidence on effects of physical activity on 1) biochemical pathways related to cancer development and progression; 2) incidence of cancers; 3) QoL parameters such as physiological, psychological and cognitive function; 4) mortality in cancer patients.

2. Research methods

A comprehensive literature review was conducted by utilising the advanced search method of the PubMed database. The queries used to find appropriate papers are represented in Table 1. Additionally, some resources were found manually from the cited articles.

The authors reviewed articles referring to the 1) physiological effects of exercise on immune, metabolic and oxidative stress; 2) performance outcomes of exercise on cognitive function, psychological and functional status of cancer patients; 3) role of PA on mortality in cancer patients. Only reliable sources were cited, and proper measures were taken to check the reliability of citations.

Query number	Query	Description
#1	"cancer" OR "tumor" OR "tumour" OR "malignancy" OR "neoplasia"	The query was used to find papers related to cancers
#2	"Immune system" OR "Inflammation" OR "immune response"	The query was used to find papers related to immune response
#3	"Oxidative stress" OR "reactive oxygen species" OR "ROS"	The query was used to find papers related to oxidative stress
#4	"insulin" OR "metabolic" OR "estrogen" OR "obesity" OR "adipose tissue"	The query was used to find papers related to metabolic
#5	"depression" OR "anxiety" OR "pshyciatric disorders" OR "mental disorders"	The query was used to find papers related to psychiatric disorders
#6	"cognitive" OR "thinking" OR "dementia" OR behavior"	The query was used to find papers related to cognitive function disorders
#7	"Cardiorespirattory fitness" OR "muscle strength" OR "muscle mass" OR "fatigue" OR "dyspnea"	The query was used to find papers related to functional status
#8	"QoL" OR "Quality of life"	The query was used to find papers related to quality of life

#9	“mortality” OR “overall survival” OR “death”	The query was used to find papers related to mortality
#10	“Exercise” OR “sport” OR “physical activity”	The query was used to find papers related to physical activity
#10	#1 AND #10 AND #2	The query was used to find papers associated to effects of physical activity on immune response in cancer patients
#11	#1 AND #10 AND #3	The query was used to find papers associated to effects of physical activity on oxidative stress in cancer patients
#12	#1 AND #10 AND #4	The query was used to find papers associated to effects of physical activity on metabolic profile in cancer patients
#13	#1 AND #10 AND #5	The query was used to find papers associated to effects of physical activity on psychiatric disturbances in cancer patients
#14	#1 AND #10 AND #6	The query was used to find papers associated to effects of physical activity on cognitive disturbances in cancer patients
#15	#1 AND #10 AND #7	The query was used to find papers associated to effects of physical activity on functional status in cancer patients
#16	#1 AND #10 AND #8	The query was used to find papers associated to effects of physical activity on quality of life in cancer patients
#17	#1 AND #10 AND #9	The query was used to find papers associated to effects of physical activity on mortality rate in cancer patients

Table 1: Search strategy and keywords used for literature identification. Column A represents the number of query in PubMed advanced search tool; Column B represents keywords used in each query; Column C represents the description of each query.

3. Results

3.1. Physical activity and metabolism

The metabolic properties of cancer cells are one of the oldest areas of research in cancer. It is believed that various metabolic activities are disrupted in tumours, which promotes their

malignant phenotype [16]. To acquire this phenotype, cancer cells need to switch to an anabolic state to produce molecules needed for replication and tumour growth [16].

This can be done by the various pathways and hormones, including the estrogen pathway, insulin and insulin-growth factor-1 (IGF-1) pathway, and leptin pathway.

The estrogen pathway is one of the most prominent in the pathogenesis of estrogen-dependent cancers such as breast cancer (BC), ovarian cancer or endometrial cancer [17]. In pre-menopausal women, estrogens are mainly produced by the ovaries, while in post-menopausal women, peripheral synthesis from aromatisation of adrenal androgens is more significant [17]. The latter process occurs in the adipose tissue and hence is related to obesity [18]. Therefore, weight gain and body mass index (BMI) are one of the major risk factors for developing estrogen-dependent tumours, including BC [18]. Since PA decreases the amount of adipose fat, it can decrease estrogens and lower the risk of BC [12].

Another pathway that promotes the development of cancers is the insulin pathway. Insulin is an anabolic hormone which promotes the growth of cells by allowing an increased availability of substrates such as glucose or amino acids. It also increases the synthesis of IGF-1, a known mitogen that promotes proliferation. Additionally, insulin increases the activity of aromatase, which increases the peripheral synthesis of estrogen, and decreases the hepatic production of sex-hormone binding globulin (SHBG), a protein responsible for estrogen binding in plasma. Reduction of SHBG consequently leads to an increase in the active (unbound) form of estrogen [12,19]. All those changes can lead to the acquisition of a malignant phenotype.

PA is an important factor in modulating the insulin pathway. It increases hepatic and muscle insulin sensitivity, promotes its uptake by those tissues and therefore decreases its plasma levels [12]. Additionally, PA decreases the levels of IGF-1 [20].

Additionally, PA modulates the leptin pathway, which is a hormone produced by adipocytes that stimulates cell proliferation. It also increases the synthesis of proteolytic enzymes such as metalloproteinases (MMPs), favouring the invasion and migration of cancer cells. This can be further facilitated by the pro-angiogenetic potential of leptin.

PA has been shown to reduce leptin levels, most likely due to reducing adiposity. Furthermore, lowering adiposity increases the levels of adiponectin, an anti-inflammatory protein that reduces the proliferation of cancer cells [12].

3.2. Physical activity and oxidative stress

Oxidative stress is defined as a disturbance in the balance between the production of reactive oxygen species (ROS) and their elimination through antioxidants. OS can be caused by various

factors, such as infection, ischemia, mental stress or due to exposure to environmental pollutants, smoking or drugs [21]. It is also associated with obesity, which is linked to a sedentary lifestyle [22,23]. OS may contribute to the development of chronic disorders such as autoimmune disorders, CVDs, neurodegenerative diseases, and ageing [13]. It is one of the most important factors of DNA damage, which can promote mutations and cancer development [12]. For example, it can cause mutation of a tumour suppressor gene - p53 [12]. Moreover, OS promotes the production of angiogenic factors such as VEGF and facilitates MMPs that promote cancer growth and metastasis [12].

During PA, the level of OS increases, causing the organism to adapt and improve its antioxidant defence systems [13]. For example, it was found that people who exercise more have increased levels of mitochondria [12]. Moreover, PA can increase superoxide dismutase (SOD) and glutathione (GSH) activity, favouring an anti-oxidative state [13]. It can also increase the plasma concentration of uric acid, a known scavenger of plasma ROS [23]. On the contrary, a sedentary lifestyle promotes proteolysis in muscles, which favours OS formation [23].

3.3. Physical activity and immunological response

The immune system is a network of biochemical processes aimed at recognising and destroying "alien" antigens such as infectious pathogens or malignancies [24]. It is comprised of cytokines, proteins and immune cells. Therefore, its proper activity is an important factor in the prevention of cancer development. Indeed, altered immune function, which can be seen in various diseases, including inborn errors of immunity (IEI) [25] or AIDS [26] has been linked to the higher incidence of the tumours [25].

Immune escape is the final phase of cancer development, where cancer cells modulate the immune system to escape from being destroyed by it [27]. For example, they can modify self-antigens to escape from T-cell recognition, changing the balance between pro-death and anti-death signals via upregulation of antiapoptotic molecules, secreting metabolites which impair the function of immune cells [27].

The immunosuppressive state in cancer patients is further aggravated by chemotherapy, which, due to its non-specific nature, destroys immune cells [28,29].

Therefore, various therapies were implemented to strengthen the immune response to destroy tumours, and the new field of immunooncology has been developed [24]. Hence, novel strategies are needed to increase immune activity to not only "fight" the cancer cells, but also to prevent infections, which are common in cancer patients [30].

It has been demonstrated in various studies that regular PA positively affects immune competence and reduces the risk of infections compared to a sedentary lifestyle [11]. For example, Bachi et al. [31] have found that physically active individuals have higher immunoglobulin M and G levels against influenza virus compared to the sedentary group. This could be explained by the fact that regular activity favours the secretion of inflammatory cytokines such as interferon-gamma (IFN-γ), tumour necrosis factor-alfa (TNF-α), interleukin-6 (IL-6) and IL-12 via Toll-like receptor (TLR) signalling pathways, and increases the level of Th1 lymphocyte [32]. However, some other evidence suggests that extensive exercise causes immunosuppressive effects due to elevated levels of cortisol [33]. Epidemiological analyses support this theory. It has been shown that the incidence of upper respiratory tract infections is generally higher during the period of heavy training and 1-2 weeks after participation in a marathon [33]. Therefore, we should advise cancer patients to limit excessive exercise in favour of moderate activity.

Various studies have assessed the immune system activity in cancer patients who undergo PA. For example, a systematic review by Fairey et al. [28] has proposed the "inverted J hypothesis", which suggests that positive benefits of PA occur with regular or moderate exercise, while exhaustive exercise may lead to a suppressed immune system. The improvements upon moderate PA are believed to be caused by an enhanced NK activity, reduced neutropenia, increased granulocyte count and reduced insulin-like growth factor (IGF-1), which can promote binding of immune cells to the cancer cell, thus helping with apoptosis [28]. As for today no study provides the direct link between the PA and reduced infections rate, although it could be suggested indirectly by the fact that PA reduces the hospital admission by 8% (AR = -0.08 (95% CI from -0.03 to -0.13) [34] and infections are responsible for approximately 31% of hospital admissions in cancer patients representing its most common cause [30].

3.4. Physical activity as a prevention against cancer

Taking together all the PA benefits, it could be logically assumed that PA, through reduction of OS, decreasing the level of estrogen and leptin-producing adipose tissue and enhancing immune activity, could decrease the incidence of cancer.

Various epidemiological studies support this theory. For example, PA is associated with a 25% reduction of BC risk and a 30-40% reduction of colon cancer risk [15]. It is consisted with the study of Rockhill et al., [35] who found that a regular physical activity for more than 7h per week reduced a BC incidence by 18% compared to those who trained less than 1h for

week (RR = 0.82; 95% CI: 0.70 - 0.97) and Wolin et al., [36] study which found that PA is associated with 24% lower risk of colon cancer (RR = 0.76; 95% CI: 0.72-0.81). Moreover various meta-analyses found that PA also reduces the risk of gastric cancer by 19% (RR = 0.81; 95% CI: 0.73-0.89) [37]; pancreatic cancer by 11% (RR = 0.89; 95% CI: 0.82-0.96) [38]; lung cancer by 21% for a normal-instensity PA (RR = 0.79; 95% CI: 0.73-0.86) and 25% for a high-instenistiy PA (RR = 0.75; 95% CI: 0.68-0.84) [39] and 35% lower odds for developing hepatocellular carcinoma (OR = 0.65; 95% CI: 0.45-0.95) [40]. Therefore, it becomes clear that PA is an effective way to prevent cancer incidence. Doctors must motivate patients to engage in PA during routine visits because it not only decreases the risk of cancer occurrence but also improves the physiological and psychological well-being of patients who have been diagnosed with cancer.

3.5 Physical activity and psychological function

Various studies have demonstrated that cancer patients are frequently affected by psychiatric conditions, including depression [41,42] and anxiety [43]. The prevalence of depression was estimated to be 27% (95% CI: 24-30%) and tends to be higher amongst females [44].

Those conditions are mainly caused by an increased stress associated with the physical *pain due to the pharmacological regimes [45]*, various contraindications and limitations in life [46], loss of healthy functioning [46], feeling of worthlessness, fear of death [46] and financial burden, often called “financial toxicity” imposed on the family [47]. The latter is especially crucial in the low-income countries such as Pakistan, Nepal or Vietnam, where people face higher depression prevalence compared to the high-income countries [41,44].

The consequences of those conditions cannot be overlooked as they lead to the worst compliance with the therapies due to lack of motivation, neglect of the doctor’s advice, and struggle with communication of crucial symptoms [41]. They can also lead to lifestyle modification and promote a sedentary lifestyle. Interestingly, depression and anxiety could also predispose to cancer development as both diseases share similar risk factors with cancers, including sedentary lifestyle, alcohol consumption and smoking [43]. Taking the profound role of psychiatric conditions in both the development and management of cancer, there is a need to implement strategies that could prevent them.

There is much evidence that PA is a beneficial factor in both prevention and management of psychiatric disorders [48,49] and improves the mood in individuals without psychiatric conditions [8]. People who exercise regularly report better self-esteem, vitality,

general well-being and satisfaction with physical appearance, all of which might be altered in cancer patients [50]. Various hypotheses explain how PA can affect individuals.

The psychological theory states that the psychological benefits are achieved by: 1) distraction where diversion from unfavourable stimuli, such as daily life struggles in cancer patients; 2) self-efficacy, which improves our mood by engaging into challenging activity and achieving new goals; 3) social interaction since mutual involvement in the same activity can form bonds between participants [8]. Taken the fact that cancer patients are commonly affected by depressive mood disorders [42], *PA, through providing distraction by not thinking about the disease and improving self-efficacy, could show promising results*. Since cancer patients are often marginalised by society [51], the additional social interaction could also improve psychological well-being.

On the other hand physiological theory explains that improvements in the mood can be improved thanks to the next molecular mechanisms: 1) increasing synaptic activities of mono-amines, which could partially work in the same manner as anti-depressive drugs and 2) release of endorphins (endogenous opioids) that have an inhibitory function on central nervous system (CNS) can provide sensation of calm [8] and reduction of pain [52]. This could reduce negative thinking in cancer patients and provide better pain management.

For example, Aydin et al, [46] have observed that 60 min aerobic and home-based exercise in patients who completed cancer therapy and were on routine controls have had improvement in psychological health parameters assessed by WHOQOL Score ($p=0.009$) and social score ($p=0.016$). The same study has shown that the exercise group had 3 times lower depression risk assessed by the Beck Depression Inventory Scale ($Z=-3.893$; $p<0.001$). Another meta-analysis demonstrated that yoga moderately decreased depression (Hedge's $g = -0.554$; 95% CI: from -0.878 to -0.231) and anxiety (Hedge's $g = -0.553$; 95% CI: from -0.781 to -0.325) symptoms compared to controls [53]. Additionally, meta-analysis by Zhang et al. [54] showed that amongst breast cancer survivors, those who performed exercise had lower depression severity (SMD = -0.63; 95% CI: from 0.93 to -0.33) compared to controls. The anxiety severity was also reduced (SMD = -0.49; 95% CI: from -0.74 to -0.23). Interestingly, the same study found that the sessions lasting less than 60 minutes had more favourable outcomes than those above 60 minutes. This could be potentially caused by the fact that cancer survivors usually have a lower tolerance for physical exercise, and prolonged activity could induce excessive fatigue and anger. The exercise was also considered to be safe, as the amount of side effects was the same between the control and cancer group [54].

Taking into consideration the psychological aspect of the patients, doctors should encourage them to undertake moderate physical exercise to improve well-being and help with depression/anxiety symptoms. This could potentially lead to a better QoL, better compliance with the therapy and ultimately better impact on survival.

3.6 Physical activity and functional status

Functional status is an individual's ability to perform normal daily activities required to maintain well-being. It is determined by the physiological capacity (muscle strength, walking distance, maximal oxygen uptake) of the organism and symptom burden (eg, fatigue, dyspnea, musculoskeletal pain). It is an important predictor of overall health condition and longevity [55].

PA seems to play an important role in the improvement of those parameters [56,57]. People who exercise tend to have fewer fractures and falls [58], can walk longer distances [59] and have improved muscle strength [57].

Cancer patients are especially prone to alterations in those parameters. On one side, the cancer itself can cause deterioration of physical health by causing a chronic inflammatory [60], compressing organs and altering their function [61] or reducing red blood cell (RBC) formation [62]. From the other side, patients who undergo cancer treatment are faced with numerous toxicities and side effects caused by chemotherapy (CTX), radiotherapy (RTX) or surgical intervention [63,64]. It can be even further aggravated by the fact that a psychological decline can cause a lack of motivation in cancer patients and promote a sedentary lifestyle. Later is in fact associated with the progression of other diseases, including CVDs [65], metabolic diseases [66] and mental health disturbances [67]. Consequently, the management of cancer/treatment side effects should be included in intra- and post-treatment care.

There are various symptoms that patients can report during/after therapy. Those include fatigue [68], decreased muscle strength [69] and cardio-respiratory efficacy [70].

Fatigue is believed to be the most common cause of physical deterioration in cancer patients. Up to 80-90% of patients undergoing RTX or CTX report fatigue [71]. It can be characterised by lack of energy, decreased physical ability and chronic tiredness [71]. Fatigue can significantly impair a patient's daily life, decrease their work activity and emotional well-being. It can be caused by various factors, including the chronic inflammation state induced by the cancer, side effects of treatments, which can cause the release of cytokines from the destroyed cells, psychological distress or muscle deterioration caused by a sedentary lifestyle. [72]. Various studies have found that PA improves fatigue in cancer patients [20,68,71]. For example, meta-analysis by Tomlinson et al. [71] has found that PA moderately decreases

fatigue (SMD = -0.45; 95% CI: from -0.57 to -0.32). Another study by Dennett et al. [68] was consistent with the findings. They have shown that exercise had a positive effect on fatigue when compared to usual care. However, an excessive PA has been associated with a lesser efficacy.

Fatigue can be especially seen in lung cancer patients, since the tumour or tumour-related interventions can reduce the amount of functional lung tissue, which leads to hypoxemia [70]. PA can partially restore such distress by increasing respiratory muscle strength [70].

Another important parameter which is reduced in cancer patients is **cardio-respiratory fitness (CRF)**. It shows the capacity of the organism to transport and use oxygen [73]. Since cancer patients have reduced diffusion capacity due to the infiltration of the lungs or damage to cardiac muscle caused by the chemotherapeutics, their cardio-respiratory fitness markers, such as the 6-minute walking test (6MWT) and peak oxygen consumption (VO_{2peak}), decrease [74].

PA seems to provide a beneficial role on CRF as indicated by the increase of 6MWT in healthy individuals [59]. Similar benefits were seen in the cancer population. For example, meta-analysis by Fong et al. [20] has shown that PA was associated with an additional 29m (95% CI: 3-55m) of walking distance in the 6MWT test. They have also observed that VO_{2peak} was increased in physically active individuals. Furthermore, an RCT study done by Edvardsen et al. [75] has shown that PA not only reported an increase in VO_{2peak}, but that the control group that did not perform PA reported a decrease in VO_{2peak} in lung cancer patients.

Another important parameter of functional status in cancer patients is **muscle mass and strength**. Loss of muscle mass is associated with the worst prognosis in chronic diseases such as diabetes, cirrhosis and CVDs [76]. In cancer, low muscle mass (sarcopenia) is linked to cachexia, driven by systemic inflammation and the presence of chronic disease [76]. This leads to various negative effects, including reduced muscle strength [70] and more severe toxicities induced by CTX [76,77]. Consequently, patients with reduced muscle mass should employ other strategies to prevent further decline in muscle mass and strength.

PA can increase muscle mass by the activation of satellite cells, enhancing protein synthesis through the mechanistic target of rapamycin **(**mTOR) pathway and modulating microRNAs to promote growth pathways [78]. Therefore, various studies have confirmed the positive role of exercise on muscle mass in cancer patients [79,80].

The effect of exercise on the musculoskeletal system can be assessed directly by measuring lean body mass (LBM), which is a measure of the body's non-fat tissue used to determine the amount of muscle mass in the organism [81] or indirectly through strength tests.

The current evidence tells us that PA has a beneficial effect on muscle mass. For example, Lønbro et al. [80] have observed that lean body mass (LBM) assessed by dual energy X-ray absorptiometry was increased in post-chemotherapy cancer patients after exercise by 0.7kg (95% CI: 0.6-2.0). Additionally, exercise improved knee extension by 17.6 kg (95% CI: 12.7-22.5), chest press by 7.0 kg (95% CI: 5.6-8.0) and leg press by 21.3 kg (95% CI: 8.2-34.4); however, the group size was relatively small. The results were consistent with meta-analysis by Koeppel et al., [82] which showed that the exercise group gained on average 0.85 kg LBM (95% CI: 0.26-1.43). Moreover, the control group has shown a decrease in LBM of 0.59kg. However, it was not statistically significant (95% CI: from -1.04 to 0.06) [80]. Additionally, it is worth noticing that the implementation of exercise with dietary advice significantly improves outcomes compared to exercise alone [83]. Those results become especially clinically relevant as a handgrip was found to be an independent prognostic factor of survival [69].

3.7 Physical activity and cognitive function

Cognitive performance is defined as the ability to execute cognitive tasks that require memory and attention to generate an appropriate response to external stimuli. Cancer-related cognitive impairment (CRCI) comprises deficits in memory retention, attention control and processing speed alterations [84]. It is confirmed by neuroimaging studies, which show grey and white matter loss in multiple brain areas in cancer patients [84]. Studies suggest that those impairments can persist up to 2 years after the treatment, and 30-40% of patients will never return to the baseline levels of cognitive function [85]. Various mechanisms were proposed to sit behind those changes. For example, some chemotherapeutics, such as platinum-based compounds, have neurotoxic effects caused by inducing an inflammatory state and destroying the blood-brain barrier [85].

PA has demonstrated a beneficial role in improving cognitive performance [86]. The mechanism behind it is similar to the mechanism of improved psychological function and counters the chemotherapy by regulation of oxidative stress and inflammation, improving blood flow via producing Vascular Endothelial Growth Factor (VEGF) and a positive effect on a range of neurotransmitters [84].

An umbrella review by Hu et al. [85] has demonstrated that PA causes moderate-to-large improvement in verbal memory assessed by the Hopkins Verbal Learning Test (HVLT). Specifically, this test checks the ability of the patient to verbally recall the words which have been read before. They have also found an improvement in processing speed and executive

function using the Trail Making Test protocol. Patients also reported an improvement in self-reported questionnaires.

3.8 Physical activity and quality of life

The quality of life is defined by the World Health Organization (WHO) as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [87]. Many factors contribute to the QoL. Amongst them are physical and psychological well-being, financial [83,88] and social status [89,90], level of healthcare in a specific country [41], and familial support [89]. *Given the fact that cancer patients show worse physiological and psychological activity and become marginalised by society,* their QoL significantly decreases [91]. This becomes a substantial problem, since the QoL influences the mortality of patients [92].

For example, Fukushima et al. [92] have observed that the overall risk of mortality increases by 6% for every unit of QoL drop (HR = 1.06; 95% CI: 1.05-1.07). The number becomes even higher for some tumours, such as lung or liver cancer, where the risk increases by 10% and 20% respectively. Interestingly, the pre-treatment QoL has proved to be the most significant factor affecting mortality (HR = 1.06; 95% CI: 1.05-1.07). Another study has found that high physical functioning stratified by QLQ-C30 score is correlated to approximately 3 times longer survival [93]. The QLQ-C30 score assesses physical, psychological and social function in patients with cancer. The group which achieved more than 66.6 points had a median survival time in months of 65.38 (95% CI: 56.02-71.52), the group which got between 33.3 and 66.6 point had a median survival of 27.24 (95% CI: 23.36-40.44) and the group which got less than 33.3 points has achieved a median survival of 20.80 months (95% CI: 13.17-72.21). Therefore, future therapeutic strategies should consider improving patients' QoL.

Various studies showed that PA positively impacts QoL in a healthy population [94], and other diseases such as depression [95] or asthma [96].

Many studies have assessed whether PA can improve the QoL of cancer patients. For example study by Lin et al. [97] has found that for every additional minute of walking per week, the QoL score was increased by 0.03 points assessed by the FACT-L score. It is worth noting that the FACT-L score focuses primarily on physical and functional abilities and does not take into consideration psychological aspects. Another meta-analysis has shown that PA improves QoL scores by 5.55 points on a 100-point scale after standardisation of results (MD = 5.55; 95% CI: 3.19-7.9) [98]. Additionally, it was found that frequent exercise (3-5 times per week) was

associated with improved peak oxygen consumption, self-esteem, and reduced fatigue and that shorter exercise provided more benefits [98]. Interestingly, frequent exercise was linked to shorter hospital stay [98], which is beneficial, since cancer treatment causes financial burden [1]. Another meta-analysis done by Sweegers et al. [99] has further evaluated the role of physical activity on self-assessed QoL of cancer patients. They found a small to moderate improvement of QoL in cancer patients who undergo exercise (g = 0.19; 95% CI: 0.13-0.26). Additionally, they found that supervised exercise showed better results than unsupervised, and that moderate-high activity better affects QoL than moderate or low-moderate activity. The duration of the session also matters; patients exercising more than 60 minutes did not show an improvement in QoL, although the number of studies was relatively small (N = 3).

3.9 Physical activity and cancer mortality

As we already established, moderate physical activity is associated with various benefits to our life by increasing the immune response, antioxidant defence mechanisms and improving metabolic equilibrium. Consequently, those molecular changes lead to better physiological and psychological parameters and QoL in cancer patients. Therefore, we hypothesised that more physically active patients would have a better prognosis in terms of cancer survival.

Indeed, PA was shown to decrease mortality in various studies (REFs). For instance, a meta-analysis done by Bettariga et al. [74] has assessed whether the muscle strength and cardio-respiratory fitness (CRF) score affect all-cause cancer mortality. The all-cause mortality was 31% lower (HR = 0.69; 95% CI 0.61-0.78) in patients with high muscle strength levels compared with those with low muscle strength levels, and better CRF results were associated with a 46% reduction of all-cause mortality (HR = 0.54; 95% CI: 0.38-0.84). Another meta-analysis, which included 777,696 patients, used metabolic equivalent of task (MET) per hour per week to measure people's activity. The higher MET was associated with the highest activity, while the lowest MET was associated with the sedentary lifestyle. People in the lowest quartile of physical activity (less than 2.5 MET-h/week) who were mostly inactive during the week and sat for more than 8h per day had a 21% increased risk (95% CI: 1.14-1.28) [100]. Interestingly, even those who sat for more than 8h per day but had a high MET-h/week, hence were physically active, have not had a higher risk of cancer death [100]. However, it is worth mentioning that the provided results evaluated only all-cause mortality, not specifically caused by the cancer.

Several other studies have assessed the relationship between PA and mortality for specific cancers. For example, Benke et al. [101] have found that post-diagnosis PA was

associated with 31% reduced risk of dying from prostate cancer (RR = 0.69; 95% CI: 0.55-0.85).

Another cohort study has provided evidence that PA provides beneficial effects on women with BC. Interestingly, it provided more benefits in women with advanced-stage cancer (RR = 0.36; 95% CI: 0.19-0.71 for those who trained for 9 or more MET-h/week) and those with positive estrogen/progesterone cancers [102]. The latter could be explained by the fact that PA, by reducing adipose tissue, can also reduce peripheral estrogen production and slow progression of the disease. However, we should notice that hormone-positive cancers generally have a better prognosis [103]. Positive role of PA on BC was found in other cohort studies involving women with BC [104–106]. Additionally, a study by Irwin et al. [104] found that lack of physical activity was associated with a 4-fold greater risk for death (HR = 0.55; 95% CI, 0.22 to 1.38 for those who were physically active vs HR = 3.95; 95% CI, 1.45 to 10.50 for physically inactive).

For colorectal cancer (CRC), it was observed that physical activity for more than 18 MET-h/week was associated with a 71% lower risk of CRC cancer-specific mortality (95% CI: 0.11-0.77) [107]. Another study found provides evidence that post-diagnosis physical activity was associated with the 42% lower risk for all-cause mortality (95% CI: 0.47-0.71) and those who had been spending more than 6 hours of leisure time sitting had 36% higher all-cause mortality compared to those who spent less than 3h sitting during the leisure time (HR = 1.36; 95% CI: 1.10-1.68) [108].

The role of PA was also assessed in a patient with palliative, recurrent malignant glioma and a Karnofsky performance status ≧ 70 [109]. PA has granted a longer survival in physically active patients. For example, patients who engaged in PA represented in 9 or more MET-h/weeks had a median survival of 21.84 months, while those less active had a median survival of 13.03 months. This provides evidence that even in palliative care, PA can provide substantial benefits [109].

4. Limitations & Discussion:

Cancer is one of the main causes of death in the XXI century and imposes a substantial health burden on our society [1]. Novel strategies should be implemented globally to reduce its incidence, improve the QoL of affected patients, and increase survival.

The role of PA has been assessed in various studies in the context of cancer management and prevention. It has been shown that more physically active people have improved immune response [31], reduced levels of OS [12], and metabolic/hormonal profile [12]. Clinically, those

changes could lead to a better physical, psychological and cognitive performance in cancer patients [46,71,85], potentially improving their quality of life and survival.

Even though, as evidenced by this study, PA provides numerous benefits for both life quality and survival for cancer patients, doctors should be cautious and keep in mind that not everyone can benefit from such implementation. PA should be adapted to the clinical status of the patient, individually taking into consideration age, global health parameters and comorbidities [72]. For example, PA can be contraindicated in patients with myocardial ischemia or severe arrhythmia which occurs during exercise [72]. Moreover, patients with respiratory distress should limit their PA intensity [72]. Bone metastases should also be taken into consideration to avoid excessive pressure on the affected bones [72]. Additionally, we should be aware that excessive physical activity is associated with the worst prognosis [68].

Finally, it should be emphasized that PA is not a single non-pharmacological remedy for the disease. The patient should also work on a proper diet, limit interaction with irritants such as smoking or pollution and sleep well.

5. Conclusions

Our review indicates that PA has a substantial role in both the prevention and management of cancers. On one side, it improves QoL in cancer patients by providing benefits in physiological, cognitive and psychological function. From the other side, improvements in such parameters positively impact patients' health, providing a decline in cancer mortality rate. Various metabolic, immune and oxidative stress pathways are believed to be engaged in this process. Further studies are needed to evaluate the role of PA in cancer patients, and novel adjustments in guidelines should be implemented on a global scale to decrease the economic and health burden caused by cancers.

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