

SMUSZKIEWICZ-RÓŻAŃSKI, Paweł, RÓŻAŃSKA-SMUSZKIEWICZ, Gabriela, RAGAN, Dagmara, DLUGOSZ, Joanna, STASZCZAK, Paweł, BARA, Maciej, KMIOTEK, Weronika, JAWORSKA, Barbara, ORONOWICZ, Radosław and JAMA, Grzegorz. Holistic approach to oncology patients with a special focus on physical activity – a literature review. *Quality in Sport*. 2024;20:53434. eISSN 2450-3118.

<https://dx.doi.org/10.12775/QS.2024.20.53434>

<https://apcz.umk.pl/QS/article/view/53434>

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.

Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).

Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.

Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

© The Authors 2024;

This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland

Open Access. This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author (s) and source are credited. This is an open access article licensed under the terms of the Creative Commons Attribution Non commercial license Share alike. (<http://creativecommons.org/licenses/by-nc-sa/4.0/>) which permits unrestricted, non commercial use, distribution and reproduction in any medium, provided the work is properly cited.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 18.07.2024. Revised: 28.07.2024. Accepted: 05.08.07.2024. Published: 14.08.2024.

Holistic approach to oncology patients with a special focus on physical activity – a literature review

Paweł Smuszkiewicz-Różański¹, Gabriela Różańska-Smuszkiewicz², Dagmara Ragan³, Joanna Długosz⁴, Paweł Staszczak⁵, Maciej Bara⁶, Weronika Kmiotek⁷, Barbara Jaworska⁸, Radosław Oronowicz⁹, Grzegorz Jama¹⁰

¹ Paweł Smuszkiewicz-Różański

Health Care Centre in Strzyżów,

700th Anniversary Street 1, 38-100 Strzyżów, Poland

<https://orcid.org/0009-0009-3178-2029>

pawels161@gmail.com

² Gabriela Różańska-Smuszkiewicz

Clinical Regional Hospital No. 2 named after St. Hedwig of Anjou in Rzeszów
Lwowska Street 60, 35-301 Rzeszów, Poland

<https://orcid.org/0009-0005-3857-8830>

gabrielarozanskaa@gmail.com

³ Dagmara Ragan

T. Marciniak Lower Silesian Specialist Hospital - Emergency Medicine Centre

General August Emil Fieldorf Street 2, 54-049 Wrocław, Poland

<https://orcid.org/0009-0002-2423-0698>

dagmara.ragan@gmail.com

⁴ Joanna Długosz

District Health Center - Specialist Hospital in Brzeziny

Maria Skłodowska-Curie Street 6, 95-060 Brzeziny, Poland

<https://orcid.org/0009-0005-0922-6190>

joanna.dlugosz123@gmail.com

⁵ Paweł Staszczak

SPZOZ University Clinical Hospital No. 1 named after Norbert Barlicki in Łódź.

dr. Stefana Kopcińskiego 22, 90-153 Łódź, Poland

<https://orcid.org/0009-0005-8324-9956>

pawel.staszczak@stud.umed.lodz.pl

⁶ Maciej Bara

Infant Jesus Clinical Hospital, Medical University of Warsaw,

William Heerlein Lindleya 4, 02-005 Warsaw, Poland

<https://orcid.org/0000-0001-7238-2237>

maaciej.bara@gmail.com

⁷Weronika Kmiotek

Clinical Regional Hospital No. 2 named after St. Hedwig of Anjou in Rzeszów

Lwowska Street 60, 35-301 Rzeszów, Poland

<https://orcid.org/0009-0009-7699-0585>

weronika55.12@o2.pl

⁸Barbara Jaworska

Independent Health Care Center of the Ministry of Interior and Administration in Lublin

Grenadierów Street 3, 20-331 Lublin, Poland

<https://orcid.org/0009-0000-9155-5084>

barbaraewajaworska@gmail.com

⁹Radosław Oronowicz

Regional Hospital named after Dr. H. Jankowski,

Szpitalna Street 16, 37-200 Przeworsk, Poland

<https://orcid.org/0009-0008-8784-3858>

radoslaw.oronowicz@gmail.com

¹⁰Grzegorz Jama

Clinical Regional Hospital No. 2 named after St. Hedwig of Anjou in Rzeszów

Lwowska Street 60, 35-301 Rzeszów, Poland

<https://orcid.org/0009-0004-8108-5428>

grzegorzjama@gmail.com

Abstract

Current global statistics indicate nearly 20 million new cancer cases and close to 10 million cancer deaths annually. Demographic forecasts predict that the annual number of new cancer cases will reach 35 million by 2050, representing a 77% increase from the 2022 levels. These statistics highlight that oncology patients will increasingly be seen by doctors of all specialties. This is a particular patient population because, primarily, they are chronically ill with a severe

disease and are treated with potent medications. Both the doctor and patient usually focus on the disease and the primary treatment, as these constitute the main therapeutic issue. Consequently, the aspect of physical activity, which is an adjunct, may not only be deprioritized but may also be entirely overlooked. Recent studies support the promotion of physical activity and exercise for adult oncology patients before, during, and after cancer treatment, across all types of cancer, including those with advanced disease. Lack of physical activity, reduced physical fitness, including exercise intolerance, and dependency are common consequences of cancer and its treatment. The vast majority of guidelines for those diagnosed with cancer suggest that physical activity is an essential part of care. Individualization and optimization of oncological treatment significantly improve prognosis for these patients. Simultaneously, there remains a continuous need for further research into the type, intensity, and duration of physical activity for cancer prevention, as well as the development of effective recommendations for patients during active cancer treatment and in remission.

Keywords: oncology patient, oncology, cancer, physical activity, exercise, health

Introduction

Current global statistics of 2022 indicate that nearly 20 million new cancer cases and close to 10 million cancer-related deaths were recorded. Projections based on demographic data suggest that the annual number of new cancer cases will reach 35 million by 2050, representing a 77% increase compared to the 2022 level [1].

Oncology patients, therefore, represent a patient group that physicians across all specialties will increasingly encounter. This is a unique group of patients because they are chronically ill with a serious disease and are treated with potent medications. Both the disease and its primary treatment typically demand the full attention of both the doctor and the patient,

as they constitute the primary medical concern. Consequently, the matter of physical activity, which is considered an additional aspect, may not only be relegated to a distant priority but may also be entirely forgotten.

Recent studies advocate for the promotion of physical activity and exercise for adult oncology patients before, during, and after cancer treatment, across all cancer types, including patients with advanced disease. Physical inactivity, reduced physical fitness, including exercise intolerance, and dependency are common consequences of cancer and its treatment. The vast majority of guidelines for individuals diagnosed with cancer suggest that physical activity is an essential component of care. An individualized approach is necessary to maximize the potential benefits of exercise. Aerobic training combined with resistance training, aimed at enhancing muscle fitness and function, can be particularly important for patients experiencing disease-related cachexia [2]. Individualization and optimization of oncological treatment significantly improve patient prognosis. Additionally, it is essential to manage side effects and avoid long-term consequences. Physical activity is recommended for every oncology patient, regardless of the type of cancer and stage of therapy, taking contraindications into account. Numerous studies have demonstrated the positive impact of physical activity and targeted exercise therapy on certain patient-related outcomes. After diagnosis, patients should be integrated into supportive exercise monitoring as soon as possible to sustainably reduce side effects related to primary therapy [3].

Statistics

The table below presents cancer statistics for the year 2022, including new cases and deaths due to cancer.

Cancer site	New cases	Deaths
Lung	2,480,301	1,817,172
Female breast	2,308,897	665,684

Colorectum	1,926,118	903,859
Prostate	1,466,680	396,792
Stomach	968,350	659,853
Liver	865,269	757,948
Thyroid	821,173	47,485
Cervix uteri	661,021	348,189
Bladder	613,791	220,349
Non-Hodgkin lymphoma	553,010	250,475
Esophagus	510,716	445,129
Pancreas	510,566	467,005
Leukemia	486,777	305,033
Kidney	434,419	155,702
Corpus uteri	420,242	97,704
Lip, oral cavity	389,485	188,230
Melanoma of skin	331,647	58,645
Ovary	324,398	206,839

Brain, central nervous system	321,476	248,305
Larynx	188,960	103,216
Multiple myeloma	187,774	121,252
Gallbladder	122,462	89,031
Nasopharynx	120,416	73,476
Oropharynx	106,316	52,268
Hypopharynx	86,276	40,917
Hodgkin lymphoma	82,409	22,701
Testis	72,031	9056
Salivary glands	55,003	23,894
Vulva	47,342	18,579
Penis	37,699	13,729
Kaposi sarcoma	35,359	15,911
Mesothelioma	30,618	25,372
Vagina	18,800	8238
All cancers excl. C44	18,730,216	9,667,298

All cancers	19,964,811	9,736,779
-------------	------------	-----------

Table No. 1 based on article [1].

Incidence and Mortality Rates by Gender and World Region

With the increase in the Human Development Index (HDI), we observe a rise in cancer incidence. In 2022, the risk of developing cancer before the age of 75 for men in low HDI conditions was around 10%, whereas in very high HDI conditions, it exceeded 30%. The overall incidence rate of all types of cancers combined was slightly higher in men (212.5 per 100,000) compared to women (186.2 per 100,000) in 2022, although the rates varied by world region. The risk of death from cancer, depending on the level of HDI, differs less, although the risk of death in the male population in high and very high HDI conditions is about 60% higher than in low and medium HDI conditions. For women, the risk varies slightly depending on the HDI level, with higher risk in low HDI conditions compared to very high HDI conditions. Regional differences in cancer incidence and mortality largely reflect differences in underlying exposure to dominant risk factors for major cancers, the distribution of related cancer types, and barriers to effective prevention, early detection, and radical treatment. [1]

Physical Activity and Health

It is widely recognized, and there is substantial research, on the impact of physical activity in preventing the development of various chronic diseases. Studies show that physical activity reduces mortality from any cause or events related to cardiovascular diseases, coronary artery disease, stroke, heart failure, overall cancer, and site-specific cancers (such as cancers of the head and neck, acute myeloid leukemia, multiple myeloma, stomach cardia, lungs, liver, endometrium, colon, breast, bladder, rectum, esophagus, prostate, and kidneys) [4].

Scientific evidence indicates that increasing regular physical activity is associated with a reduced risk of developing many types of cancer. Probable mechanisms linking physical activity to decreased cancer risk include reducing systemic inflammation, sex hormones, hyperinsulinemia, insulin-like growth factor (IGF-I), pro-inflammatory leptin, and other obesity-related cytokines, as well as significantly increasing levels of anti-inflammatory

adiponectin. Physical activity also improves immune system function and the composition and diversity of the gut microbiota. The most significant changes in the inflammatory profile are induced by high-intensity physical activity, although moderate physical activity is also important for cancer protection [5].

Lung Cancer

Lung cancer is the leading cause of cancer incidence and mortality in 2022. In that year, 2.5 million new cases and over 1.8 million deaths were recorded globally due to this disease. It ranks first among men and second among women in both incidence and mortality. The ratio of lung cancer incidence and mortality between men and women is approximately 2.

The highest incidence rates are observed in the East Asia region among men, followed by Micronesia/Polynesia and Eastern Europe, with Turkey having the highest national incidence rate among men worldwide. Among women, elevated incidence rates are seen in North America, East Asia, and Northern Europe, with Hungary having the highest national incidence rate.

This cancer is characterized by poor survival rates. Available data reveal clear geographical and temporal patterns of incidence and mortality that reflect stages of the tobacco epidemic. Another important modifying factor for the likelihood of developing the disease is the intensity and duration of smoking, type of cigarettes, and the degree of inhalation.

In transitioning countries, the epidemic is at an earlier stage; smoking among men has either recently peaked or is still increasing, leading to rising lung cancer rates. In several high-income countries, where smoking was introduced earlier, a decrease in smoking prevalence can be observed in the male population, followed by a peak and decline in lung cancer rates in the same generations. Among women, tobacco use remains in a less advanced phase compared to men. In most transitioning countries, lung cancer incidence rates among women continue to rise, with only a few countries showing signs of stabilization or decline. Tobacco remains the primary cause of lung cancer, and the disease can be largely prevented through effective tobacco control policies and regulations. [6]

Lung cancer patients often exhibit symptoms such as shortness of breath, cough, fatigue, anxiety, depression, insomnia, and pain. These persist despite advances in treatment efficacy. In addition to pharmacological interventions, non-pharmacological approaches that improve

fatigue, quality of life, cardiovascular-respiratory fitness, lung function, muscle mass and strength, and mental health in lung cancer patients include physical activity and exercise. It has been shown that physical fitness, especially cardiovascular-respiratory endurance and muscle strength, are independent predictors of survival in lung cancer patients. At the same time, lung cancer patients frequently exhibit insufficient levels of physical activity and exercise, leading to a significant decline in their quality of life. This may result in decreased functional capacity along with muscle wasting or weakness and worsening symptoms, particularly dyspnea. [7]

Research also shows that dysbiosis of the lung and/or gut microbiome, as well as their interactions, are closely related to dietary patterns and regular physical activity. The latter plays a key role in the development and progression of lung cancer. This opens the path for microbiome modulation as an adjunct therapy in lung cancer treatment. Another review emphasizes the need to consider non-pharmacological interventions as effective strategies supporting lung cancer treatment. [8]

Rehabilitation programs conducted for lung cancer patients lead to stabilization of the disease course and increased patient confidence. Exercise therapy includes aerobic exercises and resistance training. An important component of rehabilitation are functional tests such as the 6-minute walk test, chair stand test, timed up and go test, and gait speed tests, supplemented with muscle strength and mass assessment. Rehabilitation for lung cancer patients has been shown to alleviate fatigue symptoms and improve quality of life. Improvements in functional capacities have also been noted. [9] Additionally, one study found that patients receiving hospital physiotherapy had higher levels of physical activity in the early days after lung cancer surgery compared to an untreated control group. [10]

Colorectal Cancer

It is estimated that in 2022, there will be over 1.9 million new cases of colorectal cancer (including anal cancer) and 904,000 deaths, accounting for nearly one in ten cases and deaths from cancer. Colorectal cancer ranks third in terms of incidence but second in terms of mortality. Incidence rates are three to four times higher in transitioning countries compared to those that have not undergone transformation.

Incidence rates of colorectal cancer are steadily increasing in countries undergoing major transformations. Behavioral and dietary changes are the main factors contributing to the rise in cases, including relatively higher consumption of animal products and increasingly sedentary lifestyles, leading to higher rates of overweight and obesity. Alcohol consumption, smoking, consumption of red or processed meats, and obesity increase the overall risk of the disease, while calcium supplements and intake of whole grains, fiber, dairy products, and physical activity are considered protective, especially against colorectal cancer. [11]

Decreases in colorectal cancer incidence in many high-incidence countries over the past decades are believed to result from population-level changes towards healthier lifestyles (e.g., increased access to fiber sources such as fruits and vegetables) and the introduction of screening, including widespread use of colonoscopy and removal of precancerous lesions.

Analyzing the relationship between colorectal cancer and physical activity, we observe that higher levels of physical activity are associated with a lower incidence of colorectal cancer. [12][13] A study involving male healthcare workers found that a high level of recreational physical activity, particularly aerobic exercise amounting to about 30 MET-hours per week, was associated with a 31% reduction in colorectal cancer risk. [14] A prospective study involving an Asian population demonstrated that engaging in any form of vigorous or strenuous leisure-time exercise was associated with a 15% reduction in colorectal cancer risk compared to individuals who never engaged in recreational exercise. [15]

Further research is needed to capture the exact causes of the rising incidence in recent generations. However, we can link the influence of risk factors such as the increasing prevalence of obesity, lack of physical activity, and antibiotics affecting the gut microbiome, particularly during early life and/or early adulthood, to the rising incidence of colorectal cancer. [16]

Breast Cancer

Breast cancer in women is the second most common cause of cancer worldwide in 2022, with an estimated 2.3 million new cases, accounting for 11.6% of all cancer cases. It is the fourth leading cause of cancer mortality globally, with 666,000 deaths. Among women, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer deaths worldwide [1].

Increasing physical activity and reducing sedentary time are already recommended in the prevention of various cancers. Observational studies have shown that an active lifestyle is associated with a lower risk of breast cancer. However, to establish a causal relationship and assess the role of physical activity as protective against breast cancer, further studies were needed. A study utilizing individual-level data collected by the Breast Cancer Association Consortium evaluated whether lifetime physical activity or sedentary time, assessed using genotype, could be causally linked to breast cancer risk overall, pre/post-menopause, and by case groups defined based on tumor characteristics. The results provided strong evidence that higher levels of physical activity and shorter sedentary time are likely to reduce the risk of breast cancer. These results were consistent across all subtypes of breast cancer. Various types of evidence were analyzed, and it was recognized that insufficient physical activity is a modifiable risk factor for breast cancer. In summary, more widespread adoption of an active lifestyle and a greater emphasis on promoting physical activity and controlling sedentary time could reduce the burden of the most common cancer in women, which is crucial given the weight of this disease [17].

A systematic review was conducted to examine the impact of physical exercise on selected physical fitness variables in women with breast cancer (BCP) and breast cancer survivors (BCS). A comprehensive literature search included randomized controlled trials with isolated exercise interventions in women with BCP and BCS (< 5 years post-therapy). Variables regarding cardiovascular-respiratory fitness (CRF), strength (ST), fatigue (F), and health-related quality of life (HRQoL) were discussed. The review results demonstrated that physical exercise interventions appear to be a valuable strategy for both women with breast cancer and breast cancer survivors. They help prevent declines in cardiovascular-respiratory fitness, strength, and health-related quality of life. The most promising results seem to be provided by resistance training and combined interventions [18].

Subsequent Mendelian randomization analyses confirmed a potentially causal relationship between higher levels of physical activity and a lower risk of breast cancer and colorectal cancer. Based on the above data, promoting physical activity in the population is likely an effective strategy for the primary prevention of these commonly diagnosed cancers [19].

One article investigated the role of physical activity in the prevention, treatment, and prognosis of gynecological malignancies. The results suggested that physical activity likely

reduces the risk of ovarian, endometrial, and cervical cancers, with the strongest association observed for endometrial cancer. It was shown that physical activity can reduce symptom burden and increase chemotherapy completion rates [20].

In one study, preferences and opinions of older women with gynecological cancers regarding physical activity during chemotherapy were examined. The study involved women aged 60 and older who had received chemotherapy at a single facility within the past 12 months. They completed questionnaires and interviews with relevant questions. The results showed that 67% of patients agreed with the potential usefulness of physical activity interventions during chemotherapy, and 73% also indicated they would be willing to use an activity tracker during chemotherapy. Preferred forms of physical activity included aerobic activities such as walking. Patients also expressed a desire for education on the impact of physical activity on treatment symptoms and reported a need for interventions that are easily accessible and consider their treatment symptoms, as these were significant barriers to physical activity during chemotherapy [21].

Thus, it appears that survivors of gynecological cancers are motivated to increase physical activity, and lifestyle modification programs are well-received and feasible for them. Healthcare providers caring for women with gynecological cancers should advise patients on the importance of physical activity in their lives. It is valuable to discuss with these patients the health benefits of physical activity, while also considering a personalized approach [20].

Prostate Cancer

It is estimated that in 2022, there were 1.5 million new cases and 397,000 deaths from prostate cancer worldwide. Prostate cancer is the second most commonly occurring cancer globally and the fifth leading cause of cancer-related deaths among men. Advanced age, family history, and certain genetic mutations and conditions are established risk factors, although speculative roles of smoking, excessive body weight, and some dietary factors in modulating risk exist [1].

Comparing the highest and lowest levels of overall physical activity and prostate cancer risk, Europeans, North Americans, and African Americans observe a significant reduction in prostate cancer risk. The most statistically significant reduction in prostate cancer risk was seen in individuals aged 20–45 and 45–65 years [22].

The greatest reductions in prostate cancer risk occur among physically active African American and Asian men. Among various subgroup analyses, age is the only potential modifier of the relationship between physical activity and prostate cancer risk, with younger men appearing to be better protected by physical activity than older men [23].

Thyroid Cancer

Thyroid cancer ranks seventh in overall cancer incidence and fifth among women. The incidence rate is three times higher in women than in men. Mortality from this disease is significantly lower than the incidence, with an estimated 44,000 deaths recorded in 2022 for both sexes combined, placing it at 24th. Incidence rates are about seven times higher in developed countries compared to countries in transition, while the difference in mortality rates is much smaller [1].

It appears that engaging in physical activity may affect thyroid hormone levels in the blood. A study assessed the relationship between thyroid function, including antibodies against thyroid peroxidase (TPOAb), and physical activity. The results showed that free T4 levels were lowest in the group with low physical activity. TSH levels did not differ significantly between groups. However, TPOAb levels increased in the following order: moderate, low, and high physical activity. After adjusting for confounding factors, moderate physical activity was associated with high T4 levels and a significant decrease in TSH and TPOAb. However, there were no significant changes in free T4, TSH, or TPOAb levels in the high physical activity group. This study thus showed a relationship between thyroid function and moderate physical activity. Therefore, moderate-intensity physical activity should be recommended to improve thyroid function [24].

A prospective cohort study in Korea examined the relationship between physical activity and thyroid cancer (TC). The results showed that participants with the highest level of physical activity had a lower risk of TC compared to those with the lowest level of physical activity. Significant associations were stronger among women with a body mass index (BMI) ≥ 25 kg/m², individuals with primary household income, those without a family history of first-degree breast cancer, and those who did not consume alcohol or smoke. This study thus suggests that increased physical activity may have a protective effect against the development of thyroid cancer [25].

Another cohort study aimed to determine whether a healthy lifestyle can weaken the impact of genetic variants on thyroid cancer and whether it is associated with thyroid cancer risk. It included 423 patients with incidental thyroid cancer and 264,533 individuals without thyroid cancer. It was found that adhering to a healthier lifestyle weakened the negative association of genetic factors with thyroid cancer risk in individuals of European descent. The highest risk of thyroid cancer was observed in participants with a high polygenic risk score and an unfavorable lifestyle. The results of this study suggest that the harmful role of genetic factors in thyroid cancer may be mitigated by adhering to a healthier lifestyle, especially in individuals with high genetic risk. Therefore, lifestyle interventions for patients are important as they may be beneficial in preventing TC, especially in patients with high genetic predisposition [26].

In another study in the United States, the temporal variability in TC incidence at the state level was examined. The study looked at disparities in TC incidence by race, ethnicity, and age at the state level, as well as the correlation between TC incidence and obesity and physical activity. Data on thyroid cancer incidence from 2000–2017 were obtained from cancer statistics in the United States. The results showed that the incidence of TC showed a general declining trend in recent years in most states, but not in all. In 10 states, the incidence of thyroid cancer showed an increasing trend. Differences in incidence were observed at the state level by race/ethnicity and age groups. The study demonstrated that lifestyle and environmental factors may influence the trend of thyroid cancer incidence in the USA [27].

Physical activity, or rather its minimal amounts, is often associated with excessive body weight in patients. A meta-analysis showed that greater height and excessive obesity in adulthood are associated with higher incidence of most major types of thyroid cancer, including the rare but most aggressive form, anaplastic thyroid cancer. They are also associated with higher mortality from thyroid cancer [28].

A large meta-analysis of cohort study data from the Asia Cohort Consortium, including 538,857 men and women from 13 cohorts in China, Korea, Japan, and Singapore, was also conducted [29]. During the follow-up, 1132 cases of thyroid cancer were diagnosed. A positive linear relationship between BMI and thyroid cancer was observed in men, with a 25% higher risk for every 5 kg/m². In women, a weaker non-linear relationship was observed a 7% higher risk for every 5 kg/m². Another study assessed pre-pregnancy BMI and the risk of differentiated thyroid cancer in a nationwide registry-based cohort in Denmark [30]. The study included 443,403 women and identified 463 incidental thyroid cancer cases during follow-up. The results

showed that pre-pregnancy BMI was positively associated with differentiated thyroid cancer, with a 17% higher risk for every 5 kg/m². In another review, which also evaluated the relationship between obesity and differentiated thyroid cancer (DTC), it was found that the increasing incidence of differentiated thyroid cancer (DTC) is pathogenically associated with the prevalence of obesity. However, the mechanisms that could explain this association are still not well understood [31]. Understanding the etiology of thyroid cancer will require further well-organized and designed studies. However, based on the studies conducted, targeting obesity and lack of physical activity may be a good point of thyroid cancer prevention [32].

Studies suggest that physical activity may have a preventive effect on thyroid cancer. It is also worth mentioning that it may support patients who have already undergone thyroidectomy. Studies have shown that the risk of vertebral fractures decreased after starting regular exercise in patients with thyroid cancer over 40 years old who had undergone thyroidectomy [33].

Factors Affecting Physical Exercise in Cancer Patients

Many researchers have attempted to identify factors influencing physical exercise in cancer patients. In one study, patients were asked about benefits, barriers, and cues to action regarding physical activity. Patients reported numerous psychological, physical, and physiological benefits from engaging in sports. However, various barriers such as the advancement of the disease, medical procedures, and side effects related to treatment hinder exercise. Several strategies were identified that might help encourage patients to exercise. These include social support from family and friends, medical advice, and goal setting. Owning a pet can also be a motivation for physical activity. Important factors that significantly facilitate the incorporation of physical exercise into daily life include detailed information about physical activity in oncology environments, availability of physical activity specialists for consultation, and individualized programs based on patient characteristics [34]. Similar conclusions were reached by researchers assessing barriers and motivation for running in women with cancer [35]. Other studies [36] further emphasized the role of social support in managing lifestyle in cancer patients, as well as overall patient knowledge about therapeutic options, side effects of treatment, and specific guidelines for management. Concrete and clear information about the benefits of managing lifestyle is also very important.

Cancer-Related Fatigue (CRF)

Cancer-related fatigue (CRF) is the most common and debilitating side effect in cancer patients undergoing cancer treatment. It is estimated that it affects between 60% to 100% of patients and can occur as a result of the treatment or the cancer itself. Its effects persist for years after treatment and reduce the overall quality of life and level of activity of cancer patients.

A review aimed to determine whether exercise interventions can reduce CRF and improve health-related quality of life (HRQOL) in selected cancer patients. Databases searched included Clinical Key, ProQuest Nursing and Allied Health Source, Cochrane Library, Mosby's Nursing Consult, and MEDLINE. The results of most studies indicate that exercise can reduce the effects of CRF in cancer patients, leading to an overall improvement in HRQOL. No negative results regarding the impact of exercise on CRF were reported [37].

Patients who have survived testicular cancer (TCS) are at increased risk of CRF, psychosocial impairment, and poor health-related quality of life (HRQoL). One article examined the impact of high-intensity interval training (HIIT) on patient-reported outcomes in TCS. It also investigated cardiovascular endurance as a mediator of intervention effects. Patients were randomly assigned to 12 weeks of supervised HIIT or usual care (UC). Patient-reported outcomes included CRF, depression, anxiety, stress, self-esteem, sleep quality, and HRQoL assessed at baseline, post-intervention, and after 3 months of follow-up. Patients completed 99% of training sessions and achieved 98% of the target training intensity. HIIT was found to significantly improve CRF, self-esteem, and several domains of HRQoL compared to UC. CRF and vitality effects persisted during the 3-month follow-up. Changes in cardiovascular fitness mediated improvements in CRF and mental health-related quality of life. CRF effects were greater in patients with a less active lifestyle, lower fitness, higher testosterone levels, and greater clinical fatigue at the beginning of the study. In summary, high-intensity interval training significantly reduces CRF and improves mental health-related quality of life in patients who have survived testicular cancer [38].

One study hypothesized that higher CRF is directly related to low muscle mass in patients. A total of 233 patients with advanced cancer who started palliative chemotherapy for lung, colorectal, breast, or prostate cancer were examined. Skeletal muscle index (SMI) was calculated as the patient's muscle mass at L3 or T4 CT scans, adjusted for height. Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-fatigue questionnaire.

The study results showed that higher SMI was significantly associated with less CRF in men but not in women. No association was found between SMI and fatigue scores on the Functional Assessment of Chronic Illness Therapy. This may suggest that male patients might reduce cancer-related fatigue through exercise interventions aimed at increasing muscle mass [39].

Another study evaluated the feasibility, acceptability, and safety of a home-based exercise intervention to increase perceived self-efficacy in managing CRF. It involved individuals who had undergone thoracotomy for non-small cell lung cancer and were transferred from the hospital to home. Low-intensity walking exercises and balance exercises in a virtual reality environment with Nintendo Wii Fit Plus were performed. Activity started in the first week after thoracotomy and continued for 6 weeks. The results showed that physical activity had a positive impact on perceived self-efficacy in managing fatigue, walking, and balance, as well as on overall functional performance, and even reduced the severity of chronic renal insufficiency. It can be concluded that a low-intensity home-based exercise intervention for patients after thoracotomy due to non-small cell lung cancer is feasible, safe, well-tolerated, and fully acceptable, showing positive changes in self-management of chronic cancer-related fatigue. However, further research is needed to validate this potentially effective rehabilitation approach [40].

A meta-analysis was also conducted to compare four commonly recommended methods for treating cancer-related fatigue: exercise, psychological therapy, combined exercise and psychological therapy, and pharmacotherapy. Randomized clinical trials in adult cancer patients were selected. Inclusion criteria included CRF severity as an outcome and testing of exercise, psychology, exercise plus psychology, or pharmacological interventions. The primary outcome was CRF severity. Study quality was assessed using a modified 12-item version of the Physiotherapy Evidence-Based Database scale. Results showed that exercise, psychological therapies, and combined exercise plus psychological interventions improved CRF during and after primary treatment, while pharmacological interventions did not have such an effect. The results also suggested that the effectiveness of CRF treatment was related to cancer stage, baseline treatment status, experimental treatment form, experimental delivery method, psychological mode, type of control state, use of ITT analysis, and fatigue measures. It can be concluded that exercise and psychological interventions are effective in reducing CRF and surpass the available pharmaceutical options in effectiveness. Therefore, physicians should recommend exercise or psychological interventions as the first-line treatment for CRF [41].

Conclusion

Oncological patients will increasingly be seen in the offices of doctors from various specialties. It is important, in addition to applying established oncology treatment standards, not to forget the fundamentals of supporting patients with cancer. These fundamentals primarily include appropriate health education, which encompasses dietary recommendations, lifestyle interventions, and a comprehensive description of patient physical activity. Given the uniqueness of the oncological patient, providing adequate psychological support is also crucial, as it aids in mental and physical rehabilitation.

It is important to emphasize the role of collaboration between oncologists and exercise specialists in cancer treatment to develop programs tailored to patient needs. In this context, the benefits of physical exercise seem potentially greater when they constitute a multidimensional, comprehensive approach to patient well-being. Therefore, efforts should be made to develop coherent yet individualized methods for integrating physical activity into these patients' lives.

At the same time, it is essential to reiterate the ongoing need for further research on the type, intensity, and duration of physical activity to prevent certain types of cancer, as well as to develop effective recommendations for patients during active cancer treatment and in remission concerning physical activity.

Disclosure

Author's contribution

Conceptualization, PSR, DR, GRS, WK; methodology, GRS, BJ, JD; software, WK, RO; check, GRS, MB, PSR and DR; formal analysis, DR, GJ; investigation, PRS; resources, WK; data curation RO, MB, PS; writing - rough preparation, PSR, BJ, JD; writing - review and editing, GRS, PS, GJ, JD; visualization, GRS; supervision, PS, BJ, MB; project administration, PSR, GJ, RO; receiving funding, no specific funding.

All authors have read and agreed with the published version of the manuscript.

Financing statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflict of interest

The authors deny any conflict of interest

References:

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024, 74:229-63. 10.3322/caac.21834
2. Maddocks M. Physical activity and exercise training in cancer patients. *Clin Nutr ESPEN.* 2020 Dec;40:1-6. doi: 10.1016/j.clnesp.2020.09.027. Epub 2020 Oct 3. PMID: 33183519.
3. Zoth N, Böhlke L, Theurich S, Baumann FT. Körperliche Aktivität und Bewegungstherapie in der Onkologie [Physical activity and exercise therapy in oncology]. *Inn Med (Heidelb).* 2023 Jan;64(1):19-24. German. doi: 10.1007/s00108-022-01450-5. Epub 2023 Jan 3. PMID: 36594967.
4. Garcia L, Pearce M, Abbas A, Mok A, Strain T, Ali S, Crippa A, Dempsey PC, Golubic R, Kelly P, Laird Y, McNamara E, Moore S, de Sa TH, Smith AD, Wijndaele K, Woodcock J, Brage S. Non-occupational physical activity and risk of cardiovascular disease, cancer and mortality outcomes: a dose-response meta-analysis of large prospective studies. *Br J Sports Med.* 2023 Aug;57(15):979-989. doi: 10.1136/bjsports-2022-105669. Epub 2023 Feb 28. PMID: 36854652; PMCID: PMC10423495.
5. Jurdana M. Physical activity and cancer risk. Actual knowledge and possible biological mechanisms. *Radiol Oncol.* 2021 Jan 12;55(1):7-17. doi: 10.2478/raon-2020-0063. PMID: 33885236; PMCID: PMC7877262.
6. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide

- for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024 May-Jun;74(3):229-263. doi: 10.3322/caac.21834. Epub 2024 Apr 4. PMID: 38572751.
7. Avancini A, Sartori G, Gkoutakos A, Casali M, Trestini I, Tregnago D, Bria E, Jones LW, Milella M, Lanza M, Pilotto S. Physical Activity and Exercise in Lung Cancer Care: Will Promises Be Fulfilled? *Oncologist*. 2020 Mar;25(3):e555-e569. doi: 10.1634/theoncologist.2019-0463. Epub 2019 Nov 26. PMID: 32162811; PMCID: PMC7066706.
 8. Nigro E, Perrotta F, Scialò F, D'Agnano V, Mallardo M, Bianco A, Daniele A. Food, Nutrition, Physical Activity and Microbiota: Which Impact on Lung Cancer? *Int J Environ Res Public Health*. 2021 Mar 1;18(5):2399. doi: 10.3390/ijerph18052399. PMID: 33804536; PMCID: PMC7967729.
 9. Dávid L, Sebastian R, Jana L. Rehabilitation and physical activity of patients with lung cancer. *Klin Onkol*. 2022 Winter;35(1):32-37. English. doi: 10.48095/ccko202232. PMID: 35236079.
 10. Jonsson M, Hurtig-Wennlöf A, Ahlsson A, Vidlund M, Cao Y, Westerdahl E. In-hospital physiotherapy improves physical activity level after lung cancer surgery: a randomized controlled trial. *Physiotherapy*. 2019 Dec;105(4):434-441. doi: 10.1016/j.physio.2018.11.001. Epub 2018 Nov 20. PMID: 30871894.
 11. World Cancer Research Fund International/American Institute for Cancer Research."Continuous Update Project Expert Report 2018: Diet, Nutrition, Physical Activity and Prostate Cancer. 2018." (2018).
 12. Samad AK, Taylor RS, Marshall T, Chapman MA. A meta-analysis of the association of physical activity with reduced risk of colorectal cancer. *Colorectal Dis*. 2005 May;7(3):204-13. doi: 10.1111/j.1463-1318.2005.00747.x. PMID: 15859955.
 13. Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2012 Oct 17;104(20):1548-61. doi: 10.1093/jnci/djs354. Epub 2012 Aug 22. PMID: 22914790.
 14. Keum N, Bao Y, Smith-Warner SA, Orav J, Wu K, Fuchs CS, Giovannucci EL. Association of Physical Activity by Type and Intensity With Digestive System Cancer Risk. *JAMA Oncol*. 2016 Sep 1;2(9):1146-53. doi: 10.1001/jamaoncol.2016.0740. Erratum in: *JAMA Oncol*. 2019 Apr 1;5(4):579. doi: 10.1001/jamaoncol.2019.0286. PMID: 27196375; PMCID: PMC5846204.

15. Eaglehouse YL, Koh WP, Wang R, Aizhen J, Yuan JM, Butler LM. Physical activity, sedentary time, and risk of colorectal cancer: the Singapore Chinese Health Study. *Eur J Cancer Prev.* 2017 Nov;26(6):469-475. doi: 10.1097/CEJ.0000000000000369. PMID: 28542077; PMCID: PMC5620106.
16. Spaander MCW, Zauber AG, Syngal S, Blaser MJ, Sung JJ, You YN, Kuipers EJ. Young-onset colorectal cancer. *Nat Rev Dis Primers.* 2023 Apr 27;9(1):21. doi: 10.1038/s41572-023-00432-7. PMID: 37105987; PMCID: PMC10589420.
17. Dixon-Suen SC, Lewis SJ, Martin RM, et al. Physical activity, sedentary time and breast cancer risk: a Mendelian randomisation study. *Br J Sports Med.* 2022;56(20):1157-1170. doi:10.1136/bjsports-2021-105132
18. Ficarra S, Thomas E, Bianco A, Gentile A, Thaller P, Grassadonio F, Papakonstantinou S, Schulz T, Olson N, Martin A, Wagner C, Nordström A, Hofmann H. Impact of exercise interventions on physical fitness in breast cancer patients and survivors: a systematic review. *Breast Cancer.* 2022 May;29(3):402-418. doi: 10.1007/s12282-022-01347-z. Epub 2022 Mar 12. PMID: 35278203; PMCID: PMC9021138.
19. Papadimitriou N, Dimou N, Tsilidis KK, Banbury B, Martin RM, Lewis SJ, Kazmi N, Robinson TM, Albanes D, Aleksandrova K, Berndt SI, Timothy Bishop D, Brenner H, Buchanan DD, Bueno-de-Mesquita B, Campbell PT, Castellví-Bel S, Chan AT, Chang-Claude J, Ellingjord-Dale M, Figueiredo JC, Gallinger SJ, Giles GG, Giovannucci E, Gruber SB, Gsur A, Hampe J, Hampel H, Harlid S, Harrison TA, Hoffmeister M, Hopper JL, Hsu L, María Huerta J, Huyghe JR, Jenkins MA, Keku TO, Kühn T, La Vecchia C, Le Marchand L, Li CI, Li L, Lindblom A, Lindor NM, Lynch B, Markowitz SD, Masala G, May AM, Milne R, Monninkhof E, Moreno L, Moreno V, Newcomb PA, Offit K, Perduca V, Pharoah PDP, Platz EA, Potter JD, Rennert G, Riboli E, Sánchez MJ, Schmit SL, Schoen RE, Severi G, Sieri S, Slattery ML, Song M, Tangen CM, Thibodeau SN, Travis RC, Trichopoulou A, Ulrich CM, van Duijnhoven FJB, Van Guelpen B, Vodicka P, White E, Wolk A, Woods MO, Wu AH, Peters U, Gunter MJ, Murphy N. Physical activity and risks of breast and colorectal cancer: a Mendelian randomisation analysis. *Nat Commun.* 2020 Jan 30;11(1):597. doi: 10.1038/s41467-020-14389-8. PMID: 32001714; PMCID: PMC6992637.
20. Tucker K, Staley SA, Clark LH, Soper JT. Physical Activity: Impact on Survival in Gynecologic Cancer. *Obstet Gynecol Surv.* 2019 Nov;74(11):679-692. doi: 10.1097/OGX.0000000000000731. PMID: 31755545.

21. Vega B, Desai R, Solk P, McKoy JM, Flores AM, Phillips SM, Barber EL. Increasing physical activity among older adults with gynecologic cancers: a qualitative study. *Support Care Cancer*. 2024 Apr 11;32(5):282. doi: 10.1007/s00520-024-08483-6. PMID: 38600364.
22. Liu Y, Hu F, Li D, Wang F, Zhu L, Chen W, Ge J, An R, Zhao Y. Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. *Eur Urol*. 2011 Nov;60(5):1029-44. doi: 10.1016/j.eururo.2011.07.007. Epub 2011 Jul 19. PMID: 21802197.
23. Brown JC, Winters-Stone K, Lee A, Schmitz KH. Cancer, physical activity, and exercise. *Compr Physiol*. 2012 Oct;2(4):2775-809. doi: 10.1002/cphy.c120005. PMID: 23720265; PMCID: PMC4122430.
24. Lee J, Baek HS, Jo K, Kim MH, Lee JM, Chang SA, Lim DJ. The Impact of Physical Activity on Thyroid Health: Insights From Representative Data in Korea. *J Clin Endocrinol Metab*. 2024 Apr 15:dgae178. doi: 10.1210/clinem/dgae178. Epub ahead of print. PMID: 38620035.
25. Bui AQ, Gunathilake M, Lee J, Lee EK, Kim J. Relationship Between Physical Activity Levels and Thyroid Cancer Risk: A Prospective Cohort Study in Korea. *Thyroid*. 2022 Nov;32(11):1402-1410. doi: 10.1089/thy.2022.0250. Epub 2022 Nov 3. PMID: 36070439.
26. Feng X, Wang F, Yang W, et al. Association Between Genetic Risk, Adherence to Healthy Lifestyle Behavior, and Thyroid Cancer Risk. *JAMA Netw Open*. 2022;5(12):e2246311. Published 2022 Dec 1. doi:10.1001/jamanetworkopen.2022.46311
27. Chen B, Xie Z, Duan X. Thyroid cancer incidence trend and association with obesity, physical activity in the United States. *BMC Public Health*. 2022 Jul 12;22(1):1333. doi: 10.1186/s12889-022-13727-3. PMID: 35831811; PMCID: PMC9281136.
28. Kitahara CM, McCullough ML, Franceschi S, Rinaldi S, Wolk A, Neta G, Olov Adami H, Anderson K, Andreotti G, Beane Freeman LE, Bernstein L, Buring JE, Clavel-Chapelon F, De Roo LA, Gao YT, Gaziano JM, Giles GG, Håkansson N, Horn-Ross PL, Kirsh VA, Linet MS, MacInnis RJ, Orsini N, Park Y, Patel AV, Purdue MP, Riboli E, Robien K, Rohan T, Sandler DP, Schairer C, Schneider AB, Sesso HD, Shu XO, Singh PN, van den Brandt PA, Ward E, Weiderpass E, White E, Xiang YB, Zeleniuch-Jacquotte A, Zheng W, Hartge P, Berrington de González A. Anthropometric Factors and Thyroid Cancer Risk by Histological Subtype: Pooled Analysis of 22 Prospective

- Studies. *Thyroid*. 2016 Feb;26(2):306-18. doi: 10.1089/thy.2015.0319. PMID: 26756356; PMCID: PMC4754509.
29. Shin A, Cho S, Jang D, Abe SK, Saito E, Rahman MS, Islam MR, Sawada N, Shu XO, Koh WP, Sadakane A, Tsuji I, Sugawara Y, Ito H, Nagata C, Park SK, Yuan JM, Kim J, Tsugane S, Cai H, Wen W, Ozasa K, Matsuyama S, Kanemura S, Oze I, Wada K, Wang R, Yoo KY, Potter JD, Ahsan H, Boffetta P, Chia KS, Matsuo K, Qiao YL, Rothman N, Zheng W, Inoue M, Kang D. Body Mass Index and Thyroid Cancer Risk: A Pooled Analysis of Half a Million Men and Women in the Asia Cohort Consortium. *Thyroid*. 2022 Mar;32(3):306-314. doi: 10.1089/thy.2021.0445. Epub 2022 Jan 11. PMID: 34915752; PMCID: PMC8971972.
30. Sørensen SM, Urbute A, Frederiksen K, Kjaer SK. Prepregnancy Body Mass Index and Risk of Differentiated Thyroid Cancer: A Prospective Cohort Study of More than 440,000 Danish Women. *Thyroid*. 2023 Mar;33(3):365-372. doi: 10.1089/thy.2022.0259. Epub 2022 Nov 15. PMID: 36173097.
31. Matrone A, Ferrari F, Santini F, Elisei R. Obesity as a risk factor for thyroid cancer. *Curr Opin Endocrinol Diabetes Obes*. 2020 Oct;27(5):358-363. doi: 10.1097/MED.0000000000000556. PMID: 32740043.
32. Kitahara CM. Obesity, Physical Activity, and Thyroid Cancer Risk: Disentangling True Associations from Detection Bias. *Thyroid*. 2023;33(3):276-277. doi:10.1089/thy.2022.0618
33. Kim J, Han K, Jung JH, Ha J, Jeong C, Heu JY, Lee SW, Lee J, Lim Y, Kim MK, Kwon HS, Song KH, Baek KH. Physical activity and reduced risk of fracture in thyroid cancer patients after thyroidectomy - a nationwide cohort study. *Front Endocrinol (Lausanne)*. 2023 Jul 20;14:1173781. doi: 10.3389/fendo.2023.1173781. PMID: 37547303; PMCID: PMC10400320.
34. Avancini A, Tregnago D, Rigatti L, Sartori G, Yang L, Trestini I, Bonaiuto C, Milella M, Pilotto S, Lanza M. Factors Influencing Physical Activity in Cancer Patients During Oncological Treatments: A Qualitative Study. *Integr Cancer Ther*. 2020 Jan-Dec;19:1534735420971365. doi: 10.1177/1534735420971365. PMID: 33349064; PMCID: PMC7758643.
35. Avancini A, Skroce K, Tregnago D, Frada P, Trestini I, Cercato MC, Bonaiuto C, Tarperi C, Schena F, Milella M, Pilotto S, Lanza M. "Running with cancer": A qualitative study to evaluate barriers and motivations in running for female oncological

- patients. *PLoS One*. 2020 Apr 2;15(4):e0227846. doi: 10.1371/journal.pone.0227846. PMID: 32240181; PMCID: PMC7117710.
36. Yannitsos D, Murphy RA, Pollock P, Di Sebastiano KM. Facilitators and barriers to participation in lifestyle modification for men with prostate cancer: A scoping review. *Eur J Cancer Care (Engl)*. 2020 Jan;29(1):e13193. doi: 10.1111/ecc.13193. Epub 2019 Dec 3. PMID: 31797478.
37. Scott K, Posmontier B. Exercise Interventions to Reduce Cancer-Related Fatigue and Improve Health-Related Quality of Life in Cancer Patients. *Holist Nurs Pract*. 2017 Mar/Apr;31(2):66-79. doi: 10.1097/HNP.000000000000194. PMID: 28181972.
38. Adams SC, DeLorey DS, Davenport MH, Fairey AS, North S, Courneya KS. Effects of high-intensity interval training on fatigue and quality of life in testicular cancer survivors. *Br J Cancer*. 2018 May;118(10):1313-1321. doi: 10.1038/s41416-018-0044-7. Epub 2018 May 8. PMID: 29736007; PMCID: PMC5959855.
39. Neeffjes ECW, van den Hurk RM, Blauwhoff-Buskermolen S, van der Vorst MJDL, Becker-Commissaris A, de van der Schueren MAE, Buffart LM, Verheul HMW. Muscle mass as a target to reduce fatigue in patients with advanced cancer. *J Cachexia Sarcopenia Muscle*. 2017 Aug;8(4):623-629. doi: 10.1002/jcsm.12199. Epub 2017 Jun 21. PMID: 28639432; PMCID: PMC5566642.
40. Hoffman AJ, Brintnall RA, Brown JK, Eye Av, Jones LW, Alderink G, Ritz-Holland D, Enter M, Patzelt LH, Vanotteren GM. Too sick not to exercise: using a 6-week, home-based exercise intervention for cancer-related fatigue self-management for postsurgical non-small cell lung cancer patients. *Cancer Nurs*. 2013 May-Jun;36(3):175-88. doi: 10.1097/NCC.0b013e31826c7763. PMID: 23051872.
41. Mustian KM, Alfano CM, Heckler C, Kleckner AS, Kleckner IR, Leach CR, Mohr D, Palesh OG, Peppone LJ, Piper BF, Scarpato J, Smith T, Sprod LK, Miller SM. Comparison of Pharmaceutical, Psychological, and Exercise Treatments for Cancer-Related Fatigue: A Meta-analysis. *JAMA Oncol*. 2017 Jul 1;3(7):961-968. doi: 10.1001/jamaoncol.2016.6914. PMID: 28253393; PMCID: PMC5557289.

