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The role of exercise in obesity-related cancers: Current evidence and biological mechanisms

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ABSTRACT

Cancer ranks among the five leading causes of death in almost all countries and has important repercussions for individual and public health, the healthcare system, and society in general. Obesity increases the incidence of many types of cancer, but growing evidence suggests that physical activity may decrease risk for developing a variety of obesity-related cancer types, and, in some cases, may improve cancer prognosis and mortality rates. This review summarizes recent evidence on the effect of physical activity on obesity-related cancer prevention and survival. For some cancers, including breast, colorectal, and endometrial cancer, there is strong evidence for a preventative effect of exercise, but for many others, including gallbladder and kidney cancer, and multiple myeloma, evidence is inconsistent or largely lacking. Though many potential mechanisms have been proposed to explain the onco-protective effect of exercise, including improved insulin sensitivity, alterations in sex hormone availability, improved immune function and inflammation, myokine secretion, and modulation of intracellular signaling at the level of AMP kinase, the exact mechanism(s) of action within each cancer subtype remains poorly defined. Overall, a deeper understanding of how exercise can help against cancer and of the exercise parameters that can be altered to optimize exercise prescription is necessary and should be the subject of future investigation.

1. Introduction

Cancer ranks as one of the five leading causes of death in almost all countries, and constitutes the second greatest cause of death globally [1]. Nearly 20 million new cases of cancer and 10 million cancer-related deaths occur annually worldwide [2]. Among the most prevalent types of cancer, breast cancer accounts for 12% of all new cancer cases, lung cancer for 11%, prostate cancer for 7%, and non-melanoma of the skin and colon cancer for about 6% each [2]. The staggering incidence and mortality have multifactorial repercussions. A shortage of healthcare workers, which was estimated to reach 14.5 million globally in 2020, coupled with high cancer incidence, could overwhelm already stressed healthcare systems [3]. Cancer also results in an additional economic impact to both those diagnosed and their families, due to the cost of healthcare and the loss of productivity and wages [4]. This economic impact extends to a national level, as cancer care costs increase and as patients with cancer increase use of healthcare resources [5].

Certain co-morbidities, such as obesity, increase the likelihood of cancer incidence. Obesity has been associated with increased rates of at least 13 cancers, including endometrial cancer, esophageal adenocarcinoma, gastric cancer, cancer of the liver, and kidney—among others [6–12]. Preventing cancer occurrence and improving cancer outcomes is tantamount to easing the burden on patients and on healthcare systems. Beyond that, exploring cancer prevention and recurrence prevention strategies could help alleviate the staggering cancer mortality rate worldwide. Physical activity—which is important in the lifestyle

Abbreviations: AMPK, AMP-activated protein kinase; BMI, body mass index; BDNF, brain-derived neurotrophic factor; BRCA, breast cancer genes; CAR, chimeric antigen receptor; FFA, free fatty acids; GLUT, glucose transporter; Th, helper T cells; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; (IGF;, insulin-like growth factor; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; MET, metabolic equivalent of task; NKC, natural killer cells; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; Treg, regulatory T cells; SPARC, secreted protein acidic and rich in cysteine; ILC2, type 2 innate lymphoid cells.

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management of obesity—is one such strategy. By manipulating some of the risk factors for cancer, including bodily adiposity, sex hormone levels, insulin sensitivity, the balance between pro-inflammatory and anti-inflammatory cytokines (including adipokines and myokines), and the immune response, regular exercise can bring about beneficial effects on both cancer incidence and survival [13].

This review summarizes recent evidence for the effect of physical activity on obesity-related cancer prevention and survival, and explores the potential biological mechanisms behind these observations.

1.1. Physical activity effects on cancer incidence and mortality

There is ample evidence that regular exercise is associated with lower risk for developing a variety of cancer types, and in some cases also, improved cancer prognosis and mortality rates (Fig. 1 and Table 1) [14–49]. However, the characteristics of exercise that are responsible for these beneficial effects are not so well defined to allow for an optimal "anti-cancer" exercise prescription. Furthermore, given that most of these links are observational in nature, it is not entirely clear whether physical activity has direct biological effects that counter cancer initiation and progression, whether it is simply a marker of a healthier-than-average general lifestyle that carries lower cancer risk, whether the ability to exercise reflects other physiological processes that also determine cancer risk and prognosis, or whether being physically more active and fit increases the effectiveness and tolerability of standard medical cancer treatment.

1.2. Breast cancer

There is an abundance of evidence on the association between physical activity and risk of breast cancer. A 2018 meta-analysis of 38 cohort studies found that any type or amount of physical activity was associated with a 13% lower risk of breast cancer (odds ratio, OR = 0.87, 95% CI = 0.84–0.90) [14]. When stratified by menopausal status, the meta-analysis found a reduced risk in both premenopausal and postmenopausal women (premenopausal OR = 0.83, 95% CI = 0.79–0.87, postmenopausal OR = 0.91, 95% CI = 0.85–0.97) [14]. A 2022 systematic review in carriers of deleterious mutations of the BReast CAncer genes (*BRCA*) 1 and 2 included 5 studies and specifically evaluated the risk of breast cancer in younger females [15]. Four of the 5 studies

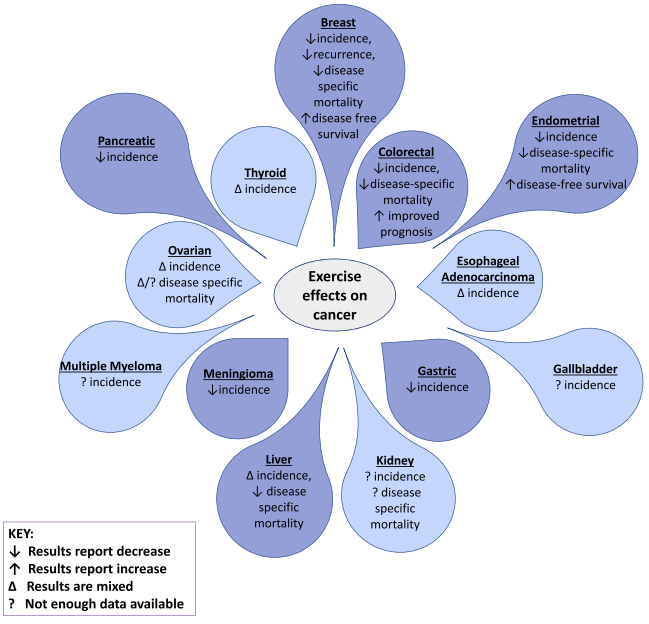

Fig. 1. Effects of regular exercise training on cancer incidence, prognosis and mortality.

Table 1
Recent studies evaluating the relationship between physical activity and cancer.

First author and year	Study characteristics	Physical activity exposure	Key results
Breast cancer			
Chen, 2019 [14]	Meta-analysis (38 prospective cohort studies)	Total, recreational, occupational, non-occupational (highest category vs lowest category)	• ↓ incidence (total OR = 0.87; premenopausal OR = 0.83; postmenopausal OR = 0.91)
Bucy, 2022 [15]	Systematic review (2 cohort studies, 2 cross-sectional studies,1 case-control study)	Any physical activity, in hours per week	• ↓ incidence in 4 out of 5 studies; no dose-response
Bigman, 2022 [16]	Case-control	Moderate to vigorous leisure time physical activity (highest quartile vs lowest quartile)	• ↓ incidence (OR = 0.51)
Zagalaz-Anula, 2022 [17]	Meta-analysis (2 randomized controlled trials, 8 prospective cohort studies, 1 case-control study)	Recreational physical activity post-diagnosis	• ↓ recurrence (RR = 0.84)
Colorectal cancer			
Hatime, 2022 [18]	Case-control	Work, household, and recreational physical activity (≥50 vs <10 MET-hours/week)	• ↓ incidence (OR = 0.72)
An, 2022 [19]	Cross-sectional	Physical inactivity (sedentary time (≥10 vs <10 h/day)	• ↑ incidence with more sedentary time (OR = 1.64)
Qiu, 2022 [20]	Meta-analysis (18 prospective cohort studies)	All physical activity (highest vs lowest level of pre-diagnosis physical activity)	• ↓ mortality (total HR = 0.81, cancer-specific HR = 0.85)
Hong, 2021 [21]	Systematic review (13 prospective cohort studies)	All physical activity (17.5–35 MET-hours/week vs lower amounts)	• ↓ mortality by 30%– 40% (physical activity post-diagnosis was more effective than pre-diagnosis)
Lee, 2021 [22]	Retrospective cohort	Vigorous, moderate intensity physical activity and walking (≥3 vs 0 times/week)	• ↓ cancer-specific mortality (colon HR = 0.85, rectal HR = 0.77)
Singh, 2020 [23]	Meta-analysis (19 randomized controlled trials)	Exercise arm vs usual care	• ↑ health-related outcomes in patients with colorectal cancer and better prognosis
Endometrial cancer			
Saint-Maurice, 2021 [24]	Prospective cohort	Leisure-time physical activity (≥6–7 vs 0 h/week)	• ↓ incidence (HR = 0.81)
Miyata, 2021 [25]	Prospective cohort	Occupational physical activity (standing or moving vs sitting)	• ↓ incidence (standing HR = 0.79, moving HR = 0.46)
Gorzelitz, 2022 [26]	Cross-sectional	Moderate- and vigorous intensity physical activity (≥1 vs 0 sessions/week)	• ↓ all-cause mortality (HR = 0.61); no clear dose-response

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Table 1 (*continued*)

First author and year	Study characteristics	Physical activity exposure	Key results
Breast cancer			
Friedenreich, 2020 [27]	Prospective cohort	All physical activity (>13–14 vs ≤5–8 MET-hours/week pre- and post-diagnosis)	• ↑ disease-free survival (pre-diagnosis HR = 0.54, post-diagnosis HR = 0.33)
Esophageal cancer			
Lam, 2017 [28]	Meta-analysis (2 cohort studies, 5 case-control studies)	Recreational and occupational physical activity (highest vs lowest level)	• No pooled estimate available but individual study incidence HR/ORs ranged from 0.7 to 1.0
Gallbladder cancer			
Pang, 2021 [29]	Prospective cohort	Occupational and non-occupational physical activity, including leisure time, household and commuting (highest vs lowest quintile)	• ↓ incidence (HR = 0.51)
Gastric cancer			
Psaltopoulou, 2016 [30]	Meta-analysis (10 cohort studies, 12 case-control studies)	Any physical activity (any vs no physical activity)	• ↓ incidence (RR = 0.81)
Gunathilake, 2018 [31]	Case-control	All physical activity (>23 vs ≤8.25 MET-hours/week)	• ↓ incidence (OR = 0.46)
Fagundes, 2021 [32]	Case-control	Physical exercise, occupational physical activity, and leisure and locomotion activity during the preceding 5, 10 and 15 years (highest vs lowest category)	• ↓ incidence by 70%– 80% (all time periods)
Kidney cancer			
Ihira, 2019 [33]	Prospective cohort	Heavy physical work or strenuous exercise, sedentary activity and walking and standing (highest vs lowest group)	• No association with incidence
Liss, 2017 [34]	Cross-sectional	Light, moderate, or vigorous exercise (any vs no physical activity)	• ↓ mortality (HR = 0.50)
Liver cancer			
Lin, 2021 [35]	Meta-analysis (5 cohort studies)	Leisure time physical activity	• No association with incidence
Lee, 2020 [36]	Meta-analysis (10 cohort studies)	Any physical activity (2–3 and ≥3 vs <2 h/week)	• ↓ incidence and mortality by 20–25%; evidence of dose-response
Baumeister, 2019 [37]	Meta-analysis (14 prospective cohort studies)	Any physical activity (high vs low levels)	• ↓ incidence (HR = 0.75)
Meningioma			
Niedermaier, 2015 [38]	Meta-analysis (4 cohort studies, 2 case control studies)	All physical activity (high vs low levels)	• ↓ incidence (RR = 0.73)
Multiple myeloma			
Marinac, 2018 [39]	Prospective cohort	Cumulative average physical activity and walking	• No association with incidence
Ovarian cancer			
Lee, 2019 [40]	Meta-analysis (18 case-control studies and 16 prospective cohort studies)	All physical activity, i.e., recreational, occupational and non-occupational (low, medium, and high amounts of physical activity vs none)	• ↓ incidence by ~10%; no dose-response
Wang, 2021 [41]	Retrospective cohort	Walking, moderate, and vigorous physical activity during early life	• No association with incidence at later life
Wang, 2021 [42]	Retrospective cohort	Leisure-time physical activity in the 8 years pre-diagnosis and 4 years post-diagnosis	• No association of pre-diagnosis with mortality, but post-diagnosis ↓ mortality by 33%
Zamorano, 2019 [43]	Retrospective cohort	Vigorous physical activity in the past 12 months (1–3 times/month, 1–2 times/week, 3–4 times/week or 5 times/week vs. never/rarely)	• No association with mortality
Pancreatic cancer			
Farris, 2015 [44]	Meta-analysis (7 case-control studies, 20 cohort studies)	Leisure-time physical activity (highest vs lowest category)	• ↓ incidence (RR = 0.89)
Park, 2022 [45]	Retrospective cohort	Vigorous physical activity (1–3 days/week, 4–5 days/week or 6–7 days/week vs none)	• ↓ incidence (HR = 0.47)
Sandhu, 2020 [46]	Case-control	Moderate and vigorous physical activity	• No association with incidence
Wu, 2018 [47]	Prospective cohort	Leisure-time, occupational, and daily living physical activity (150 min/week of moderate activity or 75 min/week of vigorous activity vs none)	• ↓ incidence (HR = 0.59)
Thyroid cancer			
Schmid, 2013 [48]	Meta-analysis (8 cohort studies, 3 case-control studies)	All physical activity (highest vs lowest level)	• No association with incidence
Chen, 2022 [49]	Retrospective	All physical activity at state level in the USA between 2000 and 2017 (% physically active citizens)	• Inverse correlation with cancer incidence in all states (r = −0.29) which was stronger in states with increasing incidence (r = −0.65)

included in the review found a reduced risk of breast cancer of up to 40% with higher levels of physical activity, but there was no dose-response relationship [15]. Another study, conducted in Nigeria, explored the association between leisure-time physical activity and breast cancer risk [16]. This case-control study found that those in the highest quartile of leisure-time physical activity had reduced odds of developing breast cancer when compared to those in the lowest quartile (OR = 0.51, 95% CI = 0.35–0.74) [16]. This study also found that those in the highest (versus the lowest) quartile had lower odds of developing triple-negative breast cancer, but not hormone-receptor positive breast cancer [16].

A meta-analysis published in 2022, including nearly 30,000 survivors of breast cancer and 11 individual research articles, explored the association between recreational physical activity and breast cancer recurrence and survivorship [17]. This meta-analysis found that post-diagnosis physical activity reduced the risk of recurrence of breast cancer by 16% (relative risk, RR = 0.84, 95% CI = 0.78–0.91) [17]. Furthermore, the authors reported a decrease in disease-specific mortality in those who engaged in any post-diagnosis physical activity when compared to those who did not (RR = 0.77, 95% CI = 0.66–0.93) [17]. All aforementioned systematic reviews and original research studies adjusted their analyses for potential demographic and lifestyle confounders (e.g., age, body mass index [BMI], age of menarche, smoking, and alcohol use).

1.3. Colorectal cancer

In a population-based case-control study which included 1516 Moroccan males and females, those who performed at least 50 MET (metabolic equivalent of task, which indicates the energy expenditure of exercise as multiple of resting metabolic rate)-hours per week of physical activity had a 28% reduced risk of colorectal cancer when compared to those who performed fewer than 10 MET-hours per week (OR = 0.72, 95% CI = 0.62–0.83) [18], confirming results from earlier studies suggesting that high levels of physical activity decrease colorectal cancer risk [50]. Interestingly, a recent cross-sectional study that examined over 33,000 participants from the Korea National Health and Nutrition Examination Survey from 2014 to 2019, found that those who were sedentary at least 10 h per day had a higher risk of developing colorectal cancer when compared to those who were sedentary fewer than 10 h per day (OR = 1.64, 95% CI = 1.22–2.21) [19]. Both studies adjusted for potential confounders. These data suggest that limiting the time spent being inactive, and not necessarily engaging in structured exercise, may also be beneficial. Still, there are no systematic reviews or meta-analyses on the effect of physical activity on colorectal cancer risk.

Two recent systematic reviews of prospective cohort studies evaluated the association between physical activity and mortality in patients with colorectal cancer [20,21]. In the first, which included meta-analysis of data, those with the highest level of pre-diagnosis physical activity had reduced all-cause mortality (summary hazard ratio, HR = 0.81, 95% CI = 0.76–0.87), and reduced colorectal cancer mortality (summary HR = 0.85, 95% CI = 0.77–0.98) when compared to those with the lowest level of pre-diagnosis activity [20]. In the second, very high levels of physical activity (17.5–35 MET hours/week) were associated with reduced colorectal cancer mortality by 30%− 40% [21]. These 2 systematic reviews adjusted for potential confounders including tumor stage, cancer treatment modality, BMI, smoking, and alcohol use. Additionally, another recent study, which utilized patients from the Korean National Health Insurance Database, found that post-surgical patients with colorectal cancer who engaged in physical activity (estimated as the weighted sum of the frequencies for walking, moderate, and vigorous activity) for ≥ 3 times per week had lower colorectal cancer mortality than those who did not exercise (colon cancer HR = 0.85, 95% CI = 0.76–0.97; rectal cancer HR = 0.77, 95% CI = 0.66–0.90) [22]. However, there was no association between physical activity and mortality in those patients who had not undergone surgery [22]. Mortality aside, lower levels of physical inactivity and/or higher levels of physical activity have been consistently linked with improvements in several health-related outcomes in patients with colorectal cancer and better prognosis [23].

1.4. Endometrial cancer

A recent study from Saint-Maurice et al. (2021), which followed almost 70,000 women from the National Institutes of Health-AARP Diet and Health Study in the United States, found that compared to sedentary women (defined as those who rarely or never engaged in leisure time physical activity), those who were physically active (defined as those who engaged in 6–7 h per week or more of leisure time physical activity) had an almost 20% lower risk (HR = 0.81, 95% CI = 0.67–0.98) of developing endometrial cancer [24]. In this study, the effect of regular exercise was largely mediated through the BMI of the women, which was lower in physically active participants [24]. Although, an earlier meta-analysis reported that the beneficial effects of regular exercise on endometrial cancer risk is likely independent of body weight [51]. Another recent study conducted in Japanese women found > 50% decreased risk of endometrial cancer among those who had occupations in which they were physically active compared to those who had occupations in which they were mostly seated or sedentary (HR = 0.46, 95% CI = 0.22–0.97) [25]. However, hours of leisure-time physical activity and walking were not associated with risk of endometrial cancer [25]. All these reviews and original research studies adjusted their estimates for potential confounders. These observations imply that the benefits of regular physical activity can be materialized not only by engaging in structured exercise but also by doing all sorts of activities, including occupational physical activity, commuting activity, etc. Furthermore, they raise the possibility that once a certain threshold level of physical activity is reached (via occupation in this case), more exercise does not provide further benefits.

A number of studies have addressed the effect of physical activity on survivorship in patients with endometrial cancer, though no systematic review or meta-analysis is yet available. A 2022 study conducted in 745 endometrial cancer patients found that those who had participated in at least one session of moderate to vigorous physical activity per week in the five years before the study had lower all-cause mortality when compared to those who did not participate in any weekly moderate to vigorous physical activity (HR = 0.61, 95% CI = 0.41–0.92) [26]. However, there was no dose-response relationship between physical activity and all-cause mortality, and the study did not investigate the effect specifically on cancer mortality [26]. Another prospective cohort study, conducted in Canada, evaluated the association of pre- and post-diagnosis physical activity on endometrial cancer survivorship [27]. The study found that those who performed ≥ 14 MET-hours per week annually pre-diagnosis had greater disease-free survival than those who performed ≤ 8 MET-hours per week annually (HR = 0.54, 95% CI = 0.30–0.96) [27]. Additionally, the study found that those who were more active post-diagnosis (≥13 MET-hours per week versus ≤5 MET-hours per week) had improved disease-free survival (HR = 0.33, 95% CI = 0.17–0.64) [27]. These data indicate that about 2 h per week of moderate-to-vigorous exercise (7 MET, e.g. running, swimming, basketball playing) or 4.5 h per week of light exercise (3 MET, e.g. yoga, most home chores, walking) are required to beneficially affect endometrial cancer survivorship.

1.5. Esophageal adenocarcinoma

A systematic review and meta-analysis from 2017, which assessed the effect of physical activity on gastroesophageal reflux disease, Barrett's esophagus, and esophageal adenocarcinoma, found 3 studies examining the potential benefit of exercise in the primary prevention of adenocarcinomas [28]. Though heterogeneity among the studies did not allow for calculating a pooled estimate, results from 1 of the 3 studies were promising [28]. The study, a prospective cohort including both

males and females from the United States [52], found a reduced risk of esophageal adenocarcinoma in those who participated in ≥ 5 weekly recreational physical activity sessions of 20 min or longer, when compared to those who participated in none (RR = 0.68, 95% CI = 0.48–0.96) [28]. The other two studies included in the review found no association [28]. All studies performed adjustment for potential lifestyle confounders. There is currently no information on the association between physical activity and survivorship for esophageal adenocarcinoma patients, indicating a need for further study on this topic.

1.6. Gallbladder cancer

Though there is evidence that obesity is a major risk factor for gallbladder cancer, there is little available evidence on the relationship between regular physical activity and gallbladder cancer risk. One available study included over 400,000 participants from the China Kadoorie Biobank, and found that the level of total physical activity (leisure-time, commuting, household, and occupational) was inversely associated with risk of gallbladder cancer when the top quintile of physical activity was compared to the bottom quintile (HR = 0.51, 95% CI = 0.32–0.80), even after adjustment for confounders [29]. No literature is currently available on the association between physical activity and survival in patients with gallbladder cancer.

1.7. Gastric cancer

A systematic review and meta-analysis of physical activity and gastric cancer published in 2016 included 10 cohort studies and 12 case-control studies with a total of over 1.6 million participants [30]. The pooled analysis found that participating in any type of physical activity was associated with a lower incidence of gastric cancer when compared to not participating in any type of physical activity (pooled RR = 0.81, 95% CI = 0.73–0.89) [30]. A more recent study from 2018, examining risk of gastric cancer in Korean patients with and without Helicobacter pylori infection, found that those who engaged in regular physical activity had a reduced risk of gastric cancer when those in the highest tertile of activity (engaging in >23 MET-hours per week of physical activity) were compared to those in the lowest tertile (engaging in ≤8.25 MET-hours per week of physical activity) (OR = 0.46, 95% CI = 0.32–0.65) [31]. Additionally, a 2021 case-control study conducted in the Amazon region of Brazil found that those with the highest levels of leisure and locomotive (commuting) activities during the previous 5, 10, and 15 years before diagnosis were 70%− 80% less likely to develop gastric cancer [32]. All these reviews and original research studies performed adjustment for potential confounders related to lifestyle. There is no literature available on the association between physical activity and survival in patients with gastric cancer.

1.8. Kidney cancer

There is little available literature on the association between regular physical activity and kidney cancer risk. However, a 15-year prospective cohort study among middle-aged Japanese males and females found physical activity was not associated with risk of kidney cancer (HR = 1.05, 95% CI = 0.74–1.49) [33]. With respect to mortality, a study utilizing patients from the US National Health Information Survey from 1998 through 2004 found that those who reported engaging in any amount of any type of physical activity had lower kidney cancer mortality than those who did not engage in any type of physical activity (HR = 0.50, 95% CI = 0.27–0.93), demonstrating a clear benefit of any type of movement for those diagnosed with kidney cancer [34]. The results in both studies persisted after adjustment for potential confounders.

1.9. Liver cancer

The effects of physical activity on liver cancer, considered to be the second most deadly cancer type, are somewhat inconsistent but generally favorable. A systematic review and meta-analysis from 2021, which included 5 cohort studies and about 2.5 million subjects, found no association between leisure-time physical activity and liver cancer risk (pooled RR = 0.92, 95% CI = 0.84–1.01), although a protective effect was seen among never smokers [35]. Two other systematic reviews with meta-analysis from 2019 and 2020 on the effect of physical activity on liver cancer risk provided more encouraging results [36,37]. The first found that, compared to those who engaging in fewer than 2 h of physical activity per week, those engaging in 2–3 h and ≥ 3 h of physical activity per week had a 23% and 26% lower risk of developing liver cancer, respectively [36]. Similarly, the second study, including 6440 liver cancer cases from 14 prospective observational studies, reported that high vs. low levels of physical activity were associated with reduced risk of liver cancer by ~25% (HR = 0.75, 95% CI = 0.63–0.89) [37]. In the meta-analysis from 2020, it was also reported that engaging in ≥ 2–3 h of physical activity per week were associated with 19%− 25% lower risk of mortality from liver cancer [36]. All these studies adjusted their analyses for confounders.

1.10. Meningioma

Risk of meningioma, a type of tumor situated around the brain and spinal column, may be affected by regular physical activity. A meta-analysis published in 2015, which included 6 studies and 2982 meningioma cases, found an inverse relationship between physical activity and incidence of meningioma (RR = 0.73, 95% CI = 0.61–0.88), which persisted even after adjustment for age and BMI [38]. There is currently no literature on the association between physical activity and meningioma survival.

1.11. Multiple myeloma

A prospective cohort study published in 2018 that included three cohorts found that physical activity was not associated with risk of developing multiple myeloma, for which BMI is the only modifiable risk factor [39]. There are currently no systematic reviews or meta-analyses on physical activity and multiple myeloma risk, and no literature on the association between physical activity and multiple myeloma survival.

1.12. Ovarian cancer

A 2019 systematic review and meta-analysis of data from 30 studies evaluated the association between physical activity and ovarian cancer risk [40]. The pooled analysis found that when compared to those who were physically inactive, those who engaged in low, medium, and high amounts of physical activity had a 9%, 9%, and 8% lower risk of developing ovarian cancer, respectively (i.e. no dose-response relationship) [40]. A more recent study, published in 2021, evaluated the association between early life physical activity and ovarian cancer risk, among two large cohorts of females from the Nurses' Health Study I and II [41]. The study found that physical activity between the ages of 12 and 22 years was not associated with later development of ovarian cancer [41]. Both studies adjusted for potential confounders.

There are no meta-analyses on the association between physical activity and survival in patients with ovarian cancer. One individual study, which included nearly 1500 females from the United States' Nurses Health Cohort I and II, reported that ovarian-cancer specific mortality was not associated with engaging in physical activity in the 8 years leading up to an ovarian cancer diagnosis [42]. A second study that used data from American women enrolled in NIH-AARP Diet and Health Study also found that pre-diagnosis physical activity was not associated with mortality from ovarian cancer [43]. In the 4 years following the diagnosis of ovarian cancer, however, those who engaged in at least 7.5 MET-hours/week of physical activity had lower mortality when compared to those who engaged in fewer than 1.5 MET-hours/week of

physical activity (HR = 0.67, 95% CI = 0.48–0.94) [42]. These findings imply that there is no legacy or memory effect of training, and any protective effect of physical activity on ovarian cancer survival is directly related to responses or adaptations that occur concurrently with exercise.

1.13. Pancreatic cancer

A 2015 systematic review and meta-analysis on the association between leisure-time physical activity and pancreatic cancer risk included 26 studies and found an ~11% lower risk (pooled RR = 0.89, 95% CI = 0.82–0.96) [44]. More recently, a retrospective cohort study, conducted in 220,357 Koreans, found that higher levels of physical activity were associated with lower risk of pancreatic cancer [45]. In this study, only those in the highest physical activity group (6–7 days per week of vigorous physical activity lasting at least 20 min per session) had a reduced risk of pancreatic cancer when compared to those in the lowest physical activity group (no vigorous physical activity), after adjusting for confounders (HR = 0.47, 95% CI = 0.25–0.89) [45]. Nonetheless, a population-based case-control study from Canada, which tracked self-reported moderate and vigorous physical activity in young-adulthood, mid-adulthood, and older-adulthood, found no significant results in any age group [46]. A third study, a prospective cohort study conducted in Chinese males and females, also found no benefit when all amounts and types of exercise were considered, but found a decreased risk of pancreatic cancer in males who engaged in 150 min/week of moderate-intensity exercise or 75 min/week of vigorous-intensity exercise (HR = 0.59, 95% CI = 0.40–0.87) [47]. These significant results persisted after confounder adjustment in males, however they were not seen in females [47]. There is currently no literature on the association between physical activity and pancreatic cancer survival.

1.14. Thyroid cancer

A systematic review and meta-analysis published in 2013 evaluated the association between physical activity and thyroid cancer risk [48]. The review included 7 cohort and case-control studies with over 900,000 participants and found no association between physical activity and thyroid cancer risk (summary RR = 1.06, 95% CI = 0.79–1.42) [48]. A more recent study, published in 2022, evaluated the average annual percent change in thyroid cancer in the United States between 2000 and 2017, and found an inverse strong correlation between thyroid cancer incidence and physical activity level (r = −0.65) in the 10 states with a persistent increasing trend of thyroid cancer incidence over the years [49]. This relationship persisted after adjusting for age (no adjustments for lifestyle confounders were made). There is no available data on the association between physical activity and survival among patients with thyroid cancer.

1.15. Biological mechanisms by which physical activity affects cancer

The effects of regular physical activity on cancer risk and mortality likely reflect biological links between exercise and the mechanisms of cancer initiation and/or progression, mediated through changes in metabolic, hormonal, inflammatory and immune functions (Fig. 2). The effects of physical activity on carcinogenesis are likely to be multifactorial and affected by individual traits such as age and sex and exercise-specific factors such as the type, intensity, and frequency of physical activity.

1.16. Improvement in insulin resistance and attenuation of hyperinsulinemia

There is growing evidence that an insulin resistant glucose metabolism is etiologically linked to tumorigenesis and associated with clinical cancer diagnoses [53,54]. In a state of insulin resistance, uptake of glucose into insulin-sensitive tissues (predominantly skeletal muscle) is decreased. The body therefore requires a greater than normal amount of insulin to maintain blood glucose concentration and avoid hyperglycemia, which is achieved by compensatory insulin secretion from the pancreas, leading to various degree of hyperinsulinemia. Insulin, besides its multiple metabolic roles, is also a key growth hormone. After binding to its receptor in the cellular membrane, insulin initiates a cascade of downstream events that activate two major signaling branches: the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT) pathway which controls metabolic homeostasis, and the mitogen-activated protein kinase (MAPK) pathway which controls cell growth and proliferation [55]. The net result is an increase in cell proliferation and an inhibition of cell apoptosis—both biological hallmarks of cancer [53,56]. Individuals with obesity often have insulin resistance and hyperinsulinemia, together with elevated levels of circulating free fatty acids (FFA) which can further augment secretion of insulin from pancreatic β-cells [57].

Physical activity can help mitigate insulin resistance and thus, alleviate hyperinsulinemia, and therefore also possibly the resulting increase in cancer risk [56]. In fact, endurance exercise and perhaps also strength exercise acutely increases insulin sensitivity for 2–3 days [58]. This effect is attributed to increased glucose transporter (GLUT)− 4 translocation to the plasma membrane and enhanced glucose uptake

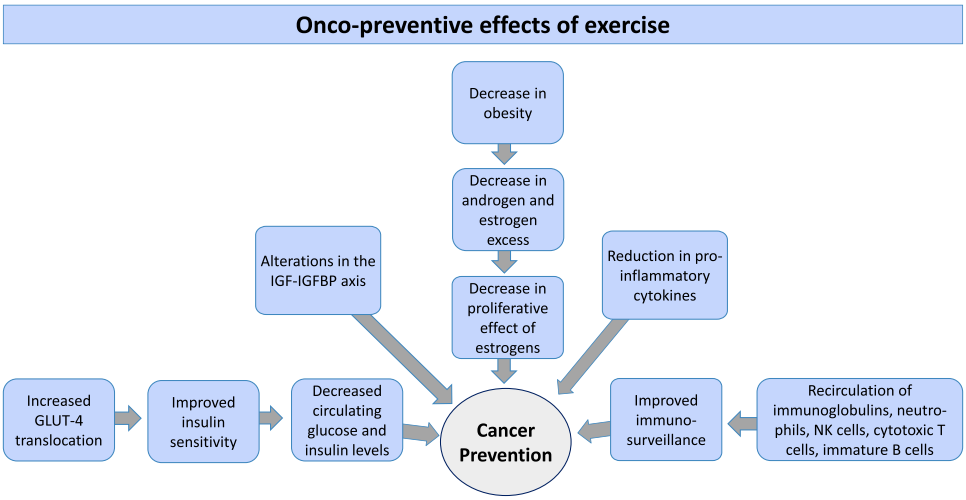

Fig. 2. Key mechanisms by which exercise may be able to protect against cancer.

from the bloodstream, which leads to a decrease in circulating blood glucose and subsequently, a decrease in insulin levels [59]. The increase in insulin sensitivity and glucose uptake in the postexercise period is generally thought to be linked to the need for replenishing skeletal muscle glycogen stores which have been depleted by prior exercise [59]. This acute insulin-sensitizing effect of exercise may be exaggerated with repeated exercise bouts (i.e. chronic training) [60], predominantly as a result of changes in body composition and particularly an increase in skeletal muscle mass [61]. Muscle is responsible for about 20% of whole-body glucose uptake during postabsorptive conditions and about 70%– 90% under postprandial conditions [62–64]. Therefore, exercise-induced increases in muscle mass can augment whole-body glucose uptake and lower plasma glucose concentrations, which can in turn decrease the need for more insulin [65–67]. In addition, exercise-induced energy deficits in individuals with obesity can lead to loss of body weight—albeit only to modest amounts in the absence of concurrent dietary energy restriction [68]—which in itself can have beneficial effects on insulin sensitivity and hyperinsulinemia [57,69]. Accordingly, the effects of physical activity on the prevention and prognosis of obesity-related cancers can partly be mediated by exercise-induced weight loss [14].

Besides changes in glucose metabolism, body composition or weight, and the availability of circulating insulin, exercise-mediated effects in the insulin-like growth factor (IGF) system could be linked to the observed reductions in cancer incidence and improvements in cancer-related outcomes and survival. The IGF axis is key in the regulation of cell proliferation, differentiation and apoptosis. Regular exercise training in cancer survivors has been associated with moderate reductions in the concentrations of IGF-1 and IGF-2 and moderate increases in the concentrations of IGF-binding proteins 1 and 3 (which binds and further reduces bioavailability of IGFs) [70], although these effects vary considerably among different cancer type survivors [71]. Similar variability has been observed in otherwise healthy individuals [72], but the reasons behind these variable responses are not clear. Thus, the degree of involvement of alterations in the IGF axis in mediating the effects of exercise on carcinogenesis warrants further clarification.

1.17. Altered sex steroid hormone milieu

Female sex hormones have a mitotic effect by promoting cellular proliferation, inhibiting apoptosis and increasing DNA damage [73]. Accordingly, elevated estrogen—but also androgen—levels in women are associated with increased risk of breast and endometrial cancers, whereas lower androgen levels in men are associated with increased prostate cancer survival [56]. Estrogens, which are crucial in the typical development of the breast epithelium, have a pro-proliferative effect at high levels [74]. Generally, androgens prevent cell proliferation; however, androgens also serve as estrogen precursors, and an excess of androgens in women allows for an increased conversion to estrogens in adipose tissue and thus, a secondary pro-proliferative effect [75]. Obesity is associated with androgen excess, increased amounts of adipose tissue, and hyperinsulinemia—which upregulates aromatase activity, i.e. the enzyme that coverts androgens to estrogens [76]—resulting in increased risk of these types of cancers [77].

Regular exercise has been associated with modest reductions in the levels of endogenous estrogens and androgens in women—both premenopausal and postmenopausal—and with increases in sex hormone binding globulin which binds and further reduces bioavailability of endogenous sex hormones [78,79]. Exercise-induced reductions in sex hormone binding globulin are also evident among men [56]. Loss of body fat induced by exercise is likely important and exaggerates these hormonal shifts, particularly among postmenopausal women [73,80]. In fact, large volumes of intense exercise that affect energy homeostasis can disrupt the hypothalamic–pituitary–gonadal axis and can result in alterations in reproductive function and menstrual disturbances (e.g. primary or secondary amenorrhea and oligomenorrhea), which can in turn reduce the cumulative lifecycle exposure to sex hormones and subsequent sex hormone-related cancer risk [73,81]. In the absence of significant deficit in energy availability or weight loss, it is possible that other biological mechanisms rather than merely sex hormone shifts are primarily important for the favorable effects of moderate-intensity exercise on cancer risk in both premenopausal [82] and postmenopausal [83] women.

1.18. Resolution of inflammation

Inflammation has been linked to the cascade of events involved in the development and progression of cancer [84]. Elevated levels of inflammatory markers—such as C-reactive protein, interleukin-6, tumor-necrosis factor-alpha, and monocyte chemoattractant protein-1—are strongly linked with cancer diagnoses [85–87]. These pro-inflammatory cytokines are also elevated in individuals with excess weight and body fat and can contribute to the evolution of obesity-related cancers [88,89]. Inflammation is associated with normal tissue repair after injury, but can also become chronic, as is the case with many autoimmune diseases and with obesity [90]. Chronic inflammation is associated with a second insult to already injured tissue, and may be involved in both cancer promotion and progression [90]. As a promoter, chronic inflammation can contribute to the neovascularization of tumors and contribute to rapid tumor growth [90]. Exercise in conjunction with diet-induced weight loss has a beneficial impact on inflammatory biomarkers associated with cancer [91]. Studies have consistently shown that regular physical activity reduces pro-inflammatory cytokines, though the mechanisms are not yet fully understood [56]. This anti-inflammatory effect may be particularly relevant for cancer patients undergoing chemotherapy that typically induces a pro-inflammatory response [92]. Results from studies in animal models support a link between physical activity, decreased inflammation and reduced tumor burden, although still very limited mechanistic insights [93].

1.19. Improved immune function

Systemic immune dysfunction is another feature of cancer, resulting in both increased cancer risk, and increased risk of infection in those diagnosed [94]. Those with impaired immune systems, as is the case with organ donation recipients and those with diseases like human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), are at increased risk of cancer likely due to suppressed immunosurveillance that would otherwise identify, target, and eliminate damaged tissue [95]. Furthermore, cancer itself is associated with altered immune function [96]. Among other tactics, cancer can halt the production of bone marrow-associated macrophages and of neutrophils, creating a tumor microenvironment that further propagates tumor growth and favors metastasis [96,97]. Obesity is also associated with impaired immune function [98]. Not only does the low-grade inflammation impair immune function, excess adiposity is associated with reduced antibody response post-vaccination, as adipose tissue is poor in immune cells that are found commonly in lean tissues including M2-type macrophages, regulatory T cells (Treg), T-helper (Th)2, and type 2 innate lymphoid cells (ILC2) [99].

Exercise has immunomodulatory effects that could alter multiple critical phases of immune system–tumor cross-talk in both tumor initiation and progression [100]. Regular exercise causes reprogramming of tissue-specific immunometabolic regulation that enhances resistance to tissue-specific events linked to tumorigenesis [97]. It significantly alters the number and function of circulating cells of the innate immune system (e.g., neutrophils, monocytes, and natural killer [NK] cells) and, to a lesser degree, of the adaptive immune system (e.g., T and B cells) [101]. Exercise favorably modifies the immunological composition of the tumor microenvironment, decreasing the proportion of innate immune cell populations (macrophages and myeloid-derived suppressor cells)

and increasing $CD3^+$ T cells and NK cells, the ratio of $CD8^+$ T cells to Treg, and the activation of $CD8^+$ T cells ($CD69^+$) [97]. Moreover, moderate to vigorous physical activity performed for 60 min or less has been showed to improve immunosurveillance—the same immune function whose lack increases cancer risk [102]. This happens through increased recirculation of immune system components, including immunoglobulins, anti-inflammatory cytokines, neutrophils, NK cells, cytotoxic T cells, and immature B cells [102]. This again demonstrates that beyond the energy deficit and associated mild weight loss, physical activity has the potential to provide immune system support to lower cancer risk and improve immune function in those with cancer. Accordingly, it has been suggested that exercise treatment could be used to improve responses to cancer immunotherapies including immune checkpoint inhibitors, dendritic cell vaccines, NK cell therapies, and adoptive T cell therapies such as chimeric antigen receptor (CAR) T cells [103].

1.20. Secretion of myokines with pleiotropic effects

The skeletal muscle is, among other things, an endocrine organ that produces and secretes a variety of proteins and peptides—collectively referred to as myokines—which can affect multiple metabolic and physiological pathways in the same tissue, adjacent tissues, or remote tissues and organs [104,105]. Myokines allow not only for communication within the muscle itself, but also for crosstalk between the muscle and other organs such as the brain, adipose tissue, bone, liver, gut, pancreas, vasculature, and skin [105]. Accordingly, they are thought to mediate, at least in part, many of the physiological adaptations to regular exercise training and its beneficial effects on a variety of chronic diseases, including cancer [106]. The type of exercise (aerobic/endurance or strength/resistance), its frequency, duration, and intensity influence the mixture and amount of myokines that are being released from skeletal muscle [107]. Since the characterization of the "prototype" myokine (interleukin 6), a number of other peptides have been identified as myokines, including interleukin 5, interleukin 8, interleukin 15, irisin, oncostatin M, secreted protein acidic and rich in cysteine (SPARC), decorin, brain-derived neurotrophic factor (BDNF), fibroblast growth factor-21, and more [105,107]. These myokines can hinder cancer development and progression either directly by inhibiting proliferation, inhibiting epithelial-mesenchymal transformation (i.e., metastasis), or promoting apoptosis; or indirectly by attenuating the tumor-promoting microenvironment than is often accompanying obesity (i.e., hyperinsulinemia, insulin resistance, hyperlipidemia, low-grade inflammation, impaired immune response) [107,108].

1.21. Modulation of intracellular signaling

AMP-activated protein kinase (AMPK) is a protein kinase expressed in muscle (and other tissues) that is considered a master regulator of metabolism [109]. When cellular energy homeostasis is disturbed (e.g., because of ATP depletion or low glucose levels due to exercise), AMPK is activated via phosphorylation by upstream kinases (e.g., liver kinase B1 and calcium/calmodulin-dependent protein kinase), and in turn phosphorylates a wide array of downstream enzymes and effectors [110]. The net result of AMPK activation is the inhibition of pathways that consume ATP (e.g., gluconeogenesis and most other anabolic processes) and the activation of pathways that generate ATP (e.g., glucose uptake and fatty acid oxidation) [109,110]. Accordingly, it is believed that AMPK activation has a critical role in mediating exercise-induced adaptations in various tissues and organs that promote health and prevent disease [110].

The relevance of AMPK to cancer is obvious: cancer is a state of altered cellular energetics, where the energy demands of the cell are increased due to rapid growth and division, whereas activation of AMPK inhibits essentially all anabolic pathways that promote cell growth [111]. Data from in vitro, preclinical and clinical studies have revealed potentially beneficial effects of genetic or pharmacological AMPK upregulation against lung cancer, colorectal cancer, liver cancer, but also other cancers, including breast cancer, prostate cancer, ovarian cancer, melanoma, and leukemia [112]. For example, metformin, one of the most commonly used antihyperglycemic agents in the management of type 2 diabetes, is associated with a 20–30% reduction in total cancer incidence and mortality [113], and the main mechanism behind this beneficial effect is thought to be its ability to activate AMPK in various tissues [114].

There are many cellular targets for AMPK, of which several are relevant to carcinogenesis. The most important downstream event is the AMPK-mediated suppression of the mammalian target of rapamycin (mTOR), a protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription [111]. Activation of mTOR is tumor-promoting because it increases anabolic processes, cell growth, cell proliferation and cell survival, whereas suppression of mTOR is tumor-suppressing because it inhibits translation and protein synthesis and eventually, cell growth [111,112]. Other cellular events that are likely involved in the antitumorigenic effects of AMPK include: i) the suppression of cyclooxygenase-2, an enzyme responsible for the formation of pro-inflammatory mediators that promote tumor growth; ii) the activation of tumor suppressor p53, a protein that prevents tumor development by enabling the cell to respond to a number of stressors (e.g., DNA damage, oncogene activation) and by inducing cell cycle arrest or senescence; and iii) the induction of autophagy (partly through mTOR inhibition), which is a catabolic process that degrades and recycles cellular components and organelles and maintains overall homeostasis [111,112,115,116].

2. Conclusions

There is a wealth of observational data supporting a link between high levels of regular physical activity and lower incidence and/or recurrence of various types of cancer. Despite abundant epidemiological evidence, the mechanisms responsible for the apparent anti-cancer effects of exercise remain poorly defined. It is entirely possible that multiple exercise-induced factors contribute to these beneficial outcomes, and the relative importance of each varies depending on the characteristics of the exercise regimen, the characteristics of the individual, and the type of cancer in question. We also still lack a clear understanding of how different exercise modalities (e.g., aerobic or resistance exercise) and amounts (e.g., duration and intensity) interact to improving disease outcomes. Although a deeper understanding of how exercise can help against cancer and of the exercise parameters that can be tweaked to optimize exercise prescription is necessary and should be the subject of future investigation, knowledge of the mechanisms and of the optimal exercise parameters is clearly not a prerequisite to promote a more physically active lifestyle among patients at risk of cancer and among cancer survivors [117]. Accordingly, understanding barriers to exercise among those individuals, educating those involved in cancer care about the benefits of regular exercise and providing guidelines to clinicians on how to effectively and safely incorporate physical activity in the day-to-day treatment of their patients is also of paramount importance.

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References

[1] F. Bray, M. Laversanne, E. Weiderpass, I. Soerjomataram, The ever-increasing importance of cancer as a leading cause of premature death worldwide, Cancer 127 (2021) 3029–3030.

[2] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (2021) 209–249.

[3] J. Lortet-Tieulent, D. Georges, F. Bray, S. Vaccarella, Profiling global cancer incidence and mortality by socioeconomic development, Int J. Cancer 147 (2020) 3029–3036.

[4] A. Alzehr, C. Hulme, A. Spencer, S. Morgan-Trimmer, The economic impact of cancer diagnosis to individuals and their families: a systematic review, Support Care Cancer 30 (2022) 6385–6404.

[5] K.R. Yabroff, J. Lund, D. Kepka, A. Mariotto, Economic burden of cancer in the United States: estimates, projections, and future research, Cancer Epidemiol. Biomark. Prev. 20 (2011) 2006–2014.

[6] B. Lauby-Secretan, C. Scoccianti, D. Loomis, Y. Grosse, F. Bianchini, K. Straif, Body fatness and cancer — viewpoint of the iarc working group, N. Engl. J. Med 375 (2016) 794–798.

[7] M.M. Dougan, S.E. Hankinson, I.D. Vivo, S.S. Tworoger, R.J. Glynn, K.B. Michels, Prospective study of body size throughout the life-course and the incidence of endometrial cancer among premenopausal and postmenopausal women, Int. J. Cancer 137 (2015) 625–637.

[8] C. Hoyo, M.B. Cook, F. Kamangar, N.D. Freedman, D.C. Whiteman, L. Bernstein, L.M. Brown, H.A. Risch, W. Ye, L. Sharp, A.H. Wu, M.H. Ward, A.G. Casson, L. J. Murray, D.A. Corley, O. Nyrén, N. Pandeya, T.L. Vaughan, W.H. Chow, M. D. Gammon, Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium, Int. J. Epidemiol. 41 (2012) 1706–1718.

[9] Y. Chen, L. Liu, X. Wang, J. Wang, Z. Yan, J. Cheng, G. Gong, G. Li, Body mass index and risk of gastric cancer: a meta-analysis of a population with more than ten million from 24 prospective studies, Cancer Epidemiol. Biomark. Prev. 22 (2013) 1395–1408.

[10] Y. Chen, X. Wang, J. Wang, Z. Yan, J. Luo, Excess body weight and the risk of primary liver cancer: an updated meta-analysis of prospective studies, Eur. J. Cancer 48 (2012) 2137–2145.

[11] F. Wang, Y. Xu, Body mass index and risk of renal cell cancer: a dose-response meta-analysis of published cohort studies, Int J. Cancer 135 (2014) 1673–1686.

[12] X. Fang, J. Wei, X. He, J. Lian, D. Han, P. An, T. Zhou, S. Liu, F. Wang, J. Min, Quantitative association between body mass index and the risk of cancer: a global Meta-analysis of prospective cohort studies, Int J. Cancer 143 (2018) 1595–1603.

[13] M. Jurdana, Physical activity and cancer risk. Actual knowledge and possible biological mechanisms, Radio. Oncol. 55 (2021) 7–17.

[14] X. Chen, Q. Wang, Y. Zhang, Q. Xie, X. Tan, Physical activity and risk of breast cancer: a meta-analysis of 38 cohort studies in 45 study reports, Value Health 22 (2019) 104–128.

[15] A.M. Bucy, C.I. Valencia, C.L. Howe, T.J. Larkin, K.D. Conard, E.W. Anderlik, S. I. Valdivi, J.W. Bea, Physical activity in young BRCA carriers and reduced risk of breast cancer, Am. J. Prev. Med. 63 (2022) 837–845.

[16] G. Bigman, S.N. Adebamowo, K.-D.T. Yawe, M. Yilkudi, O. Olaomi, O. Badejo, A. Famooto, E. Ezeome, I.K. Salu, E. Miner, I. Anosike, B. Achusi, C. Adebamowo, Leisure-time physical activity is associated with reduced risks of breast cancer and triple negative breast cancer in Nigerian women, Cancer Epidemiol. 79 (2022), 102195.

[17] N. Zagalaz-Anula, M.J. Mora-Rubio, E. Obrero-Gaitán, R. Del-Pino-Casado, Recreational physical activity reduces breast cancer recurrence in female survivors of breast cancer: a meta-analysis, Eur. J. Oncol. Nurs. 59 (2022), 102162.

[18] Z. Hatime, K. El Kinany, I. Huybrechts, N. Murphy, M.J. Gunter, M. Khalis, S. D. Meimouna, H.A. Boudouaya, A. Benslimane, A. El Asri, M. Abkari, K. Bendahhou, M.Z. Ismaili, K. El, Rhazi, Association of physical activity and sedentary behavior with colorectal cancer risk in moroccan adults: a large-scale, population-based case–control study, Asian Pac. J. Cancer Prev. 23 (2022) 1859–1866.

[19] S. An, S. Park, Association of physical activity and sedentary behavior with the risk of colorectal cancer, J. Korean Med. Sci. 37 (2022), e158.

[20] S. Qiu, C. Jiang, L. Zhou, Physical activity and mortality in patients with colorectal cancer: a meta-analysis of prospective cohort studies, Eur. J. Cancer Prev. 29 (2020) 15–26.

[21] J. Hong, J. Park, Systematic review: recommendations of levels of physical activity among colorectal cancer patients (2010-2019), Int J. Environ. Res Public Health 18 (2021) 2896.

[22] M. Lee, Y. Lee, D. Jang, A. Shin, Physical activity after colorectal cancer diagnosis and mortality in a nationwide retrospective cohort study, Cancers 13 (2021) 4804.

[23] B. Singh, S.C. Hayes, R.R. Spence, M.L. Steele, G.Y. Millet, L. Gergele, Exercise and colorectal cancer: a systematic review and meta-analysis of exercise safety, feasibility and effectiveness, Int J. Behav. Nutr. Phys. Act. 17 (2020) 122.

[24] P.F. Saint-Maurice, J.N. Sampson, K.A. Michels, S.C. Moore, E. Loftfield, K. McClain, M.B. Cook, B. Trabert, C.E. Matthews, Physical activity from adolescence through midlife and associations with body mass index and endometrial cancer risk, JNCI Cancer Spectr. 5 (2021) pkab065.

[25] H. Miyata, K. Shirai, I. Muraki, H. Iso, A. Tamakoshi, Associations of body mass index, weight change, physical activity, and sedentary behavior with endometrial cancer risk among japanese women: the Japan collaborative cohort study, J. Epidemiol. 31 (2021) 621–627.

[26] J.S. Gorzelitz, A. Trentham Dietz, J.M. Hampton, R.J. Spencer, E. Costanzo, K. Koltyn, R.E. Gangnon, P.A. Newcomb, L.A. Cadmus-Bertram, Mortality risk and physical activity across the lifespan in endometrial cancer survivors, Cancer Causes Control 33 (2022) 455–461.

[27] C.M. Friedenreich, L.S. Cook, Q. Wang, R.L. Kokts-Porietis, J. McNeil, C. Ryder-Burbidge, K.S. Courneya, Prospective cohort study of pre- and postdiagnosis physical activity and endometrial cancer survival, J. Clin. Oncol. 38 (2020) 4107–4117.

[28] S. Lam, A.R. Hart, Does physical activity protect against the development of gastroesophageal reflux disease, Barrett's esophagus, and esophageal adenocarcinoma? A review of the literature with a meta-analysis, Dis. Esophagus 30 (2017) 1–10.

[29] Y. Pang, J. Lv, C. Kartsonaki, C. Yu, Y. Guo, H. Du, D. Bennett, Z. Bian, Y. Chen, L. Yang, I. Turnbull, H. Wang, H. Li, M.V. Holmes, J. Chen, Z. Chen, L. Li, Association of physical activity with risk of hepatobiliary diseases in China: a prospective cohort study of 0.5 million people, Br. J. Sports Med 55 (2021) 1024–1033.

[30] T. Psaltopoulou, I. Ntanasis-Stathopoulos, I.G. Tzanninis, M. Kantzanou, D. Georgiadou, T.N. Sergentanis, Physical activity and gastric cancer risk: a systematic review and meta-analysis, Clin. J. Sport Med 26 (2016) 445–464.

[31] M.N. Gunathilake, J. Lee, A. Jang, I.J. Choi, Y.I. Kim, J. Kim, Physical activity and gastric cancer risk in patients with and without helicobacter pylori infection in a Korean population: a hospital-based case-control study, Cancers (Basel) 10 (2018) 369.

[32] M.A. Fagundes, S.V. Peres, P.P. Assumpção, M.P. Curado, Physical activity and gastric cancer risk: a case-control study in the Amazon region of Brazil, Eur. J. Cancer Prev. 30 (2021) 437–441.

[33] H. Ihira, N. Sawada, T. Yamaji, A. Goto, T. Shimazu, M. Inoue, M. Iwasaki, S. Tsugane, Physical activity and subsequent risk of kidney, bladder and upper urinary tract cancer in the Japanese population: the Japan Public Health Centre-based Prospective Study, Br. J. Cancer 120 (2019) 571–574.

[34] M. Liss, L. Natarajan, A. Hasan, J.L. Noguchi, M. White, J.K. Parsons, Physical activity decreases kidney cancer mortality, Curr. Urol. 10 (2017) 193–198.

[35] Z.Z. Lin, Y.C. Xu, C.X. Liu, X.L. Lu, F.Y. Wen, Physical activity and liver cancer risk: a systematic review and meta-analyses, Clin. J. Sport Med 31 (2021) 86–90.

[36] J. Lee, Associations between physical activity and liver cancer risks and mortality: a systematic review and meta-analysis, Int. J. Environ. Res. Public Health 17 (2020) 8943.

[37] S.E. Baumeister, M.F. Leitzmann, J. Linseisen, S. Schlesinger, Physical activity and the risk of liver cancer: a systematic review and meta-analysis of prospective studies and a bias analysis, J. Natl. Cancer Inst. 111 (2019) 1142–1151.

[38] T. Niedermaier, G. Behrens, D. Schmid, I. Schlecht, B. Fischer, M.F. Leitzmann, Body mass index, physical activity, and risk of adult meningioma and glioma: A meta-analysis, Neurology 85 (2015) 1342–1350.

[39] C.R. Marinac, B.M. Birmann, I.M. Lee, B.A. Rosner, M.K. Townsend, E. Giovannucci, T.R. Rebbeck, J.E. Buring, G.A. Colditz, Body mass index throughout adulthood, physical activity, and risk of multiple myeloma: a prospective analysis in three large cohorts, Br. J. Cancer 118 (2018) 1013–1019.

[40] J. Lee, Physical activity, sitting time, and the risk of ovarian cancer: a brief research report employing a meta-analysis of existing, Health Care Women Int. 40 (2019) 433–458.

[41] T. Wang, D.E. Jake-Schoffman, M.K. Townsend, C. Vinci, W.C. Willett, S. S. Tworoger, Early life physical activity and risk of ovarian cancer in adulthood, Int J. Cancer 149 (2021) 2045–2051.

[42] T. Wang, M.K. Townsend, A.H. Eliassen, K.L. Terry, M. Song, M.L. Irwin, S. S. Tworoger, Prediagnosis and postdiagnosis leisure time physical activity and survival following diagnosis with ovarian cancer, Int. J. Cancer 149 (2021) 1067–1075.

[43] A.S. Zamorano, A.R. Hagemann, L. Morrison, J.A. Lee, L.M. Liao, L.A. Brinton, Y. Park, A.T. Toriola, Pre-diagnosis body mass index, physical activity and ovarian cancer mortality, Gynecol. Oncol. 155 (2019) 105–111.

[44] M.S. Farris, M.H. Mosli, A.A. McFadden, C.M. Friedenreich, D.R. Brenner, The association between leisure time physical activity and pancreatic cancer risk in adults: a systematic review and meta-analysis, Cancer Epidemiol. Biomark. Prev. 24 (2015) 1462–1473.

[45] S.K. Park, J.Y. Jung, C.M. Oh, M.H. Kim, E. Ha, Y. Kim, D.J. Nam, J.H. Ryoo, Daily vigorous intensity physical activity and its preventive effect on pancreatic cancer, Cancer Res. Treat. 54 (2022) 873–881.

[46] J. Sandhu, V. De Rubeis, M. Cotterchio, B.T. Smith, L.E. Griffith, D.R. Brenner, A. Borgida, S. Gallinger, S. Cleary, L.N. Anderson, Trajectories of physical activity, from young adulthood to older adulthood, and pancreatic cancer risk; a

population-based case-control study in Ontario, Canada, BMC Cancer 20 (2020) 139.
[47] L. Wu, W. Zheng, Y.B. Xiang, Y.T. Gao, H.L. Li, H. Cai, X.O. Shu, Physical activity and pancreatic cancer risk among urban Chinese: Results from two prospective cohort studies, Cancer Epidemiol. Biomark. Prev. 27 (2018) 479–487.
[48] D. Schmid, G. Behrens, C. Jochem, M. Keimling, M. Leitzmann, Physical activity, diabetes, and risk of thyroid cancer: a systematic review and meta-analysis, Eur. J. Epidemiol. 28 (2013) 945–958.
[49] B. Chen, Z. Xie, X. Duan, Thyroid cancer incidence trend and association with obesity, physical activity in the United States, BMC Public Health 22 (2022) 1333.
[50] S.C. Moore, I.M. Lee, E. Weiderpass, P.T. Campbell, J.N. Sampson, C.M. Kitahara, S.K. Keadle, H. Arem, A. Berrington de Gonzalez, P. Hartge, H.O. Adami, C. K. Blair, K.B. Borch, E. Boyd, D.P. Check, A. Fournier, N.D. Freedman, M. Gunter, M. Johannson, K.T. Khaw, M.S. Linet, N. Orsini, Y. Park, E. Riboli, K. Robien, C. Schairer, H. Sesso, M. Spriggs, R. Van Dusen, A. Wolk, C.E. Matthews, A. V. Patel, Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults, JAMA Intern Med. 176 (2016) 816–825.
[51] D.W. Voskuil, E.M. Monninkhof, S.G. Elias, F.A. Vlems, F.E. van Leeuwen, A. Task, Force physical, cancer, physical activity and endometrial cancer risk, a systematic review of current evidence, Cancer Epidemiol. Biomark. Prev. 16 (2007) 639–648.
[52] M.F. Leitzmann, C. Koebnick, N.D. Freedman, Y. Park, R. Ballard-Barbash, A. Hollenbeck, A. Schatzkin, C.C. Abnet, Physical activity and esophageal and gastric carcinoma in a large prospective study, Am. J. Prev. Med. 36 (2009) 112–119.
[53] E. Orgel, S.D. Mittelman, The links between insulin resistance, diabetes, and cancer, Curr. Diab Rep. 13 (2013) 213–222.
[54] E. Chiefari, M. Mirabelli, S. La Vignera, S. Tanyolac, D.P. Foti, A. Aversa, A. Brunetti, Insulin resistance and cancer: in search for a causal link, Int J. Mol. Sci. 22 (2021) 11137.
[55] E. Choi, S. Kikuchi, H. Gao, K. Brodzik, I. Nassour, A. Yopp, A.G. Singal, H. Zhu, H. Yu, Mitotic regulators and the SHP2-MAPK pathway promote IR endocytosis and feedback regulation of insulin signaling, Nat. Commun. 10 (2019) 1473.
[56] A. McTiernan, Mechanisms linking physical activity with cancer, Nat. Rev. Cancer 8 (2008) 205–211.
[57] E. Fryk, J. Olausson, K. Mossberg, L. Strindberg, M. Schmelz, H. Brogren, L. M. Gan, S. Piazza, A. Provenzani, B. Becattini, L. Lind, G. Solinas, P.A. Jansson, Hyperinsulinemia and insulin resistance in the obese may develop as part of a homeostatic response to elevated free fatty acids: a mechanistic case-control and a population-based cohort study, EBioMedicine 65 (2021), 103264.
[58] F. Magkos, L.S. Sidossis, Exercise and insulin sensitivity. Where do we stand? You'd better run!, US Endocrinol. 4 (2008) 23–26.
[59] L.B. Borghouts, H.A. Keizer, Exercise and insulin sensitivity: a review, Int J. Sports Med. 21 (2000) 1–12.
[60] G. Perseghin, T.B. Price, K.F. Petersen, M. Roden, G.W. Cline, K. Gerow, D. L. Rothman, G.I. Shulman, Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subjects, N. Engl. J. Med 335 (1996) 1357–1362.
[61] J. Paquin, J.C. Lagace, M. Brochu, I.J. Dionne, Exercising for insulin sensitivity - is there a mechanistic relationship with quantitative changes in skeletal muscle mass? Front Physiol. 12 (2021), 656909.
[62] A.D. Baron, G. Brechtel, P. Wallace, S.V. Edelman, Rates and tissue sites of non-insulin- and insulin-mediated glucose uptake in humans, Am. J. Physiol. 255 (1988) E769–E774.
[63] E. Ferrannini, O. Bjorkman, G.A. Reichard Jr., A. Pilo, M. Olsson, J. Wahren, R. A. DeFronzo, The disposal of an oral glucose load in healthy subjects. A quantitative study, Diabetes 34 (1985) 580–588.
[64] F. Magkos, D.N. Reeds, B. Mittendorfer, Evolution of the diagnostic value of "the sugar of the blood": hitting the sweet spot to identify alterations in glucose dynamics, Physiol. Rev. 103 (2023) 7–30.
[65] J.W. Ryder, A.V. Chibalin, J.R. Zierath, Intracellular mechanisms underlying increases in glucose uptake in response to insulin or exercise in skeletal muscle, Acta Physiol. Scand. 171 (2001) 249–257.
[66] K. Hejazi, G.R. Mohammad Rahimi, S.K. Rosenkranz, Effects of exercise training on inflammatory and cardiometabolic risk biomarkers in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials, Biol. Res. Nurs. (2022), 10998004221132841.
[67] K. Hejazi, A. Wong, Effects of exercise training on inflammatory and cardiometabolic health markers in overweight and obese adults: a systematic review and meta-analysis of randomized controlled trials (in press), J. Sports Med. Phys. Fit. (2022), https://doi.org/10.23736/S20022-24707.23722.14103-23734).
[68] R.J. Verheggen, M.F. Maessen, D.J. Green, A.R. Hermus, M.T. Hopman, D. H. Thijssen, A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: distinct effects on body weight and visceral adipose tissue, Obes. Rev. 17 (2016) 664–690.
[69] F. Magkos, G. Fraterrigo, J. Yoshino, C. Luecking, K. Kirbach, S.C. Kelly, L. de Las Fuentes, S. He, A.L. Okunade, B.W. Patterson, S. Klein, Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity, Cell Metab. 23 (2016) 591–601.
[70] J.F. Meneses-Echavez, E.G. Jimenez, J.S. Rio-Valle, J.E. Correa-Bautista, M. Izquierdo, R. Ramirez-Velez, The insulin-like growth factor system is modulated by exercise in breast cancer survivors: a systematic review and meta-analysis, BMC Cancer 16 (2016) 682.
[71] J.L. Devin, K.A. Bolam, D.G. Jenkins, T.L. Skinner, The influence of exercise on the insulin-like growth factor axis in oncology: physiological basis, current, and future perspectives, Cancer Epidemiol. Biomark. Prev. 25 (2016) 239–249.
[72] J. Frystyk, Exercise and the growth hormone-insulin-like growth factor axis, Med Sci. Sports Exerc 42 (2010) 58–66.
[73] K.L. Campbell, Sex hormones, cancer and exercise training in women, in: A. C. Hackney (Ed.), Sex Hormones, Exercise and Women, Cham: Springer International Publishing Switzerland, 2017, pp. 209–225.
[74] P. Bhardwaj, C.C. Au, A. Benito-Martin, H. Ladumor, S. Oshchepkova, R. Moges, K.A. Brown, Estrogens and breast cancer: Mechanisms involved in obesity-related development, growth and progression, J. Steroid Biochem Mol. Biol. 189 (2019) 161–170.
[75] G. Secreto, A. Girombelli, V. Krogh, Androgen excess in breast cancer development: implications for prevention and treatment, Endocr. Relat. Cancer 26 (2019) R81–R94.
[76] J.F. Randolph Jr., S. Kipersztok, J.W. Ayers, R. Ansbacher, H. Peegel, K. M. Menon, The effect of insulin on aromatase activity in isolated human endometrial glands and stroma, Am. J. Obstet. Gynecol. 157 (1987) 1534–1539.
[77] R. Pasquali, C. Oriolo, Obesity and androgens in women, Front Horm. Res. 53 (2019) 120–134.
[78] K. Ennour-Idrissi, E. Maunsell, C. Diorio, Effect of physical activity on sex hormones in women: a systematic review and meta-analysis of randomized controlled trials, Breast Cancer Res 17 (2015) 139.
[79] C.T.V. Swain, A.E. Drummond, L. Boing, R.L. Milne, D.R. English, K.A. Brown, E. H. van Roekel, S.C. Dixon-Suen, M.J. Lynch, M.M. Moore, T.R. Gaunt, R. M. Martin, S.J. Lewis, B.M. Lynch, Linking physical activity to breast cancer via sex hormones, part 1: the effect of physical activity on sex steroid hormones, Cancer Epidemiol. Biomark. Prev. 31 (2022) 16–27.
[80] E.M. Monninkhof, M.J. Velthuis, P.H. Peeters, J.W. Twisk, A.J. Schuit, Effect of exercise on postmenopausal sex hormone levels and role of body fat: a randomized controlled trial, J. Clin. Oncol. 27 (2009) 4492–4499.
[81] N.I. Williams, H.J. Leidy, B.R. Hill, J.L. Lieberman, R.S. Legro, M.J. De Souza, Magnitude of daily energy deficit predicts frequency but not severity of menstrual disturbances associated with exercise and caloric restriction, Am. J. Physiol. Endocrinol. Metab. 308 (2015) E29–E39.
[82] A.J. Smith, W.R. Phipps, A.Y. Arikawa, M. O'Dougherty, B. Kaufman, W. Thomas, K.H. Schmitz, M.S. Kurzer, Effects of aerobic exercise on premenopausal sex hormone levels: results of the WISER study, a randomized clinical trial in healthy, sedentary, eumenorrheic women, Cancer Epidemiol. Biomark. Prev. 20 (2011) 1098–1106.
[83] A. McTiernan, S.S. Tworoger, C.M. Ulrich, Y. Yasui, M.L. Irwin, K.B. Rajan, B. Sorensen, R.E. Rudolph, D. Bowen, F.Z. Stanczyk, J.D. Potter, R.S. Schwartz, Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial, Cancer Res 64 (2004) 2923–2928.
[84] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, Inflamm., Cancer, Cell 140 (2010) 883–899.
[85] S. Suzuki, R. Katagiri, T. Yamaji, N. Sawada, T. Imatoh, H. Ihira, M. Inoue, S. Tsugane, M. Iwasaki, N. Sawada, S. Tsugane, M. Iwasaki, M. Inoue, T. Yamaji, R. Katagiri, Y. Miyamoto, H. Ihira, S.K. Abe, S. Tanaka, T. Moriya, T. Minamizono, Y. Shirai, H. Kuniyoshi, T. Yoshimi, H. Sonoda, T. Tagami, T. Ando, T. Kimura, Y. Kokubo, K. Yamagishi, T. Mizoue, K. Nakamura, R. Takachi, J. Ishihara, H. Iso, T. Kitamura, I. Saito, N. Yasuda, M. Mimura, K. Sakata, M. Noda, A. Goto, H. Yatsuya, Association between C-reactive protein and risk of overall and 18 site-specific cancers in a Japanese case-cohort (Japan Public Health Center-based Prospective Study Group), Br. J. Cancer 126 (2022) 1481–1489.
[86] X. Wang, Y. Lin, Tumor necrosis factor and cancer, buddies or foes? Acta Pharm. Sin. 29 (2008) 1275–1288.
[87] G. Tian, J. Mi, X. Wei, D. Zhao, L. Qiao, C. Yang, X. Li, S. Zhang, X. Li, B. Wang, Circulating interleukin-6 and cancer: a meta-analysis using Mendelian randomization, Sci. Rep. 5 (2015) 11394.
[88] M. Visser, L.M. Bouter, G.M. McQuillan, M.H. Wener, T.B. Harris, Elevated C-Reactive Protein Levels in Overweight and Obese Adults, JAMA 282 (1999) 2131–2135.
[89] F.R. Greten, S.I. Grivennikov, Inflammation and cancer: triggers, mechanisms, and consequences, Immunity 51 (2019) 27–41.
[90] L.M. Coussens, Z. Werb, Inflammation and cancer, Nature 420 (2002) 860–867.
[91] A.S. Anderson, A.G. Renehan, J.M. Saxton, J. Bell, J. Cade, A.J. Cross, A. King, E. Riboli, F. Sniehotta, S. Treweek, R.M. Martin, A. Anderson, R. Beeken, J. Cade, A. Cross, A. King, R. Martin, G. Mitrou, E. Riboli, J. Saxton, A. Renehan, U.K.N. C. On, behalf of the, C. Nutrition, Cancer prevention through weight control—where are we in 2020? Br. J. Cancer 124 (2021) 1049–1056.
[92] A.E. Hiensch, S. Mijwel, D. Bargiela, Y. Wengstrom, A.M. May, H. Rundqvist, Inflammation mediates exercise effects on fatigue in patients with breast cancer, Med Sci. Sports Exerc 53 (2021) 496–504.
[93] E.A. Murphy, R.T. Enos, K.T. Velazquez, Influence of exercise on inflammation in cancer: direct effect or innocent bystander? Exerc Sport Sci. Rev. 43 (2015) 134–142.
[94] M.R. Shurin, Cancer as an immune-mediated disease, Immunotargets Ther. 1 (2012) 1–6.
[95] J.M. Rice, Immunosuppression, in: R.A. Baan, B.W. Stewart, K. Straif (Eds.), Tumour Site Concordance and Mechanisms of Carcinogenesis, International Agency for Research on Cancer, Lyon, 2019, pp. 159–163.
[96] H. Gonzalez, C. Hagerling, Z. Werb, Roles of the immune system in cancer: from tumor initiation to metastatic progression, Genes Dev. 32 (2018) 1267–1284.

[97] G.J. Koelwyn, X. Zhuang, T. Tammela, A. Schietinger, L.W. Jones, Exercise and immunometabolic regulation in cancer, Nat. Metab. 2 (2020) 849–857.
[98] F.P. de Heredia, S. Gómez-Martínez, A. Marcos, Obesity, inflammation and the immune system, Proc. Nutr. Soc. 71 (2012) 332–338.
[99] D.L. de Frel, D.E. Atsma, H. Pijl, J.C. Seidell, P.J.M. Leenen, W.A. Dik, E.F.C. van Rossum, The impact of obesity and lifestyle on the immune system and susceptibility to infections such as COVID-19, Front Nutr. 7 (2020), 597600.
[100] G.J. Koelwyn, E. Wennerberg, S. Demaria, L.W. Jones, Exercise in regulation of inflammation-immune axis function in cancer initiation and progression, Oncol. (Williston Park) 29 (2015) 908–920.
[101] N.P. Walsh, M. Gleeson, R.J. Shephard, M. Gleeson, J.A. Woods, N.C. Bishop, M. Fleshner, C. Green, B.K. Pedersen, L. Hoffman-Goetz, C.J. Rogers, H. Northoff, A. Abbasi, P. Simon, Position statement. Part one: immune function and exercise, Exerc Immunol. Rev. 17 (2011) 6–63.
[102] D.C. Nieman, L.M. Wentz, The compelling link between physical activity and the body's defense system, J. Sport Health Sci. 8 (2019) 201–217.
[103] M.P. Gustafson, C.M. Wheatley-Guy, A.C. Rosenthal, D.A. Gastineau, E. Katsanis, B.D. Johnson, R.J. Simpson, Exercise and the immune system: taking steps to improve responses to cancer immunotherapy, J. Immunother. Cancer 9 (2021).
[104] B.K. Pedersen, T.C. Akerstrom, A.R. Nielsen, C.P. Fischer, Role of myokines in exercise and metabolism, J. Appl. Physiol. 103 (2007) 1093–1098.
[105] M.C.K. Severinsen, B.K. Pedersen, Muscle-organ crosstalk: the emerging roles of myokines, Endocr. Rev. 41 (2020) 594–609.
[106] C. Hoffmann, C. Weigert, Skeletal muscle as an endocrine organ: the role of myokines in exercise adaptations, Cold Spring Harb. Perspect. Med 7 (2017).
[107] Q. Huang, M. Wu, X. Wu, Y. Zhang, Y. Xia, Muscle-to-tumor crosstalk: the effect of exercise-induced myokine on cancer progression, Biochim Biophys. Acta Rev. Cancer 2022 (1877), 188761.
[108] A. Papadopetraki, M. Maridaki, F. Zagouri, M.A. Dimopoulos, M. Koutsilieris, A. Philippou, Physical exercise restrains cancer progression through muscle-derived factors, Cancers (Basel) 14 (2022).
[109] D.G. Hardie, K. Sakamoto, AMPK: a key sensor of fuel and energy status in skeletal muscle, Physiol. (Bethesda) 21 (2006) 48–60.
[110] H.R. Spaulding, Z. Yan, AMPK and the adaptation to exercise, Annu Rev. Physiol. 84 (2022) 209–227.
[111] A. Gonzalez, M.N. Hall, S.C. Lin, D.G. Hardie, AMPK and TOR: The yin and yang of cellular nutrient sensing and growth control, Cell Metab. 31 (2020) 472–492.
[112] W. Li, S.M. Saud, M.R. Young, G. Chen, B. Hua, Targeting AMPK for cancer prevention and treatment, Oncotarget 6 (2015) 7365–7378.
[113] C.S. Sondergaard, P.N. Esquivel, M. Dalamaga, F. Magkos, Use of antihyperglycemic drugs and risk of cancer in patients with diabetes, Curr. Oncol. Rep. 25 (2023) 29–40.
[114] N. Chomanicova, A. Gazova, A. Adamickova, S. Valaskova, J. Kyselovic, The role of AMPK/mTOR signaling pathway in anticancer activity of metformin, Physiol. Res 70 (2021) 501–508.
[115] G. Rehman, A. Shehzad, A.L. Khan, M. Hamayun, Role of AMP-activated protein kinase in cancer therapy, Arch. Pharm. 347 (2014) 457–468.
[116] Z. Wang, N. Wang, P. Liu, X. Xie, AMPK and cancer, Exp. Suppl. 107 (2016) 203–226.
[117] K.R. White, J. Lu, Z. Ibrahim, P.A. Furth, Enabling exercise prescription for survivors of cancer, Sci. Rep. 11 (2021) 9557.