Influence of Exercise on Inflammation in Cancer: Direct Effect or Innocent Bystander?

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MURPHY, E.A., R.T. ENOS, and K.T. VELÁZQUEZ. Influence of exercise on inflammation in cancer: direct effect or innocent bystander? Exerc. Sport Sci. Rev., Vol. 43, No. 3, pp. 134–142, 2015. We propose the hypothesis that the benefits of exercise on inflammation in cancer are a result of a direct effect on inflammatory cytokines, including interleukin-6, tumor necrosis factor-α, and monocyte chemoattractant protein 1, that are critical for cancer growth as well as a bystander effect of the established relationship between exercise and cancer. Key Words: exercise, physical activity, colon cancer, breast cancer, inflammation

INTRODUCTION

According to the World Health Organization, physical inactivity is the fourth leading risk factor for mortality globally; it is responsible for 6% of all deaths worldwide. Specifically, physical inactivity has emerged as a leading behavioral risk factor for certain cancers. In fact, the American Cancer Society speculates that the increase in cancer incidence among the younger population is, at least in part, caused by a sedentary lifestyle as rates of cancer incidence in individuals younger than 50 yr are on the rise. Conversely, physical activity has been linked to a reduced risk for various cancers; epidemiological studies indicate an inverse association between physical activity and cancer risk, and controlled experiments in rodent models substantiate these claims. For example, our research supports an exercise-induced decrease in tumorigenesis in mouse models of breast cancer and colon cancer (25,28,34). However, the mechanisms responsible for this relationship have not yet been established.

The mechanisms for a beneficial effect of physical activity on cancer risk are likely to be complex and multifaceted; several interrelated mechanisms including adiposity, energy balance, adipokines, insulin, estrogen, and immune function have all been investigated as possible contributing factors. Recently, it has been suggested that a physical activity–induced reduction in inflammation may play a significant role. Inflammation has been linked to every event involved in the development and progression of cancer, and physical activity has been reported to reduce inflammatory processes. Research from our laboratory supports this association as we have seen a decrease in inflammatory mediators with physical activity in rodent models of cancer that has been linked to decreased tumorigenesis (25,28). However, whether the benefits of physical activity on inflammation in cancer are a result of a direct effect on inflammatory pathways that are critical for cancer growth or merely just a bystander effect of the established relationship between physical activity and cancer has not yet been elucidated firmly.

The purpose of this article is to propose the hypothesis that exercise has both a direct and an indirect effect on inflammatory cytokines (interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein 1 (MCP-1)) that leads to decreased tumorigenesis. Although beneficial effects of physical activity have been observed for most, if not all, malignancies, the majority of this evidence to date has been centered on colon cancer and breast cancer. This is not surprising given the prevalence of these cancers and their propensity to be altered by lifestyle factors. Thus, this article will focus largely on the available evidence for the benefits of physical activity on breast cancer and colon cancer.

BENEFITS OF PHYSICAL ACTIVITY ON CANCER

Although not all, the majority of literature supports a beneficial effect of various modes of physical activity on cancer risk. A preponderance of this evidence comes from observational epidemiological studies and controlled experiments in rodent models.
Colon Cancer

Colon cancer is the third most common malignancy and the fourth most common cause of cancer mortality, identifying it as a significant global health concern. Physical inactivity has been reported to account for a substantial number of all colon cancer cases, whereas physical activity has been associated with a reduced risk. In fact, it has been estimated that high levels of physical activity may reduce the risk for colon cancer by as much as 50%. This presents an enormous potential for chemoprevention.

The majority of physical activity studies in rodents have used the ApcMin/+ mouse model of intestinal tumorigenesis, arguably the most widely used genetic mouse model for cancer studies that involve the gastrointestinal tract. Colbert et al. (6) examined possible sex-specific differences for physical activity using this model and found a decrease in polyp development in male, but not female, mice after 8 wk of treadmill running. More recently, Mehl et al. examined the influence of exercise mode on tumorigenesis in the ApcMin/+ mouse by comparing treadmill running with wheel running using both male and female mice. It was reported that 9 wk of treadmill running decreased total intestinal polyps as well as the number of large polyps (>2 mm) after treadmill exercise in male mice but no change in total polyp number (Fig. 1A, B). Similar results were reported by Basterfield and Mathers (5) who found a decrease in the number of large polyps after 10 to 12 wk of treadmill exercise but not for wheel running. These findings for a benefit of treadmill running on tumorigenesis in the ApcMin/+ mouse were corroborated in a chemically induced (azoxymethane) mouse model of colon cancer; it was reported that 6 wk of treadmill exercise suppressed the generation of aberrant crypt foci in the colon (1). However, in contrast to the findings of Baltgalvis et al. (3) and Basterfield and Mathers (5), a recent study reported that voluntary exercise did reduce the number of intestinal tumors in ApcMin/+ as well as azoxymethane/dextran sodium sulfate–treated mice (20).

Based on the available animal literature, it seems that physical activity is effective at reducing tumor size, multiplicity, or both in most, but not all, studies. Furthermore, treadmill running seems to be a more efficient mode of exercise than wheel running for reducing colon tumorigenesis. This effect likely is to be attributed, at least in part, to differences in the intensity of the exercise; although, in general, mice in activity wheels run longer distances compared with their treadmill-running counterparts, the exercise intensity tends to be greater with treadmill running. In the study by Baltgalvis et al. (3), wheel runners ran approximately three times more than treadmill runners but only treadmill running reduced polyp number. Another possible explanation for this disparity could be changes in energy balance. In the same study, wheel runners consumed approximately 25% more food than the control mice, whereas there was no difference in calorie consumption of treadmill mice, placing them in a state of negative caloric balance (3), which is known to decrease tumorigenesis. Interestingly, there may be interactions between physical activity and sex in the ApcMin/+ mouse because several studies have reported the benefits of physical activity in male but not female mice (3,6). However,
the mechanisms for these effects were not explored in the aforementioned investigations. Although estrogen may be an obvious potential mechanism, as it stands, its role in colon cancer is unclear; some studies have implicated estrogen as being protective in colon cancer whereas others have suggested it to be an independent risk factor. Thus, this makes it difficult to speculate on any interaction between physical activity and estrogen in colon cancer. Nonetheless, the current literature indicates that sex is an important factor when investigating the effects of physical activity on tumorigenesis, at least in the ApcΔmin mouse.

The human data mostly have mirrored the animal findings. In the Melbourne Collaborative Cohort Study, a prospective cohort study of 41,528 Australians, participants with incident cases of colorectal cancer were interviewed about their physical activity. Among the 526 identified cases of colorectal cancer, those who had engaged in physical activity had an improved disease-specific survival (15). Similarly, a recent study in a multiethnic colon cancer screening population of 982 patients examined the relationship between exercise and the prevalence of polyps. It was reported that exercising for 1 h wk⁻¹ or more was associated with a lower prevalence of polyps and adenomas when compared with those who exercised less or not at all (33). Although the majority of the literature supports an inverse correlation between physical activity and colon cancer risk, there is a literature base that has failed to report a relationship. For instance, Meyerhardt et al. (26) examined colorectal cancer-specific and overall mortality according to predefined physical activity categories before and after diagnosis and by change in activity after diagnosis by a prospective observational study of 573 women with stage I to III colorectal cancer. It was reported that prediagnosis physical activity was not predictive of mortality (26). Interestingly, however, increasing levels of exercise after diagnosis of nonmetastatic colorectal cancer reduced cancer-specific mortality (26). To address the inconsistencies in human literature, a recent meta-analysis of seven prospective cohort studies was performed. It was concluded that physical activity, both prediagnosis and postdiagnosis, is associated with better prognosis of colorectal cancer (17).

Although animal data and epidemiological literature largely support an inverse relationship between physical activity and risk for colon cancer, there is an overall lack of clear evidence on the specific details underlying the optimal mode, intensity, and duration of exercise, which may explain the inconsistencies across studies. Furthermore, studies using a randomized controlled trial design to determine the benefits of physical activity in patients with colorectal cancer currently are nonexistent.

Breast Cancer

Breast cancer currently is the second most commonly diagnosed cancer and the leading cause of cancer-related death in women in the United States. Undoubtedly, there is an underlying genetic origin to certain breast cancer cases. However, many, and perhaps the majority of incidents, are linked to behavioral or lifestyle risk factors. Accumulating epidemiological evidence, as well as controlled experimental studies using mouse models, indicates a relationship between physical activity and reduced breast cancer risk.

The most common rodent model used in physical activity prevention studies has been chemically induced mammary tumorigenesis (e.g., 7,12-dimethylbenzanthracene, N-nitrosomethylurea). A large body of this work has been done by Zhu et al. (38), whose work has demonstrated convincingly that voluntary wheel-running activity is effective at reducing breast cancer incidence, multiplicity, and burden. However, although the majority of studies have reported a positive influence of exercise training on tumor number, growth, and incidence using chemically induced models, there also have been a number of studies that have reported negative findings. Genetically engineered mouse models to study the relationship between exercise and breast cancer risk have been used in several recent studies; these models are thought to mimic the spontaneous development of breast cancer in humans more closely. We used the C3(1)SV40Tag mouse model of breast cancer to examine the effects of exercise on mammary tumorigenesis. Our initial study incorporated a treadmill-running protocol where we reported a reduction in tumor number and volume with exercise (28) (Fig. IC, D). We followed this up with a second study to examine the influence of voluntary wheel-running activity on mammary tumorigenesis using the same mouse model. Voluntary wheel running reduced tumor volume per tumor (~40%) but interestingly was associated with increased tumor number (34). To our knowledge, there have been only two other studies that have examined the effects of exercise on breast cancer using genetically engineered mouse models (7,12). Goh et al. (12) examined the effects of voluntary wheel running on tumor progression in the transgenic polyoma middle T oncoprotein (PyMT) mouse model of invasive breast cancer. Voluntary wheel running significantly reduced tumor sizes compared with nonrunners after 3 wk of running, and the distance run was correlated negatively with tumor size (12). On the contrary, Colbert et al. (7) reported a detrimental effect of both treadmill and wheel-running activity on mammary tumorigenesis in a p53-deficient (p53⁻/⁻):MMTV-Wnt-1 mouse model of breast cancer. Treadmill running increased the rate of tumor development and the proportion of mice with multiple carcinomas and decreased survival time, whereas wheel running resulted in an increased incidence and multiplicity of mammary carcinomas (7), which may have resulted from an exercise-induced increase in the expression of the Wnt-1 transgene or an interaction between p53 dosage and exercise (7).

In general, the majority of the available animal data support the notion that physical activity decreases the risk for breast cancer. Furthermore, it seems that increasing exercise intensity enhances the likelihood of inhibiting tumorigenesis, whereas lower exercise intensities result in inhibition, no effect, or enhancement of a tumorigenic response. Most of the data supporting these conclusions come from studies using chemically induced mammary tumorigenesis where any reported inconsistencies likely are caused by methodological issues with respect to the dose, timing, route, and type of carcinogen. This is not surprising given the relative dearth of studies using transgenic animals; appropriate transgenic models for exercise studies have yet to be considered extensively as to date only three models, which have resulted in inconsistent findings, have been used.

There have been a large number of epidemiological investigations that have explored the relationship between breast cancer and physical activity. On average, a 25% reduction in
breast cancer risk for physically active women compared with the least active women has been estimated. These associations appeared to be the strongest for recreational activity, activity sustained across the lifetime or done after menopause, and activity that is of moderate to vigorous intensity and performed regularly. For example, the relationship between physical activity and breast cancer risk was evaluated in 3424 women of the French E3N cohort. A linear decrease in the risk of breast cancer was observed with increasing amounts of moderate and vigorous recreational activities (36). Similarly, using NHANES data, it was found that moderate- to vigorous-intensity activity has significant inverse associations with biomarkers associated with breast cancer risk, whereas sedentary time may contribute independently to breast cancer risk (22). Furthermore, there is a growing body of literature that supports an improved overall and breast cancer risk, whereas sedentary time may contribute

vigorous recreational activities (36). Similarly, using NHANES data, it was found that moderate- to vigorous-intensity activity has significant inverse associations with biomarkers associated with breast cancer risk, whereas sedentary time may contribute independently to breast cancer risk (22). Furthermore, there is a growing body of literature that supports an improved overall and breast cancer-specific survival for women who are physically active. In one study, a cohort of 1231 women diagnosed with breast cancer was followed for a minimum of 8.3 yr for any cancer progression and a minimum of 10.3 yr for deaths (10). Both moderate- and vigorous-intensity activity decreased the risk of breast cancer death and moderate-intensity activity decreased the risk of a recurrence, progression, or new primary cancer (10). Of further significance is the emerging evidence that supports a benefit of physical activity on the side effects of anticancer therapy, radiation, surgery, and recovery after chemotherapy; in general, physical activity has been reported to increase quality of life during various breast cancer treatment regimens.

Based on the epidemiological evidence, it is clear that moderate to vigorous activity provides the greatest benefit to breast cancer risk and breast cancer–specific survival. However, specific details on the optimal mode, intensity, and duration of exercise as well as the timing of exercise in relation to menopause are still lacking. Furthermore, there is a clear need for randomized controlled trials to substantiate the findings reported in the epidemiological and animal literature.

ANTINFLAMMATORY EFFECTS OF PHYSICAL ACTIVITY IN CANCER

Given the well-documented benefits of physical activity on tumorigenesis, a quest for the mechanisms responsible for this effect has ensued. However, this has not transpired without challenges. Namely, the mechanisms responsible for the benefits of physical activity on cancer risk are complex and likely to be multifaceted given the very broad pleotropic effects of exercise. Thus, several interrelated factors including adiposity, energy balance, insulin, adipokines, estrogen, and immune function as well as inflammation likely are to be involved, making it difficult to determine the relative contribution of each mechanism.

Inflammation and Cancer

Inflammation plays a significant role in the development and progression of cancer (13). Data from our laboratory support this notion. For instance, we recently examined the timing and magnitude of inflammation in relation to tumorigenesis in the ApcMin/+ mouse at 8, 12, 16, and 20 wk of age (23). We reported an increased mRNA expression of MCP-1, IL-1β, IL-6, and TNF-α in the mucosal tissue that is evident at 12 wk of age (Fig. 2) and is consistent with the increase in polyp number that occurs at this time (23). Further increases in the inflammatory response (i.e., during wk 16 and 20) seemed to be associated with a change in polyp size but not number (23). Of the inflammatory mediators measured, MCP-1 seemed to be the most responsive (23). We believed that this warranted further investigation into the role of this chemokine on inflammatory responses and tumorigenesis in this model. Therefore, we performed a follow-up study to examine the role of MCP-1 on inflammation and tumorigenesis by crossing the ApcMin/+ mouse with an MCP-1–knockout mouse (24). MCP-1 deficiency decreased overall polyp number and abundance of large polyps, which was consistent with a reduced expression of inflammatory cytokines in the intestinal tissue and polyps as well as circulating levels of IL-6 (24).

We performed a similar study to examine the role of MCP-1 on breast cancer in the C3(1)SV40Tag mouse model of mammary tumorigenesis using a pharmacological approach (35). To inhibit MCP-1, we used bindarit (2-(((1-benzyl-indazol-3-yl) methoxy)-2-methyl propionic acid), a well-characterized small synthetic indazolic derivative best known for its transcriptional inhibition of the monocyte chemoattractant subfamily of CC chemokines including MCP-1/CCL2 (27). Bindarit treatment reduced tumor number but did not affect tumor size, tumor weight, or tumor latency in C3(1)/SV40Tag mice (35). Within the tumor, mRNA expression of bindarit’s primary targets, MCP-1 and IL-12/p35, was significantly decreased, and this was consistent with trends for reduced expression of TNF-α, IL-6, and IL-10 (35).

Given the well-established role of inflammation in cancer, it has become a target for cancer prevention and therapy. As such, we recently have seen an increase in the investigation of antiinflammatory chemoprevention strategies in cancer including physical activity.

Interleukin-6

IL-6 is a cytokine that has been associated with poor prognosis in various cancers including that of the colon and breast. For example, Baltgalvis et al. (4) used IL-6–knockout mice and plasma-based IL-6 overexpression to examine the role of IL-6 in tumorigenesis and reported that ApcMin/+IL-6-/- mice had a decrease in overall polyp number, whereas overexpression of IL-6 increased polyp burden (4). Similarly, we have documented an increase in circulating levels of IL-6 in a mouse model of breast cancer (28).

Several studies have addressed the effects of physical activity on IL-6 in colon cancer models. A study by Mehl et al. reported a decrease in circulating IL-6 in male ApcMin/+ mice after treadmill running that was associated with a decreased polyp number. Interestingly, IL-6 also was decreased in male mice exposed to wheel-running activity as well as female mice that underwent both treadmill exercise and wheel-running activity, but there was no benefit on tumorigenesis in these treatment groups implicating that exercise can decrease IL-6 independent of any effects on tumorigenesis. Given the age-induced increase in intestinal inflammation and associated elevated risk for colon cancer, a recent study examined the
effects of voluntary wheel running on IL-6 expression in intestinal lymphocytes in older adult mice (31). Although other inflammatory mediators were reduced with voluntary exercise, there was no reported reduction in IL-6 (31). To our knowledge, there are no studies that have examined IL-6 levels after an exercise intervention in colon cancer patients or survivors.

Although limited, there have been a few investigations that have examined the relationship between exercise, IL-6, and breast cancer. For example, we examined the effects of daily treadmill running on circulating IL-6 in the C3(1)SV40Tag mouse model of breast cancer and found a significant decrease in plasma IL-6 after 20 wk of training (Fig. 3A), which was consistent with a reduction in tumor number and volume (28). Similarly, it has been demonstrated that voluntary wheel-running activity is effective at reducing plasma IL-6 in a chemically induced rat model of breast cancer (37,38). Although the limited animal literature shows positive findings, the available epidemiological evidence is less convincing. For example, the Yale exercise and survivorship study investigated the effects of 6 months of aerobic exercise on IL-6 levels in postmenopausal breast cancer survivors (19). Although there were no significant effects of the exercise intervention on circulating IL-6 levels, interestingly, secondary analyses revealed a significant reduction in IL-6 among exercisers who reached 80% of the intervention goal compared with those who did not (19).

**Tumor Necrosis Factor-α**

Another inflammatory cytokine with protumorigenic properties is TNF-α, although its role remains somewhat controversial. Based on the available literature, it seems that TNF-α is more detrimental during the early stages of carcinogenesis and at lower sustained doses, whereas antitumor effects have been reported at higher doses. Nonetheless, the majority of evidence supports a negative effect of TNF-α in tumorigenesis given its role in promoting inflammatory processes.

Like IL-6, some, but not all, studies have reported a reduction in TNF-α with physical activity. In a mouse model of chemically induced colon cancer, it was reported that 6 wk of regular treadmill exercise results in a decrease in TNF-α in the colon and plasma, and this was consistent with a suppression of aberrant crypt foci (1). Similarly, it was found that voluntary wheel running reduces TNF-α expression in intestinal lymphocytes of older adult mice, which may have implications for colon cancer (31). Although the sample size was relatively
small, a 12-wk home-based exercise program resulted in a significant decrease in circulating TNF-α levels in patients with stage II to III colorectal cancer (21).

In a chemically induced rat model of breast cancer, it was reported that voluntary wheel running reduced tumor burden, which was associated with a decrease in circulating levels of TNF-α among other cancer-related biomarkers (38). In a recent pilot study, stage I, II, or IIIA breast cancer survivors were randomized to either a 3-month physical activity intervention or control treatment. After the exercise intervention, there was a small but nonsignificant decrease in TNF-α (32). In the Yale exercise and survivorship study, postmenopausal breast cancer survivors underwent a 6-month aerobic exercise regimen, but there were no reported changes in TNF-α levels (19). Similarly, in the Alberta Physical Activity and Breast Cancer Prevention Trial, a randomized control trial in healthy postmenopausal women to examine the effects of moderate to vigorous aerobic exercise on circulating inflammatory markers, there was no statistically significant decrease in TNF-α after 12 months on the exercise intervention (11). Similar to IL-6, the animal data support an inverse relationship between physical activity and TNF-α, whereas the human literature remains largely inconsistent.

Monocyte Chemoattractant Protein 1

Although the evidence for a role of MCP-1 in cancer is considerable, there currently is very limited work on the relationship between exercise and MCP-1 in cancer models. In fact, to our knowledge, any investigation of an effect of exercise on MCP-1, at least for colon cancer and breast cancer, is limited to work performed in our laboratory. We examined the effects of exercise on macrophage chemoattractants, including MCP-1, in the ApcMin/+ mouse model of intestinal tumorigenesis. Treadmill exercise for 12 wk resulted in a decrease in the number of large polyps, but there was no significant decrease in MCP-1 or any of the other chemotactic proteins measured (25). On the contrary, we recently examined the effects of daily treadmill running on circulating MCP-1 levels in the C3(1)SV40Tag mouse model of breast cancer and found a significant decrease in plasma MCP-1 after 20 wk of training (Fig. 3B), which was linked to a reduction in tumor number and volume (28). Additional studies in rodents as well as clinical investigations are necessary to establish a potential relationship between physical activity and MCP-1 in cancer.

Direct Effects and/or Innocent Bystander?

Although the available studies are limited and not all investigations have reported a decrease in inflammatory mediators with physical activity, there certainly is evidence to support the hypothesis that the benefits of physical activity on tumorigenesis are associated with a decrease in inflammatory markers. What is not clear, however, is whether these benefits are a result of a direct effect on inflammatory pathways that are essential for tumorigenesis or purely just a bystander effect of the recognized relationship between physical activity and cancer?

The evidence from controlled experimental studies in animals to date is limited to data that simply support an association between physical activity, reduced tumor burden, and decreased inflammation. Mechanistic studies to determine whether physical activity is influencing tumorigenesis via a direct effect on certain inflammatory mediators are just not available. The human literature is even scarcer with the majority of the few existing studies limited to measurement of inflammatory mediators in cancer survivors after physical activity interventions. There is, however, a literature base to support an anti-inflammatory effect of physical activity in nondiseased models. Thus, it is certainly possible that physical activity directly can influence inflammatory pathways. However, given the very broad pleiotropic effects of physical activity, it is likely that physical activity is affecting several interrelated pathways that are known to influence cancer development and progression (Fig. 4).

INTERRELATED MECHANISMS FOR BENEFITS OF PHYSICAL ACTIVITY IN CANCER

Adiposity

Adiposity, energy balance, insulin, adipokines, estrogen, and immune function all have been reported to affect the tumorogenic response and are known to be altered by physical activity. Interestingly, these factors have been shown to influence the inflammatory response and may support a possible indirect effect of physical activity on inflammatory processes in cancer.

Adiposity

Both the animal and epidemiological literature supports an association between obesity and cancer risk; this relationship is particularly strong for colon cancer and for postmenopausal breast cancer (14). We have reported previously that the
high-fat diet–induced increase in body weight, body fat percent, and fat mass in the Apc<sup>Min/+</sup> mouse is associated with an increase in the number of large polyps (9).

A likely contributor to the benefits of exercise on cancer risk is alterations in body composition and specifically a reduction in fat mass. In a rodent study, we reported an exercise-induced reduction in body weight in a mouse model of breast cancer, and this was consistent with a decrease in tumor number and volume (28). Although we did not explore the relative importance of changes in body composition on cancer progression, the findings support a potential role for reduced body weight as a possible contributing factor for the deceased tumor burden. Furthermore, we recently reported a significant decrease in waist-to-hip ratio in a population of obese individuals after a 1-yr diet and physical activity intervention (16). Importantly, in both of the aforementioned studies, we report a decrease in circulating inflammatory mediators that may be linked to the exercise-induced changes in body composition. Given the strong associations between obesity and cancer risk, a physical activity-induced decrease in adiposity is a very likely contributor to the benefits of exercise on tumorigenic responses and may influence the reported anti-inflammatory effects of exercise in cancer models.

**Energy Balance**

The concept of energy balance, whether an individual consumes and expends the same amount of energy, has been associated with disease risk, including cancer. Energy balance has become an important concept in the etiology of cancer given its association with adiposity and adiposity-related inflammation. Thus, high-energy intake may increase the risk of colon and breast cancers, whereas high-energy expenditure has been associated with a reduced risk.

Energy is expended through the basal metabolic rate, the thermic effect of digesting food, and physical activity. Thus, increasing energy expenditure through physical activity is likely to decrease cancer risk. As elimination of excess fat is linked to a decrease in proinflammatory cytokines, this process will result almost certainly in decreased inflammation. Using a rat model of chemically induced breast carcinogenesis, the effects of diet restriction and different intensities of wheel-running activity were compared to examine the effects of limiting energy availability on breast cancer (38). The energetics interventions inhibited the carcinogenic response, resulting in a reduction in cancer incidence, multiplicity, and burden (38), which was associated with a decrease in inflammatory cytokines. However, given the broad pleotropic effects of exercise, it is difficult to independently attribute energy expenditure to the findings on carcinogenesis and inflammation. Nonetheless, energy expenditure through physical activity is likely to influence cancer risk, which may be mediated through a reduction in inflammatory processes.

**Insulin**

Imbalances in metabolic mediators have been linked to a heightened risk for cancer. Evidence indicates that insulin resistance and its accompanying pathological conditions are associated with various cancers. Interestingly, there is now evidence to suggest that insulin resistance may even promote inflammation. Thus, improvements in insulin signaling may decrease inflammation.

Aerobic activity is known widely to improve metabolic outcomes including insulin resistance, fasting blood glucose and insulin, and insulin-like growth factors (IGF) and their binding proteins. A recent study reported that IGF-1 levels are lowered and specifically the IGF/IGFB3 ratio in a carcinogenic mouse model of colon cancer, which was associated with decreased tumorigenesis (20). Similarly, Zhu et al. (38) reported a decrease in IGF-1 and IGFB3 levels after wheel running in rats exposed to a breast cancer carcinogen, which
Interestingly were associated with a decrease in inflammatory mediators. Of the biomarkers measured, the IGF/IGFBP3, IGF-1, and IGFBP3 levels were considered to be of great value in predicting cancer outcomes, along with the adipokines (38). Given the ability of physical activity to improve insulin-related biomarkers, it is likely that these factors contribute to the benefits of exercise on cancer risk that may be linked to reduced inflammation.

**Adipokines**

Adipose-derived hormones (adipokines) have been identified as potential mediators of the effects of exercise on cancer risk. Adiponectin has been reported to be associated negatively with cancer risk, whereas leptin has been linked to increased risk for cancer. Both of these adipokines are known to be influenced by exercise and thus have the potential to play a role in exercise-induced modulation of tumorigenic responses. Furthermore, there is evidence to support a link between adipokines and inflammation in cancer models.

Several studies have examined the benefits of exercise on adiponectin in the settings of breast cancer, whereas investigations in colon cancer virtually are nonexistent. In a rat model of breast cancer, increased adiponectin was associated with reduced tumor burden after wheel-running activity (38). Inflammatory outcomes also were reported to be decreased in this study (38). In a pilot study of breast cancer survivors, a decrease, albeit nonsignificant, in adiponectin was found after a 3-month physical activity intervention (32). For leptin, Colbert et al. (6) reported an increase in leptin, which was associated with a reduced polyp number in male ApcMin/+ mouse. Furthermore, leptin has been implicated as an important biomarker in predicting the carcinogenic response after wheel running in a rat model of breast cancer (38). Based on the available evidence, it is clear that adipokines are linked to the tumorigenic response and even possible that modulation of the adipokine profile via physical activity may lead to a reduction in inflammatory processes.

**Estrogen**

There is a large literature base dedicated to the investigation into the role of estrogen on various cancers. In general, higher levels of endogenous estrogens are associated with an increased risk for postmenopausal breast cancer. The data for colon cancer risk are less clear; although some studies have implicated estrogen as being protective in colon cancer, others have conveyed no change. Future investigations using knockout mice and/or antibodies are necessary to examine a mechanistic relationship between estrogen and cancer risk.

**Immune Function**

Immune evasion is an emerging hallmark of cancer. A competent immune system is necessary not only for prevention of cancer development but also to slow its progression. This has led to a large body of research devoted to investigating immunotherapy for cancer. Interestingly, physical activity has been reported to enhance immune function and thus may be a potential mechanism for its benefits on cancer risk. As inflammation is an important aspect of the immune response, it is likely to be altered with changes in immune function.

We previously have reported a benefit of exercise on immune function in various mouse models, including cancer models. For example, we have shown that moderate exercise can increase the cytotoxicity of macrophages to B16 melanoma cells and decrease their metastatic spread in vivo (29). Similarly, we have reported an increase in natural killer cell activity with moderate exercise training (8). Thus, immune system alterations with exercise are likely to be a contributing factor in reducing cancer risk.

**Other Factors**

Given the broad pleotrophic effects of physical activity, other factors also likely are to play a role in the benefits of exercise on tumorigenesis. For example, it has been postulated that the exercise-induced production of novel myokines such as secreted protein acidic and rich in cysteine (SPARC) can alter the mechanisms involved in cancer pathogenesis. A recent study reported that low-intensity exercise reduced aberrant crypt foci growth in a chemically induced mouse model of colorectal cancer. However, these effects were lost in SPARC-deficient mice, implicating a role of this myokine on the benefits of exercise in colorectal cancer. Furthermore, exercise enhanced apoptosis in colon mucosal cells, but again, these effects were not evident in SPARC-deficient mice (2). Furthermore, in a prostate cancer model, it has been reported that exercise can alter genes responsible for metastatic dissemination in the primary tumor with a shift toward a suppression of distant metastasis (18). These reports provide further evidence for the complexity of the interaction between physical activity and cancer risk.

**CONCLUSIONS**

The evidence to support a benefit of exercise on cancer risk is convincing, especially for breast cancer and colon cancer, both of which heavily are influenced by lifestyle factors. What is less clear are the mechanisms that are responsible for these effects. Based on the animal literature, we are limited to conclude that the current evidence merely supports a link between physical activity, reduced tumor burden, and decreased inflammation. The human literature is less obvious, with some studies reporting reduced inflammation, whereas others convey no change. Future investigations using knockout mice and/or antibodies are necessary to examine a mechanistic link between physical activity, inflammation, and cancer. What will be more challenging will be the determination of...
whether physical activity is influencing tumorigenesis via a direct effect on inflammatory pathways as opposed to indirect effects as discussed earlier. Given that many of the interrelated factors that are affected by exercise can, in turn, influence inflammatory processes and tumorigenesis, it will be difficult to attribute these potential mechanisms independently to the findings on inflammation and carcinogenesis. The likely scenario is that exercise is affecting several, if not all, of these interrelated pathways including inflammatory pathways, adiposity, energy balance, adipokines, insulin, estrogen, and immune function, leading to a decrease in inflammation and subsequent tumorigenesis.

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