



The Pioneering Hypotheses of Exercise Effects on Tumor Growth - Systematic Review

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Abstract

Introduction: Over the past seventy years, the relationship between physical exercise (PE) and cancer has been researched extensively, but the biological changes associated with PE and its probable influence on the tumor growth and patient survival are still uncertain.

Aim: The objective of this study was to identify and analyze pioneering hypotheses in relation to the effect of PE and tumor growth in experimental animal models.

Methods: We conducted a descriptive historic review of the literature through PRISMA protocol by Virtual Health Library on electronic databases MEDLINE, LILACS, IBECs and SciELO. The inclusion criterion was experimental studies that submitted animals to exercise and sought to explicate the relationship between exercise and tumor growth through biological mechanisms.

Results: The pioneering hypotheses indicated that PE effects on tumor growth were due to energy-related metabolic factors which inhibit tumor growth. PE inhibits tumor growth through (a) alternative consumption of energy otherwise available in the development of tumor cells or (b) secretion of substances produced by muscle contraction in fatigue. However, there are other determining factors related to life experiences.

Conclusion: There is preliminary evidence of PE being beneficial in tumor inhibition, but acknowledge that the mechanisms involved in the effects of exercise on tumor growth remain uncertain, possibly due to the wide variety of tumor types and biological intra-individual variation.

Keywords: Neoplasms; Cancer; Physical exercise

Introduction

Cancer is a major public health problem worldwide and is the second leading cause of death in the United States. In 2016, the 1,685,210 estimated new cases of invasive cancer were reported in the US [1]. Cancer is widely considered to be a cell-autonomous genetic disease that results from alterations in oncogenes, tumor-suppressor genes and genome-stability genes [2]. Basically, tumor cells acquire a common set of properties including unlimited proliferation potential, self-sufficiency in growth signals, and resistance to anti-proliferative and apoptotic cues [3].

Over the past seventy years, researchers have investigated the relationship between cancer and physical exercise (PE) [4]. In the last three decades, changes in the areas of oncology and kinesiology have resulted in rapid advances in interventions for cancer survivors. Some of this work has focused upon PE in prevention and rehabilitation [5].

Several experimental studies of interventions have been developed with human beings. These attest to various PE protocols, and include evidence of feasibility and physical exercise guidelines

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Table 1: Study, objectives, methods, main results and pioneering hypothesis of experiments with animal models on the effects of exercise on development of selected cancer in MEDLINE, LILACS, and SciELO IBECs.

STUDY	AIM	METHOD	OUTCOMES	PIONEERING HYPOTHESIS
Rusch, Kline [21]	To investigate the influence of forced exercise on the rate of tumor growth on a series of male mice	EG1: 16h continuously in rotating cages x 8h resting (1 week before TI); EG2: 2h exercising x 1h resting throughout 24h (2 weeks after TI); CG: no exercise.	EG1, EG2 < tumor growth trend than CG.	Tumor cells do not develop with little or no power available, after the body suppress the energy needed for exercise.
Rashkis [22]	To investigate the effect of stress on inoculated tumor inhibition in Swiss mice	Swim for 14 days; 2 types of tumours with different time of swimming.	EG > 20% lifetime than CG.	The development of tumors is hindered when the body is subjected to a systematic stress - EF, having catabolic character and therefore inhibitor.
Hoffman et al. [23]	To determine whether a mitosis-inhibiting substance produced by fatigued muscles could inhibit tumor growth in male Wistar rats.	EG: daily for 3 wk: electric shock stimulated (20 feet) + 20 min swim + revolving drum at nights (5.4 miles per 12h)	The tumor weight in EG was lower than in the control group, indicating lower cancer development in EG.	Tumor inhibition occurs due to a substance produced by muscle fatigue, not only related to energy imbalance.
Newton [24]	How differential early treatment would compare and interact with later exercise in affecting the response to implanted tumor cells in rats	CG and EG with and without stress, subjected to exercises prior and post TI	Rats to exercise and stress had lower tumor development.	The development of tumor is modifiable by conditioning factors in the life experience of the bodies and inducing agents or tumor inhibitors (PE).

PE: Physical Exercise; EG: Experimental Group; CG: Control Group; h: Hours; TI: Tumor Inoculation; wk = Weeks

for cancer patients and survivors [4,6-13]. However, the primary effects of exercise on tumor growth and progression remain relatively poorly understood. Primary effects that have been identified include biological changes in tumor cells or the tumor micro-environment that are a direct consequence of exercise, such as alteration in oxidative status and gene expression [14]. In animal models, exercise has been show influence modulation of the micro-environment of mammary tumor development [15]. The authors found that exercise training promoted tumor vascularization and growth in tumors with higher volume, but reduced the number of mammary tumors and aggressiveness, and increased latency period in female Sprague-Dawley rats. This study indicates that, although involved complex and poorly understood variables (such as tumor volume), there is a preliminary indication of the benefits of PE [16].

We consider that the elucidation of the molecular mechanisms underlying the association between exercise and cancer is of paramount importance in optimizing the safety and efficacy of exercise in cancer control [17]. It may have important implications for inhibiting tumor metastasis and improving the efficacy of conventional cancer therapies [17]. The molecular mechanisms underlying the exercise-tumor-genesis relationship are complex, and proposed explanations remain speculative [17].

In the context of the recent and rapidly accruing research in this area, it is timely to review previous findings and addressing future directions. On this basis, our aim was to explore the pioneering hypotheses and related findings published on the effects of exercise on tumor growth in experimental animal models through a systematic review.

Method

This is a descriptive historic review that analysed the primary hypotheses published in literature about the effect of exercise on tumor growth in experimental animal models. We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) protocol on MEDLINE, LILACS, IBECs eSciELO databases throughVirtual Health Library – Regional Portal. We searched articles published from 1981, the point from which the original and first study with cancer patients and exercise was undertaken [5]. The primary search terms used were “cancer” and interchangeable terms such as “tumor” and “neoplasm”, combined with secondary terms

“physical exercise”, “exercise” and “physicalactivity” in title, abstract or subject.

The inclusion criterion was experimental studies that submitted animals to exercise and sought to explicate the relationship between exercise and tumor growth through biological mechanisms. The search also included references of selected studies and in *Cancer Research, Science e Psychological Reports* journals.

Results

We initially identified 352 articles. Four pioneer experimental studies using animal models, and which focused upon the relationship between exercise and tumor growth were selected for this review (see Figure 1).

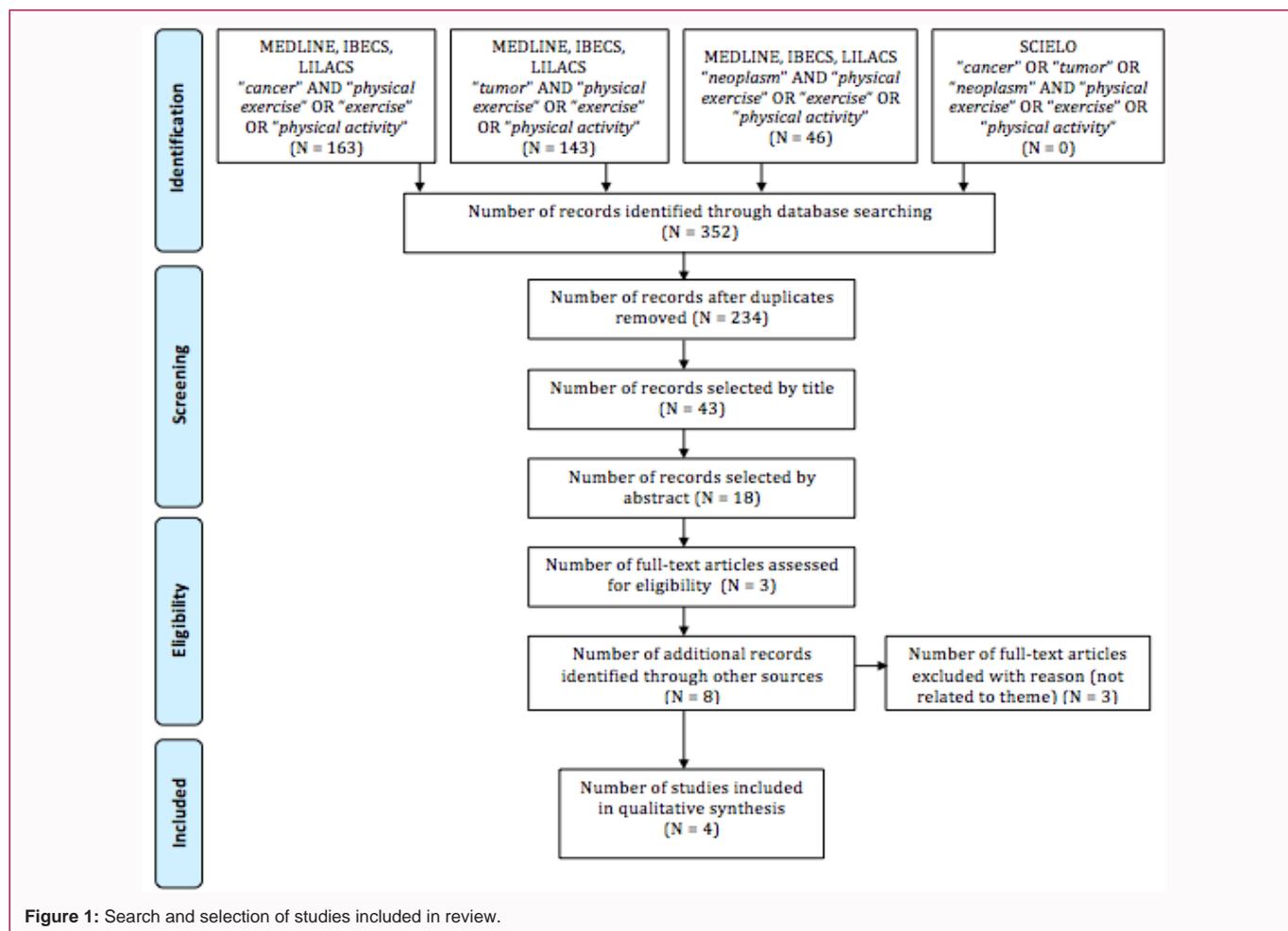
PRISMA model adapted from Liberati et al. [18].

The primary hypotheses used in animal models that considered the relationship between exercise and cancer were published between 1944 and 1962. The studies used mice and rats as models and are described below (see Table 1).

Rusch, Kline - 1944

The first publication on the subject of exercise effects on tumor growth was Rusch and Kline [19] study in 1944. The authors investigated the influence of forced exercise on tumor growth rates in mice bearing transplantable tumors. The authors believed it would be possible to inhibit tumor growth by subjecting animals to forced exercise. The exercise, and consequently energy bodily requirements, were found to inhibit the neoplastic cell development because there remained little, or no excess energy. Young adult ABC male mice were divided into two groups: one group was subjected to forced exercise, and the other group was control situation. After a preliminary 1 or 2 weeks-period of exercise, Rusch and Kline²¹ subcutaneously inoculated transplantable fibrosarcoma on the abdominal region in all mice. The original fibrosarcomas were obtained from the ear of a mouse, which received continued ultraviolet irradiation.

The experiment was conducted with two series of mice. In the first series, 100 mice were divided into two groups of 50 each (exercise and control). Exercise was induced by rotating cages for 16 hours continuously and was followed by a rest period for the remaining 8 hours of the day. In this series, the exercise was started 1 week before



the mice were inoculated with the sarcoma. In the second series, composed of 40 mice in each group, the exercising group was rotated for 2 hours at a time with an alternate 1-hour rest period throughout the 24-hour period. The exercise was started 2 weeks before tumor inoculation and continued for the duration of the experiment. The results showed more retardation of tumor growth trend in exercise groups than in control groups. In the first series, the tumor size was 0.43 to 2.42 units, while the second series was 0.16 to 1.53 units. The control groups showed improvement of 0.58 to 3.21 and 0.28 to 2.33 units, respectively. The hypothesis of Rusch and Kline was confirmed, and they concluded it was possible to inhibit the tumor growth in animals through exercise because of the utilization of excess energy [19].

Rashkis - 1952

The second identified published study was Rashkis [19], in 1952. The study investigated the effect of stress (forced swimming) on inoculated tumor inhibition in Swiss mice. The hypothesis was that organisms under stress would show less tendency to develop experimentally produced tumors than normal controls because of stress catabolic (inhibitor effect). In the first tests, 25-young adult male Swiss albino mice made up the experimental group. These were submitted to 17 days of forced swimming with progressive duration (i.e. from one and a half hour to four hours daily, with 15 minutes increased per day). After intraperitoneally tumor inoculation the mice were forced to swim 34-hours during 14 days.

The duration of sessions was decreased from four and a half

hours to 15 minutes daily. Discontinued swimming was necessary in the experimental group because of the tumor growth, which also increased the danger of mice deaths by drowning. The average of survival time in the experimental group was 18 days, 20% more than control group. A second experiment consisted of sarcoma inoculation by methylcholanthrene in mice and investigated the stress effect in different ways. The experimental group was forced to swim until exhaustion (i.e. during 5 to 36 days). This method of exercise was tested in periods according to tumor inoculation: pre, post, and both pre and post. The post-inoculation group was forced to swim for less time and showed the greatest survival rate. The group that was submitted to more time of swimming was exhausted and developed a leucocytosis infection. Thus, the results showed that there was a likelihood that imposed stress (i.e. exercise) promoted the inhibition on tumor growth[20].

Hoffman et al. - 1962

In 1962, Hoffman et al. [21] tried to determine whether a mitosis-inhibiting substance produced by fatigued muscles could inhibit tumor growth in male Wistar rats. The animals were divided into two exercise groups: (I) with no substance injection and (II) with fatigue substance (F-Substance) injection. A third group was composed of fifteen tumor-bearing animals confined in individual cages to keep activity at a minimum as a control condition. The exercise experiment consisted of Walker 256 tumors transplanted by injection subcutaneously into the right thigh of 24 animals that were posteriorly exercised daily for 3 weeks. The experiment consisted

of: (a) the animal being first conditioned by electric shock to run continually in a 20-foot runway; (b) after a brief rest, the animal was forced to swim, starting with a 20-minute period and increasing by 20 minutes per day to a maximum of 4 hours; (c) the animal was placed in a revolving drum where it ambulated each night for a recorded distance of 5.4 miles over 12 hours.

The injection experiments by Hoffman et al. [21] used male Wistar and Sprague-Dawley rats that received inoculations of the Walker 256 tumor or the Murphy lymphosarcoma. The F-substance was produced through electric stimulation on the rectus femoral muscle of the rat. This was applied to produce contraction to the point of fatigue. The substance was injected subcutaneously when the smallest tumor in the control animals reached a size of 2 cm. in diameter, 7-10 days following transplantation [21].

The results showed that in the (a) experiment, the tumor weight in control rats exceed tumor weight of the exercised animals in every instance. In several cases, there was complete tumor regression in the exercised animals. In the (b) experiment, the weight of tumors of the control animals in every instance was also larger than in the animals given injections, and there were also cases of complete tumor regression in injection group.

The authors [21] concluded that a tumoristic factor may be produced by muscle contraction and this tumoristic effect of exercise may not be due entirely to a divergence of energy from tumor growth during exercise. They identified no decreased mitotic activity of the tumors by histological examination. The study could not explain the nature of the substance and the mechanism of its action in retarding tumor growth [21].

Newton - 1965

Newton [22] believed the tumor growth development could be modified by tumor-inhibitors and life experiences. The hypothesis in this study was that social isolation and minimum physical activity could contribute to fast tumor development. The experiment considered how differential early treatment would compare and interact with later exercise in affecting the response to implanted tumor cells in rats. Newton [24]. Compared infantile-manipulated (x) with non-manipulated groups (c). The manipulation was a stressor defined as early treatment, which consisted of removing pups from the nest by tweezer and placing them in a separate cardboard container for 3 min. daily from 2-to-7 days of age.

Six groups were created Ax, Bx, Cx and Ac, Bc, and Cc. The A groups were not submitted to exercise. The B groups were exercised (through 138 hours of walking exercise over 10 days) post tumor inoculation. The C groups exercised prior to inoculation (for 50 hours over a period of 5 days) and after (138 hours of walking exercise over 10 days). All animals were inoculated subcutaneously in the right flank at 50 days of age with a Walker 256 tumor. The results showed that exercise retarded tumor growth. This was even more so when it was combined with infantile manipulation. Overall mortality was delayed only by manipulation, and was not postponed by exercise. Manipulated rats exercised only after implantation presented with a shorter survival time than those manipulated and exercised prior to and following cell inoculation. Pre-implantation exercise apparently conditioned manipulated animals against inflammation of exercise that followed inoculation [22].

Discussion

An important further step in the field of 'exercise and cancer'

addresses the translation from scientific findings into practice. Until now, the optimal type, frequency, duration and intensity of exercise training for cancer patients remain largely unknown [23]. In animal models, physical exercise has been shown to suppress tumor initiation and progression. The neurotransmitter dopamine is closely related to movement and exhibits antitumor properties [24].

The primary hypotheses in experimental animal models revealed the effects of exercise on tumor growth related to metabolic energetic factors and stress. One possible interpretation of this is (a) exercise retards tumor growth by using energy of tumor cells or secretion of substance produced in muscular fatigue, and (b) exercise could be tumor inhibitor or inductor agent, together with other additional conditioners and factors related to life experiences within individuals. Generally, the studies presented here showed decreased tumor growth in animals submitted to exercise. Rusch and Kline²¹, Rashkis²² and Hoffman et al. [21] investigated exercise as an agent associated to energetic metabolism of tumor cells. However, Newton [22] suggested the existence of more factors modulating tumor growth, and factors related to life experiences of individuals would also modulate tumor growth.

Alterations to cellular metabolism should be considered a crucial hallmark of cancer [25]. Tumor cells utilise increased glucose uptake and lactate extrusion by tumors, and consequent pH decreases in surrounding tissues, even in presence of ample oxygen – the Warburg effect [26]. The Warburg effect has been demonstrated in different types of tumors and the concomitant increase in glucose uptake has been exploited clinically for the detection of tumors [27]. We consider that the findings of Rusch and Kline [19] and Hoffman et al. [21] studies can plausibly be justified based upon the Warburg Effect.

Steiner et al. [28] investigated whether voluntary physical activity, initiated prior to the development of mammary tumors, could attenuate tumor development and growth in mouse model of breast cancer. Voluntary wheel running activity was more effective in preventing progression of tumor growth as opposed to inhibiting tumor initiation, independent of an energy imbalance, and possibly because of minimized stress placed on the animal by voluntary exercise. In another study, the same authors found reduced tumor volume and reduction in plasma concentration of inflammatory substances in mice post-exercise; an apparent benefit of exercise training on breast cancer progression mediated by its anti-inflammatory potential [29].

Exercise is a stressor to the human body, and the magnitude of this stress appears to be related to the volume and intensity of exercise to which the individual is exposed [30]. According Justice [31], the type of tumor and the time of stress application are crucial on tumor induction. Several hypotheses have been generated to explain the stress-cancer relationship: (a) *stress-inhibition*, stress administered during tumor development slows tumor growth of non-viral origin; (B) *stress-recovery after the stress is stopped*, the tumor grows more rapidly than in animals not subjected to stress; (C) *facilitating the immune-*, viral tumors grow faster during exposure to the stressor due to immunosuppression; (D) *immune-recovery after stress stopping*, there is a recovery of the immune system which inhibits the development of viral tumors. Studies presented by Justice [31] using PE as a stressor showed the amount of exercise imposed on rats and effects in tumorigenesis can have a protective or tumor-inducing role.

If exercise results in significant muscle damage, inflammatory processes can play an important role in production of free radicals,

oxidative stress inducers, and consequently DNA damage, tumorigenesis, and increase mitosis of tumor cells [31]. The classical theory of tumorigenesis involves a multistage process: (a) initiation of the tumor, by consequences of the initial interaction of the tissues with the carcinogen; (B) promotion of the tumor, by processes that facilitate the expression of the phenotype started in the tissue; and (c) tumor progression, in which there is proliferation and invasion of other tissues, with changes in gene expression and DNA damage of tumor cells [32].

Paradoxically, regular PE can be beneficial in preventing tumorigenesis through changes in hormone levels, growth factors, and reduction of obesity. Further, it may reduce pro-inflammatory mediators and reduce chronic inflammation [32]. Thus, despite the increased production of free radicals, regular PE and higher levels of physical activity assist in balancing oxidative damage in DNA repair [33]. The chronic effect of PE results in the neuroendocrine system adaptations that may cause reduction in stress hormones responses, and lead to reduced baseline levels of stress hormones [30]. Cook et al. [34] found symptoms and exacerbated inflammatory responses in male-mice placed on systematic PE forced to moderate intensity and attenuated in those who practiced PE voluntarily. Jones et al. [17] justify the training effect by aerobic PE on the reduction of tumor development speed by increasing vascularity in the tumor cells, "normalizing" the inside of the affected tissue. As hypoxia in tumor tissues decreases due to the increased blood supply, fewer metastases occur, so the tumor development is reduced [17].

The pioneering experiments reviewed with animals were reliant upon unethical and unviable PE protocols for humans. There is a clear difference between current and pioneer experiments. Currently, several factors are considered and analyzed to explain the effects of exercise on cancer, that are usually associated with the immune system. Pioneering hypotheses considered isolated factors, as stress, energy or substances only. The advances in science and technology will ultimately allow greater depth of knowledge in this area, but the preliminary advances have produced comparable findings in considering pioneering work to recent studies. These include evidence on the role of inflammatory markers of the immune system and body responses to stress.

The pioneering hypotheses of experimental animal models (that the effects of physical exercise have an inhibitory influence on tumor growth) justified this relationship by energy metabolism. Currently, studies show that PE can have protective or cancer-inducing effect, depending on the intensity, duration, and type of exercise. The mechanisms involved in PE effects on tumor growth are in an early stage of developing understanding and remain unclear, possibly due to the heterogeneous nature of tumors and biological intra-individual variation. The view that there is a relationship between the amount of PE and tumor grow will be the subject of further work.

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