Pre-clinical investigations of physical activity and cancer: a brief review and analysis

Henry J. Thompson
Cancer Prevention Laboratory, Colorado State University, 1173 Campus Delivery, Fort Collins, CO 80523, USA
Tel: +1 970 491 7748; Fax: +1 970 491 3542; Email: henry.thompson@colostate.edu

There is substantial evidence that physical inactivity is an important risk factor for a number of chronic diseases, including cancer. As consequences of physical inactivity on cancer risk and treatment efficacy surface, there is increasing interest in determining the benefits of a physically active lifestyle and of exercise as a component of that lifestyle. In the cancer research field, the spectrum of research activities includes pre-clinical studies and clinical and population-based interventions; of these approaches, pre-clinical experiments combining animal cancer models with physical activity (PA) have been underutilized. Clarifying the amounts and types of PA that inhibit carcinogenesis is best done in animals, where mechanistic inquiry and biomarker evaluation of the protected state can be carried out in a more favorable environment than in clinical populations. The expertise required to integrate models for investigating PA with those used to study carcinogenesis is not trivial, but mastery of these models is likely to result in highly translatable pre-clinical findings that advance this important field of investigation. This brief review and analysis is intended to focus attention on the issues and opportunities associated with the pre-clinical investigations of PA and cancer.

Introduction

Broadly considered, physical activity (PA) is simply defined as skeletal muscle contraction that results in a quantifiable expenditure of energy (1). As such, investigations into the effects of PA on various aspects of carcinogenesis in human populations involve an effort to quantify a very heterogeneous set of PA exposures. Although such efforts are difficult and many limitations are widely recognized (2), there is substantial evidence supporting the existence of an inverse relationship between PA and cancer incidence and cancer-related mortality, although the latter has been the topic of limited investigation (3). What is important to recognize, given the growing volume of population-based data, is that key translational questions remain unanswered; namely, what are the types, frequencies, durations and intensities of PA that prevent and control cancer (3). Despite considerable speculation, there is little compelling evidence regarding the mechanisms that account for the inhibition of carcinogenesis by PA (4,5). Because of the complexity and heterogeneity of activity in people, animal models for carcinogenesis and PA present the opportunity to study work rate, length per activity bout and bouts per week in controlled environments. However, the number of pre-clinical studies on PA and cancer is limited. This brief review is intended to focus attention on the issues and opportunities associated with the investigations of PA on the carcinogenic process using animal models.

PA models

An important advantage of using an animal model to study PA is that it permits the investigator to better define the activity and relate it to a specific subset of exposures that comprise the constellation of PA behaviors typically observed in human populations on a daily basis. Very few investigators working with animal models have attempted to clearly define the human PA exposures that they model, and this has limited the ability to relate the pre-clinical work to clinical observations.

Although a detailed survey of methods used to quantify human PA exposures is beyond the scope of this review, several general points are useful to consider in categorizing activity in human populations and drawing parallels in pre-clinical models. One approach used in epidemiological research is to categorize PA exposures by whether they are occupational or recreational; within those broad categories, PA is further described by its type, frequency, duration and intensity. Another approach used in human populations is to define PA in terms of its volume (determined by frequency, duration and intensity) and to report PA in terms of daily energy expenditure per unit time. The above are readily modeled in animal experiments that allow control over the environment. Other clinical investigators focus on a subset of PA that is referred to as exercise. Exercise is defined as ‘planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness’. Physical fitness refers to a physiologic state of well-being that allows one to meet the demands of daily living or that provides the basis for sport performance, or both. Health-related physical fitness includes cardiovascular fitness, musculoskeletal fitness, body composition and metabolism (3). In population studies, PA and physical fitness are frequently treated as being interchangeable, with fitness commonly being treated as a more accurate albeit indirect measure of PA. Measures of fitness that can be assessed in animal studies include aerobic capacity, lactate load, heart rate and enzyme activities such as citrate synthase.

Two of the most commonly used animal models for PA are voluntary running on an activity wheel and forced running on a treadmill. Each is considered briefly.

Activity wheel

The typical protocol permits the animal to decide when to run in the wheel, and the animal determines the frequency,
duration and intensity of the activity. For these reasons, this type of PA is described as voluntary. Since there is nothing planned or structured by the investigator and free access is given to the wheel, it does not meet the formal definition of exercise. This distinction is consistent with the way investigators have quantified wheel running, i.e. the distance run or exercise. This distinction is consistent with the way investigators have quantified wheel running, i.e. the distance run or energy expended. Measurements of physical fitness as outlined above have not been determined.

Activity wheels are easy to implement but have considerable start-up expense in providing enough wheels to gain adequate statistical power when conducting a carcinogenesis experiment. A significant limitation of currently available, commercially produced activity wheels is that they do not permit collection of data on rates of walking and running in the wheels and this diminishes the ability to quantify key characteristics of the activity: frequency, intensity and duration over a 24 h period. Other issues to be considered if this approach is used are the general decline in voluntary activity over time observed in experiments of several months duration and the considerable intra- and inter-animal variation that occurs in daily running activity in a group of animals.

**Treadmill**

The most widely used PA model to improve rodent physical fitness through exercise is running on a variable speed, incline-adjustable treadmill. The use of the treadmill permits the greatest flexibility in studying the effects of exercise duration and frequency because this is determined by the investigator. Exercise intensity is also specified and can be regulated by adjusting the belt speed of the treadmill as well as its incline. An exercise training protocol is developed by the investigator and animals are reinforced to induce compliance with the training program; treadmill running is frequently referred to as forced exercise. The use of this approach has raised issues about reinforcement-associated stress because negative reinforcement is used and need for reinforcement increases with increasing intensity and duration of the training protocol. This results in potential confounding between exercise and its reinforcement. Other than the expense of the treadmill, additional factors that should be considered in the selection of this model are: (i) the amount of energy expended on a daily basis, attributable to treadmill running, is a small percentage of the animals resting metabolic rate; and (ii) animals need to be continuously monitored during running to minimize the risk of injury and to assure adherence to the exercise training protocol.

**Other PA models**

As reviewed in (6), a few investigators have used alternative activity models that include swimming and running of groups of animals in revolving drums. Both methods are considered forced exercise, but they use different reinforcement strategies. Areas of PA that have been neglected in carcinogenesis research are resistance training and access to a static PA device, e.g. alley-way running.

**PA model summary**

When investigators select a model to study activity, they should define the simulation in terms of type, frequency, duration and intensity. In addition, the assessment of animal fitness using one or more established methods would further inform thinking regarding the different categories of activity and in so doing enhance the translation of pre-clinical findings to the human setting.

**Carcinogenesis models**

A detailed analysis of PA–carcinogenesis models that have been studied has been thoroughly evaluated in a number of recent papers (7). Overall, animal models of carcinogenesis can be divided into the following categories: spontaneously occurring, chemical-, radiation-, or virus-induced, genetically-engineered and transplantable tumors. The categories of spontaneously occurring and radiation- or virus-induced models have virtually no studies relating to the effects of PA on carcinogenesis and only a few studies have used transplantable tumors. Rather, the literature is populated primarily with studies using chemically-induced models and more recently with genetically engineered mouse models. Work done using chemically-induced rodent models for cancer research has primarily been focused on two organ sites, breast and colon; in general, PA has been reported to inhibit the carcinogenic process in parallel with work reported in human populations. The advantages of chemically-induced models include the ability to investigate stage-specific effects, the well defined parallels between animal models and the human disease, and the understanding of the cellular and molecular mechanisms that underlie tumor development. PA studies involving the use of transgenic and/or knock-out models of carcinogenesis are fewer in number and primarily focused on intestinal tumors. Using a model such as the APCMin mouse, PA has been reported to have little effect on tumorigenesis, although the findings are mixed (9–11). Such models may be more mechanistically useful in complementing work conducted in chemically-induced systems where robust effects have been observed. The investigation of cancer progression using transplant models is the least studied dimension of the PA–cancer relationship, but given the increasing interest and use of PA interventions during and after cancer treatment, the value of investigations using such systems is assuming increasing importance.

**Other considerations**

Of the many factors that should be carefully considered in designing pre-clinical experiments and interpreting their results, two factors merit particular attention: PA-associated stress and the temporal framework of the physiologic response to a bout of PA. Relative to stress, there are clear differences in the types of stress that accompany voluntary running in an activity wheel versus forced running on a treadmill; this topic has been reviewed (7). However, it is uncertain whether these differences are as follows: (i) sufficient in their type or amount to meaningfully affect the carcinogenic process and (ii) based on how the stressors experienced by exercising rodents compare with the stress associated with various human PA exposures. Clarifying this issue will require careful characterization of the chemical and biological nature of the induced stress while considering that there are significant differences in stress responses among species including those between rats and mice. In considering physiological responses to PA, it is critical to differentiate between whether the variables being investigated represent acute responses to a bout of PA or if they are chronic.
adaptations that characterize different levels of physical fitness (12,13).

Mechanisms

There is a paucity of compelling data about the mechanism(s) that accounts for the reported inhibitory effects of PA on the carcinogenic process, although there is an abundance of speculation about what these mechanisms may be and the topic has been reviewed (14). Of the various candidate mechanisms that have been advanced, those most commonly cited include: reductions in fat stores, activity-related changes in sex hormone levels, altered immune function, effects on insulin and insulin-like growth factors, reduced free radical generation and direct effects on the tumor. For colon cancer, there have been efforts to link physiological changes associated with PA such as decreased intestinal transit time, altered prostaglandin ratios and lowered bile acid secretion to cancer inhibition but such efforts are weakened because the relationship of these physiological changes to colon carcinogenesis are poorly understood (7). For breast cancer, a primary focus of inquiry has been on alterations in sex hormone metabolism, but available experimental data do not provide strong support for this as an obligatory mechanism (5,15,16).

Considering how mechanistic work has progressed in highly relevant and related investigations of protection against cancer by dietary energy restriction (17,18), logical areas of inquiry that have not been adequately studied include: cellular processes (cell proliferation, apoptosis and angiogenesis), metabolic processes (glucose homeostasis, inflammation and cellular oxidation) and signaling pathways (e.g. signaling mediated via AMP-activated protein kinase and phosphoinositide-3 kinase) that PA exposures are known to modulate directly and indirectly in a number of tissues in addition to skeletal muscle.

Research opportunities

As noted above, the emergence of physical inactivity as an important factor in affecting cancer risk, and possibly cancer prognosis, places renewed emphasis on questions that have dominated the field for almost two decades: how much PA is enough, what type is best, and when during the life cycle is it important. However, as work in the field progresses this list of questions is being refined and expanded. Table I contains a list of questions that should be considered for investigation using pre-clinical models for PA and cancer.

Current issue

This issue of Carcinogenesis features two papers that investigate the effects of PA on the carcinogenic process. Both studies were conducted using voluntary wheel running of mice as the PA model. In the paper of Colbert et al. (10), the energy balance dependent effects of PA were studied in male C57Bl6 APCMin mice using wheel running to create an energy deficit in comparison to sedentary control animals fed ad libitum. As noted by the authors, this is a follow-up to their previous report that treadmill exercise had little impact on tumor development in this model for intestinal tumorigenesis, a finding that differs from the work reported in (11). Although a reduction in the number and size of intestinal polyps was observed in the wheel running energy-restricted mice, and evidence of an inverse association between distance run and polyp numbers per mouse was noted, the observed increase in body fat composition in the wheel run mice, and the lack of correlation among frequently measured biomarkers for cancer risk and tumor outcome, illustrate the complexities of work in the area and the paucity of definitive mechanistic data providing insights about causal links between PA and the carcinogenic response. In the paper of Michna et al., (10), the experiment was designed to study energy balance independent effects of PA on UVB-induced skin carcinogenesis, a cancer site for which little evidence of PA effects has been reported. This study reports a reduction in skin tumor occurrence in group housed SKH-1 mice given free access to an activity wheel. Although body weights did not vary between treatment groups, intra-dermal fat thickness was reduced in animals provided with access to activity wheels. The authors note the constraints placed on data interpretation due to the need to group house wheel running animals to increase the number of animals that could be studied. Their work highlights how the resource demands for the equipment required to do PA-carcinogenesis research can impact the design of experiments and interpretation of results.

Concluding remarks

The consequences of physical inactivity versus the benefits of an active lifestyle are perceived to be large but quantification of those benefits and establishment of causal mechanisms remains elusive. Pre-clinical studies have been underutilized in this field but have the potential to make significant contributions by clarifying the amounts and types of PA that inhibit carcinogenesis and by providing an avenue for mechanistic studies that establish cause and effect relationships, as well as identify candidate biomarkers for monitoring the “PA-protected state” in clinical populations. The experience required to integrate models for investigating PA with those used to study carcinogenesis are demanding but will likely result in highly translatable pre-clinical findings that advance this important field of investigation.

Table I. Questions for investigation using pre-clinical models for physical activity (PA) and cancer

- What is more important to modulating carcinogenesis by PA: its type (e.g. aerobic versus resistance training), intensity, duration, or frequency?
- Are there effects of PA, per se, on the development of cancer that are directly or indirectly related to skeletal muscle contraction, independent of its effects on energy balance? How does degree of physical fitness affect cancer risk or response to treatment and treatment outcome?
- Is the protective activity of PA due solely to its effects on energy balance and if present are such effects dependent on body fat mass and/or its location?
- If energy balance is perturbed to the same degree by either decreasing energy intake via the diet or increasing energy expenditure by PA, do these approaches have comparable effects on the carcinogenic response?
- What are the causal mechanisms that explain the linkages among PA and the carcinogenic process? Specifically, which cellular processes, biochemical mediators and signaling pathways are causally involved?
- Can the mechanisms identified explain organ site specific effects of PA on the carcinogenic process? That is, why do some cancer sites appear to be protected against cancer by PA whereas others are not affected?
- Do the mechanisms elucidated provide for the identification of biomarkers that can be used to determine whether an individual has achieved and/or is maintaining a PA-mediated cancer protected state?
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References


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