Effect of Exercise Intensity and Duration on the Induction of Mammary Carcinogenesis

Henry J. Thompson

AMC Cancer Research Center, Denver, Colorado 80214

Abstract

Physical activity is defined as bodily movement due to skeletal muscle contraction that results in quantifiable energy expenditure. Both epidemiological and laboratory data indicate that the level of physical activity in which an individual engages may affect cancer risk. Exercise is distinguished from other types of physical activity by virtue of the fact that the intensity, duration, and frequency of the activity(ies) is specifically designed to improve physical fitness. Based on available data, a role for exercise in specifically reducing cancer risk has been conjectured and is referred to as the exercise-cancer hypothesis. However, the amount of scientific evidence in support of this hypothesis is still quite limited, and there are conflicting reports about the nature of the association. The exercise-cancer hypothesis was evaluated in two experimental animal models for breast cancer using treadmill running as the exercise paradigm. The data presented indicate that both the intensity and duration of exercise affect the development of experimentally induced breast cancer. In general, as exercise intensity increased, the likelihood that such physical activity inhibited carcinogenesis increased. Exercise at lower intensities resulted in either inhibition, no effect, or enhancement of the tumorigenic response depending on the duration of exercise. Inhibitory conditions of exercise affected both the initiation and promotion/progression stages of the disease process.

Introduction

Much like the consumption of foods, people are constantly making choices about the amount, type, and frequency of physical activity in which they engage. These choices have demonstrable effects on a number of disease processes, most notably those of the cardiovascular system, and certain patterns of physical activity also are associated with increased longevity (1). These observations have raised the general question of whether or not similar physical activity choices also alter the risk for cancer. A number of excellent reviews of the epidemiological literature regarding the effects of physical activity on cancer have been published in recent years (2—4), and there is considerable concordance in the conclusions that have been reached. The strongest associations exist for cancer of the colon for which there is convincing evidence of an inverse trend with increased longevity (1). These observations have raised the general question of whether or not similar physical activity choices also alter the risk for cancer. A number of excellent reviews of the epidemiological literature regarding the effects of physical activity on cancer have been published in recent years (2—4), and there is considerable concordance in the conclusions that have been reached. The strongest associations exist for cancer of the colon for which there is convincing evidence of an inverse trend with increased longevity (1).

Definition of Physical Activity

Physical activity is defined as skeletal muscle contraction that results in a quantifiable expenditure of energy (6). There are three primary components of physical activity that can be varied and that may have different effects relative to carcinogenesis. They are the intensity (work-rate), the duration (length per activity bout), and the frequency (times per week) of the activity(ies) that is performed. Other attributes of physical activity also can be considered and are reviewed by Caspersen (6). The various types of physical activity in which individuals engage also can be subdivided into two major categories, occupational and recreational. The characteristics of each are summarized in Table 1. It should be noted that exercise represents a subset of activities listed under the category of recreational activity and is distinguished from other types of physical activity in that exercise is planned and designed to improve physical fitness.

Exercise and Breast Carcinogenesis

Only one major epidemiological study of physical activity and breast cancer has been reported (7). In that investigation, mailed, self-administered questionnaires obtained from college alumni were used, and the analysis of that data indicated that former collegiate athletes were leaner, more likely to have exercised before college, and to be doing exercise as adults. These former athletes were found to have a lower relative risk for breast cancer than those individuals that indicated that they were non-athletes. In other studies, findings have varied and include failure to detect an association between participation in collegiate athletics and breast cancer (8) and an elevation in the proportionate mortality for breast cancer in the lowest among four categories of occupational activity (9). Of potential importance are the results of an analysis of NHANES I data that showed an inverse association between nonrecreational activity and breast cancer for postmenopausal women and a direct association for premenopausal women (10). However, as noted by Sternfeld (5), available evidence currently is insufficient to conclude whether active women experience a decreased incidence of breast cancer compared with inactive women.

While a definitive evaluation of the exercise-cancer hypothesis based on both prospective epidemiological studies and intervention trials is an important goal, the results of such studies are not likely to be available in the immediate future. While unavoidable, this situation is unfortunate because the potential impact of such information on lifestyle choices of women of all ages is considerable. A complementary and more timely alternative approach to either population or clinical studies is the investigation of this exercise-cancer hypothesis in appropriate model systems for both breast cancer and exercise. My laboratory has conducted a series of experiments over the last several years that address the exercise-cancer hypothesis in two widely recognized models for mammmary carcinogenesis induced in the rat by injection of either MNU, or DMBA. The usefulness of these models for the study of breast cancer has been detailed in several papers (11—13). The effects of the intensity and duration of treadmill exercise on chemically induced mammary carcinogenesis has been investi-
Gated on the initiation and promotion/progression stages of mammary carcinogenesis. Our reasons for choosing treadmill running versus other models for exercise are detailed in by Thompson (14).

**Effects of Exercise on the Initiation Phase of Mammary Carcinogenesis**

Carcinogenesis initiation is operationally defined as the time at which carcinogen exposure occurs and a period of time thereafter during which the initial cellular events in response to the carcinogen are complete. In rodent models of chemically induced mammary carcinogenesis, initiation is generally defined to be complete within 7 days of carcinogen administration. In order to study the effects of intensity and duration of exercise on this phase of carcinogenesis, exercise training was started at an early age given that in most carcinogen dosing regimes, carcinogen is administered at 50 days of age and that failure to inject animals by 75 days of age is complicated by developmental changes in the mammary glands that render them refractory to carcinogenic insult (15). Because of this, there are limits on the intensity of exercise that can be investigated. The effects of exercise were investigated in female Sprague-Dawley rats. They were randomized into exercise training groups one day postweaning, i.e., at 22 days of age, and were trained until 7 days after carcinogen administration. The exercise conditions are reported in terms of the incline and the beltspeed at which the animals ran. These conditions (incline and beltspeed) define exercise intensity. The effects of exercise on the initiation phase of mammary carcinogenesis are summarized in Table 2. These data show that running for 15 or 300 min at a beltspeed of 20 m/min and an incline of either 1 or 7.5 degrees had no effect on MNU-induced mammary carcinogenesis, whereas a reduction in mammary tumor occurrence induced by DMBA was observed at the higher exercise intensity. DMBA is a procarcinogen that requires metabolic activation by the mixed function oxidase system, whereas MNU is a direct acting carcinogen (11). These data indicate that the activation of DMBA during metabolism via the mixed function oxidase system is likely to have been affected by the higher intensity exercise protocol that was used. The fact that MNU-induced mammary carcinogenesis was unaffected indicates that the levels of exercise studied are unlikely to be affecting the response of the mammary gland to carcinogenic insult. The effects of exercise in the DMBA model are consistent with other published work that has shown that exercise can affect xenobiotic metabolism (16, 17). These findings suggest the potential value of more detailed studies of the effect(s) of exercise on carcinogen metabolism.

**Effects of Exercise on the Promotion/Progression Phase of Mammary Carcinogenesis**

In rat mammary carcinogenesis models, it is not possible to distinguish between tumor promotion and tumor progression as it is in other systems, e.g., the skin system. Promotion/progression is operationally defined to begin 7 days following carcinogen administration. We have published a number of reports on the effects of exercise intensity and duration on this phase of MNU-induced mammary carcinogenesis (14, 18-21). The results of these experiments are summarized in Table 3. Low intensity, short duration activity has been observed to enhance the rate of mammary tumor occurrence. This observation was made at an intensity level below that studied in the anti-initiation work discussed above. With increasing intensity and duration of exercise, evidence of a dose-dependent protective effect against mammary carcinogenesis was obtained (Table 3). However, in our opinion it is premature to identify the levels of exercise intensity and duration that are required for inhibition of carcinogenesis. It should be noted that the dose responsive relationship noted here (Table 3) is contrary to that reported by Cohen (22) in which a bimodal effect of exercise was hypothesized, i.e., low intensity and high intensity exercise enhanced, whereas moderate intensity exercise inhibited mammary carcinogenesis. We cannot currently reconcile these observations other than to indicate that the hypothesized relationship between physical activity

<table>
<thead>
<tr>
<th>Exercise conditions</th>
<th>MNU-induced carcinogenesis</th>
<th>DMBA-induced carcinogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise incline (degree)</td>
<td>Belt speed (m/min)</td>
<td>Duration (min)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>300</td>
</tr>
</tbody>
</table>

*The value is calculated as 1- [(average number of cancers per rat in the experimental group) divided by (the average number of cancers per rat in the control group)] × 100. A negative sign preceding this number indicates inhibition of carcinogenesis. A positive sign preceding this number indicates enhancement of carcinogenesis.

*Data were subjected to the Kruskal Wallis test, one-sided P value Assuming a x2 distribution.
EXERCISE AND MAMMARY CARCINOGENESIS

Table 3 Effects of treadmill exercise on the promotion/progression stage(s) of mammary carcinogenesis

<table>
<thead>
<tr>
<th>Exercise conditions</th>
<th>MNU-Induced Carcinogenesis</th>
<th>DMBA-induced carcinogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise incline (degree)</td>
<td>Belt speed (ml/min)</td>
<td>Duration (min)</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>1</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>

Exercise incline: 1°; Beltspeed: 20 ml/min; Duration: 15 min; Dose MNU: 5 mg/kg; Change in mammary carcinogenesis: 53.4% increase; Statistical significance: P < 0.05.

<table>
<thead>
<tr>
<th>Exercise conditions</th>
<th>Exercise incline (degree)</th>
<th>Belt speed (ml/min)</th>
<th>Duration (min)</th>
<th>Dose DMBA (ng)</th>
<th>Change in mammary carcinogenesis (%)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1°</td>
<td>20</td>
<td>15</td>
<td>5</td>
<td>Control +53.4%</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>1</td>
<td>1°</td>
<td>20</td>
<td>15</td>
<td>5</td>
<td>Control +53.4%</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>9</td>
<td>1°</td>
<td>20</td>
<td>30</td>
<td>37.5</td>
<td>Control –85%</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>9</td>
<td>1°</td>
<td>20</td>
<td>30</td>
<td>37.5</td>
<td>Control –85%</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

A negative sign preceding this number indicates inhibition of carcinogenesis. A positive sign preceding this number indicates enhancement of carcinogenesis.

and cancer presented by Cohen (22) is more likely to relate to differences in duration rather than intensity of exercise. It is important not to confuse these terms. Intensity is defined by the speed of running and the incline that is traveled, not by the distance run. Clearly more work is required to further define the quantitative dimensions of the effects of exercise on the promotion/progression stage of this disease process.

Issues to Be Considered in Laboratory Investigations of the Exercise-Cancer Hypothesis

Laboratory experiments in which the effect of physical activity on the occurrence of cancer have been studied are few in number (reviewed in Ref. 22). A significant limitation in much of the published work is that little attention has been given to assessing whether the physical activity performed actually improved physical fitness, thus fulfilling the criteria for exercise. Another limitation is that in many cases the level of activity was so strenuous that exercise-specific effects could not be dissociated from those attributable to altered growth and/or reduced caloric intake. Thus, for the majority of work published prior to 1980, it can only be stated that exhaustive levels of physical activity are associated with cancer inhibitory activity.

In the late 1980s, a number of studies were published concerning the effects of treadmill exercise and activity wheel running on the development of breast or colon cancer in widely used experimental models for these diseases (reviewed in Ref. 22). The interpretation of these studies also is complicated by less dramatic but statistically significant effects on growth and/or carcass composition associated with activity wheel running. In these experiments, modest levels of tumor inhibition were observed. In two studies in which neither growth nor carcass composition were affected, short duration treadmill running was associated with an accelerated rate of tumor occurrence (18, 19). Consequently it currently is not possible to conclude whether exercise exerts energy metabolism independent effects on carcinogenesis. This is a critical question to resolve.

An additional consideration is the potential role that stress may play in accounting for the effects of exercise on carcinogenesis. In this regard, it is noteworthy that in the science of exercise physiology that exercise is defined as the application of a stress to a muscle. Thus, by definition, exercise is stress. Because of this, debates as to whether a particular exercise regimen is stressful would appear to have little merit. Rather, more detailed studies are needed to characterize the chemical nature of the stress associated with various types of physical activity so that its components and their effects on carcinogenesis can be systematically evaluated.

Conclusion

Work to date indicates that the exercise-cancer hypothesis is amendable to systematic evaluation and that this can best be accomplished by considering the components of exercise intensity, duration and frequency. Data exist to indicate that both the initiation and promotion/progression phases of mammary carcinogenesis are affected by exercise. In our opinion, the following questions merit further investigation: how much exercise is sufficient to inhibit carcinogenesis; what type is best; how frequent is it necessary; when during the life cycle and disease process is exercise important; and are there beneficial effects against cancer that can be maintained in the absence of a continued program of exercise? Until such questions are answered, there is a need for practical guidelines about the role that exercise plays as a component of a healthy life style. It is suggested that variety and moderation in the choice of exercise activities is prudent and that an individual’s overall level of physical activity should be such that, in concert with caloric intake, an appropriate body weight is maintained. With regard to the question of how much and what type of exercise are desirable, it is recommended that the guidelines of the American College of Sports Medicine and the American Heart Association be considered (23, 24).

References


1962s


Effect of Exercise Intensity and Duration on the Induction of Mammary Carcinogenesis

Henry J. Thompson


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/54/7_Supplement/1960s

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.