Impact of Physical Activity on Intestinal Cancer Development in Mice

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ABSTRACT Observational epidemiology supports the hypothesis that variation in diet and other lifestyle exposures accounts for a large part of the variation in incidence of colorectal cancer (CRC). Physical inactivity is associated strongly with enhanced CRC risk, but no human intervention studies have shown causality. This paper reviews data from all available studies of the effects of exercise interventions on intestinal neoplasia using rat and mouse models. All 5 published studies of effects of increased physical activity (both forced and voluntary) using carcinogen-treated rat models show strong protection against CRC by greater physical activity. In contrast, there is little convincing evidence of reduced intestinal neoplasia after increased physical activity in the 3 published studies using ApcMin mice (which develop multiple intestinal polyps spontaneously) although the nature and amounts of physical activity imposed in rats and mice were similar. Major differences in protocol between the 2 groups of studies are that the rat studies were much longer (at least 20 wk and in most cases 38 wk compared with ≤9 wk for the mouse studies) and the primary endpoint was colorectal carcinoma (rats) rather than small bowel adenomas (mice). The epidemiological evidence for protection against adenoma formation by increased physical activity is weaker than that for carcinoma. The limited evidence available suggests that, compared with rats, mice may show a greater compensation for energy expenditure in exercise through reduction in nonexercise physical activity, thus ameliorating effects. The resulting smaller effects on body weight and body fatness may limit changes in intestinal neoplasia in ApcMin mice. J. Nutr. 135: 3002S–3008S, 2005.

KEY WORDS: • bowel cancer • physical activity • rats • Min mice • body fat

Observational epidemiology supports the hypothesis that variation in diet and other lifestyle exposures accounts for a large part of the variation in incidence of colorectal cancer (CRC). Although quantification of both habitual dietary intake and of habitual exercise poses substantial technical challenges (1), the available evidence suggests that the population attributable risk of physical inactivity for colon cancer is 13–14% (2). This is of the same order as the population attributable risks due to a Western eating pattern or to not using aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) (both ~12%) and considerably greater than the risk due to a family history of bowel cancer (2). The evidence supporting a protective effect of physical activity against colon cancer is more consistent than that for rectal cancer (2). However, physical activity is a very heterogeneous exposure and little is known about the effects of particular types of physical activity on bowel cancer risk. The limited evidence available suggests that higher intensities of activity carried out over longer periods are more protective (3) but the optimum type of exercise or its intensity, frequency, or duration required to minimize CRC risk is unknown.

Those with higher BMI are at enhanced CRC risk and of cancer at several other sites (4), with the risk of death from colon cancer increasing more strongly and linearly in men than in women (5). Accumulation of abdominal fat (as indicated by greater waist circumference) was a stronger predictor of both proximal and distal cancer than was BMI in the Framingham Study (6). Because increased adiposity results from a sustained imbalance of energy intake over energy expenditure, greater physical activity, and therefore greater energy expenditure, may have its beneficial effects on bowel cancer risk through lowering BMI. However, evidence exists that a high BMI is associated with higher colon cancer risk in sedentary but not in physically active men (7), suggesting that raised adiposity and physical inactivity are independent risk factors for bowel cancer.

Although the epidemiological evidence supports the hypothesis that greater physical activity protects against CRC,
such evidence can be challenged because of the problems in assessing exposure and the possibility of uncontrolled confounding (1). No human intervention trials with CRC as the outcome have tested this hypothesis largely because of logistical and financial considerations. Interventions with surrogate endpoints would be an attractive alternative but, except for adenoma recurrence (8,9), surrogate endpoints for bowel cancer are poorly developed. Data from the Polyp Prevention Trial suggest that recent physical activity is not associated with polyp recurrence (10). Improved immune function may help prevent CRC (11) and some evidence shows that moderate-intensity exercise may improve immune function whereas high-intensity, prolonged physical training may depress immune function (12). A Program Promoting Exercise and an Active Lifestyle (the APPEAL Study) is the only randomized controlled clinical trial of which we are aware that is testing the effects of enhanced physical activity on biomarkers of bowel cancer risk; the latter include cell kinetics in the colorectal mucosa and circulating concentrations of insulin, insulin-like growth factor-1, and insulin-like growth factor binding protein-3 (12). The intention was to recruit 100 men and 100 women aged 40–75 y to a moderate-intensity exercise program for 1 y (12). At the time of writing, outcomes from the APPEAL study had not been published.

Although well-designed and -conducted observational studies can provide strong evidence for associations, unequivocal evidence of causality requires intervention studies. This review considers the evidence from experiments using rodent models in which the amount of physical activity undertaken was modified and the occurrence of intestinal neoplasia was quantified.

Animal models

Experimental studies of the effect of exercise on intestinal tumorigenesis have been restricted to studies in rodents. As summarized in Tables 1 and 2, we found 8 published studies, 5 of which used rats and 3 of which used mice. The rat studies (published between 1987 and 1994) predate the mouse studies, which were published from 2000 onwards. In all the rat studies, colon cancer was induced by carcinogen administration using 1,2-dimethylhydrazine (DMH) or azoxymethane (AOM). Rats exposed to an appropriate dosing regime with either agent develop 1 or more tumors in the large bowel although tumors in the small bowel and at other extraintestinal sites are observed less frequently (17). All studies used male Fischer (in most cases) F344 rats except for Andrianopoulos et al. (13), who used male Sprague-Dawley rats.

In contrast, the 3 mouse studies all used both male and female ApcMin mice, which carry a germline nonsense mutation at codon 850 in the Apc gene and develop multiple intestinal neoplasms spontaneously (21,22). This mutation in the Apc gene (the gatekeeper gene for bowel cancer) truncates the protein product, inhibiting interaction with and the normal catabolism of β-catenin resulting in constitutive activation of the Wnt signal transduction pathway and chromosomal instability (23). ApcMin mice develop numerous adenomas throughout the intestine but, in most circumstances, most of these neoplasms are in the small bowel (22). In addition to their utility for studies of intestinal tumorigenesis per se, ApcMin mice have proved to be very useful in investigation of the neoplastic and antineoplastic effects of a wide range of substances and exposures including NSAIDs (24,25), chemotherapeutic agents (26), and several dietary components (27–30). Numbers, sizes, and intestinal distribution of polyps are readily modifiable by exogenous factors in ApcMin mice with some dietary factors inducing and others preventing the formation of intestinal polyps (31).

<table>
<thead>
<tr>
<th>Rat strain and sex</th>
<th>Type of exercise</th>
<th>Exercise protocol</th>
<th>Study duration</th>
<th>Time of AOM or DMH administration</th>
<th>Tumor incidence</th>
<th>Tumor multiplicity (tumors/rat)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control Exercise</td>
<td>Control Exercise Reference</td>
</tr>
<tr>
<td>Sprague-Dawley</td>
<td>Wheel</td>
<td>Free access to wheel 33 cm diameter</td>
<td>20 wk after last DMH injection</td>
<td>Exercise begun at same time as DMH injections</td>
<td>93</td>
<td>55</td>
</tr>
<tr>
<td>male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n = 20</td>
<td>n = 11</td>
</tr>
<tr>
<td>F344</td>
<td>Treadmill</td>
<td>60 min/d @ 24 m/min 7° gradient 5 d/wk</td>
<td>38 wk after last AOM injection</td>
<td>Exercise applied after last AOM injection</td>
<td>66</td>
<td>41</td>
</tr>
<tr>
<td>male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n = 27</td>
<td>n = 27</td>
</tr>
<tr>
<td>F344</td>
<td>Treadmill</td>
<td>5 h/d @ 7 m/min 5 d/wk</td>
<td>38 wk after last AOM injection</td>
<td>Exercise applied after last AOM injection</td>
<td>78</td>
<td>53</td>
</tr>
<tr>
<td>male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n = 32</td>
<td>n = 32</td>
</tr>
<tr>
<td>F344</td>
<td>Treadmill</td>
<td>5 h/d @ 7 m/min 5 d/wk</td>
<td>38 wk after last AOM injection</td>
<td>Exercise applied after last AOM injection</td>
<td>37²</td>
<td>0²</td>
</tr>
<tr>
<td>male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n = 30</td>
<td>n = 30</td>
</tr>
</tbody>
</table>

1 Numbers after ± refer to SD.
2 Carcinomas only.
3 Total neoplasms.
4 Corn-oil-fed group only. There was no significant (P > 0.05) effect of exercise in coconut-oil-fed group.
Exercise interventions

Two modes of exercise intervention have been used: “forced” exercise in which the animals were trained to run on treadmills and voluntary exercise in which the animals were allowed free access to running wheels in their home cages. Except in the 2 Danish studies (16,17), treadmill running for both rats and mice was at a relatively high speed (18–24 m/min) on a gradient of 5–7% for up to 1 h/d on 5 d per wk (14,18,19) or 6 d/wk (20). This is equivalent to ~5.4–7.2 km/wk. Thorling et al. (16,17) made treadmills from acrylic plastic drums that were rotated at 7 m/min, allowing rats to walk quickly with short stops and catch up with a brief run (16). The animals were placed in these drums for 7 m/min, allowing rats to walk quickly with short stops and catch up with a brief run (16). The animals were placed in these drums for 7 h/d, allowing rats to walk quickly with short stops and catch up with a brief run (16). The animals were placed in these drums for 7 h/d, allowing rats to walk quickly with short stops and catch up with a brief run.

The other studies used wheels (see Tables 1 and 2 for details) in which the animals were free to run as little or as much as they chose at any time throughout the study. One study used a combination of wheel running (for the first 3 wk) followed by treadmill running (for the remaining 5 wk) (19). Only one study provided a direct comparison of effects of treadmill versus wheel running on intestinal tumorigenesis and did so using ApcMin mice (20). No study appears to have investigated the effects of the imposed exercise on nonexercise physical activity (NEPA), that is, the amount of physical activity (e.g., walking, fighting, or cage climbing) undertaken by the experimental animals in the periods between bouts of treadmill or wheel running.

Do exercise regimens impose stress on the experimental animals?

Psychosocial factors including stress-induced immunosuppression or dysregulation may play a role in the initiation and progression of tumors (32). Oxidative stress leading to DNA damage appears to be a risk factor for CRC (33) as it is for the process of aging and for many age-associated degenerative diseases (34). Forcing rats to swim to exhaustion with a weight equivalent to 2% of body weight tied to the tail produced an almost 3-fold increase in the number of aberrant crypt foci (a precursor lesion of CRC) in the colon of unstained Wistar rats treated with DMH (35). DMH was injected subcutaneously immediately after the single bout of exhaustive swimming and aberrant crypt foci were scored 15 d later. The authors hypothesize that the unaccustomed exhaustive physical activity may have increased free radical generation leading to damage to DNA and to other cell macromolecules (35).

Andrianopoulos et al. (13) chose a voluntary wheel-running protocol for their studies “in order to minimize confounding of activity with physiological or emotional stress” whereas Thorling et al. (16) justified their forced treadmill running protocol on the grounds that “there was no indication of stress, when returned to the cages from the treadmill.” However, other studies showed that forced treadmill running (and endurance training in humans) results in chronic stress-like changes in the hypothalamic-pituitary-adrenal (HPA) axis (36–41), one of the principal neuroendocrine stress systems. Furthermore, substantially enlarged adrenal medullas (i.e., the main source of adrenaline, another important stress mediator) have been observed in both humans after high-intensity exhaustive exercise (42) and rats after forced treadmill or swim exercise (43,44). In contrast, voluntary exercise does not evoke such a profound hyperactivity of the HPA axis both in terms of glucocorticoid and adrenaline secretion and hyper trophy of the adrenal gland [for review see (45)]. In a recent study, it was shown that voluntary exercise does not evoke the chronic stress-like changes in the HPA axis as seen after forced exercise (46,47). Rather, long-term voluntary exercise results in a reorganization of the HPA axis including its neural control by central nervous system structures that allows the organism to present a more differentiated response to physically versus psychologically stressful stimuli (46,47). Furthermore, as compared with the sedentary controls, the voluntarily exercising mice showed significantly decreased anxiety-related behavior (48) and improved sleep quality (49). Thus, overall it appears that allowing animals to voluntarily exercise increases their stress resistance in terms of stress hormone secretion, emotionality, and sleep (45–49). One important factor why forced exercise is aversive and stressful for the animals whereas voluntary exercise is not is the fact that forced exercise is usually conducted during the day time, when nocturnal animals such as rats and mice are normally sleeping. Thus, the forced-exercise paradigm causes sleep deprivation, which is known to be stressful (47). Voluntary wheel running follows the normal physical behavior of the animal; mice (and rats; S. K. Droste and J.M.H.M. Reul, unpublished results) run (as much as pleases them) mainly during the first half of the dark (i.e., active) period (45,49).

A 16-mo study of unlimited wheel-running exercise in...
Sprague-Dawley rats compared with sedentary animals with no access to physical activity showed that the exercising animals had lower body weight (50). In addition, in the absence of an exogenous carcinogen, the exercising rats had only half the number of sporadic kidney tumors and the mean size of tumors was only one third of that seen in the sedentary rats (50).

**Effects of exercise on intestinal tumorigenesis**

In all 5 carcinogen-treated rat studies, animals exposed to an exercise regime had reduced large bowel tumor incidence (Table 1). The most dramatic protection was observed in the second study by Thorling et al. (17) where there were no carcinomas in the large bowel of exercised rats fed high-fat diets (containing 23% corn oil) compared with 37% of animals with carcinomas in the control group. However, the numbers of animals with moderate and severe dysplasia were similar for the 2 groups (17). For the other studies, tumor incidence was reduced by 32–52% in the exercised rats (Table 1). In addition to more tumor-free rats in the exercise groups, tumor multiplicity was reduced in all studies although not all differences were statistically (P < 0.05) significant. In the study by Thorling et al. (17) there appeared to be a substantial difference in the effects of the exercise regime between animals fed different types of fat. There was no significant diminution in either tumor incidence or tumor multiplicity when the fat content of the high-fat diet was provided largely by coconut oil (21%) in contrast with the absence of carcinomas in exercised rats fed the high-corn-oil diet. The anatomical distribution of neoplasms along the colon also appeared to be modified by the type of fat in the high-fat diets (17). There was no obvious difference in the degree of protection against CRC afforded by treadmill running versus wheel running in the rat studies.

In contrast with the strong evidence for a protective effect of exercise reported in the rat studies, 2 of 3 mouse studies (18,19) failed to detect a significant effect of exercise on food intake (measured as number of adenomas per mouse intestine) (Table 2). Treadmill running reduced intestinal tumorigenesis (as number of adenomas per mouse intestine) (Table 2). In addition to more tumor-free rats in the exercise groups, tumor multiplicity was reduced in all studies although not all differences were statistically (P < 0.05) significant. In the study by Thorling et al. (17) there appeared to be a substantial difference in the effects of the exercise regime between animals fed different types of fat. There was no significant diminution in either tumor incidence or tumor multiplicity when the fat content of the high-fat diet was provided largely by coconut oil (21%) in contrast with the absence of carcinomas in exercised rats fed the high-corn-oil diet. The anatomical distribution of neoplasms along the colon also appeared to be modified by the type of fat in the high-fat diets (17). There was no obvious difference in the degree of protection against CRC afforded by treadmill running versus wheel running in the rat studies.

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**Possible confounding effects—food intake, body weight, and body fatness**

For the 3 rat studies where data are available (15–17), the exercise intervention was associated with increases in food intake of 13–25% and, for 4 of 5 studies, with 7–24% lower body mass (Table 3). In contrast, the exercise interventions in ApcMin mice had more modest effects on body mass and body fat content and, in most cases, differences from the sedentary controls were not significant (Table 4). The exception was the study of Colbert et al. (19) where the exercise intervention led to a 9% decrease in body mass (P < 0.01) and 11% decrease in body fat content (P < 0.05) of female mice but had no detectable effect on either variable in males. After 4 wk of wheel running, male C57BL/6N mice showed no changes in body weight but abdominal fat mass was significantly decreased (46). Wheel-running but not treadmill-running mice ate more food than controls in the study by Mehl et al. (20) but there were no reports of altered food intake in the other ApcMin mouse studies (Table 4). No changes in food intake were observed in wheel-running C57BL/6N mice (46).

The more modest effects of exercise in the ApcMin mice compared with the rats is somewhat surprising given the similarity in the amounts of imposed (treadmill) exercise undertaken (14,18–20). The drum-walking and drum-running rats of Thorling et al. (16,17) traveled up to twice as far as the treadmill-running rats or mice in the other studies (10 vs. 5.4–7.2 km/wk) but this was much less than the distances run by the wheel-running ApcMin mice (on average 33 km/wk) (20). The wheel-running rats studied by Reddy et al. (15) averaged 3–30 km/wk at different times during the 38-wk study.

One possible explanation for the apparently divergent results observed for the 2 rodent species is that they had different behavioral responses to the exercise intervention. The treadmill-running ApcMin mice (especially the male mice) reduced

### TABLE 3: Effects of exercise on food intake, body mass, and body fat content in AOM- or DMH-treated rats

<table>
<thead>
<tr>
<th>Rat strain and sex</th>
<th>Type of exercise</th>
<th>Exercise protocol</th>
<th>Study duration</th>
<th>Food intake by exercised rats as % control</th>
<th>Body mass of exercised rats as % control</th>
<th>Body fat content of exercised rats as % control</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sprague-Dawley male</td>
<td>Wheel</td>
<td>Free access to wheel 33 cm diameter</td>
<td>20 wk after last DMH injection</td>
<td>na</td>
<td>93%</td>
<td>na</td>
<td>13</td>
</tr>
<tr>
<td>F344 male</td>
<td>Treadmill 60 min/d @ 24 m/min 7° gradient</td>
<td>5 d/wk</td>
<td></td>
<td>na</td>
<td>82%</td>
<td>na</td>
<td>14</td>
</tr>
<tr>
<td>F344 male</td>
<td>Wheel</td>
<td>Free access to wheel 13.5 inch diameter</td>
<td>38 wk after last AOM injection</td>
<td>113%</td>
<td>106%</td>
<td>na</td>
<td>15</td>
</tr>
<tr>
<td>Fischer male</td>
<td>Treadmill 5 h/d @ 7 m/min 5 d/wk</td>
<td></td>
<td></td>
<td>122%</td>
<td>76%</td>
<td>36%</td>
<td>15</td>
</tr>
<tr>
<td>F344 male</td>
<td>Treadmill 5 h/d @ 7 m/min 5 d/wk</td>
<td></td>
<td></td>
<td>125%</td>
<td>83%</td>
<td>na</td>
<td>17</td>
</tr>
</tbody>
</table>

1 na, data not available.
their NEPA and so maintained a similar energy balance despite their greater energy expenditure during the daily forced running. Unfortunately, no published study provides data on NEPA.

**Are Apc<sup>Min</sup> mice resistant to the beneficial effects of increased physical activity on intestinal tumorigenesis?**

Despite the evident plasticity of the phenotype of Apc<sup>Min</sup> mice when exposed to pharmaceutical and dietary agents (24, 25, 28–31), the limited evidence to date suggests that the imposition of exercise regimens has only modest effects on intestinal tumorigenesis in this mouse model. In addition, what protection is apparent seems to be restricted to male mice (20). Because only males were used in the 5 published rat studies (Table 1), no comparison of this putative sex effect in mice with that in rats is possible. There are several possible explanations for the apparent resistance of Apc<sup>Min</sup> mice to the beneficial effects of increased physical activity on intestinal tumorigenesis: 1) As discussed above, the exercise regimens used with the mice appeared to have milder effects on total energy expenditure (perhaps through reduced NEPA), which limited any potential benefit gained from lower body mass. Others demonstrated that dietary (caloric) restriction reduces polypl multiplicity in Apc<sup>Min</sup> mice (30,51) as does in DMH-treated rats (14). 2) The beneficial effects of increased physical activity may be restricted to tumorigenesis in the large bowel with little or no effect on small bowel neoplasia, which is the predominant form in Apc<sup>Min</sup> mice. However, this seems unlikely because the pharmaceutical and dietary agents that modulate small intestine polyposis in Apc<sup>Min</sup> mice have similar effects on colonic tumors in carcinogen-treated animals (52). 3) Increased physical activity may reduce the development of carcinomas (the main endpoint in the carcinogen-treated rat studies) but not adenomas (polyps; the major neoplastic lesion in Apc<sup>Min</sup> mice). The epidemiological evidence for a protective effect of increased physical activity is stronger for carcinomas than for adenomas (2) and there appeared to be no effect of higher habitual physical activity on adenoma recurrence in the Polyp Prevention Trial (10). 4) The timing of the exercise interventions in the Apc<sup>Min</sup> mice may not have been optimal for suppressing tumor development especially because the benefits of chronic exercise in prevention of cancer appear to be greater if the exercise is performed before initiation of the tumor (53). Because every cell in the Apc<sup>Min</sup> mouse body has only 1 functioning copy of the Apc gene, sporadic events causing the loss of the second copy, and thus the initiation of tumorigenesis, occur early in the life course. Indeed, greater effectiveness of interventions with dietary or pharmaceutical agents in Apc<sup>Min</sup> mice were reported when the interventions were begun in utero or early in postnatal life (26,27,54). However, in the carcinogen-treated rat studies (Table 1) where greater physical activity was associated with reduced tumorigenesis, the exercise regimens were started after the administration of the carcinogen (i.e., after induction of neoplasia). This suggests that the timing of physical activity protocols in the Apc<sup>Min</sup> mouse studies was not responsible for the limited effect on intestinal tumor development in this model.

**Mechanisms of action**

Some possible biological mechanisms by which increased physical activity may reduce CRC risk were summarized by Friedenreich and Orenstein (55). However, these focus on physiological changes (e.g., decreased gastrointestinal transit time, altered prostaglandin ratios, and lowered bile acid secretion) where the mechanistic link (if any) with the known biological basis of tumorigenesis (56) is poorly understood. Tumors develop because of aberrant gene expression resulting from genomic damage including mutations, chromosomal rearrangements, telomere shortening, and abnormal epigenetic markings. Interventions that reduce neoplastic risk are likely to do so because they protect the genome against damage, upregulate apoptosis of damaged cells, improve immunosurveillance, or enhance genomic repair mechanisms (11,57).

Inflammation is emerging as a unifying link between a range of exposures, including increasing age and greater body fatness, and neoplastic risk. Some of the strongest evidence for a link between inflammation and cancer is provided by ulcerative colitis where those with ulcerative colitis have an ~10-fold greater risk of CRC (58). Both naturally occurring (e.g., the Cotton-top tamarin) and chemically induced animal models of colitis (33) support the concept that inflammation may be causal for CRC. Expression of inflammation-associated genes including cyclooxygenase-2 (COX-2) and nitric oxide synthase-2 (NOS-2) is upregulated in both inflamed mucosa and in colonic tumors (58). Crossing the Apc<sup>Δ716</sup> mouse

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**TABLE 4**

*Effects of exercise on food intake, body mass and body fat content in Apc<sup>Min</sup> mice*

<table>
<thead>
<tr>
<th>Type of exercise</th>
<th>Exercise protocol</th>
<th>Study duration</th>
<th>Food intake by exercised mice as % control</th>
<th>Body mass of exercised mice as % control</th>
<th>Body fat content of exercised mice as % control</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treadmill</td>
<td>60 min/d @ 18–21 m/min 5% gradient, 5 d/wk</td>
<td>Start at age 4 wk; 7 wk</td>
<td>104%</td>
<td>105%</td>
<td>P &gt; 0.05</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Wheel and treadmill</td>
<td>Free access to wheel then 45 min/d @ 20 m/min, 5% gradient, 5 d/wk</td>
<td>Start at age 5–6 wk; 3 wk wheel running, 5 wk on treadmill</td>
<td>na</td>
<td>0.91</td>
<td>Difference in body mass was significant (P &lt; 0.01) for females only</td>
<td>0.89</td>
</tr>
<tr>
<td>Treadmill</td>
<td>60 min/d @ 18 m/min, 5% gradient, 6 d/wk</td>
<td>Start at 3.5 wk; 9 wk</td>
<td>No effect of exercise</td>
<td>1.04</td>
<td>P &gt; 0.05</td>
<td>na</td>
</tr>
<tr>
<td>Wheel</td>
<td>Free access to wheel 9.5 inch dia.</td>
<td>Start at 4 wk; 9 wk</td>
<td>Exercising mice ate more than controls</td>
<td>0.97</td>
<td>P &gt; 0.05</td>
<td>na</td>
</tr>
</tbody>
</table>

¹ na, data not available.
(which develops multiple intestinal adenomas spontaneously) with a mouse in which the Cox-2 gene was knocked out resulted a huge reduction in numbers of intestinal neoplasms (59). A similar but less dramatic response was seen when the activity of the COX-2 enzyme was inhibited using a COX-2 selective drug (59). These data are in accord with observations from both observational (60) and intervention studies (9,61) in humans where frequent and prolonged consumption of NSAIDs appears to prevent adenoma formation or progression to CRC in some individuals. Greater physical activity, especially when accompanied by lower body fatness, may contribute to slower bowel cancer risk by reducing the inflammatory stimulus experienced by the gut mucosa.

Because both dietary (caloric) restriction and increased physical activity reduce intestinal neoplasia in rat (14) and ApcMin mouse models (20,30,51), important mechanistic information about the processes responsible for this protection may be learned from analysis of changes in gene expression in target tissues in the 2 intervention models. This hypothesis is stimulated by the outcomes of microarray profiling of global gene expression in energy-restricted rodents, suggesting that at least some of the age-associated changes in gene expression can be retarded or reversed by reducing the amount of food available (62,63). This dietary maneuver also attenuated the age-associated induction of genes encoding inflammatory and stress responses in mouse brain (62). Even relatively short periods of food restriction (2–8 wk) produced a rapid and progressive shift in gene expression in liver towards that seen in animals exposed to long-term energy restriction (64). Although there are a few reports of global changes in gene expression after exercise, these focus on changes in gene expression in skeletal muscle in response to increased physical activity (65–67) and, to our knowledge, there are as yet no published reports of global changes in gene expression in other tissues, and in particular in the gut epithelium, after chronic exercise regimens in animal models. There is a substantial opportunity to apply transcriptomic and proteomic approaches to investigate global patterns of gene expression in the intestinal mucosa of rodent models in which the natural history of neoplasia has been retarded by greater physical activity and by food restriction. Better understanding of the mechanisms through which physical activity protects against CRC would provide the basis for sound public health advice and for the development of novel intervention strategies.

In conclusion, this review confirms that the apparent protection against bowel cancer afforded by increased physical activity reported in human observational studies has been confirmed by experimental exercise studies in carcinogen-treated rat models. In these studies it appears that reduced body fatness may contribute to the reduction in cancer risk. In contrast, there is little evidence that exercise (voluntary or forced) alters tumor multiplicity in the ApcMin mouse model even though many other interventions, most notably dietary interventions, were shown to be chemopreventive in such mice. Further investigation of the putative resistance of ApcMin mice to the beneficial effects of exercise may help reveal genetic, behavioral, or other modifying factors that limit the impact of increased physical activity on colorectal tumorigenesis with implications for human interventions aimed at lowering bowel cancer risk by increasing physical activity.

LITERATURE CITED


