Chapter 7
Carcinogenicity

Human studies

As reviewed in Chapter 5, the associations between cancer risk and both overweight and physical activity suggest that weight control and physical activity generally offer benefits in terms of cancer risk rather than hazards.

The observational epidemiology of the relationship between BMI and cancer risk is sufficient to describe the possible adverse effects of lifetime weight control. Studying the consequences of intentional weight loss on cancer risk among persons who are overweight or obese has been more difficult because few people in the population have lost substantial amounts of weight and maintained that weight loss over time. The limited evidence available does not suggest an adverse effect of intentional weight loss on cancer risk, however. In addition, short-term studies of weight loss show that intermediate markers of cancer risk, such as estrogen levels, are affected in directions that would be likely to reduce long-term cancer risk.

Epidemiological studies that have examined long-term associations between changes in body weight in adulthood and overall mortality risk have not shown increased cancer risk from intentional weight loss (Williamson & Pamuk, 1993). Weight fluctuation resulting from repeated attempts to lose weight, a common finding among those who are overweight, is associated with increased risk for heart disease, stroke, diabetes and hip fracture, but has not been found to be consistently associated with increased risk of cancer (Lindblad *et al.*, 1994; French *et al.*, 1997).

For some cancer sites for which there is an inverse association between adiposity and cancer risk, factors such as alcohol, tobacco and/or pre-existing illness are likely to confound the associations. For example, overweight is associated with reduced risk for lung cancer and for cancers of the head and neck largely because those who abuse tobacco or alcohol are both less obese and at increased cancer risk due to their tobacco and alcohol habits. Reduced body weight can also be a sign of pre-existing cancer or of illnesses that increase cancer risk. Weight loss due to occult malignancies can be substantial for months or years before cancer diagnosis, and chronic conditions such as cirrhosis and chronic lung disease can lead to both chronic weight loss and increased risk for cancers at sites such as the lung, oral cavity and liver.

Among premenopausal women, there is an inverse association between BMI and breast cancer risk (see Chapter 5). The mechanisms responsible for this association are uncertain, but may well be related to the anovulation that accompanies excess weight. Reducing the prevalence of overweight among premenopausal women in the population by avoiding excess weight gain and/or by maintaining weight loss might improve the anovulation associated with overweight and thereby result in increased rates of premenopausal breast cancer.

The existing evidence on the relationship between physical activity and cancer risk shows either benefits or no association in nearly all studies. Evidence for an adverse effect of physical activity is seen rarely in epidemiological studies (for example, Mink *et al.*, 1996).

Experimental models

While no evidence was available to the Working Group that either energy restriction or conditions of physical activity are capable of inducing cancer *per se*, conditions of restriction and exercise have been reported to increase the carcinogenic response in some defined model systems of chemical induction of cancer.

Weight control

Energy restriction, but not restriction of total diet, in the range of 10–40% of *ad-libitum* intake, when imposed chronically, is associated with inhibition of tumour development in most but not all experimental model systems in which it has been evaluated. On the other hand, there are several reports that when energy restriction was interrupted with periods of refeeding, loss of the protective effect against cancer and/or enhancement of tumour development occurred in model systems for breast, colon and liver cancer (Pollard *et al.*, 1984; Lagopoulos *et al.*, 1991; Mehta *et al.*, 1993; Harris *et al.*, 1995; Tagliaferro *et al.*, 1996). Studies showing enhancement of tumours or of tumour markers are summarized in Table 53. Such experimental protocols have been referred to as energy cycling, patterned calorie restriction or cyclic food restriction, and such patterns of eating have parallels in human populations. In these studies, all of which involved the promotion phase of tumorigenesis, a variety of cyclic feeding patterns were investigated, but invariably

Table 53. Studies of increased mammary cancer and liver foci in cyclic-fed rodents

Organ site/ species/ strain (sex)	Age at beginning of study (wk)	No. of animals per group	Carcinogen exposure	Dietary restriction	Timing of restriction	Carcinogenic effect	Summarized effect	Reference
Mammary cancer								
Rat								
Sprague-Dawley (F)	3	50–56	25 mg/kg bw MNU at 50 days of age, i.p.	33% energy restricted	11 days following MNU, for 18 weeks AL control Meal-fed Meal-fed, cyclic restricted	Mammary cancer incidence: 54% 57% 63% ($p <$ 0.0001 vs AL)	Increased cancer incidence with meal-fed cyclic restricted	Tagliaferro *et al.* (1996)
Liver foci								
Mouse								
Swiss OF1 (M/F)	Weanling	16–18	0.5 µmol/g bw NDEA at wk 0, i.p.	Cereal-based diet, 30% diet restricted	Up to 36 weeks AL throughout DR throughout AL-24 wk/DR-12 wk DR-24 wk/AL-12 wk	No. of foci/group 338 115 175 173	DR throughout inhibited DR-24 wk/ AL-12 wk increased compared with DR throughout	Lagopoulos *et al.* (1991)

MNU, *N*-methyl-*N*-nitrosourea; NDEA, *N*-nitrosodiethylamine; i.p., intraperitoneal; DR, dietary restriction; AL, *ad libitum*

led to loss of protective activity against cancer relative to that which was observed in chronically restricted controls. In other fields of inquiry, a similar pattern of energy cycling is referred to as weight cycling. Rodent models have been used to study the effects of weight cycling on propensity for obesity, development of insulin resistance, effects on diabetes and cardiovascular disease (Lu *et al.*, 1995; Lauer *et al.*, 1999; Sea *et al.*, 2000).

Physical activity

While physical activity protocols have resulted in inhibition of experimentally induced carcinogenesis, certain protocols have led to enhancement of the carcinogenic response (Table 54).

Thompson *et al.* (1988) investigated the effects of low-intensity, short-duration treadmill running on induction of mammary carcinogenesis. Female Sprague-Dawley rats were maintained on a 5% (w/w) corn oil diet (AIN-76A) from 21 to 64 days of age. At 50 days of age, they received either 5 mg 7,12-dimethylbenz[*a*]anthracene (DMBA) or the vehicle. Fourteen days after DMBA intubation, they were randomized into three groups: 5% fat (w/w), sedentary; 24.6% fat (w/w), sedentary; or 24.6% fat (w/w), exercised on a motor-driven treadmill at a belt speed of 20 m/min and a 1° incline for 15 min per day on five days per week for 18 weeks (moderate exercise). Animals fed the high-fat diet had higher incidence and multiplicity of breast cancers than the low-fat group. Moderate treadmill exercise increased the incidence and number of cancers and shortened latency in comparison with the sedentary high-fat and low-fat diet groups. Body composition was not altered by the exercise regime imposed, although the exercised animals weighed more than either sedentary group.

To control better for the non-training effects of treadmill running, Thompson *et al.* (1989b) fed female Sprague-Dawley rats a purified 5% fat diet (AIN-76A) from 21 to 64 days of age. At 50 days of age, they were administered 5 mg DMBA intragastrically. Fourteen days later, they were divided into three diet groups: 5% fat as corn oil, 24.6% fat as corn oil, or 24.6% fat as a mixture of palm (21.8%) and corn oil (2.8%). The combination of palm and corn oil provided the same amount of linoleic acid per gram as the 5% corn oil diet. Half of the animals receiving each diet were exercised on a treadmill at a speed of 20 m/min with a 1° incline for 15 min per day on five days per week, and were designated as the moderate-intensity treadmill exercise group. The remaining half were exercised at a speed of 2 m/min with a 1° incline for 15 min per day on five days per week, and were designated as a low-intensity sham control. The experiment was terminated 154 days after DMBA treatment. The median tumour-free time was significantly shortened by moderate-intensity exercise in rats receiving the 24.6% fat, corn oil-formulated diet in comparison with the sham-treated rats receiving the same diet (43 days versus 62 days, $p = 0.028$). Similarly, tumour appearance was more rapid in rats that exercised at moderate intensity and consumed the low-fat corn oil diet than in the low-fat diet-fed sham-exercised group (57 days versus 67 days, $p = 0.046$). Exercise exerted no effect on the rate of tumour appearance in rats that received the 24.6% palm and corn oil mixture. Mean body weight gains were similar in all groups, although moderate-intensity exercised rats consistently weighed more than sham-exercised rats consuming the same diet. Gross carcass composition was unaffected by either the level of exercise or the amount of dietary fat consumed.

In another study, female Sprague-Dawley rats were subjected to an exercise protocol (treadmill 18 m/min at 15% incline for 60 min per day five times per week) from 21 to 50 days of age and given one injection of 37.5 mg/kg bw *N*-methyl-*N*-nitrosourea (MNU) at 50 days of age. At 22 weeks after MNU treatment, the tumour incidence, multiplicity and latency period were not different, but the growth rate of tumours in the exercise group was significantly greater than in the sedentary group (0.107 ± 0.025 versus 0.043 ± 0.009 g/day) and the final tumour weights were greater after exercise (3.2 ± 0.74 versus 1.2 ± 0.34 g) (Whittal-Strange *et al.*, 1998).

Using a different model system, Craven-Giles *et al.* (1994) investigated the modulation of pancreatic foci, an intermediate biomarker for pancreatic cancer, by treadmill running. As reported in Chapter 5, the burden of pancreatic foci was increased by treadmill running.

Table 54. Studies of increased carcinogen-induced tumours due to physical activity and exercise in experimental animals

Organ site/ species/strain (sex)	Age at beginning of study (wk)	Study type	No. per group	Carcinogen exposure/ diet	Type of exercise	Results	Reference
Mammary gland							
Rat							
Sprague-Dawley (F)	3	Post-initiation	28–35	5 mg DMBA at 50 days, p.o. 24.6% fat	Treadmill at 64 days for 18 weeks	Increase of tumour incidence	Thompson *et al.* (1988)
Sprague-Dawley (F)	3	Post-initiation	34–55	5 mg DMBA at 50 days, p.o.	Treadmill at 64 days for 140 days		Thompson *et al.* (1989b)
				Corn oil 5% fat	High versus low	Decrease of latency	
				Corn oil 24.6% fat	High versus low	Decrease of latency	
				Corn/palm oil 24.6% fat	High versus low	No effect	
Sprague-Dawley (F)	3	Pre-initiation	40	37.5 mg/kg bw MNU at 50 days, i.p., killed at 24 weeks	Treadmill from 21 to 50 days	Increase of tumour growth	Whittal-Strange *et al.* (1998)
Pancreas							
Rat							
Lewis (M)	2	Post-initiation	10–19	30 mg/kg azaserine at 14 days, i.p.	Treadmill from 13 to 31 weeks	Increase of acidophilic acinar cell foci	Craven-Giles *et al.* (1994)

Experiments in which decreased tumour incidence was observed are presented in Chapter 5.
DMBA, 7,12-dimethylbenz[a]anthracene; MNU, *N*-methyl-*N*-nitrosourea; i.p., intraperitoneal; p.o., orally