

Chapter 9

Summary of data

Characteristics, occurrence, trends and analysis of weight and physical activity

The prevalence of overweight (body mass index (BMI) between 25 and 30 kg/m²) and obesity (BMI of 30 kg/m² or higher) is increasing rapidly worldwide. In many countries overweight and obesity co-exist with undernutrition. The increase in prevalence is especially rapid in developing countries undergoing an economic transition to a market economy. Obesity is largely preventable through changes in lifestyle. The fundamental causes of the obesity epidemic are societal, resulting from an environment that promotes sedentary lifestyles and over-consumption of energy.

These changes in lifestyle and the resulting positive energy balance leading to weight gain and increased rates of obesity are all implicated in the changing patterns of morbidity, that usually start with a rapid increase in diseases such as type II diabetes mellitus and cardiovascular diseases, followed later by an increase in rates of various types of cancer such as cancer of the breast and colon.

The BMI provides the most widely accepted measure of the degree of overweight and obesity. It can be used to estimate the prevalence of obesity within a population and to estimate the health risks associated with it. However, the BMI may represent different levels of fatness and body fat distribution depending on age, sex and ethnicity.

Accumulation of body fat in the abdominal area (abdominal fat distribution) represents a particular risk for many of the metabolic consequences of obesity. Therefore, measurement of the

waist circumference provides a simple and practical method, in addition to BMI, to identify individuals and populations at risk for obesity-associated illness.

The classification of overweight and obesity by BMI categories is complicated in children and adolescents by rapid changes of height and weight during growth. There is an emerging consensus on how to use BMI in children and adolescents, but there is still little comparable information on prevalence. Despite the methodological problems, the available cross-sectional and longitudinal data suggest that the prevalence of overweight and obesity are also rapidly increasing in these age-groups all over the world.

There are many ways to assess physical activity, ranging from precise techniques such as calorimetry and direct observation, to electronic monitoring devices. However, usually only job classification has been used to describe physical activity behaviours in large, representative populations. Job classifications of employed adults, however, are of limited value when misclassification is known to exist, or in populations where work-related energy expenditure is not very prevalent, as in developed countries. Recall surveys for occupational, leisure-time and household activity have been devised with a variety of time-frames from one week to a lifetime. Such surveys range in complexity from global attributions of activity and other single-item reports of general activity participation, to detailed quantitative histories.

Elucidation of the associations of physical activity with disease risk and

with weight control depends crucially on having reliable valid measures of the major types of physical activity in its various contexts. It is known that strenuous physical activity is recalled with greater accuracy than light or moderate activity, while recall of recent activities is more accurate than that of activities at an earlier point in time.

Data on the prevalence and time-trends in physical activity patterns and sedentary behaviour are available mainly from affluent industrialized societies. These data focus mainly on participation in leisure-time physical activity. For the vast majority of countries worldwide, notably most developing nations, population data on physical activity participation are unavailable. In these countries, economic transition involves large numbers of people moving away from traditionally active rural lifestyles to cities and other urban environments. In such settings, they are likely to be much less physically active. Such changes in physical activity are affecting an increasing proportion of the world's population.

Intervention trials aimed at promoting weight reduction or physical activity have so far yielded disappointing results in terms of long-term changes, probably because of the complex range of social and behavioural factors that interact in determining the relevant habits. However, it is generally agreed that prevention of overweight and obesity and promotion of physical activity should receive high priority in the public health area. Prevention of overweight and obesity and promotion of physical activity should begin early in life and require individual action and

responsibility, but also structural changes in the physical, economic, political and socioeconomic environments.

At present, our limited understanding of variation in susceptibility to obesity is a powerful justification for the development of strategies which are population-based rather than selectively targeted at high-risk individuals.

Metabolic consequences of overweight and physical activity

Human studies

Weight reduction and physical activity have strong and independent effects on various metabolic factors related to cancer risk. These effects vary somewhat by age, gender and menopausal status. Furthermore, physical activity has effects that are unrelated to those of body weight. Most studies have been conducted in Caucasian persons residing in western countries.

BMI

BMI is positively associated with insulin and inversely with IGFBP-1 and IGFBP-2 levels, in men and in both pre- and postmenopausal women. However, a BMI above 30 kg/m² ("obesity") is associated with a mild decrease in absolute IGF-I concentrations, compared with normally nourished but non-obese subjects. BMI is positively related to plasma-free IGF-I, unbound to any IGF-binding protein.

In both men and women, BMI is inversely related to plasma levels of sex-hormone-binding globulin (SHBG). However, the relationships of BMI to total and bioavailable androgens and estrogens depend on gender and menopausal status. In men and postmenopausal women, BMI correlates directly with estrone and with total and bioavailable estradiol levels. In premenopausal women, it is also related to higher estrone concentrations, but not to total or bioavailable estradiol levels. In men, increasing BMI is associated with decreased levels of total plasma testosterone, and a BMI above 30 kg/m² is also

associated with a decrease in bioavailable testosterone, unbound to SHBG. In women, BMI shows no clear association with plasma total testosterone, except in women with polycystic ovary syndrome (PCOS), in whom obesity increases total plasma androgen levels. However, BMI is positively associated with free testosterone concentrations in both pre- and postmenopausal women.

Weight reduction

Weight reduction in overweight and obese men and women has consistently been shown to lead to reduced insulin and glucose levels and to improve insulin sensitivity; it is accompanied by a rise in SHBG levels. Such findings were observed in both men and women and whatever method was used to reduce weight (low-energy or very low-energy diets, other changes in dietary composition, exercise, drugs or by-pass surgery). In obese women with PCOS, weight loss is usually associated with reduced plasma concentrations of total and bioavailable androgens (androstenedione, testosterone) as well as estrone. However, inconsistent effects on androgens and estrogens have been observed

with weight reduction in normo-androgenic premenopausal women.

Physical activity

Most studies on the effects of physical activity on hormone concentrations have addressed the short-term consequences (0–2 hours after exercise). Strenuous aerobic exercise acutely decreases plasma insulin and increases serum SHBG and total and free testosterone concentrations. In the longer term, an increase in physical activity lowers fasting plasma insulin concentration and improves insulin sensitivity, but long-term effects on SHBG and total or bioavailable sex steroids are less clear. Exercise acutely increases absolute concentrations of IGF-I and IGFBP-1, while the longer-term effects of increased regular exercise are unclear.

Experimental models

Physiological, metabolic and hormonal changes occur in experimental systems when energy balance is modulated either by altering energy intake using dietary approaches or by increasing energy expenditure through modulation of physical activity.

Metabolic syndrome – important to act on !

'Metabolic syndrome' occurs commonly in middle-aged men. It is variously defined as a combination of elevated blood glucose, elevated triglycerides, low levels of HDL cholesterol, systolic or diastolic hypertension, and obesity. Other characteristics included in the definition are central obesity (waist circumference or waist hip circumference ratio) and elevated levels of insulin (hyperinsulinaemia).

This 'metabolic syndrome' is important, as this clustering of risk factors is associated with increased risk of the development of coronary heart disease, type II diabetes and certain types of cancer. The favourable trends in the reduction in the rate of heart attack and stroke over the past 30 years in western countries may ultimately be reversed as the consequences of the increase in diabetes and obesity become manifest in middle-aged and older adults.

Weight control

Physiological changes associated with lowering dietary intake include a lower body weight with lower adiposity or fat mass, extended mean and maximal life-span, increased water consumption, decreased urinary output, decreased average body temperature, improved tolerance of high temperatures, decreased ability to withstand cold, decreased blood pressure with bradycardia and delayed puberty. Metabolic effects include lower activity of the enzymes involved in glycolysis, an increase in enzymes involved in gluconeogenesis and changes in fatty acid metabolism. Endocrine effects include reduced levels of growth hormone, prolactin and sex-steroids, inhibition of sex-specific cytochrome P450s and elevated levels of glucocorticoids.

Physical activity

Physiological changes accompanying increased physical activity include loss of body weight and adiposity, reduced blood pressure, a relative increase in heart size as body weight decreases and delayed puberty.

Metabolic effects include inhibition of glycolysis in trained animals, and increased plasma levels of fatty acids and protein. Endocrine effects include alterations in growth hormone dependent on type of activity, acute increases in catecholamines and glucocorticoids, reductions in sex steroids (dependent on the intensity and duration of the activity), increased glucocorticoids and catecholamines and reduced sex steroids (with exhausting exercise).

A lack of long-term studies evaluating combinations of controlled dietary intake and controlled physical activity is noted. This is especially important since combinations of physical activity and dietary restriction may influence mortality rates.

Cancer-preventive effects

Human studies

Body weight

Colon cancer. Both case-control and cohort studies have shown positive associations between various measures of adiposity and risk of colorectal neoplasia. Studies have been consistent in many, mostly developed, countries. The association is much less evident for rectal cancer than for colon cancers. There is an approximately linear trend of colon cancer risk from BMI 23 to 30 kg/m², with a risk increase across this range of about 25% among women and about 50% among men. A similar relationship is seen also for colon adenomas, the precursor lesions for colon cancer, but the association is stronger for larger adenomas than for smaller adenomas. The association is similar for time periods early and late in adulthood and is largely independent of other known risk factors for colon cancer. These patterns suggest an effect of factors related to adiposity on the promotion of colon cancer.

Premenopausal breast cancer. In populations with a high incidence of breast cancer, the overall association between BMI and breast cancer risk among premenopausal women is inverse. This has been documented in numerous cohort and case-control studies that have carefully controlled for many reproductive and lifestyle factors. This reduction in risk with overweight is modest and does not appear to be observed until a BMI of 28 kg/m². Despite this reduced breast cancer incidence risk, however, the breast cancer mortality rate is not lower among heavier premenopausal women.

Postmenopausal breast cancer. More than 100 studies over nearly 30 years in populations in many countries have established that increased body weight increases breast cancer risk among postmenopausal women. Nearly all of

these studies have shown that this association is largely independent of a wide variety of reproductive and lifestyle risk factors, and recent studies have indicated that it is independent of the effect of physical activity. The association between overweight and breast cancer appears to increase in a stepwise fashion with advancing age after the menopause.

The large majority of cohort and case-control studies have shown positive associations, although the increase in risk with BMI has been somewhat modest. Above a BMI of 24 kg/m², breast cancer incidence rates increase among postmenopausal women, with the greatest slope of increase in risk across higher BMI levels being seen in low- and moderate-risk countries. This suggests that increases in BMI now being observed in countries previously at low risk for breast cancer may be a major factor contributing to future increases in breast cancer rates in those countries. Further, while risk ratios have levelled off at BMI levels near 28 kg/m² in high-risk countries, this is not the case in low- to moderate-risk countries, where risk has continued to increase across a wider range of body weight. The association between BMI and breast cancer is stronger among women who have never used postmenopausal hormone replacement therapy, suggesting that the increased breast cancer risk from overweight may be mediated by the elevations in endogenous estrogen production among heavier women.

Adult weight gain has been shown to be a strong and consistent predictor of postmenopausal breast cancer risk. As with the studies on BMI and breast cancer, adjustment for many breast cancer risk factors, including physical activity, does not weaken this association, which is particularly strong among women who have never used hormone replacement therapy.

Endometrial cancer. A positive association of endometrial cancer with body weight has been observed in nearly all of 25 epidemiological studies, including in studies conducted in Asia, Europe and North America, and among pre- and postmenopausal women. Overweight or obese women appear to be at a 2–3-fold increased risk of endometrial cancer. Adult weight gain appears to be a better predictor of risk than current weight and to be associated with risk in a linear dose-dependent fashion.

Prostate cancer. Among more than 25 studies that have examined the association between body weight and prostate cancer, no consistent pattern of association has emerged. These studies have included a variety of populations in North America, Europe and Asia, and considered weight at different life periods and body fat distribution. Some studies also focused on the more aggressive forms of the disease which may be less subject to screening detection bias. In sum, the absence of a clear pattern of association across many studies suggests the absence of an important association between body weight and the risk of prostate cancer.

Kidney cancer. Nearly all studies of renal-cell cancer (17 out of 19) have observed a more than twofold higher risk among obese men and women compared with persons of normal weight. This association is not seen in studies of cancer of the renal pelvis. The studies have been conducted in Australia, China, Europe and the United States. Obesity has been consistently observed to be associated with increased renal cancer risk in a dose-related manner among both men and women, with an approximately 2–3-fold increase in risk among those with BMI of 30 kg/m² or greater.

Lung cancer. Body weight has been observed to be inversely associated with

lung cancer. However, in most studies, this association is substantially confounded by cigarette smoking history, and in some studies this inverse association was less consistently shown among never-smokers. Thus, the inverse association between body weight and lung cancer risk is difficult to interpret as causal because of the interrelationships between weight and the use of tobacco and tobacco-related chronic lung disease.

Oesophageal cancer. Obesity has been shown to be associated with increased risk for adenocarcinomas of the lower oesophagus and of the gastric cardia. There have been few such studies, but their findings have been consistent, suggesting a two-fold or greater increased risk for those with BMI over 25 kg/m².

Thyroid cancer. Obesity has been suggested to be associated with a modest increase in risk for cancer of the thyroid in a majority of 13 studies, mostly conducted among women.

Other cancers. There is a paucity of epidemiological data on body weight and cancers of the ovary, testis, liver, pancreas, gallbladder, head and neck cancers, and cancers at many other sites. The evidence from studies conducted in various countries for these sites is inconsistent and does not allow any conclusion to be drawn on possible associations with overweight or obesity.

Intervention trials with intermediate-effect biomarkers. Weight reduction in postmenopausal women has been shown to be associated with reduction of dense areas in mammograms in one clinical trial of a low-fat diet with minimal weight loss.

Physical activity

Colorectal cancer. Approximately 50 studies have examined the association between physical activity and colon

cancer and some of these examined both colon and rectal cancer. These studies have almost uniformly shown that increasing levels of activity are associated with an approximately 40% reduction in risk of colon cancer, independent of BMI. Studies including rectal cancer indicate much weaker associations. Considerable consistency in associations has been detected using different methods for estimation of activity in many different populations, in America, Asia and Europe. Increasing levels of activity, whether in intensity, frequency or duration, seem to be associated with greater reduction in risk. It appears that activities performed at a more intense levels and sustained over many years are associated with the greatest risk reduction. The precise amount of activity needed to reduce colon cancer risk is not clear, however, due to the variety of methods used to estimate activity. It has been estimated that at least 30 minutes per day of more than moderate-level physical activity might be needed to see the greatest effect in risk reduction.

Breast cancer. Most of the more than 30 epidemiological studies, conducted in Asia, Europe and North America, demonstrated lower breast cancer risk among the most physically active women. In 8 of 14 cohort studies and in 14 of 19 case-control studies, lower breast cancer risk was seen among women who were most active. The decrease in risk of breast cancer was, on average, about 20–40%. Evidence for a linear trend in effect of increasing activity with decreasing risk of breast cancer was found in most of the studies that examined the dose-response relationship. These associations were observed for both occupational and recreational activity, among pre- and postmenopausal women, for activity measured at different periods in life and for different levels of intensity of activity. Activity that is sustained throughout lifetime, or at a

minimum performed after menopause, may be particularly beneficial in reducing breast cancer risk. Although there are only limited data on the effect of physical activity in different ethnic and racial groups, it appears that physical activity does have similar effects within different populations. An effect of physical activity on breast cancer risk is biologically plausible since physical activity has a direct effect on the prevention of weight gain and postmenopausal obesity, both established breast cancer risk factors, but physical activity seems to have an effect on breast cancer risk independent of that of body weight. It has been estimated that breast cancer risk reduction begins at levels of 30–60 minutes per day of moderate-intensity to vigorous activity in addition to the usual levels of occupational and household activity of most women. Although lifetime physical activity is desirable, beginning recreational physical activity after menopause can probably be beneficial for both weight control and breast cancer risk reduction.

Endometrial cancer. Ten studies of populations in Asia, Europe and North America have been quite consistent in suggesting a moderately strong protective effect of physical activity on endometrial cancer. In most studies, this effect appeared to be independent of the association with body weight. An effect of physical activity on endometrial cancer is biologically plausible since it has a direct effect on the prevention of weight gain, an established risk factor for this disease.

Prostate cancer. About twenty epidemiological studies conducted in North America, Europe and Asia were considered in assessing the relationship of physical activity to prostate cancer. Although the data are inconsistent, a majority of studies found an inverse association with physical activity. The observed effect has been moderately strong and sometimes observed only in

subgroups. Although additional data are needed, the available evidence suggests that physical activity may protect against prostate cancer.

Kidney cancer. The results of studies regarding the association between physical activity and renal-cell cancer are inconsistent for both occupational and leisure physical activity.

Lung cancer. Five of seven studies of physical activity and lung cancer demonstrated a decreased risk of lung cancer among the most physically active subjects. This effect could well be confounded by smoking and/or by chronic lung disease, as these factors both tend to reduce physical activity and are associated with increased lung cancer risk. Given these factors, and the limited amount of data available, the evidence for an association between physical activity and lung cancer is inconclusive.

Other cancers. The few epidemiological data on physical activity and cancers of the ovary, testis, liver, oesophagus, pancreas, gall-bladder and other cancer sites are inconsistent and do not allow any conclusion to be drawn on possible associations with physical activity.

Intervention trials with intermediate effect biomarkers. The data on effects of physical activity on intermediate effect markers for cancer from intervention studies are limited. Results of several intervention studies on training effects on menstrual and reproductive factors in girls and young women have been published. Most were very small and uncontrolled studies. In general, it appears that a greater effect of training is observed when body weight is decreased and when exercise is strenuous and prolonged. Data on exercise effects on other biomarkers of cancers from intervention studies are not available.

Population attributable risk

The proportions of some common cancers that are attributable to elevated body weight and to inadequate physical activity are substantial. The population attributable risk estimates for elevated BMI and for inadequate physical activity are derived from relative risk estimates that have been adjusted using multivariate methods, with many of the relative risks for elevated BMI having been adjusted for physical activity, and most of the physical activity estimates having been adjusted for BMI. To the extent that the measures of BMI and physical activity are accurate, those attributable risks should be largely independent, so that the attributable risk estimates for BMI and physical activity can be approximately summed to express an estimate of their joint impact on cancer risk. If physical activity is imprecisely measured, the amount of cancer risk attributable to physical activity will be underestimated, and residual confounding is possible. Nevertheless, the sum of the effects of elevated body weight and inadequate physical activity for many cancer sites is clearly substantial. For colon cancer, for which approximately 11% is attributable to BMI and 13–14% to physical inactivity, the combined effect of these two factors accounts for about a quarter of the cases. For postmenopausal breast cancer, for which 9–11% is attributable to BMI and 11% to physical inactivity, the combined effects account for about one fifth of the cases. Although the risks attributable to physical activity have not been quantitatively estimated for endometrial cancer, it is likely that with a 39% attributable risk for BMI alone, the combined effects might well account for approximately half of the cases. The attributable risks for BMI alone are 25% for kidney cancer and 37% for oesophageal cancer. Therefore, for many of the common cancers, between one quarter and one third of the cases may be attributable to the combined

effects of elevated body weight and inadequate physical activity.

Experimental studies

Weight control

Cancer and premalignant lesions

Restriction of energy intake in the range of 10–40% of the amount consumed by control animals fed *ad libitum* inhibited the development of cancer in the majority of experimental model systems for carcinogenesis, including spontaneous and chemically induced cancers of the mammary gland, liver and pituitary gland, chemically induced cancers of the colon and skin, as well as spontaneous and genetically induced lymphomas. However, some types of tumour were not inhibited by energy restriction, including chemically induced ductular carcinomas of the pancreas. Limited evidence of cancer prevention was available for chemically induced tumours of the prostate and spontaneous and chemically induced tumours of the acinar pancreas. The inhibitory activity in these models has been reported to be proportional to the duration and magnitude of the restriction imposed. It is important to note that cancer-preventive activity generally coincided with a slower rate of growth or the absence of weight gain rather than with weight loss. While some evidence implies a role of body fat in accounting for these effects, other results suggest that the effects are not due to body fat *per se*. Thus, in terms of the cancer-preventive effects of weight control, the role of energy restriction is prominent. Both the initiation and the post-initiation stages of chemically induced mammary carcinogenesis have been reported to be inhibited by energy restriction. However, the protective effects of energy restriction maintained during the post-initiation stage of carcinogenesis are greater in magnitude and have been most consistently observed in a wide spectrum of model systems. The effects of dietary restriction on carcinogenesis closely parallel the

effects of energy restriction observed for the mammary gland, acinar pancreas and liver. Further, energy restriction, irrespective of whether fat or carbohydrate is reduced, is more effective than a simple reduction in fat intake at constant energy intake in preventing mammary and skin carcinogenesis. However, feeding a high-fat restricted diet generally dampens prevention by under-feeding of cancer at these sites. Overall, the available evidence indicates that a reduced rate of growth and a smaller size for age as achieved by restricting energy intake prevent the development of cancer in laboratory animal models.

Intermediate biomarkers

The effects of energy restriction on intermediate biomarkers have been investigated for colon, liver, pancreas and mammary gland. Markers studied included cell proliferation, aberrant crypt foci, glutathione *S*-transferase-positive foci, pancreatic acinar foci and epidermal growth factor. In general, changes in these markers paralleled the reported effects of energy restriction on cancer end-points.

Physical activity

Cancer and premalignant lesions.

Investigations of the effect of physical activity on cancer prevention in chemically induced or spontaneous tumour models have relied primarily on providing animals with access to an activity wheel (voluntary activity) or on exercising animals using a treadmill (involuntary activity). The effects of such activity on tumour development have varied, with reports of inhibition, no effect and enhancement of the carcinogenic response. Chemically induced rat mammary tumour induction was inhibited by voluntary but not involuntary activity. Colon tumour yield was reduced by voluntary activity in rats in two studies. Spontaneous intestinal tumours in Min mice were not affected by in

voluntary activity. In one study, rat liver tumour induction was clearly inhibited by involuntary exercise. Pancreatic ductular tumour induction was not inhibited by voluntary exercise. In general, when physical activity has been shown to protect against cancer, the magnitude of the effect has been modest. Studies of voluntary activity have more commonly reported protection than studies in which treadmill running was investigated. However, clear-cut exercise dose effects have not been shown. Thus, from experimental studies, the type of physical activity and the conditions of exercise intensity, duration and frequency that consistently and reproducibly inhibit tumour development have yet to be defined.

Intermediate biomarkers

The effects of two types of physical activity, free access to an activity wheel and treadmill running, on intermediate biomarkers for liver, pancreatic or mammary gland cancer have been investigated. The markers studied include glutathione *S*-transferase-positive hepatic foci, pancreatic acidophilic and basophilic foci and cell proliferation and development in the mammary gland. Whereas changes in marker activity generally reflected a protective effect of access to a running wheel against liver cancer, marker responses in pancreas and mammary gland failed to provide clear evidence for protection by physical activity in these organs.

Mechanisms of cancer prevention

Weight control

Humans

One major class of mechanisms that may form a physiological and causal link between excess body weight, physical inactivity and cancer risk is alterations in endogenous hormone metabolism.

Obesity and lack of physical activity are causes of insulin resistance and chronic hyperinsulinaemia. Chronic hyperinsulinaemia, in turn, is related to a

host of metabolic alterations including elevated blood glucose levels, decreased levels of IGF-binding proteins (IGFBP-1 and -2) and of SHBG, and increases in free plasma IGF-I unbound to IGF-binding proteins and bioavailable androgens and estrogens unbound to SHBG. In addition, adiposity leads to increased peripheral formation of estrogens from androgen precursors, and hence to higher absolute estrogen concentrations in men and postmenopausal women. In some premenopausal women, hyperinsulinaemia may lead to ovarian overproduction of androgens and, in extreme cases, to chronic anovulation and a drop in ovarian progesterone production.

This global pattern of obesity-associated endocrine alterations, or specific aspects of it, may be causally related to increased risk of cancers of the endometrium and breast. The most firmly established epidemiological evidence is for a relationship between bioavailable estrogens in postmenopausal women and breast cancer risk. In addition, there is substantial evidence that elevated estrogen concentrations also increase endometrial cancer risk in postmenopausal women. Before menopause, endometrial cancer risk appears to be increased especially in women with severe ovarian hyperandrogenism, who have frequent anovulatory cycles and hence low ovarian progesterone production. The roles of endogenous sex hormones in the etiology of premenopausal breast cancer, and of endogenous hormones in general in relation to ovarian cancer, are less clear. Current evidence shows no clear relationship between total and bioavailable plasma androgens and risk of prostate cancer, nor with anthropometric indices of adiposity.

Exogenous hormones for postmenopausal replacement therapy have been generally found to increase breast cancer risk, but may either increase or

decrease risk of endometrial cancer, depending on the type of hormone preparation used. This, combined with favourable hormonal changes observed after weight loss, strongly suggests that weight loss in obese postmenopausal women may decrease the risk of these cancers.

There is some evidence that chronic hyperinsulinaemia may increase the risk of colon cancer, and chronically elevated insulin levels may also contribute to the development of endometrial cancer. Furthermore, there is indirect evidence to suggest that chronic hyperinsulinaemia and related metabolic alterations may also increase risk of cancers of the pancreas and kidney.

Relatively independently of obesity, elevations in circulating IGF-I, either as absolute concentrations or relative to levels of IGFBP-3, its major plasmatic binding protein, appear to be related to increased risk of prostate cancer and premenopausal breast cancer, and possibly cancers of the colorectum and lung. Although prolonged fasting and energy malnutrition cause a dramatic drop in total IGF-I levels, obesity is not related to an increase, but rather also to a mild decrease in IGF-I, compared with the normally nourished non-obese state.

Frequent gastro-oesophageal reflux, which is often related to obesity, may increase the risk of Barrett's oesophagus and its progression towards oesophageal adenoma.

Experimental studies

Energy restriction has been reported to inhibit the initiation and post-initiation (promotion/progression) stages of carcinogenesis, although in some model systems it is without protective activity. Energy restriction modulates the activity of proteins in both phase I and phase II drug-metabolizing systems as well as the processes involved in DNA repair. Collectively, these effects are likely to

work in concert to account, at least in part, for the inhibitory effects of energy reduction during carcinogenic initiation. In the majority of model systems evaluated, energy restriction modulates the post-initiation stages (promotion/progression) of carcinogenesis. Mechanisms likely to account for protective activity include inhibition of cell proliferation and/or the induction of apoptosis. Candidate molecules that may mediate these effects include sex steroids, glucocorticoids and insulin-like growth factors and their binding proteins. The signal transduction pathways and the specific components of cell cycle and cell death machinery involved in these processes are beginning to be elucidated. Limited information is available on the role of angiogenesis or modulation of the immune function in relation to the protective activity of energy restriction.

Physical activity

Humans

Mechanisms by which weight loss due to physical activity could have cancer-preventive effects have been described above. Other proposed mechanisms through which especially physical activity might decrease cancer risk, but for which there is no direct epidemiological evidence, include enhanced immune function, decreased intestinal transit time and effects on bile acid metabolism.

Experimental studies

While physical activity has been shown to inhibit the development of cancer in several model systems, the number of mechanistic investigations is limited. Areas investigated include modulation of immune function and endocrine status, but results are inconclusive. While other mechanisms have been hypothesized, relevant data from studies under experimental conditions of physical activity shown to inhibit tumour development were not available.

Other beneficial effects*Weight control***All-cause mortality**

Studies on all-cause mortality in relation to BMI are associated with methodological problems. In the general population, the association between BMI and all-cause mortality follows a U-, J- or reverse J-shaped relationship. In studies with good control for confounding, BMI in the normal range showed the lowest risk. The current observational data do not indicate that weight loss lowers risk of all-cause mortality.

Cardiovascular disease

High BMI and weight gain increase risk for cardiovascular diseases. Limited evidence exists from observational studies that weight loss decreases risk of cardiovascular disease. This is supported by the proven benefits of weight reduction in intervention trials among high-risk individuals.

Effects on morbidity

Both BMI status and weight gain increase risks of hypertension, type II diabetes, insulin resistance, dyslipidaemia and numerous other overweight-related conditions. Intentional weight loss of 5–10% resulting from lifestyle changes improves surrogate markers of cardiovascular diseases and reduces the risk of hypertension and type II diabetes in overweight high-risk individuals. Maintained weight loss also reduces risks of many other obesity-related diseases and quality of life.

Physical activity

Physical activity has important health benefits above and beyond improved weight control. The level of physical activity is inversely associated with all-cause mortality rates in middle-aged and older men and women. This relationship is linear, at least up to an energy expenditure in activity of about 14.7 MJ (3500 kcal) per week, with little further benefit

at higher levels. This is equivalent to brisk walking at 6.4 km/h for about 8.5 h. Physical inactivity and low levels of fitness are also associated with higher rates of coronary heart disease, stroke, type II diabetes, hypertension and (in a smaller number of studies) gallbladder disease.

The compelling evidence related to coronary heart disease from studies published over more than 50 years in different populations is buttressed by evidence of plausible mechanisms. The relationship between level of physical activity or fitness is strong, graded and independent of other risk factors. Moderate-intensity activities such as cycling and brisk or fast walking decrease coronary heart disease risk, but more vigorous exercise probably confers more benefit. The dose–response relationships for the other health outcomes mentioned above are less clear. In women, physical activity may decrease the risk of hip fracture through effects on bone mineral density and/or through decreasing the risk of falls.

Carcinogenicity*Weight control***Human studies**

The associations between cancer risk and both overweight and physical activity suggest generally that weight control and physical activity offer benefits in terms of cancer risk rather than hazards (see above). Although the observational epidemiology of the relationship between BMI and cancer risk is sufficient to conclude no adverse effects of lifetime weight control on cancer risk, there have been insufficient studies of the consequences on cancer risk of major intentional weight loss to estimate either the benefits or the risks. For some cancer sites for which an inverse association has been observed between adiposity and cancer risk, factors such as alcohol, tobacco and/or pre-existing illness probably confound the

associations. Among premenopausal women, there is an inverse association between BMI and breast cancer risk, perhaps induced by mechanisms related to anovulation. Reducing the prevalence of overweight among premenopausal women improves the anovulation associated with overweight and might thereby result in increased rates of premenopausal breast cancer.

Experimental studies

Loss of cancer-preventive activity and/or frank enhancement of the carcinogenic response has been observed in model systems for the breast, colon and liver with some cyclic feeding protocols, in which periods of restricted energy intake were alternated with periods of *ad libitum* feeding.

*Physical activity***Humans**

No clear evidence is available of any increase in cancer risks directly associated with physical activity.

Experimental studies

While physical activity has generally been reported to either inhibit or have no effect on carcinogenesis in experimental models, conditions of treadmill running have been reported to increase the carcinogenic response in the mammary gland and the level of intermediate biomarkers in the pancreas.

Other adverse effects*Health effects***Weight control***Human studies*

Adverse effects of weight loss include risk of gall-stones, eating disorders, malnutrition and sarcopenia, in addition to adverse effects specific to use of weight-loss drugs. Obesity and weight gain seem to protect against loss of bone mineral density, and weight loss decreases bone mineral density and may increase fracture risk.

Experimental studies

Few potential adverse conditions have been identified to be associated with underfeeding experimental animals to control weight gain. However, animals in these protocols have elevated glucocorticoid hormone levels that may negatively affect bone mineral density and cell cycle of normal cells. Furthermore, in some dietary restriction studies, animals exhibited bradycardia, leukopenia and an inability to tolerate cold. However, it is unclear if these observations are due to reduced energy intake or the reduction of other dietary constituents with these protocols. Dietary restriction may reduce intake of cancer-protective constituents to an extent that diminishes the cancer-preventive effect of the energy restriction.

Physical activity*Human studies*

Most of the risks from physical activity are evident only when people engage in high volumes and/or intensities of exercise. Strenuous exercise can trigger myocardial infarction, but the short-term increase in risk during and soon after a session is largely restricted to individuals who are unaccustomed to this. The risk of orthopaedic injury seems to be related to volume and intensity of exercise. Prior sports-related injuries may predispose to the development of osteoarthritis of the knee and hip. Exercise, particularly running in a cold

environment, may trigger exercise-induced asthma in susceptible individuals. Among young women, intensive training may lead to menstrual dysfunction characterized by oligomenorrhoea. Women reporting extended periods of oligomenorrhoea or amenorrhoea have lower vertebral bone mineral density which may increase their subsequent risk of osteoporotic fracture. The extent to which these changes are reversible is not known.

Experimental studies

None of the adverse effects of exercise training noted in humans has been studied in animal models under conditions of exercise that have been shown to prevent the development of cancer in an experimental tumour model system.

*Reproductive and developmental effects***Weight control***Human studies*

A minimum ratio of fat to lean mass is normally necessary for menarche and the maintenance of female reproduction. Excessive leanness (as indicated by a BMI below 18.5 kg/m²) has been associated with a decreased likelihood of fecundity due to anovulatory menstrual cycles or a shortened luteal phase.

Experimental studies

In mice, dietary restriction can make female mice enter anestrus, by decreas-

ing gonadotropin-releasing hormone with consequent decreases in the hormones it stimulates. Lower levels of dietary restriction can inhibit fertility in male and female mice. Higher levels are needed to depress fertility in rats.

Physical activity*Human studies*

Physical activity can result in women becoming amenorrhoeal and puberty can be delayed. In men, heavy exercise can lead to drops in the reproductive axis hormones in the short-term, and in chronic exercisers there is also some evidence of a decrease.

Experimental studies

In rats, moderate exercise can disrupt estrous cycling. In male rats, the results for chronic effects are inconsistent.

Genetic and related effects

There are no data on effects of either weight control and/or exercise in inducing mutations or other genetic end-points. There is some evidence that, although specific organs can have lower levels of oxidative damage, plasma and urine measures of oxidative damage can be increased by dietary restriction in rats. Also, increased mitochondrial DNA damage and lipid peroxidation have been found after training to exhaustion in humans and in chronic training in rats.