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ABSENCE OF EXCESS BODY FATNESS

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5. SUMMARY OF DATA

5.1 Exposure data

Obesity is the accumulation of excess body fat. Body mass index (BMI) is commonly used as a proxy measure of body fatness, because it correlates strongly with both absolute body fat and body fat percentage. BMI is calculated by dividing the body weight (in kilograms) by the square of the height (in metres). In adults, overweight is defined as BMI ≥ 25 kg/m^2 and obesity as BMI ≥ 30 kg/m^2. Obesity can be further classified by severity into class I (30–34.9 kg/m^2), class II (35–39.9 kg/m^2), and class III (≥ 40 kg/m^2). In children younger than 5 years, overweight and obesity are defined as a weight-for-height more than 2 standard deviations (SD) and more than 3 SD, respectively, above the WHO Child Growth Standards median. In children and adolescents from age 5 years to younger than 19 years, overweight and obesity are defined as a BMI-for-age more than 1 SD and more than 2 SD, respectively, above the WHO Growth Reference median.

In 2014, an estimated 640 million adults were obese, 6 times the number in 1975. In 2013, 110 million children and adolescents aged 2–19 years were obese, twice the number in 1980. The estimated prevalence of obesity in 2014 was 10.8% in men, 14.9% in women, and 5.0% in children. Obesity in adults and children is prevalent in countries with high, middle, or low income, and globally more people are overweight or obese than are underweight. Inequalities between and within countries play a major role in the burden of obesity. In addition, recent estimates have highlighted the double burden of malnutrition (the coexistence of undernutrition and overnutrition) in some low-income countries. Perceptions about the magnitude of body weight and about body weight change may vary according to personal beliefs, contextual factors, and cultural norms.

Body weight appears to have a very modest genetic component; it is estimated that about 3% of the population variation in BMI can be explained by known genetic variants, highlighting the important role of modifiable risk factors in the development of overweight and obesity. Current evidence indicates that excess energy intake (food and drinks) and, to a lesser extent, physical inactivity are the major risk factors for excess body fatness and body weight gain throughout life. Global economic development has an impact on the built environment and on sociocultural factors, with major effects on food availability, patterns of food intake, and levels of physical activity. The most notable stimuli for excess energy intake are the availability, the frequency of consumption, and the portion sizes of energy-dense foods and drinks. Enhanced urbanization, more labour-saving devices, and increased concerns about outdoor safety have led to decreases in physical activity and increases in time spent sedentary, in the household, in transportation, and in the employment (or unemployment) and leisure domains, thereby decreasing overall energy expenditure.

Studies investigating dietary patterns in relation to body weight control and obesity have found that diets characterized by increased intake of energy-dense and highly processed foods that are high in added sugars, fat, and salt and low in fibre are positively related to weight gain, whereas diets that consist largely of nutrient-dense foods, such as the traditional Mediterranean diet, are inversely related to weight gain and obesity. Meal patterns and sleep duration may also affect the risk of excess body fatness. Other factors that have the potential to influence energy balance, apparently to a lesser extent, are internal regulatory control of hunger, satiety, and metabolic homeostasis, the fermentation activity of the microbiome and its impact on the metabolism, production, and storage of fatty acids, and endocrine disruptors.

Throughout the life-course, there are a range of critical time points and transition events that affect body weight and body weight change. Perinatal factors, including maternal body weight and weight gain during pregnancy, birth weight, infant feeding practices, and early growth trajectories, have been consistently shown to affect body fatness in infancy, childhood, and later life. Body weight changes have also been observed during the transition from school to higher education or to employment, the transition from single status to marriage or cohabitation, the postpartum period, and changes in employment or unemployment status. Body weight gain is also associated with smoking cessation, a range of comorbidities, and use of certain medications.

There are a large number of anthropometric measurement techniques for body fatness. BMI is the most widely used measure to assess overall body fatness, because weight and height are easy and inexpensive to measure and can be assessed accurately (even by self-report), and because BMI is strongly correlated with overall body fatness and enables comparisons across studies. However, BMI does not differentiate between lean mass and fat mass, the relative proportions of which vary between individuals and with age, sex, and race/ethnicity. Waist circumference is widely used as an indirect measure of abdominal obesity, because it is strongly correlated with total abdominal fat mass and with abdominal visceral fat, which is highly metabolically active and is more difficult to assess.

More sophisticated assessment methods (e.g. bioelectrical impedance, dual-energy X-ray absorptiometry, and magnetic resonance imaging) can provide more accurate estimates of body composition and body fat distribution, but their use in epidemiological studies is limited because of associated costs and concerns about radiation exposure, and they are therefore not typically used in population-based assessments. In children and adolescents, BMI (referenced to appropriate growth standards and recommended cut-offs) is the preferred measure.

5.2 Cancer-preventive effects in humans

The evidence from studies addressing body fatness and cancer risk has rapidly expanded. With continued follow-up of cohorts around the world, there are now data for many cancer sites from hundreds of prospective studies and case–control studies. Pooled analyses and meta-analyses have also been carried out, facilitating the evaluation of associations with less common cancers. Most studies have measured body fatness using BMI. A smaller number have used other measures, most importantly waist circumference, and fewer still have assessed changes in weight over time.

5.2.1 Cancer of the colorectum

For cancers of the colon and rectum, evidence from more than 30 prospective studies and about 10 case–control studies published after 2000 confirmed a positive dose–response relationship between BMI and risk. This association

was observed consistently across studies and geographical regions. The association was weaker in women than in men, and was weaker for cancer of the rectum than for cancer of the colon. For cancer of the colon, there was a statistically significant increase in risk of about 10% per 5 kg/m^2 increase in BMI in women and of 25% per 5 kg/m^2 increase in men. Waist circumference was also positively associated with risk of cancer of the colon (and was less consistently associated with cancer of the rectum). Results from two studies using Mendelian randomization were consistent with these findings.

5.2.2 Cancer of the oesophagus

(a) Adenocarcinoma of the oesophagus

For adenocarcinoma of the oesophagus, evidence from 10 prospective studies and 10 case–control studies published after 2000 confirmed a statistically significant positive dose–response relationship between BMI and risk. This association was observed in almost all studies, in men and women, and across geographical regions. Compared with BMI < 25 kg/m^2, the relative risk was about 1.5 for overweight, 2.4 for obesity class I, 2.8 for obesity class II, and 4.8 for obesity class III, estimated from a pooled analysis of 10 case–control studies and 2 cohort studies. Results from a study using Mendelian randomization were consistent with these findings.

(b) Squamous cell carcinoma of the oesophagus

Squamous cell carcinoma of the oesophagus was examined in nine individual prospective studies, several case–control studies, and one meta-analysis published after 2000. In all studies, BMI was inversely associated with risk of cancer. Residual confounding by tobacco smoking is likely to account for the inverse associations.

5.2.3 Cancer of the stomach

(a) Cancer of the gastric cardia

For cancer of the gastric cardia, evidence from 10 prospective studies and several case–control studies indicated a statistically significant positive dose–response relationship between BMI and risk. This association was observed in men and women and across geographical regions. Compared with normal body weight, the relative risk was about 1.2 for overweight and about 1.8 for obesity, estimated from a meta-analysis of seven prospective studies.

(b) Non-cardia gastric cancer

Findings from more than 10 prospective studies and several case–control studies showed a weak relationship, or no relationship, between BMI and risk of non-cardia gastric cancer.

5.2.4 Cancer of the liver (hepatocellular carcinoma)

There was evidence from more than 20 prospective studies and several case–control studies that BMI is positively associated with risk of either hepatocellular carcinoma or cancer of the liver overall. This association was reported in studies from Asia, Europe, and the USA. Compared with normal body weight, the relative risk was about 1.5 for overweight and about 1.8 for obesity, estimated from a meta-analysis of 26 prospective studies of cohorts of the general population.

5.2.5 Cancer of the gall bladder

For cancer of the gall bladder, evidence from more than 10 individual prospective studies and a comprehensive meta-analysis of 12 prospective and 8 case–control studies indicated a statistically significant positive dose–response relationship between BMI and risk. Compared with normal body weight, the relative risk was about 1.2 for

overweight and about 1.6 for obesity, estimated from the meta-analysis.

5.2.6 Cancers of the biliary tract

For cancers of the biliary tract, the evidence was inconsistent.

5.2.7 Cancer of the pancreas

For cancer of the pancreas, evidence from more than 20 prospective studies, more than 10 case–control studies, and several large pooled analyses of cohorts indicated a statistically significant positive dose–response relationship between BMI and risk. This association was observed in the large majority of studies and was found in both men and women. Compared with normal body weight, the relative risk was about 1.2 for overweight and about 1.5 for obesity, estimated from a pooled analysis of 14 cohorts.

5.2.8 Cancer of the lung

For cancer of the lung, the results of about 20 prospective studies and about 10 case–control studies consistently suggested an inverse association between BMI and risk, but studies in non-smokers generally showed no association. Because tobacco smoking is strongly related to both cancer of the lung and reduced body weight, residual confounding by tobacco smoking is likely to account for the inverse associations. Results from two studies using Mendelian randomization were inconsistent with these findings in that they showed a positive association between BMI and risk of cancer of the lung; however, these results are difficult to interpret because of concerns about failure to account for smoking status.

5.2.9 Cancer of the breast in women

More than 30 prospective studies and about 400 case–control studies published after 2000 provided data on the association between BMI and risk of cancer of the breast in women. In postmenopausal women, very consistent positive associations were observed with BMI measured in adulthood. This association was most pronounced in women not using hormone replacement therapy (HRT) and for estrogen receptor-positive tumours. This association was not consistently observed in Hispanic women. A large meta-analysis in postmenopausal women estimated a statistically significant relative risk of about 1.12 per 5 kg/m^2 in women not using HRT, but no association was found in women using HRT. Waist circumference and adult body weight gain, both from age 18 years and from age 50 years, were also positively associated with risk of cancer of the breast in postmenopausal women.

In premenopausal women, consistent inverse associations were observed between BMI and risk; however, positive associations between waist circumference and body weight gain and risk have been reported. Results from a study using Mendelian randomization were not consistent with a positive association between adult BMI and risk of cancer of the breast in postmenopausal women.

5.2.10 Cancer of the breast in men

For cancer of the breast in men, results from a pooled analysis of 11 case–control studies indicated an association between BMI and risk, whereas pooled risk estimates based on 10 cohort studies did not.

5.2.11 Cancer of the endometrium

For cancer of the endometrium, evidence from more than 20 prospective studies and 30 case–control studies published after 2000

confirmed a statistically significant positive, exponential dose–response relationship between BMI and risk. This association was observed in all cohort and case–control studies and was consistent across geographical regions. The association was particularly pronounced for type 1 cancer of the endometrium: compared with normal body weight, the relative risk for type 1 endometrial cancer was about 1.5 for overweight, about 2.5 for obesity class I, about 4.5 for obesity class II, and about 7.1 for obesity class III, estimated from the most recent pooled analysis of 10 cohorts and 14 case–control studies. Meta-analyses showed a stronger association between BMI and risk of cancer of the endometrium in never-users of HRT than in ever-users (relative risk per 5 kg/m^2, 1.18 in ever-users vs 1.90 in never-users). Results from a study using Mendelian randomization were consistent with these findings.

5.2.12 Cancer of the cervix

For cancer of the cervix, the evidence was inconsistent.

5.2.13 Cancer of the ovary

Evidence from more than 15 prospective studies and more than 30 case–control studies indicated a positive dose–response relationship between BMI and risk of epithelial cancer of the ovary. Based on a pooled analysis of 47 studies, the relative risk in never-users of HRT was about 1.1 for overweight and about 1.2 for obesity, compared with normal body weight. There was no association in users of HRT. Results from a study using Mendelian randomization were consistent with these findings.

5.2.14 Cancer of the prostate

For cancer of the prostate, evidence from about 50 prospective studies and more than 40 case–control studies suggested a positive association between BMI and risk of fatal cancer of the prostate. There was no consistent association between BMI and incidence of total, non-aggressive (non-advanced), or aggressive (advanced) cancer of the prostate. Results from three studies using Mendelian randomization were also inconsistent.

5.2.15 Cancer of the testis

One cohort study and more than 10 case–control studies have addressed the relationship between BMI and risk of cancer of the testis. The association between BMI and risk of cancer of the testis was inconsistent, and a meta-analysis did not identify sources of heterogeneity.

5.2.16 Cancer of the kidney (renal cell carcinoma)

For cancer of the kidney (renal cell carcinoma), evidence from about 20 prospective studies and 10 case–control studies published after 2000 confirmed a positive dose–response relationship between BMI and risk. This association was observed in almost all studies and was consistent in men and women and across geographical regions. Compared with normal body weight, there was a statistically significant relative risk of about 1.3 for overweight and about 1.8 for obesity, estimated from the most recent meta-analysis of 21 cohort studies. Results from a study using Mendelian randomization were consistent with an association between BMI and risk of cancer of the kidney.

5.2.17 Cancer of the urinary bladder

Findings from more than 20 prospective cohorts and 4 case–control studies indicated inconsistent relationships between BMI and risk of cancer of the urinary bladder. Residual confounding by tobacco smoking could not be excluded.

5.2.18 Primary tumours of the brain and central nervous system

For meningioma, five prospective studies and two case–control studies showed a consistent positive association between BMI and risk.

For glioma, five cohort studies and two case–control studies, with only moderate sample sizes, reported inconsistent associations between BMI and risk.

5.2.19 Cancer of the thyroid

For cancer of the thyroid, evidence from more than 10 prospective studies and 10 case–control studies indicated a positive dose–response relationship between BMI and risk. The relative risk per 5 kg/m^2 was 1.17 in men and 1.04 in women, both statistically significant, estimated from a pooled analysis of 22 prospective studies.

5.2.20 Tumours of the haematopoietic system

(a) Lymphoid tumours

For multiple myeloma, there was substantial evidence from at least 20 prospective studies and several case–control studies and meta-analyses or pooled analyses showing positive associations between BMI at baseline and risk. The association appeared to be dose-related and was observed for overweight and obesity. From a pooled analysis of 20 cohorts, the relative risk of multiple myeloma mortality was 1.15–1.24 for overweight, about 1.23 for obesity class I, and about 1.52 for obesity class II or higher, compared with normal body weight.

For diffuse large B-cell lymphoma, findings from nine individual prospective studies and two case–control studies, as well as meta-analyses or pooled analyses, suggested a positive association between BMI and risk, but the results were not fully consistent. Compared with normal body weight, the relative risk was about 1.1 for overweight and about 1.3 for obesity, estimated from a meta-analysis of 10 cohort studies.

For Hodgkin lymphoma, cohort studies generally found non-significant positive associations with obesity compared with normal BMI; the relative risk was about 1.4, estimated from a meta-analysis of five prospective studies. Findings from case–control studies were largely null.

For non-Hodgkin lymphoma and B-cell lymphoma as a group, findings for an association between BMI and risk from individual studies and meta-analyses were inconsistent. The inconsistency within the broader category of B-cell lymphoma may be due to heterogeneity among subtypes. There were too few studies on T-cell lymphoma to enable conclusions to be drawn.

(b) Other haematopoietic malignancies

For total leukaemia and myeloid leukaemia, findings for an association between BMI and risk from individual studies were inconsistent.

5.2.21 Cancers of the head and neck

Epidemiological studies on this heterogeneous group of cancers have examined associations between BMI and risk of cancers of the oral cavity, pharynx (i.e. nasopharynx, oropharynx, and hypopharynx), larynx, and salivary glands. Evidence from five prospective studies, two case–control studies, and four meta-analyses or pooled analyses that examined BMI in relation to cancers of the head and neck overall was inconsistent. Several studies examined associations between BMI and risk of cancer of the oral cavity, pharynx, or larynx specifically, and the findings from these studies were also inconsistent. Some of the inconsistencies for these cancers might be explained by residual confounding by tobacco use and/or alcohol consumption.

5.2.22 Malignant melanoma

For cutaneous malignant melanoma, eight prospective studies showed no clear relationship between BMI and risk. A weak positive relationship was suggested by the results of nine case–control studies and one pooled analysis of eight case–control studies.

5.2.23 Excess body fatness in early life and subsequent cancer risk

Studies that have evaluated relationships between excess body fatness in childhood, adolescence, and early adulthood (age ≤ 25 years) and subsequent cancer risk include studies that directly measured weight and height in childhood, studies that determined body shape in early adulthood by recall, and studies that determined trajectories of body shape from childhood to late adulthood. Collectively, these studies indicated positive associations with several cancer types known to be associated with excess body fatness in middle and later adulthood, except for cancer of the breast in postmenopausal women (see Section 5.2.9); there was some evidence for an inverse association between excess body fatness in early life and subsequent risk of cancer of the breast in postmenopausal women.

5.2.24 Excess body fatness in cancer survivors

A large number of studies have evaluated the relationship between BMI at the time of diagnosis of cancer and cancer-related mortality. The data were most consistent for cancer of the breast, for which high BMI has been associated with an increased risk of cancer-related mortality in individual reports and meta-analyses. Data were fewer and/or less consistent for other malignancies. The effect of intentional body weight loss after cancer diagnosis on cancer mortality has been tested in one intervention trial.

5.2.25 Sustained weight loss and cancer risk

The few observational studies that have evaluated body weight loss, and in particular sustained body weight loss, in relation to subsequent cancer risk are limited to observational studies on weight loss in relation to incidence of cancer of the breast and on the impact of intentional weight loss after bariatric surgery on cancer risk in morbidly obese patients. Findings from cohort studies of weight loss and cancer of the breast were inconsistent, in part reflecting the problem of distinguishing between intentional and unintentional weight loss.

In studies of large series of morbidly obese patients who underwent bariatric surgery and with sufficient follow-up, sustained substantial body weight loss is associated with reduced risk of subsequent cancer, especially for cancer of the endometrium.

5.3 Cancer-preventive effects in experimental animals

5.3.1 Excess body weight

Numerous models in experimental animals have been developed to study the association between obesity and cancer of the mammary gland, colon, liver, prostate, skin, pancreas, endometrium of the uterus, and haematopoietic system. Most such animal models are genetically manipulated (transgenic) animals: animals are either genetically modified to induce carcinogenicity and fed a modified diet to induce obesity, or genetically modified to induce obesity and administered chemicals to induce cancer.

For cancer of the mammary gland, the association between obesity and cancer was tested in five studies in genetically obese mice, five studies of diet-induced obesity in mice, two studies of chemically induced obesity in mice, four studies in genetically obese rats, and one study in obesity-prone rats. In all studies except one, obesity

increased the incidence of hyperplastic alveolar nodules and/or of tumours of the mammary gland, shortened tumour latency, and/or increased tumour volume and growth rate.

For cancer of the colon, the association between obesity and cancer was tested in six studies in genetically obese mice, including one study using a transgenic model of carcinogenicity, one study of diet-induced obesity in mice, and three studies in transgenic obese rats. In all studies, obesity increased the incidence of pre-neoplastic aberrant crypt foci and/or of tumours of the colon (primarily adenocarcinoma), and/or increased tumour size and multiplicity.

For cancer of the liver, the association between obesity and cancer was tested in five studies in genetically obese mice, four studies of diet-induced obesity in mice, and one study in diabetic obese rats. In all studies except one, obesity increased the incidence of hepatocellular tumours (adenoma and carcinoma), shortened tumour latency, and/or increased tumour volume and growth rate.

For cancer of the prostate, the association between obesity and cancer was tested in five studies of diet-induced obesity in mice, including three studies using a transgenic model of carcinogenicity, two studies in genetically obese mice, and one study of chemically induced obesity in mice. In most studies, obesity enhanced the development of pre-neoplastic prostatic intraepithelial neoplasia and of adenocarcinoma, leading to more advanced disease, and/or increased tumour volume.

For cancer of the skin, the association between obesity and cancer was tested in four studies in genetically obese mice and two studies of diet-induced obesity in mice. In all studies, obesity shortened latency, increased multiplicity, and/or accelerated the progression of subcutaneously injected melanoma cells or of tumours of the skin induced by ultraviolet light.

For cancer of the pancreas, the association between obesity and cancer was tested in four studies of diet-induced obesity in mice and one study in two models of genetically obese mice. In the three studies of genetically induced tumours of the pancreas in the diet-induced obesity model, obesity increased the incidence of pancreatic intraepithelial neoplasia and of pancreatic ductal adenocarcinoma. In the other two studies (one in transgenic mice and one of diet-induced obesity), subcutaneous injection of syngeneic pancreatic tumour cells led to the development of significantly larger tumours and higher metastatic rates in obese mice than in lean mice.

For cancer of the endometrium of the uterus, the association between obesity and cancer was tested in one study of diet-induced obesity in mice. In that study, obesity increased the incidence of pre-neoplastic glandular epithelial hyperplasia and adenocarcinoma.

For cancers of the haematopoietic system, the association between obesity and cancer was tested in two studies of diet-induced obesity in mice. In both studies, obesity shortened latency for the development of acute lymphoblastic leukaemia.

Overall, the data showed that obesity in rodents promotes tumorigenesis and increases the age-specific incidence of cancers of the mammary gland, colon, liver, pancreas, prostate (advanced stage cancer), and skin.

5.3.2 Dietary/calorie restriction

(a) Cancer of the mammary gland

More than 40 studies in several different mouse and rat models have evaluated the effect of dietary restriction on the development or progression of tumours of the mammary gland. Overall, most studies showed that dietary restriction decreased the incidence of mammary tumours, extended latency, and/or decreased tumour burden.

Six recent studies in various transgenic mouse models indicated that the pattern of restriction is also important in the protective

effect of dietary restriction. Periods of intermittent restriction had a stronger effect in the prevention of mammary tumours than did the same overall degree of restriction implemented in a prolonged fashion. One study using a model of chemically induced mammary tumours in rats showed similar results.

In general, dietary restriction interventions were implemented in young animals (shortly after weaning, or up to age 9–10 weeks), and then maintained throughout the course of the study. This approach usually led to a lower rate of body weight gain than in animals fed ad libitum. Only two studies have addressed the issue of body weight loss induced by dietary restriction in obese animals and its impact on the development of tumours of the mammary gland. In both studies, body weight loss reduced the development or progression of tumours.

Recently, several studies in mice and rats have used chemical mimetics of calorie restriction (metformin, buformin, phenformin, and 2-deoxyglucose) to assess prevention of tumours of the mammary gland. Protective effects were observed in two of three studies in the HER2/neu mouse model with metformin, as well as in three of five studies in the rapidly emerging tumour model in rats (one study each using 2-deoxyglucose, buformin, or phenformin); metformin had no effect in the remaining two studies.

In addition, several studies were conducted in strains that have different responses to high-fat diets with regard to the rate of body weight gain, thus providing the opportunity to evaluate the effect of body weight independent of diet. In these studies, lower body weight was accompanied by longer tumour latency.

(b) Cancer of the colon

Several models in rats and mice using either chemical carcinogens or allografts to induce tumours of the colon have been developed. Nine studies have assessed the effect of dietary restriction on the development or progression of such tumours. In all three studies using allografts, dietary restriction significantly reduced tumour growth. In three of four studies using a model of chemically induced tumours, dietary restriction reduced the incidence of adenoma and carcinoma of the colon. In one study in the genetically obese Zucker rat, dietary restriction did not have an impact on body weight, and had no protective effect on the development of chemically induced aberrant crypt foci. Similarly, no effect was observed in one study using a transgenic mouse model.

(c) Cancer of the liver

In three lifespan studies in different strains of male and female mice, 40% dietary restriction reduced the incidence of spontaneous liver tumours, mostly hepatocellular adenoma or carcinoma. The reduction did not always reach statistical significance in all analyses (adenomas, carcinomas, or adenomas and carcinomas combined), because of the small numbers of animals and the low incidence of tumours in animals fed ad libitum. In two studies of chemically induced liver tumours in mice, 30% or 40% dietary restriction significantly reduced the incidence of hepatocellular tumours, mostly carcinomas.

(d) Cancer of the pancreas

In all three studies using transgenic mouse models to induce tumours of the pancreatic duct, 25–30% dietary restriction decreased the incidence and severity of pre-neoplastic pancreatic lesions or carcinoma and/or increased survival. In one study using a model of chemically induced carcinogenesis in rats, in which animals were "meal-fed" (i.e. fed ad libitum for 5–6 hours per day, resulting in 10–15% dietary restriction), similar results were observed. In one of three lifespan study in rats, dietary restriction reduced the incidence of spontaneously occurring islet cell tumours. In one study using a model of chemically induced carcinogenesis

in Syrian golden hamsters, 20% or 40% dietary restriction had no effect. In one study in mice injected with pancreatic tumour cells, dietary restriction inhibited tumour growth.

(e) Cancer of the skin

Lifespan studies in mice and rats that have assessed the effect of dietary restriction on tumours of the skin gave inconclusive results because of the low incidence of spontaneously occurring tumours. Nine studies using carcinogen-induced models have assessed the effect of a range of levels (15–50%) of dietary restriction at the initiation, promotion, or progression phase. In all studies, all levels of dietary restriction inhibited the development of skin papilloma, the progression of papilloma to carcinoma, or the multiplicity of these tumours when dietary restriction was imposed at the promotion phase and/or thereafter.

In one study using a B16 melanoma cell line injected subcutaneously into mice, dietary restriction inhibited tumour growth.

(f) Cancer of the pituitary gland

Tumours of the anterior pituitary gland are prevalent in old female mice and in old male and female rats. In all five lifespan studies in mice or rats, 35% and 40% dietary restriction reduced the incidence of spontaneous tumours of the pituitary gland.

In two studies using the estrogen-induced prolactinoma models in female and male F344 rats, 40% dietary restriction inhibited the increase in the weight of the pituitary gland, which is used as an index of tumour growth in this model. Dietary restriction had no effect in three studies using this model in either male Holtzman rats or female ACI ovariectomized rats.

(g) Cancer of the prostate

The transgenic animal models used to study cancer of the prostate are characterized by the development of highly aggressive disease. Eight studies examined the impact of dietary restriction on development of cancer of the prostate: five in transgenic animals, two in models of hormonally induced tumours, and one of spontaneous tumours. In three studies in transgenic animals, dietary restriction reduced the incidence of adenocarcinoma or high-grade lesions. In one study using a model of hormonally induced cancer, dietary restriction reduced the incidence of adenocarcinoma. The one study of spontaneous tumours showed a reduction in incidence of adenocarcinoma with dietary restriction. All studies initiated dietary restriction in young animals (aged 3–9 weeks) and reported attenuated weight gain compared with control animals.

(h) Cancers of the haematopoietic system

Malignant lymphoma and histiocytic sarcoma commonly occur in old mice. In three of five lifespan studies in male or female mice, dietary restriction reduced the incidence of lymphoma and/or histiocytic sarcoma. In one study using knockout $p53^{-/-}$ mice (prone to cancer in many organs), dietary restriction resulted in a moderate reduction in the incidence of lymphoma, and a significant delay of death due to lymphoma. In one lifespan study in $B10C3F_1$ mice, dietary restriction also increased the mean lifespan of mice with lymphoma.

Mononuclear (large granular) cell leukaemia is prevalent in old F344/N rats, and the incidence and severity of disease increase with increased longevity. One 2-year study in F344/N rats showed a significant reduction in the incidence of large granular cell leukaemia with 7–20% dietary restriction. In another lifespan study, 40% dietary restriction had no significant effect. To address the issue of increased lifetime incidence of leukaemia, one study assessed the onset rate of leukaemia, and reported a significant 20% reduction with 40% dietary restriction, although the lifetime incidence did not differ from that in the group fed ad libitum.

5.4 Mechanistic and other relevant data

A short summary of the data is presented at the end of each chapter of Section 4.

The Working Group assessed which cellular and molecular mechanisms known to be dysregulated during the carcinogenesis process are causally linked with obesity, and assessed the relevance of each mechanism for cancer overall, as well as – when sufficient data were available – for individual organ sites. The findings and levels of evidence are summarized below, by the strength of the evidence of the mechanism.

The currently available data in humans and experimental models are consistent with the effects of intentional weight loss on cancer risk being mediated, at least in part, by regulation of the balance between cell proliferation and apoptosis in carcinogenic progression. The cellular machinery that accounts for such regulation includes proteins involved in the G1/S cell cycle transition and apoptotic induction, whether via the intrinsic (mitochondrial) or extrinsic pathways.

5.4.1 Sex hormone metabolism

Estrogen levels correlate with amount of body fat in postmenopausal women. Estrogens play a significant role in cancers of the breast and endometrium, and there are consistent data in humans to demonstrate that women with higher levels of estrogen have an increased risk of these malignancies. For other tumours, the role of sex hormones is less clear. For cancer of the colorectum, estrogen may be anti-tumorigenic and therefore would not represent a mechanism linking adiposity with this cancer. Data linking sex hormones with cancers of the prostate and ovary are inconsistent and may be dependent on tumour subtype. There was little evidence that sex hormones play a role in the development of other obesity-related cancers, such as those of the kidney, pancreas, oesophagus, or liver.

Overall, there is *strong* evidence that the sex hormone-mediated pathway is a major mechanism underlying the link between obesity and certain cancers.

5.4.2 Inflammation

Obesity leads to subclinical inflammation. Several clinical and experimental studies indicate that intentional weight loss by behavioural interventions, bariatric surgery, or pharmacological approaches can reverse obesity-associated inflammatory changes. The most established marker of inflammation in these studies, and the most consistently responsive to intentional weight loss, is C-reactive protein, but it is unclear whether C-reactive protein is a true biological mediator of inflammation and cancer or a marker of other aspects of inflammation. Other markers related to inflammation – including interleukin-6, tumour necrosis factor alpha (TNF-α), prostaglandins, cyclooxygenase-2 (COX-2), leptin, and adiponectin – either have inconsistent associations or have not yet been adequately studied. The obesity-associated pro-inflammatory state appears to be triggered by adipose tissue dysregulation resulting from excess triglyceride accumulation in adipocytes, leading to the recruitment and reprogramming of macrophages and other immune cells that interact with the lipid-engorged adipocytes to increase secretion of multiple cytokines and other inflammatory mediators. The chronic reinforcement of this pro-inflammatory state leads to remodelling of adipose tissue, including infiltration of lipids into the liver, pancreas, and other tissues to create a pro-tumorigenic environment. In addition, several emerging contributors to the obesity-associated pro-inflammatory state, including activation of the COX-2/prostaglandin pathway as a result of increased cytokine levels, and the obesity-induced increase in

inflammation-related molecules from the microbiome, also probably play an important role.

The findings support a role for the inflammatory process in the development of cancers of the breast and colorectum, and to a lesser extent of cancer of the ovary. Data for other sites are sparse. Overall, there is *strong* evidence that inflammation is a major mechanism underlying the link between obesity and certain cancers.

5.4.3 Insulin and insulin-like growth factor

Insulin and insulin-like growth factor 1 (IGF-1) are growth factors that activate the mammalian target of rapamycin (mTOR)/phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, which have mitogenic and anti-apoptotic effects. Hyperinsulinaemia and insulin resistance are common in obese individuals and can raise levels of bioavailable IGF-1 through suppression of IGF-binding proteins.

From epidemiological studies, there is *strong* evidence for a role for insulin in the development of cancer of the endometrium. There is *moderate* evidence linking insulin to cancer of the breast, whereas recent pooled analyses and meta-analytical approaches indicate a role for IGF-1 in the development of cancer of the breast. There is *moderate* to *strong* evidence that both insulin and IGF-1 play a role in cancer of the colorectum. For prostate cancer, there is *moderate* evidence that higher levels of IGF-1 increase the risk of this malignancy, whereas the evidence for insulin is heterogeneous. For other tumour sites, the data are much more limited and inconsistent. Overall, there is *moderate* evidence that insulin and IGF-1 play a role in obesity-induced cancer.

5.4.4 Epigenetic alterations

Structural modifications of DNA, including epigenetic alterations, play an important role in tumorigenesis. However, few studies have investigated the role of epigenetics in mediating the effects of obesity on cancer. Currently, there is *weak* evidence.

5.4.5 Oxidative stress

Oxidative stress can affect DNA integrity and has been linked to obesity, metabolic syndrome, and cancer. However, evidence of the involvement of oxidative stress in obesity-induced cancer is limited by methodological issues. Currently, there is *weak* evidence.

5.4.6 DNA repair

The role of DNA repair function in cancer risk is well established for cancers of the colorectum, breast, endometrium, and skin. Several studies point towards a link between increased BMI and DNA mismatch repair deficiencies. In spite of this, a causal link with obesity and weight control is lacking, because of methodological challenges. Currently, there is *weak* evidence.

5.4.7 Telomeres

Telomere maintenance is directly linked to immortalization. Likewise, inherited disruptions in telomere maintenance have emerged as predictors of cancer predisposition at numerous cancer sites. Evidence from several studies indicates that obesity is inversely associated with telomere length. Overall, telomere shortening may be a relevant emerging mechanism linking obesity to risk of cancer. Currently, there is *weak* evidence.

5.4.8 Other mechanisms

For several mechanisms or mechanistically linked conditions that are potentially related to obesity and cancer, i.e. vitamin D status, the gut microbiome, gut hormones, non-alcoholic fatty liver disease, immune function, and cancer stem cell enrichment, currently, there is *weak* evidence.