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Nutrition, metabolic factors and cancer risk

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Excess body weight (adiposity) and physical inactivity are increasingly being recognized as major nutritional risk factors for cancer, and especially for many of those cancer types that have increased incidence rates in affluent, industrialized parts of the world. In this review, an overview is presented of some key biological mechanisms that may provide important metabolic links between nutrition, physical activity and cancer, including insulin resistance and reduced glucose tolerance, increased activation of the growth hormone/IGF-I axis, alterations in sex-steroid synthesis and/or bioavailability, and low-grade chronic inflammation through the effects of adipokines and cytokines.

Key words: nutrition; physical activity; glucose metabolism; insulin; IGF-I; sex hormones; adipokines; inflammation.

International comparisons and time-trend analyses of age-standardized cancer incidence rates, combined with results from studies on migrants from low- to high-risk areas, clearly implicate a 'Western' lifestyle, typical of affluent societies, in the development of many forms of cancer. Tumour types that have highly increased incidence rates in these societies include cancers of the breast, endometrium, ovary, prostate, colorectum, pancreas, and kidney.[1] Besides alcohol consumption, reproductive behaviour and child-bearing patterns, there is strong evidence to suggest that nutrition in particular plays a key role in the development of many of these tumours.

From a nutritional perspective, a 'Western' lifestyle is characterized by low levels of physical activity, and a diet rich in energy-dense foods that contributes a high percentage of nutritional energy from (saturated) fats, sugars and other refined carbohydrates, and has a high proportion of dietary protein of animal origins. The combination of this

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type of diet with low levels of physical activity is the cause of an ever increasing prevalence of obesity and high body fatness. In its recent second report, an international panel convened by the World Cancer Research Fund concluded that higher intakes of foods with elevated energy density (with an energy content of more than about 225–275 kcal/100 g, such as processed foods with high sugar or fat content) are associated with an increased risk of cancer, whereas higher intakes of low energy-dense foods (e.g. vegetables, fruits, and foods containing dietary fibres) are associated with a reduced risk.[2] This international panel also concluded that there was convincing evidence that excess body weight increases the risks of cancers of the colon, kidney (renal cell tumours), endometrium, breast (postmenopausal women only), and adenocarcinomas of the oesophagus, confirming and extending similar conclusions by an earlier international expert panel convened at the International Agency for Research on Cancer.[3] It is increasingly being speculated that the association between specific food consumption patterns and cancer risk could be largely the result of their effect on nutritional energy balance, excess body weight, and adiposity. Although the relative risks for these various cancers associated with overweight or obesity are modest and mostly vary between 1.5 and 2.0, due to the high prevalence of obesity in Europe and the USA, the proportions of these cancers that potentially can be attributed to excess weight has been estimated to vary between about 20% for breast or colon cancers, to 40–50% for tumours of the kidney and endometrium.[4] Another tumour type for which risk may be moderately increased among overweight or obese individuals are B-cell lymphomas, according to several recent studies.[5]

A growing number of prospective cohort studies has examined relationships of endocrine and metabolic serum markers with cancer risks. While initial studies focused mostly on sex-steroid hormones (androgens, oestrogens, progesterone)[6], more recent studies have also devoted special attention to the roles of insulin and glucose metabolism[7], as well as of insulin growth factor-1 (IGF-I).[8] Still more recently, endocrine mediators of chronic inflammation have also been implicated in tumour development.[9]

Each of these endocrine and metabolic factors has a well-documented relationship to nutrition, including obesity, physical inactivity, or some specific dietary factors. It is now well recognized that not only is adipose tissue an organ for storage of energy, it also expresses important endocrine functions via the production of 'adipokines' involved in the regulation of many metabolic pathways[10], including the metabolism of sex steroids, inflammatory mechanisms, and insulin signalling. Physical activity, on the other hand, has been shown to improve insulin sensitivity and to reduce chronic inflammation, but also to affect circulating levels of IGF-I and sex steroids.[11] Finally, some specific dietary factors have also been consistently related to endocrine and metabolic factors.

In this review we will examine some key biological mechanisms that may provide important metabolic links between nutrition, physical activity and cancer, including insulin resistance and reduced glucose tolerance, increased activation of the growth hormone/IGF-I axis, alterations in sex-steroid synthesis and/or bioavailability, and low-grade chronic inflammation.

INSULIN RESISTANCE AND GLUCOSE METABOLISM

Insulin resistance is an inadequate biological response of adipose tissue, muscles and liver to normal levels of insulin, particularly in terms of glucose uptake and metabolism. In insulin-resistant states, the uptake of glucose by skeletal muscle and liver is

reduced, whereas hepatic gluconeogenesis is increased. As a consequence, fasting-state blood glucose levels tend to increase, which in turn causes compensatory increases in pancreatic insulin secretion and increased circulating insulin levels.

Nutritional determinants of insulin resistance

One major determinant of insulin resistance is excess body weight and adiposity. An excess of adipose tissue, especially in the abdominal region, leads to elevated blood concentrations of free fatty acids and of endocrine factors such as tumour necrosis factor (TNF) α, leptin and resistin, and low concentrations of adiponectin. Each of these metabolic changes has been implicated in reduction of insulin sensitivity (see below).

Physical activity, by contrast, contributes to the prevention of insulin resistance. In intervention trials, exercise training generally led to improvement in insulin sensitivity in previously sedentary people.[11–13] Quite independently of changes in body weight or composition, acute exercise enhances glucose uptake and insulin sensitivity in skeletal muscles by increasing blood flow and glucose transport to the muscle during exercise, by reducing intramuscular stores of lipids and glycogen, and by insulin-independent increases in the glucose uptake capacities of skeletal muscle.[14,15] In the longer term, regular physical activity also contributes to improved insulin sensitivity by avoidance of excessive weight gains.

Besides factors related to nutritional energy balance, the effects of specific dietary constituents on the regulation of insulin action have also been explored. Results from intervention studies on the effect of high-fat diets on insulin resistance – reviewed by McAuley and Mann[16] – have been quite inconsistent. Most of studies found no clear relationship between high-fat diet and insulin resistance, although in some studies with more extreme intakes of fat a reduction in insulin sensitivity was observed. More evidence of an effect of dietary fat on insulin sensitivity comes from animal studies where the fat composition seems to be particularly relevant. The majority of these studies showed an improvement of insulin action after increased dietary intakes of long-chain unsaturated n-3 fatty-acids, and lower insulin sensitivity when diets were rich in saturated, monounsaturated, or n-6 polyunsaturated fatty acids.[17] In humans, observational studies have also shown associations of higher saturated fatty-acid intakes with higher plasma insulin concentrations[16], and intervention studies have shown that replacement of saturated fat by monounsaturated fat may increase insulin sensitivity.[18,19] However, at very high fat intakes ($>$37% of total energy as fat) no such differential effects of fatty acid composition are observed. The beneficial effect of n-3 fatty acids on insulin sensitivity has not been clearly confirmed in human studies.[16]

High-carbohydrate diets, and particularly diets rich in high-glycaemic-index foods that contain rapidly digestible carbohydrates, have also been implicated in the development of insulin resistance. The glycaemic index (GI) is a standardized measure of the postprandial glycaemic response to the consumption of a given amount of test food compared to a control food (i.e. white bread or glucose).[20] The regular consumption of high-GI foods leads to repeated postprandial hyperglycaemia and hyperinsulinaemia, which in turn can cause an increase in plasma free fatty acids, impaired β-cell function (glucotoxicity) and insulin resistance.[21] In a meta-analysis of all existing prospective studies, Barclay and colleagues observed an overall 20% increased risk of type-2 diabetes (a consequence of insulin resistance) for subjects whose diets had the highest average GI, compared to the 20% of subjects whose diets had lowest GI.[22]

By contrast, diets rich in fibres have been associated with improved insulin sensitivity. However, as diets with high intake of dietary fibres also tend to have a lower

average glycaemic index, it is difficult to establish an independent effect of dietary fibre itself on insulin sensitivity.[22] Nonetheless, a recent meta-analysis of human intervention studies showed that positive effects of dietary fibres on insulin sensitivity were as strong as, and independent of, the effects observed for low GI.[23] Furthermore, in a report from 2003, an international expert panel convened under the auspices of the World Health Organization and the Food and Agriculture Organization qualified the protective effect of dietary fibres against type-2 diabetes as 'probable'.[24]

Finally, there is also some evidence for a possible protective effect of dairy products against insulin resistance, which could be confined, however, to subjects in excess weight. In a prospective study on more than 3000 adults, Pereira and colleagues, for instance, observed among overweight individuals a 70% reduction in risk of developing insulin resistance with high consumption of dairy products ($\geq$35 times per week) compared to people with low consumption ($<$10 times per week).[25] In normal-weight individuals, by contrast, no association was observed between insulin resistance and consumption of dairy products.[25,26]

Chronic hyperinsulinaemia and cancer

In the mid 1990s, several investigators independently hypothesized that chronically elevated fasting and non-fasting plasma insulin levels could be a metabolic link between nutrition-related lifestyle factors and development of cancers of the colorectum[27,28], breast[29] or endometrium.[30,31] These hypotheses were based on two sets of observations. On the one hand, many established or suspected nutritional risk factors for cancer (low physical activity, excess body weight, low dietary fibre intakes, high intakes of saturated fats and high-GI foods) had also been related to reduced insulin sensitivity and/or increased pancreatic insulin secretion. On the other hand, there was increasing experimental evidence that insulin could favour tumour development, either directly through its cognate receptor on the (pre-)tumour target tissue, or indirectly by increasing the biological activity of other hormones and growth factors.

The insulin receptor is a tyrosine kinase that transactivates the ras/raf/MAP-kinase and phosphatidyl-inositol/Akt (protein-kinase B) pathways, which are central in the control of cellular growth, proliferation and apoptosis. The central role of these in tumour development is illustrated by the presence, in these pathways, of numerous proto-oncogenes that are frequently mutated and constitutively activated in tumours, providing cells with a strong selective growth advantage, as well as tumour suppressor genes, such as PTEN, that in tumours are frequently inactivated.[32,33] Second, as discussed further in sections below, hyperinsulinaemia can increase the synthesis and/or biological availability of other endogenous hormones such as IGF-I or sex-steroid hormones (androgens, oestrogens and progesterone) that in turn can enhance tumour development.[4]

Since the formulation of the 'insulin hypothesis', many prospective studies have been conducted that address the possible relationship of blood insulin concentrations with the risk of developing cancer.[34] In a meta-analysis of existing prospective studies, circulating levels of insulin or C-peptide (a marker for pancreatic insulin secretion) have been associated with an increased risk of cancers of the colorectum and pancreas. These estimates remained after adjustment for BMI, indicating that the relationships between risk and insulin levels could not be entirely accounted for by indirect associations with adiposity. Besides cancers of the colorectum and pancreas, endometrial cancer risk has also been clearly associated with prediagnostic insulin or C-peptide levels.[35,36] Regarding

breast cancer, some[37] but not all[38] prospective studies have shown a direct relationship between risk and serum C-peptide levels, but only among older, postmenopausal women.

These various observations are in line with those from studies relating type-2 diabetes mellitus – a state of extreme glucose intolerance that generally is characterized by both hyperglycaemia and hyperinsulinaemia – to increased risks of cancers of the pancreas, endometrium, colon, liver and kidney (renal cell tumours)[39–43] and, more recently, increased risk of B-cell lymphomas.[44] Furthermore, large prospective cohort studies have shown increased risks particularly of cancers of the pancreas, endometrium, liver, bile duct, and in some studies also colorectum and breast, among non-diabetic women and men who have comparatively elevated fasting and/or 2-hour post-load blood glucose concentrations.[45–48] Interestingly, among diabetic patients the use of blood glucose- and insulin-lowering drug metformin was associated with up to 30% reductions in overall cancer incidence.[48,49] However, this apparent tumour-preventive effect could also be due to direct activation of AMP-activated kinase (AMPK), a metabolic master switch controlling anabolic versus catabolic processes in cells depending on cellular energy status, at the level of (pre-)tumour target cells.[50]

INSULIN-LIKE GROWTH FACTOR-I

IGF-I and at least six different IGF-binding proteins are synthesized in many tissue types throughout the body, where these peptides exert autocrine and paracrine effects on cellular growth, proliferation and apoptosis. In addition, IGF-I and its binding proteins are also secreted into the circulation, and IGF-I thus can also be seen as a classical hormone. Most IGF-I and its binding proteins that are in the circulation is produced by the liver, and almost all circulating IGF-I (>98%) is bound to the IGF binding proteins (IGFBPs). More than 85% of circulating IGF-I is bound in a ternary complex with IGFBP-3 – the major plasmatic IGF binding protein – and a glycoprotein called 'acid-labile subunit' (ALS). IGF-I bioactivity is the overall result of endocrine, paracrine and autocrine effects of IGF-I and IGFBP on their cellular receptors. IGF-I bioactivity is believed to increase generally when total IGF-I concentrations rise. To a large extent, however, IGF-I bioactivity is also determined by the IGF binding proteins, which regulate the efflux of circulating IGF-I through the capillary barrier, as well as the availability of IGF-I at a tissue level for binding to its receptor.[51]

At the target-cell level, IGF-I binds to its receptor (IGF-1R) and activates intracellular signalling pathways for cell proliferation and survival.[52] As in the case of insulin, this includes both the Ras/Raf/MAP-kinase and PI3K/AKT pathways, inducing mitogenic and metabolic responses. However, insulin receptor activation leads more predominantly to metabolic (e.g. cell-growth-stimulating) effects, whereas the activation of IGF-1R more predominantly causes activation of mitogenic pathways.[53]

Determinants of IGF-I

In liver, and most other tissues, the principal physiological stimulus for the synthesis of IGF-I is provided by growth hormone (GH). However, IGF-I synthesis can be strongly modulated by other endocrine and nutritional factors, which in fact may be the more important determinants of the wide variation in plasma IGF-I concentrations that can be observed between individuals. In particular energy balance and intakes of essential amino acids play an important role in the regulation of IGF-I synthesis.[54,55] Fasting

leads within days to immediate and strong (>60%) reductions in circulating IGF-I levels, and also chronic energy malnutrition is associated with strongly reduced levels.[54–56] In well-nourished populations, however, the relationship between nutritional energy balance and total circulating IGF-I levels is more complex. Large-scale cross-sectional studies indicate a non-linear relationship between IGF-I levels and BMI, where IGF-I levels rise with increasing BMI values up to about 25–26 kg/m^2, but then progressively fall with further increasing BMI values.[57,58]

Substantial evidence suggests that the effects of nutritional energy balance on hepatic IGF-I synthesis and availability of circulating IGF-I are mediated, at least in part, by differences in pancreatic insulin secretion. Insulin sensitizes liver cells to the stimulatory effects of growth hormone on IGF-I synthesis by increasing GH-receptor levels, and by enhancing cellular protein synthesis in general (reviewed in [54]). In addition to these permissive effects on IGF-I synthesis, insulin augments IGF-I bioactivity by inhibiting the production of IGFBP-1 and IGFBP-2 in the liver and in other tissues, and in cross-sectional studies excess adiposity and circulating insulin levels generally are found to be negatively correlated with blood levels of both IGFBP-1 and IGFBP-2, and positively with levels of free IGF-I – a small fraction of about 1–2% of circulating IGF-I that is unbound to any IGF-binding proteins.[54] Although most cross-sectional studies have shown linear increases in plasma insulin levels with increasing BMI, the non-linear relationship of BMI with circulating IGF-I levels can be explained by a progressive increase in negative feedback control of free circulating IGF-I on pituitary GH secretion. Thus, above a certain threshold of BMI and plasma insulin concentrations, the reduction in the GH stimulus to hepatic IGF-I synthesis may become stronger than the GH-sensitizing effects of insulin at the hepatic level.[54]

Besides nutritional energy balance, there is substantial evidence from animal experiments[59], human intervention studies[56] and observational studies comparing vegans with lacto-ovo-vegetarians and omnivorous individuals[60,61] that IGF-I synthesis also depends on the intake of essential amino acids from animal proteins. Further cross-sectional studies in humans[62–65] have shown a direct association particularly between dairy food consumption, especially milk, and circulating IGF-I levels, suggesting that calcium intake could also be an important dietary determinant. In some but not all of the latter studies, associations with intake levels of total energy, carbohydrates, various types of fat, some vitamins, red meat, poultry or fish, were also reported.

Regarding physical activity, a large number of small human intervention studies[54,66] have, with few exceptions, shown an acute but transient (slight) increase in levels of IGF-I immediately during and after a bout of exercise. This increase could be due to an acute rise in pituitary GH secretion, but might also be explained by losses of body liquids due to transpiration and a contraction of the volume of blood plasma. The longer-term effects of regular exercise may depend on intensity and duration. In some studies, an increase in regular exercise (training) over a period of several weeks to 6 months caused a rise in basal plasma IGF-I in elderly subjects as well as in younger men and women. However, prolonged exercise that results in a strongly negative energy balance for a number of days, as in the case of marathon running, have also been reported to decrease IGF-I levels for at least a number of days afterwards.[54,66]

IGF-I and cancer

A vast body of experimental evidence indicates that IGF-I can enhance tumour development. IGF-I has well-documented mitogenic and anti-apoptotic activities on a great

variety of cell types cultivated in vitro.[67] In addition, studies on genetically engineered mice have shown, for example, increased spontaneous skin-tumour development in mice that over-express IGF-I in basal epidermal cells[68,69], which could be offset by caloric restriction. By contrast, mice with a primary deficiency in the production of growth hormone or IGF-I, or in responsiveness to growth hormone, show reduced aging (longer lifespan) and reduced tumour formation.[70] Likewise, caloric restriction also reduces the spontaneous or carcinogen-induced formation of various tumours, such as leukaemias or bladder tumours, and this reduction in tumour yield can also be largely offset by restoring serum IGF-I concentrations.[71,72] Liver-specific *IGF1*-deficient (knockout) mice provided an experimental model for studies of the effects of circulating IGF-I. While these mice had normal growth patterns, reflecting sufficiency of local tissue synthesis of IGF-I for growth, they have strongly reduced circulating IGF-I levels, and in various experiments these mice also showed reduced tumour formation or growth in the mammary gland[73] or colon.[74,75]

In humans, many prospective cohort studies have examined relationships between circulating IGF-I and its binding proteins and risks of various forms of cancer.[76–85] Globally, these studies have shown moderate increases particularly in the risk of prostate cancer, but possibly also in the risks of breast and colorectal cancers, with increasing levels of circulating IGF-I (measured either as absolute concentrations or relative to IGFBP-3 – the principal plasmatic IGF-binding protein).

A recent pooled analysis of prospective cohort study data worldwide, including data from about 3300 prostate cancer cases and 4450 controls, showed approximately a 40% increase in prostate cancer risk for men in the top 20% of circulating IGF-I levels, as compared to those in the lowest 20% (Roddam et al, in press). Another meta-analysis of prospective cohort studies published up to 2004 also showed an increased risk of colorectal cancer among men and women with higher IGF-I levels[82,83], which was confirmed by one more recent prospective study[82,83], but not by several other recent studies.[84,86] In a very large case–control study nested within the EPIC cohort, including over 1100 cases of colorectal cancer and 1100 controls, there was no association of IGF-I with cancer risk (Rinaldi, personal communication).

In the earliest studies on breast cancer, an approximate two-fold increase in risk was observed especially among younger and premenopausal women who had high IGF-I levels.[87] However, the association among premenopausal women was not confirmed by three more recent prospective cohort studies[79,80,88], although two of these did show an increased risk of breast cancer among women who were older and postmenopausal at diagnosis.[79,88] A more detailed review of the epidemiological evidence concerning the association between IGF-I and cancer is presented in a separate chapter (see Chapter 7).

SEX STEROIDS AND SEX-HORMONE BINDING GLOBULIN (SHBG)

Determinants of sex steroids and SHBG

In postmenopausal women, excess weight and obesity are well-known determinants of oestrogens. In contrast to premenopausal women, for whom the ovaries are the major site of blood and tissue concentrations of oestrogen production, in postmenopausal women oestrogens are produced by the peripheral conversion of ovarian and adrenal androgens in adipose tissue. As a result, a strong correlation is observed between the level of adipose tissue and oestrogen levels, and many cross-sectional

studies have shown a positive association between BMI and oestrone and oestradiol levels after menopause.[57,89,90] SHBG, by contrast, generally is found to be strongly negatively associated with BMI in both pre- and postmenopausal women. The latter can be explained by a BMI-related increase in insulin levels, plus the fact that insulin is a key negative regulator of hepatic SHBG synthesis.[29] No association is generally observed between androgens and obesity in women, except for women with polycystic ovary syndrome (PCOS), a relatively frequent endocrine disorder characterized by ovarian androgen excess and frequent anovulation, which is estimated to affect 3–6% of premenopausal women. In women with PCOS, obesity is in fact associated with higher levels of circulating testosterone and androstenedione, as a result of enhanced stimulation of ovarian androgen synthesis by insulin.[91]

In men, excess body weight, as measured by higher BMI levels, is generally associated with a decrease in testosterone levels.[92] This relationship can be largely explained by insulin-induced reductions in circulating SHBG, and by a narrow co-regulation between circulating SHBG and testosterone levels through negative feedback control of free testosterone on the pituitary secretion of luteinizing hormone, which provides the principal stimulus for testicular androgen synthesis.[92]

Besides body weight and adiposity, there is increasing evidence that also physical activity can influence total and/or bioavailable plasma sex hormone concentrations in both women and men, although it is not entirely clear whether long-lasting effects can be achieved independently of changes in body weight and composition.[11] Among postmenopausal women, cross-sectional studies have shown lower serum concentrations of oestradiol, oestrone and androgens at higher levels of physical activity, even after adjustment for BMI.[93–95] Likewise, a large physical activity intervention trial showed significant decreases of serum oestrogens (oestradiol, oestrone, free oestradiol) after 3 months of moderate-intensity aerobic exercise (5 days a week) compared to a control group, and this effect persisted up to 12 months among women who lost body fat.[96] In women who lost body fat, there was also a statistically significant decrease in testosterone and free testosterone in exercisers compared with controls.[97] For premenopausal women, only a few intervention trials of this type have been conducted so far. Among men, an intervention study showed increased serum levels of SHBG and dihydrotestosterone, but no effects on testosterone, free testosterone, 3α-androstanediol glucuronide (ADiol-G, a plasma marker for conversions within tissues of testosterone into the more strongly androgenic dihydrotestosterone, DHT), or oestradiol, in middle-aged to older men who participated in a year-long, moderate-intensity aerobic exercise program. In the latter study, it is likely that the increase in SHBG was a result of improved insulin sensitivity, and that the increase in DHT was a consequence of greater plasmatic SHBG binding capacity.[98]

Regarding diet, it has been speculated that the intake of dietary fibres could lower circulating oestrogen levels by decreasing weight, or by increasing faecal excretion of oestrogens.[99] A number of cross-sectional and human dietary intervention studies have shown a 20–30% decrease in oestrogen levels among postmenopausal women who switched to a diet enriched in fibres.[100,101] In further studies, this reduction was observed independently of fat intake, and in the absence of changes in body weight.[102] In an Italian intervention study, also among postmenopausal women, a comprehensive dietary intervention strategy was used that combined reductions in the intake of total fat and refined carbohydrates, with an increase in the ratio of n-3 over n-6+ saturated fatty acids and with increased intakes of foods rich in dietary fibre. This comprehensive dietary change induced significant reductions in serum of testosterone, fasting C-peptide (as a marker of pancreatic insulin secretion), glucose,

and insulin area after glucose tolerance test, significant increases in serum SHBG, IGFBP-1 and IGFBP-2, but no changes in total IGF-I.[103,104] Also among men, dietary interventions have proved to influence endogenous hormone levels, showing, for example, reductions in serum and urinary androgens and SHBG after an 8-week intervention with diet low in fats and rich in dietary fibre.[105] A complicating factor in several of these and similar studies, however, is that often participation in dietary interventions lead to some (often transient) weight loss, leaving some residual doubt as to whether dietary composition itself can influence endogenous hormone levels independently of changes in body composition.

Circulating sex steroid concentrations and cancer risk

Sex steroids play a role in the regulation of cell differentiation, mitosis and apoptosis, and have been shown to promote growth of cancer cells.[106] The relationships between these hormones and risks of cancer, particularly tumours in organs sensitive to sex steroids such as breast, ovary, endometrium and prostate, have been studied extensively by epidemiologists.

Among postmenopausal women, elevated serum concentrations of both androgens (androstenedione, testosterone) and oestrogens (oestrone, oestradiol) have been consistently associated with an increased risk of breast cancer, with greater than two-fold risk ratios for women in the highest fifth of serum hormones levels compared to those in the lowest fifth.[107–109] In premenopausal women, at least two prospective studies also demonstrated an increased risk of breast cancer in association with elevated serum testosterone concentrations.[110–112] By contrast, these studies could not all demonstrate a clear relationship between breast cancer risk and prediagnostic serum oestrogen levels[110,113–115], possibly because of the large within-person variations in the blood levels of these hormones during the menstrual cycle. Nevertheless, one recent study showed an association between premenopausal breast cancer and oestradiol and free oestradiol serum levels among women who gave blood in the follicular phase of their menstrual cycle.[111] The relationships between endogenous sex steroid levels and breast cancer risk are examined in detail in Chapter 3.

Besides breast cancer, prospective cohort studies have also shown increased risks of endometrial cancer in relation to elevated circulating levels of oestrogens and androgens, and reduced levels of SHBG, among postmenopausal women.[116–118] Among premenopausal women, no clear associations with endogenous sex hormone levels have been reported so far, possibly because prospective cohort studies counted only small numbers of cases in this younger subgroup. Regarding ovarian cancer, relationships between risk and endogenous sex hormone levels, as reported from prospective cohort studies, have been inconsistent. Some small studies, with very small numbers of incident cases, showed a positive association of androgen or oestrogen levels with risk[119,120], whereas other studies showed no significant association.[121,122]

Among men, almost 20 different prospective studies have addressed the possible relationships between androgen levels in the circulation and risk of developing prostate cancer, but overall did not show any such relationship. A recent pooled re-analysis of these existing prospective cohort data worldwide, including 3886 men with incident prostate cancer and 6438 control subjects, showed a very modest inverse association between SHBG and prostate cancer risk (relative risk for the highest versus lowest quintile of SHBG levels = 0.86; 95% confidence interval: 0.75–0.98), but no significant association with either total or bioavailable androgens, nor with levels of circulating

oestrogens.[123] The absence of any effect of circulating sex hormone levels, however, does not rule out that androgenic activity within the prostate (e.g. through local conversion of testosterone into the more potent androgen DHT) could have an impact on prostate cancer development. A detailed review of the association between androgens and prostate cancer risk is presented in Chapter 5.

ADIPOSITY AND CHRONIC INFLAMMATION

Adipose tissue has long been regarded mainly as a reservoir for the storage and release of fatty acids. Since the mid 1990s, however, this view progressively has been challenged through a series of novel discoveries which showed that adipose tissue acts as a complex endocrine organ through the release of a number of important endocrine signalling factors, including leptin[124], tumour necrosis factor-α (TNF-α)[125], resistin, visfatin, adiponectin, omentin[126], and other hormonal factors.[127] In addition, it was discovered that the infiltration of macrophages in the obese adipose tissue also results in the secretion of various cytokines[128], including the interleukins 1β and 6 (IL-1β, IL-6), and macrophage-inhibiting factor (MIF).[10,129–132] In cross-sectional studies, BMI and other measures of adiposity have been found to be directly correlated with circulating levels of these various adipose tissue hormones and cytokines[133–138] as well as with C-reactive protein (CRP, a protein secreted by the liver in response to pro-inflammatory signals).[139] Conversely, weight reduction studies have shown decreases in circulating levels of these various proteins.[140,141]

Contrary to the various adipokines and cytokines described above, plasma adiponectin levels generally decrease with increasing adiposity[142,143], and generally rise during and after weight loss.[140,144,145] Adiponectin is an adipokine with anti-inflammatory and also anti-diabetic, anti-atherogenic, and anti-angiogenic properties.[126,146]

Through the metabolic effects of adipose tissue, excess body weight has been shown to generate a condition of systematic low-grade inflammation.[126,147] In addition, the various adipokines and cytokines have also been shown to play an important role in insulin sensitivity and glucose metabolism. High concentrations of TNF-α, IL-6, and IL-1β and low concentrations of adiponectin all have been shown to have deleterious effects on glucose homeostasis and pancreatic β-cell function, sustaining insulin resistance and hyperglycaemia[148–150], and several of these factors are now also recognized to be major regulators of insulin sensitivity in liver, skeletal muscle and other tissues[151–154] through the modification of cellular signal transduction pathways downstream of the insulin receptor.[125,155–157] There is also increasing evidence that these pro-inflammatory factors play an important role in the progression from normal to impaired glucose tolerance, and eventually to type-2 diabetes. Individuals who develop type-2 diabetes generally display features of low-grade inflammation years in advance of disease onset. This low-grade inflammation – mediated by increased levels of inflammation mediators such as TNF-α, IL-6, IL-1β, and CRP[158] – may contribute to the pathogenesis of type-2 diabetes via the development of insulin resistance, pancreatic β-cell damage and other mechanisms.[125,159] Conversely, hyperglycaemia can further induce inflammatory processes e.g. through the formation of advanced glycation end products (AGE)[160] and oxidative stress (glucose toxicity)[161], thereby establishing a vicious cycle.

Adiponectin, by contrast, improves hepatic glucose uptake, reduces gluconeogenesis, improves pancreatic β-cell glucose sensing and insulin secretion, and suppresses the formation of high-glucose-induced reactive oxygen species in vascular endothelial

and other cells.[162] These latter metabolic actions of adiponectin appear to be in large part mediated by the activation of AMP-activated protein kinase (AMPK).[162,163] In cross-sectional studies in humans, low adiponectin levels are generally associated with increased fasting plasma levels of glucose[164] as well as insulin.[164,165]

Inflammatory factors and cancer

In response to tissue injury or chronic inflammation, inflammatory cells produce pro-inflammatory cytokines (TNF-α and IL-1β) that control and mediate the inflammatory process. TNF-α and IL-1β induce the translocation of the cellular transcription factor NF-κB (nuclear factor κB) to the nucleus where it activates genes for immune and inflammatory response, cell proliferation and apoptosis regulation.[166] NF-κB activation leads to cyclo-oxygenase (COX)-2 expression, prostaglandin production, and inflammatory cytokine release (e.g. IL-6).[167] In case of normal (i.e. not chronic) inflammation, this process is immediately followed by the production of anti-inflammatory cytokines. Chronic low-grade inflammation, however, induces cell division and increases the concentration of free radicals, which can lead to DNA damage.[9]

In epidemiological studies, chronic inflammatory states have been associated with increased risks of several types of cancer, including cancer of the lung, oesophagus, stomach, pancreas, cervix, bladder, prostate and colorectum.[168,169] Conversely, non-steroidal anti-inflammatory drugs (NSAIDs) have shown anti-proliferative effects on endometrial cancer cells in vitro[170,171], and the use of NSAIDs was associated with a risk reduction of several cancers, including gastric cancer[172], colon cancer[173], prostate cancer[174], breast cancer[175], and ovarian cancer.[176] Also for endometrial cancer, the results from one recent case–control study showed a significant reduction of risk among obese women who were aspirin users compared to obese non-users.[177]

Only relatively few studies so far have addressed the possible relationships between blood levels of pro-inflammatory cytokines and inflammatory markers and cancer risk. Most studies have addressed the relationship of CRP with risk of colorectal cancer[178–181], and with one exception[178] showed an increase in risk among women or men with elevated serum CRP concentrations, with odds ratios between 1.6 and 2.9 for high versus low levels. In two small prospective studies, pre-diagnostic levels of CRP – but also of IL-6 and TNF-α – were found to be associated with overall cancer risk, all organ sites combined[168,179,182,183], and in one recent study elevated CRP was associated with an increased risk of ovarian cancer.[184] In addition, elevated CRP levels have been found to be inversely associated with survival in cancer patients.[185] For adiponectin, in several case–control and prospective cohort studies elevated circulating levels have been found to be related to reduced risks of cancers of the large bowel (colorectum)[186], stomach[187], breast[188–191], and endometrium[192–195] – up to 60% lower risk of cancer for the 20–25% subjects who had highest adiponectin levels, compared to those with lowest concentrations.[186,195]

CONCLUSIONS

Excess body weight (adiposity) and lack of physical activity increasingly are being recognized as major nutritional risk factors for cancer, and especially for many of those cancer types that have increased incidence rates in affluent, industrialized parts of the world. In addition, evidence is mounting that the effects of these risk factors to tumour development are mediated by hormonal and metabolic, physiological

mechanisms which, depending on the type of tumour, may include increased blood levels of glucose, insulin, IGF-I and sex hormones. More recent study results have indicated low levels of adiponectin and increased circulating levels of pro-inflammatory cytokines as factors that may contribute to tumour development. With the ever rising worldwide prevalence of sedentary lifestyles, overweight and obesity, it becomes increasingly important to understand the physiological mechanisms that link these risk factors to cancer development, so as to allow improved and more targeted strategies for both prevention and treatment.

Practice points

- excess body weight and adiposity are major risk factors for cancers of the breast (postmenopausal women only), endometrium, colon, pancreas, kidney (renal cell tumours), and oesophagus (adenocarcinomas), as well as B-cell lymphomas
- higher levels of regular physical activity reduce the risks of cancers of the colon and breast, and possibly of other tumour types
- possible endocrine and/or metabolic links between excess body weight, physical inactivity and cancer risks include insulin resistance and hyperinsulinaemia (colon, endometrium, pancreas, B-cell lymphoma), increased blood glucose levels (cancers of the pancreas, kidney, endometrium, liver, colon), increased ovarian androgen production (endometrial cancer among premenopausal women), and increased blood and tissue levels of oestrogens (cancers of the breast and endometrium), among postmenopausal women
- additional physiological mechanisms linking excess adiposity to cancer risk include alterations in the release of adipokines and cytokines by adipocytes and macrophages, resulting in a state of low-grade chronic inflammation
- higher blood levels of IGF-I have been related to increased risks of cancers of the prostate and breast, and possibly of the colorectum; circulating levels of total IGF-I, however, do not generally present a clear, direct relationship with measures of adiposity
- some specific aspects of diet (e.g. higher intakes of refined carbohydrates, lower intakes of dietary fibre, higher levels of consumption of dairy products) have been linked to either increased or reduced blood levels of insulin, sex hormones or IGF-I; current evidence, however, does not clearly relate these same aspects of diet to specific cancer risks

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