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Energy balance and cancer: the role of insulin and insulin-like growth factor-I

R. Kaaks* and A. Lukanova
International Agency for Research on Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France

Recent theories propose that a Western lifestyle may increase cancer risk through alterations in the metabolism of insulin and insulin-like growth factors (IGF; McKeown-Eyssen, 1994; Giovannucci, 1995; Kaaks, 1996; Werner & LeRoith, 1996). Insulin regulates energy metabolism, and increases the bioactivity of IGF-I, by enhancing its synthesis, and by decreasing several of its binding proteins (IGFBP; IGFBP-1 and -2). Insulin and IGF-I both stimulate anabolic processes as a function of available energy and elementary substrates (e.g. amino acids). The anabolic signals by insulin or IGF-I can promote tumour development by inhibiting apoptosis, and by stimulating cell proliferation. Furthermore, both insulin and IGF-I stimulate the synthesis of sex steroids, and inhibit the synthesis of sex hormone-binding globulin (SHBG), a binding protein that regulates the bioavailability of circulating sex steroids to tissues. The present paper reviews epidemiological findings relating the risk of cancers of the colo-rectum, pancreas, breast, endometrium and prostate to body size (obesity, height) and physical activity, and discusses the relationships between obesity and physical activity and plasma levels of insulin, IGF-I and IGFBP. Subsequent sections review epidemiological findings relating cancer risk to indices of chronic hyperinsulinaemia, and to plasma levels of IGF-I and IGFBP. Conclusions are that chronic hyperinsulinaemia may be a cause of cancers of the colon, pancreas and endometrium, and also possibly of the breast. On the other hand, elevated plasma IGF-I, as total concentrations or relative to levels of IGFBP-3, appears to be related to an increased risk of prostate cancer, breast cancer in young women, and possibly colo-rectal cancer. For cancers of the endometrium, breast and prostate, these findings are discussed in the context of relationships between insulin and IGF-I and levels of bioavailable sex steroids.

Cancer: Insulin: Insulin-like growth factors: Energy balance

Age-standardized incidence rates of cancers of the colon, rectum, pancreas, breast, endometrium, and prostate are up tenfold in Western Europe, North America or Australia compared with most parts of Africa or South-East Asia (International Agency for Research on Cancer, 1997). Other forms of cancer that are frequent in Western countries, but which will not be discussed further in the present review, are cancers of the gall bladder and kidney. Increases in the incidence rates of these cancers in migrants moving from low-risk to high-risk (Western) areas, and the strong increases in these incidence rates in Western countries during the course of the 20th century, show that the incidence rates depend largely on environmental (i.e. non-genetic) risk factors, including lifestyle.

Among the lifestyle factors most strongly implicated in the aetiology of each of these various forms of chronic disease are low physical activity and an energy-dense diet rich in total and saturated fats and rapidly-digestible carbohydrates (World Cancer Research Fund/American Institute for Cancer Research, 1997). In addition, overweight or obesity, reflecting an excessive energy intake relative to total energy expenditure, is associated with an increased risk of several forms of cancer, whereas physical activity has been regularly reported to be protective. Animal experiments have shown a strongly protective effect of chronic energy restriction against tumour development (Weindruch, 1992; Kritchevsky, 1999).

Physiological mechanisms that might mediate the effects of energy balance on cancer risk include reductions in endogenous free radical formation and oxidative damage, enhanced DNA repair, enhanced immune response, alterations in the activity of carcinogen-metabolizing enzymes, or

Abbreviations: GH, growth hormone; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin.

***Corresponding author:** Dr R. Kaaks, fax +33 4 72 73 83 61, email kaaks@iarc.fr

alterations in endogenous hormone metabolism (Fishbein, 1991; Frame *et al*. 1998). Regarding hormonal factors, attention has focused mostly on sex steroid metabolism (Key *et al*. 2001). More recently, however, insulin, insulin-like growth factor (IGF)-1 and IGF-binding proteins (IGFBP) have also received much interest from epidemiologists and basic researchers. Reasons are that both insulin and IGF-I can enhance tumour development by stimulating cell proliferation, and by inhibiting apoptosis (Jones & Clemmons, 1995; Werner & LeRoith, 1996). Furthermore, blood and tissue concentrations of insulin, IGF-I, and several of the IGFBP (especially IGFBP-1, -2 and -3) are intricately related to nutritional status and energy balance, and are central to the regulation of anabolic processes as a function of available energy and essential nutrients (e.g. amino acids; Clemmons & Underwood, 1991; Straus, 1994; Thissen *et al*. 1994).

The present paper will briefly review the epidemiological evidence for associations between cancer risk and anthropometric indices of overweight or obesity, and physical activity levels. The relationships between obesity and physical activity levels and plasma insulin, IGF-I and IGFBP are discussed. There will be an overview of results from epidemiological studies relating cancer risk to indices of chronic hyperinsulinaemia (history of non-insulin-dependent diabetes; blood insulin measurements), and to plasma levels of IGF-I and IGFBP. Findings relating cancers of the endometrium, breast and prostate to levels of insulin and IGF-I are discussed in the context of relationships between these peptides and levels of bioavailable sex steroids. Finally, major conclusions are presented together with a global discussion of the findings presented in the present review.

Obesity, physical activity and cancer risk

Overweight and obesity

A large number of epidemiological studies have addressed the possible relationships between cancer risk and BMI (weight/height^2), as an anthropometric index of excess body weight and obesity.

Endometrial cancer risk is positively associated with BMI (Hill & Austin, 1996; Goodman *et al*. 1997). This association is quite strong; relatively-severe obesity (BMI > 35 kg/m^2) is observed in a large proportion of patients with endometrial cancer, and has been associated with a four- to fivefold increase in risk. For breast cancer, by contrast, the relationship between risk and BMI (Hunter & Willett, 1993; Ballard-Barbash, 1994) is more complex, and appears to depend on menopausal status. In premenopausal women BMI shows no positive association, or possibly even a weakly inverse association with breast cancer risk (Ursin *et al*. 1995). By contrast, BMI has been associated with an increased risk of breast cancer diagnosed many years after the menopause.

As for the digestive tract cancers, colon cancer risk, particularly, appears to be positively related to BMI (Giovannucci, 1995; Giacosa *et al*. 1999). This association, however, is more defined in men than in women, possibly because in men BMI is a stronger indicator than in women of intra-abdominal body fat stores, which are an important determinant of insulin resistance and chronic hyperinsulinaemia (see p. 94). Rectal cancer risk, on the other hand, appears to be unrelated to BMI (Giovannucci, 1995; Giacosa *et al*. 1999). For pancreatic cancer, eleven studies conducted so far have examined the relationships between risk and BMI (Ji *et al*. 1996; Weiderpass *et al*. 1998; Silverman *et al*. 1998), and four of these (Friedman & Van Den Eeden, 1993; Møller *et al*. 1994; Ji *et al*. 1996; Silverman *et al*. 1998) have shown a positive association.

For prostate cancer, a large number of case–control and prospective cohort studies have been conducted to relate risk to BMI, and collectively these studies have provided fairly strong evidence against the presence of any such relationship (Kolonel, 1996).

Physical activity

The association between physical activity and cancer risk has been studied extensively for cancers of the colon, rectum, breast and prostate, while a smaller number of studies have examined a possible association for cancers of the endometrium.

For cancers of the digestive tract, numerous case–control and cohort studies have shown an inverse association between estimated physical activity levels and colon cancer risk particularly, in both men and women (Colditz *et al*. 1997; McTiernan *et al*. 1998; Moore *et al*. 1998). This inverse association was consistent across studies with widely-differing methods of measuring physical activity levels, ranging from occupational histories to questionnaire assessments or detailed diaries of recreational and non-recreational activity. For rectal cancer risk, by contrast, the evidence for an inverse association with physical activity levels is much weaker, and was observed in only a small proportion of cohort and case–control studies. As for pancreatic cancer risk, the possible relationship with physical activity has not been addressed so far by epidemiological studies (McTiernan *et al*. 1998; Moore *et al*. 1998).

For breast cancer, a large number of case–control and cohort studies have been conducted, as in the case of colon cancer, using diverse methods of assessing habitual physical activity levels. The vast majority of these studies have shown an inverse relationship between physical activity and breast cancer risk (McTiernan *et al*. 1998; Moore *et al*. 1998; Gammon *et al*. 1998). The association between breast cancer risk and physical activity levels during early adulthood was also addressed in several studies (Gammon *et al*. 1998; Wyshak & Frisch, 2000), and was also found to be inverse. For endometrial cancer risk, three case–control studies, but no cohort studies so far, have also shown an inverse association with physical activity levels (McTiernan *et al*. 1998).

For prostate cancer, the results from eleven cohort studies and nine case–control studies were inconclusive; some studies showed a decrease in risk, whereas other studies showed an adverse effect (McTiernan *et al*. 1998; Moore *et al*. 1998).

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Energy balance, insulin metabolism and the insulin-like growth factor-I–insulin-like growth factor-binding protein system

Obesity, physical inactivity and insulin resistance

Insulin resistance is a state of reduced response of tissues, skeletal muscle, liver and adipose tissue, to the physiological actions of insulin. In order to compensate for insulin resistance, and to maintain blood glucose levels within acceptable limits, plasma insulin levels rise permanently, even in the fasting state. Except for some rare inherited forms, insulin resistance generally develops as a consequence of increased hepatic and muscular uptake, and oxidation of fatty acids instead of glucose for energy metabolism (DeFronzo, 1988; Bjorntorp, 1994; Belfiore & Iannello, 1998; Randle, 1998). One major determinant of insulin resistance is obesity, particularly an increase in intra-abdominal body fat stores (Bjorntorp, 1992; Abate, 1996), from where free fatty acids are easily mobilized and released regularly into the circulation. A second major determinant is physical inactivity (Koivisto *et al*. 1986; Grimm, 1999). In the short term, physical activity generally improves insulin sensitivity through mechanisms that are independent of any substantial change in body weight. In the long term, regular exercise ('training') may improve insulin sensitivity, also, through the prevention or reduction of excess body weight and obesity.

Insulin-like growth factor-I, insulin-like growth factor-binding proteins and insulin-like growth factor-I bioactivity

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 modulated by interactions of IGF-I with at least six different IGFBP (Jones & Clemmons 1995), which regulate the efflux of circulating IGF-I through the capillary barrier, as well as the binding of IGF-I to its tissue receptors.

Although IGF-I and IGFBP are produced in practically all human tissues, most IGF-I and IGFBP in blood plasma are produced in the liver. Over 90 % of circulating IGF-I is complexed with IGFBP-3, together with another glycoprotein, acid-labile subunit. IGFBP-3 has a very high affinity for IGF-I, and the large IGF-I–IGFBP-3–acid-labile subunit complex cannot pass through the capillary barrier to target tissues. IGFBP-5, which has an even higher affinity than IGFBP-3 for IGF-I, may form a similar IGF-I–IGFBP-5–acid-labile subunit complex (Twigg & Baxter, 1998). Practically all the remaining IGF-I is bound to IGFBP-1, -2, -4 and -6, which have lower binding affinities for IGF-I (compared with IGFBP-3 and IGFBP-5), do not form complexes with acid-labile subunit, and are small enough to cross the endothelial barrier. Thus, a decrease in plasma IGFBP-3, with a transfer of IGF-I to smaller IGFBP not complexed with acid-labile subunit, is believed to increase IGF-I availability to its tissue receptors. Reductions in plasma concentrations of the smaller IGFBP, and particularly IGFBP-1 and -2, are also thought to increase the bioavailability of circulating IGF-I (Jones & Clemmons, 1995).

At the tissue level, binding proteins have been proposed mostly to inhibit receptor binding, by complexing IGF-I. Nevertheless, results from *in vitro* studies suggest that, depending on the relative concentrations of IGF-I and IGFBP, and perhaps depending also on tissue type, certain IGFBP (e.g. IGFBP-1, -2, -3, -5) may actually enhance IGF-I binding to its receptors (Jones & Clemmons, 1995). Furthermore, it is possible that certain IGFBP exert effects also through their own specific receptors (Jones & Clemmons, 1995). For example, for IGFBP-3 it has been shown that, while it may inhibit the anti-apoptotic action of IGF-I by decreasing availability of IGF-I for binding to its receptor, it can itself stimulate apoptosis of breast, prostatic and endometrial cancer cells *in vitro* through a IGFBP-3-specific binding site on the cell membrane (Gill *et al*. 1997; Karas *et al*. 1997; Rajah *et al*. 1997; Rechler, 1997).

Energy balance and the insulin-like growth factor-I system

The principal factor enhancing the production of IGF-I and IGFBP-3, its major plasma binding protein, is growth hormone (GH; Clemmons & Underwood, 1991; Straus, 1994; Thissen *et al*. 1994; Jones & Clemmons, 1995). In addition to GH, however, insulin appears to be central to the regulation of IGF-I bioactivity as a function of available dietary energy (Straus, 1994; Thissen *et al*. 1994).

Insulin enhances GH-stimulated IGF-I synthesis in at least two ways. First, *in vitro* studies have shown that insulin increases GH receptor levels in the liver (Baxter & Turtle, 1978; Tollet *et al*. 1990), which could also be the case in other tissues. This stimulatory effect on GH receptor levels is also reflected in positive correlations between fasting insulin levels and levels of GH-binding protein, the external domain of the GH receptor, which is split off and released into the circulation (Baumann & Mercado, 1993). Second, insulin enhances protein synthesis in general, by stimulating the cellular uptake of amino acids (Straus, 1994; Thissen *et al*. 1994). In addition to these permissive effects of insulin on the GH-stimulated synthesis of IGF-I, insulin augments IGF-I bioactivity by inhibiting the production of IGFBP-1 and IGFBP-2 in the liver and in other tissues (Suikkari *et al*. 1988; Boni-Schnetzler *et al*. 1990; Conover & Lee, 1990; Suwanichkul *et al*. 1994; Lee *et al*. 1997). A second hormonal factor with a strong regulatory effect on IGFBP-1, increasing its levels, is cortisol (Unterman, 1993; Lee *et al*. 1997).

Table 1 summarizes relationships reported in the literature between plasma insulin, GH, IGF-I and IGFBP under conditions of insulinopenia (energy restriction, insulin-dependent diabetes mellitus), and under conditions of insulin excess (obesity, most cases of non-insulin-dependent diabetes mellitus).

The low endogenous production (and hence hepatic concentrations) of insulin during prolonged fasting or insulin-dependent diabetes mellitus causes reductions in GH receptor levels (Baxter & Turtle, 1978; Baxter *et al*. 1981; Merimee *et al*. 1982; Postel-Vinay *et al*. 1982; Maes *et al*. 1983; Straus & Takemoto, 1990; Baumann & Mercado, 1993; Mercado & Baumann, 1995), and hence resistance to

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Table 1. Plasma insulin, growth hormone (GH), insulin-like growth factor (IGF)-I and IGF-binding proteins (IGFBP) in relation to states of hypoinsulinaemia (chronic energy restriction, insulin-dependent diabetes mellitus (IDDM)) and hyperinsulinaemia (obesity, non-insulin-dependent diabetes mellitus (NIDDM))

					IGFBP			
	Fasting insulin	GH	GHBP	IGF-I	-1	-2	-3	Free IGF-I
Energy restriction; IDDM	↓	↑	↓	↓↓	↑	↑	↓	↓↓
Obesity; NIDDM	↑	↓	↑	~↓	↓	↓	~	↑

GHBP, GH-binding protein; ↓, decrease; ↑, increase; ~, no association.

the GH stimulation of IGF-I synthesis and decreases in plasma IGF-I levels (Clemmons *et al*. 1981; Caufriez *et al*. 1984; Tanaka *et al*. 1985; Clemmons & Underwood, 1991; Counts *et al*. 1992; Hochberg *et al*. 1992; Golden *et al*. 1994; Thissen *et al*. 1994; Dunger & Cheetham, 1996; Argente *et al*. 1997). In addition, such hypoinsulinaemic states are associated with a decrease in IGFBP-3 (Clemmons & Underwood, 1991; Counts *et al*. 1992; Golden *et al*. 1994; Thissen *et al*. 1994; Bereket *et al*. 1995*a,b*, 1999; Dunger & Cheetham, 1996). Finally, prolonged fasting and insulin-dependent diabetes mellitus cause a sharp rise in plasma levels of GH in compensation for the GH resistance (Clemmons & Underwood, 1991; Thissen *et al*. 1994; Dunger & Cheetham, 1996), and also cause rises in IGFBP-1 (Counts *et al*. 1992; Bereket *et al*. 1995*b*, 1999; Dunger & Cheetham, 1996; Argente *et al*. 1997) and IGFBP-2 (Counts *et al*. 1992; Argente *et al*. 1997; Bereket *et al*. 1999). Increased secretion of cortisol is a second mechanism through which fasting leads to elevated IGFBP-1 levels.

The chronically-hyperinsulinaemic state, as in obesity or non-insulin-dependent diabetes mellitus, leads to reductions in IGFBP-1 (Clemmons & Underwood, 1991; Thissen *et al*. 1994; Frystyk *et al*. 1995; Wabitsch *et al*. 1996; Argente *et al*. 1997; Nam *et al*. 1997; Nyomba *et al*. 1997) and IGFBP-2 (Wabitsch *et al*. 1996; Argente *et al*. 1997; Nam *et al*. 1997), and therefore increases in free IGF-I (Frystyk *et al*. 1995; Nam *et al*. 1997; Nyomba *et al*. 1997). Furthermore, the hyperinsulinaemic state causes a reduction in plasma GH (Gama *et al*. 1990; Cordido *et al*. 1991; Prelevic *et al*. 1992; Frystyk *et al*. 1995; Veldhuis *et al*. 1995; Rasmussen *et al*. 1995*a*,*b*; Morales *et al*. 1996; Bernardi *et al*. 1998), which can be explained largely by an increased negative feedback on pituitary GH secretion by free IGF-I (Tannenbaum *et al*. 1983; Chapman *et al*. 1998), plus an increased sensitivity to GH, and thus a reduction in GH requirements for synthesis of a given amount of IGF-I. Compared with normal-weight and non-diabetic subjects, the plasma total IGF-I levels either remain stable (Gama *et al*. 1990; Cordido *et al*. 1991; Rasmussen *et al*. 1994, 1995*a,b*; Frystyk *et al*. 1995; Nam *et al*. 1997) or slightly decrease (Copeland *et al*. 1990; Gama *et al*. 1990; Marin *et al*. 1993; Chang *et al*. 1994; Hu *et al*. 1994; Veldhuis *et al*. 1995), whereas for IGFBP-3 some mild increase (Frystyk *et al*. 1995; Rasmussen *et al*. 1995*a,b*), decrease (Wilson, 1992), or no difference (Bang *et al*. 1994; Rasmussen *et al*. 1995*a,b*; Nam *et al*. 1997; Bernardi *et al*. 1998) has been reported.

It is noteworthy that fasting and insulin-dependent diabetes mellitus, on the one hand, and obesity and non-insulin-dependent diabetes mellitus, on the other hand, exert opposite effects on plasma levels of all peptides (GH-binding protein, GH, IGFBP-1, IGFBP-2, and free IGF-I), except total IGF-I. Thus, the effects of insulin on the IGF-I–IGFBP system can explain almost all the observations in energy-restricted states, although they do not explain why in generally-well-nourished populations some subjects have substantially higher total plasma IGF-I concentrations (and higher cancer risk; see p. 97) than other subjects.

Apart from insulin, other factors affecting pituitary GH secretion will also have a major impact on total plasma IGF-I levels. The control of pituitary GH secretion is complex, and involves many internal physiological variables, including hypoglycaemia (Casanueva, 1992; Vance *et al*. 1992), mechanisms related to stress response (cold exposure, fright), thyroid hormones (Giustina & Wehrenberg, 1995) and sex steroids (Wehrenberg & Giustina, 1992; Ho *et al*. 1996).

Physical activity and the insulin-like growth factor-I system

The effects of physical activity on circulating levels of IGF-I and IGFBP have been studied intensively in recent years. A large number of small human intervention studies (Bang *et al*. 1990; Cappon *et al*. 1994; Schwarz *et al*. 1996; Hornum *et al*. 1997; Nguyen *et al*. 1998; Bermon *et al*. 1999; Chadan *et al*. 1999; Wallace *et al*. 1999; Elias *et al*. 2000), with some exceptions (Hopkins *et al*. 1994; Kraemer *et al*. 1995; Schmidt *et al*. 1995; Bonnefoy *et al*. 1999), have shown an acute but transient increase in levels of IGF-I immediately during and after a bout of exercise, and this increase may be explained by an acute rise in pituitary GH secretion (Cappon *et al*. 1994; Kraemer *et al*. 1995; Schmidt *et al*. 1995; Di Luigi *et al*. 1997; Hornum *et al*. 1997; Wideman *et al*. 1999). Two studies have shown an increase in IGF-I (Nguyen *et al*. 1998; Wallace *et al*. 1999), although another study did not (Bermon *et al*. 1999), and demonstrated a simultaneous increase in IGFBP-3 levels. One study in prepubertal children, however, showed a reduction in IGF-I levels (Scheett *et al*. 1999). Another relatively consistent finding is a dramatic (in some studies more than tenfold) increase in IGFBP-1 after a single more-prolonged episode of exercise (Hopkins *et al*. 1994; Nguyen *et al*. 1998; Scheett *et al*. 1999; Wallace *et al*. 1999). This increase in IGFBP-1 was independent of variations in circulating insulin, and may be explained by an exercise-induced rise in cortisol levels. The main function of the increase in IGFBP-1 may be to diminish the hypoglycaemic action of IGF-I. Findings for IGFBP-3 were more variable,

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some studies showing an acute rise after exercise (Schwarz *et al*. 1996; Wallace *et al*. 1999), whereas other studies showed no change (Bermon *et al*. 1999).

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 (Bonnefoy *et al*. 1999) as well as in younger men and women (Roelen *et al*. 1997; Koziris *et al*. 1999), and also increased IGFBP-3 levels in one of these studies (Koziris *et al*. 1999). Other studies in elderly men, however, showed no effect on IGF-I after 6 months of endurance training (Nicklas *et al*. 1995; Vitiello *et al*. 1997). Intensive exercise during prolonged periods of several hours, e.g. marathon running, was found to decrease circulating levels of IGF-I, as well as IGFBP-3 (Koistinen *et al*. 1996). Studies on adolescents, who have the highest basal IGF-I levels when compared with other age-groups, showed a significant decrease in plasma levels of IGF-I and IGFBP-3 after an increase in physical activity levels for 3 d (Jahreis *et al*. 1991) to several weeks (Eliakim *et al*. 1998).

Taken together, these observations show that a short bout of exercise, at least in adults, causes an acute transient increase in IGF-I and a dramatic increase in IGFBP-1, whereas physical training may also increase total circulating IGF-I levels. Prolonged exercise that results in a strongly negative energy balance for a number of days, e.g. marathon running, may decrease IGF-I levels for at least a number of days afterwards. In children and adolescents both short-term and regular exercise might decrease IGF-I.

Chronic hyperinsulinaemia and cancer risk

For several organ sites, a substantial number of epidemiological studies have been conducted to examine whether a history of diabetes is related to increased cancer incidence (see below). A limitation of many of these studies is that often they lacked detail as to whether diabetes was of early onset (type 1) or adult onset (type 2), and whether or not the subjects depended on insulin injections. Nevertheless, the vast majority (> 80 %) of diabetic subjects are generally of the adult-onset type, which typically develops after a long period of insulin resistance and pancreatic insulin hypersecretion. Furthermore, even after the first clinical symptoms of diabetes, type 2 diabetic subjects generally continue to produce insulin in greater amounts than non-obese and non-diabetic subjects, although not high enough to overcome insulin resistance and maintain normal glucose homeostasis (DeFronzo, 1988). Thus, even in the absence of detailed information about the type of diabetes and insulin dependence, associations between cancer risk and previous history of diabetes may be taken as indirect evidence for chronic hyperinsulinaemia as a possible risk factor. In addition to studies relating cancer risk to diabetes, several more recent studies, discussed later, (pp. 97–99), have also examined the possible relationships between cancer risk and plasma levels of insulin, or C-peptide (a marker of pancreatic insulin secretion).

Endometrial cancer is among the cancers most strongly related to a previous history of diabetes. Epidemiological studies have consistently shown increases in endometrial cancer risk among diabetic women (O'Mara *et al*. 1985; Adami *et al*. 1991; Moseson *et al*. 1993; La Vecchia *et al*. 1994; Weiderpass *et al*. 1997, 2000; Wideroff *et al*. 1997; Shoff & Newcomb, 1998; Parazzini *et al*. 1999; Niwa *et al*. 2000). In addition to these studies, one large case–control study showed an increase in endometrial cancer risk in post-menopausal women (Troisi *et al*. 1997) with elevated serum levels of C-peptide. A similar but much smaller study also showed higher fasting insulin levels in thirty-two post-menopausal patients with endometrial cancer compared with eighteen controls (Rutanen *et al*. 1994).

Cancer of the pancreas is a second type of cancer for which risk has consistently been found to be related to a previous history of diabetes. The large majority of prospective cohort studies and case–control studies showed an increase in risk in subjects who developed diabetes mellitus at least 1 year before the diagnosis of cancer (Everhart & Wright, 1995; Wideroff *et al*. 1997; Calle *et al*. 1998; Weiderpass *et al*. 1998; Silverman *et al*. 1999). In a formal meta-analysis, this association was significant ($P < 0{\cdot}05$), and remained so when restricted to data on subjects who had developed diabetes at least 5 years before the diagnosis of pancreatic cancer (Everhart & Wright, 1995). Given that, generally, pancreatic cancers progress very fast, it was unlikely that the diabetes mellitus existing several years earlier was a consequence of the pancreas tumour, e.g. due to local tumour infiltration, rather than a possible cause. So far, no prospective studies have been conducted to estimate risk directly as a function of plasma insulin or C-peptide measurements. Nevertheless, one cohort study recently showed a twofold increase in pancreatic cancer mortality in men and women with high (> 11·1 mmol/l) compared with low (< 6·6 mmol/l) plasma glucose levels 2 h after a standard oral glucose load (Gapstur *et al*. 2000). Elevated post-load glucose levels are indicative of insulin resistance, and generally are associated with increased pancreatic insulin secretion in both the fasting and non-fasting states (DeFronzo, 1988).

A third form of cancer that appears to be related to chronic hyperinsulinaemia is cancer of the colon. First, a number of studies have shown a positive association between diabetes and increased risk of colon cancer (in some studies, cancers of the colon and rectum combined; McKeown-Eyssen, 1994; Giovannucci, 1995; La Vecchia *et al*. 1997; Le Marchand *et al*. 1997; Will *et al*. 1998; Hu *et al*. 1999). In addition, in a recent cohort study men and women who had elevated fasting plasma glucose concentrations, and who had increased 2 h plasma levels of both glucose and insulin during an oral glucose tolerance test, were found in subsequent years to experience an almost twofold higher risk of developing colo-rectal cancer (Schoen *et al*. 1999). Another recent cohort study, in New York women, showed an approximately fourfold increase in risk, especially of colon cancer, when comparing subjects in the highest and lowest quartiles of serum C-peptide levels (Kaaks *et al*. 2000).

For breast cancer, epidemiological studies have provided no consistent evidence for a positive relationship with diabetes (Kaaks, 1996); some studies showed an increase in risk (Weiderpass *et al*. 1997), but most other studies showed no association (O'Mara *et al*. 1985; Adami *et al*. 1991; Moseson *et al*. 1993; La Vecchia *et al*. 1994; Wideroff *et al*.

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1997; Sellers *et al*. 1998; Weiss *et al*. 1999). One complication in studies on breast cancer, however, is that diabetes and hyperinsulinaemia might have diverging relationships with breast cancer risk before and after menopause, as also in the case of obesity. Unfortunately, none of the studies on breast cancer and diabetes provided separate relative risk estimates by menopausal status or age. While the possible relationship with diabetes thus remains unsettled, two case–control studies did show a positive association between breast cancer risk and plasma C-peptide or insulin levels. This association was observed in both premenopausal (Bruning *et al*. 1992; Del Giudice *et al*. 1998) and postmenopausal (Bruning *et al*. 1992) women, which is intriguing, as obesity (generally a major determinant of circulating insulin levels) appears to be related to a mild decrease in breast cancer risk before menopause.

Prostate cancer risk was unrelated to a previous history of diabetes in case–control and prospective cohort studies (Ragozzino *et al*. 1982; O'Mara *et al*. 1985; Adami *et al*. 1991; Smith *et al*. 1992; La Vecchia *et al*. 1994; Steenland *et al*. 1995; Wideroff *et al*. 1997; Giovannucci *et al*. 1998; Will *et al*. 1999). Furthermore, prostate cancer risk was not found to be associated with fasting plasma insulin levels in one prospective cohort in northern Sweden. Collectively, these observations provide fairly strong evidence against a relationship between prostate cancer risk and chronic hyperinsulinaemia.

Cancer risk in relation to blood levels of insulin-like growth factor-I and insulin-like growth factor-binding protein-3

Since the mid 1990s, a number of case–control and prospective cohort studies have addressed the possible relationships between cancer risk and circulating levels of IGF-I and IGFBP-3, while a few studies have also addressed the possible relationships between cancer risk and levels of IGFBP-1 and IGFBP-2.

For breast cancer four of five case–control studies (Peyrat *et al*. 1993; Bruning *et al*. 1995; Bohlke *et al*. 1998; Del Giudice *et al*. 1998; Petridou *et al*. 2000), and two prospective cohort studies (Hankinson *et al*. 1998; Toniolo *et al*. 2000) have shown an increase in breast cancer in women with elevated total plasma IGF-I, or with elevated IGF-I for given levels of IGFBP-3. In all studies, this relationship between risk and total plasma IGF-I was found exclusively for women developing breast cancer before the average age at menopause, and remained after adjustment for age, family history of breast cancer, height, BMI, or serum C-peptide.

For prostate cancer two case–control studies and two prospective cohort studies have shown an increase in prostate cancer risk in men with elevated plasma IGF-I. In the Physicians' Health Study prostate cancer risk increased with increasing plasma concentrations of IGF-I (Chan *et al*. 1998). In a multivariate analysis adjusting for IGFBP-3, this association was even stronger, whereas IGFBP-3 was inversely related to risk after adjustment for effects on disease risk due to IGF-I. Another prospective cohort study, in Northern Sweden, also showed an increase in prostate cancer risk with increasing plasma levels of total IGF-I, and this increase in risk was particularly strong in men who provided their blood sample at age 40–50 years, and who developed a prostate tumour below age 60 years (relative risks and 95 % CI of 1·00, 2·97 (95 % CI 0·84, 10·49) and 4·30 (95 % CI 1·19, 15·50) respectively for tertiles of IGF-I). In this study, however, adjustment for IGFBP-3 did not further increase relative risk estimates (Stattin *et al*. 2000). In addition to these two cohort studies, prostate cancer risk was shown to be positively related to total circulating IGF-I levels in two case–control studies (210 and fifty-two cases respectively; Mantzoros *et al*. 1997; Wolk *et al*. 1998).

For colo-rectal cancer, three cohort studies (Ma *et al*. 1999; Giovannucci *et al*. 2000; Kaaks *et al*. 2000) showed very mild statistically non-significant increases in risk with increasing plasma or serum levels of total IGF-I. Nevertheless, in two of the three studies (Ma *et al*. 1999; Giovannucci *et al*. 2000), risk showed a much stronger, and statistically significant ($P < 0{\cdot}05$) increase in relation to IGF-I after adjustment for circulating levels of IGFBP-3. On the other hand, in the third cohort study, plasma levels of IGFBP-1 and IGFBP-2 were also measured, and were found to be inversely related to colo-rectal cancer risk (Kaaks *et al*. 2000). Finally, in one case–control study (Manousos *et al*. 1999) colo-rectal cancer risk was associated positively with IGF-I and inversely with IGFBP-3, although none of these relationships reached statistical significance.

As for endometrial cancer, one small study comparing thirty-two patients and eighteen control subjects showed (Rutanen *et al*. 1994) reduced plasma levels of both IGF-I and IGFBP-3 in the patient group. As no adjustment for BMI was made, it cannot be ruled out that this inverse association was due to the higher degree of obesity in the patient group, because severe obesity can reduce circulating IGF-I levels (see also p. 95). In a second small case–control study, including twenty-three patients and twenty-seven controls, the patient group was found to have increased total plasma IGF-I, and decreased IGFBP-1, and these associations remained after adjustment for the effects of BMI on disease risk (Ayabe *et al*. 1997).

For pancreatic cancer, no studies so far have addressed the possible relationships between risk and plasma levels of IGF-I or IGFBP.

Insulin, insulin-like growth factor-I, sex steroid metabolism, and cancers of endometrium, breast and prostate

A large body of evidence shows that insulin and IGF-I are very central to the regulation of circulating levels of total and bioavailable sex steroids. Insulin and IGF-I both inhibit the production of sex hormone-binding globulin (SHBG) by liver cells *in vitro* (Plymate *et al*. 1988; Singh *et al*. 1990; Crave *et al*. 1995), and cross-sectional studies show negative correlations between plasma SHBG and insulin (Pugeat *et al*. 1991), and more weakly also between plasma SHBG and IGF-I (Lonning *et al*. 1995; Erfurth *et al*. 1996; Pfeilschifter *et al*. 1996; Vermeulen *et al*. 1996).

In addition to the inhibition of SHBG synthesis, *in vitro* studies have shown that insulin and IGF-I both stimulate the synthesis of sex steroids, particularly androgens, in

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ovarian (Barbieri *et al*. 1988; Cara, 1994), testicular (Lin *et al*. 1986; De Mellow *et al*. 1987; Bebakar *et al*. 1990) or adrenal tissue. On a more detailed level, these effects on steroidogenesis appear to be explained by an enhanced activity of the CYP11A1 enzyme, which catalyses the first and rate-limiting step (cholesterol side-chain cleavage) in the formation of all steroid hormones, and of the 17-α-hydroxylase and 17,20-lyase activities of the CYP17 protein, which catalyse the first two steps in the formation specifically of sex steroids (Magoffin *et al*. 1990; Urban *et al*. 1990; Magoffin & Weitsman, 1993*a*,*b*; Stein *et al*. 1995; Chuzel *et al*. 1996; Penhoat *et al*. 1996; DeMoura *et al*. 1997; Mesiano *et al*. 1997; Kristiansen *et al*. 1997).

In premenopausal women with functional ovarian hyperandrogenism (polycystic ovary syndrome; PCOS) obesity and plasma insulin levels are positively associated with total plasma levels of testosterone and androstenedione (Dunaif, 1999; Poretsky *et al*. 1999). In these hyperandrogenic women plasma androgen levels can be decreased by improving insulin sensitivity through weight loss (Kopelman *et al*. 1981; Bates & Whitworth, 1982; Kiddy *et al*. 1989; Pasquali *et al*. 1997), or by the use of insulin-lowering drugs (Ehrmann, 1999; Pugeat & Ducluzeau, 1999). In normo-androgenic pre- and post-menopausal women relationships between hyperinsulinaemia and total circulating androgen levels are less clear. Nevertheless, because of decreases in plasma SHBG levels, obesity and hyperinsulinaemia are generally associated with indices of bioavailable testosterone in normo-androgenic women as well as in women with PCOS. In post-menopausal women, particularly, this increase in bioavailable androgens may be a major cause of increased tissue concentrations of oestrogens, formed by local conversion of the androgens. These regulatory effects of insulin and IGF-I on the synthesis of SHBG and sex steroids may thus have important implications for the development of cancer, particularly of the endometrium and breast, but possibly also at other organ sites.

Case–control studies have shown an increase in endometrial cancer risk in women with low plasma SHBG, high plasma androgens and, particularly after menopause, comparatively elevated total and bioavailable plasma oestrogens formed peripherally from androgens of either ovarian or adrenal origin. Women with ovarian hyperandrogenism may be at increased risk, especially before menopause, as shown by frequent case reports of PCOS in young women developing endometrial cancer (Grady & Ernster, 1996), and case–control (Dahlgren *et al*. 1991; Shu *et al*. 1991; Niwa *et al*. 2000) and cohort (Coulam *et al*. 1983) studies show an increased endometrial cancer risk in PCOS patients. A theory that very successfully explains most observations relating endometrial cancer risk to endogenous and exogenous sex steroids, as well as to other risk factors (obesity, PCOS) is the 'unopposed oestrogen' hypothesis (Key & Pike, 1988*a*; Grady & Ernster, 1996). This theory stipulates that risk is increased among women who have normal or elevated plasma bioavailable oestrogens and low plasma progesterone, so that the effects of oestrogens are insufficiently counterbalanced by those of progesterone. A defect in endogenous progesterone production may be related to energy balance and hyperinsulinaemia through the development of ovarian hyperandrogenism. PCOS is a relatively frequent endocrine disorder, with an estimated prevalence of about 4–8 %, and in premenopausal women is associated with frequent anovulatory menstrual cycles, and hence with impaired luteal-phase progesterone synthesis.

With regard to sex steroids and breast cancer, a popular theory is that risk is increased particularly in women with elevated plasma and breast tissue levels of oestrogens ('estrogen excess' hypothesis; Key & Pike, 1988*b*; Bernstein & Ross, 1993). This theory fits observations from prospective studies that breast cancer risk is increased in post-menopausal women who have low circulating SHBG, elevated plasma androgens (androstenedione, testosterone), and hence elevated plasma levels of total and bioavailable oestradiol (Thomas *et al*. 1997). The theory also fits the observations that in elderly post-menopausal women obesity is associated with increased breast cancer risk. After menopause, adipose tissue (including that of the breast) becomes the major source of oestrogen production. In addition, as described earlier, obesity and associated hyperinsulinaemia increase levels of bioavailable androgens, the direct precursors for oestrogen synthesis. A second theory relating breast cancer risk to endogenous sex steroid metabolism stipulates that, compared with an exposure to oestrogens only (as in post-menopausal women not using exogenous progestogens), risk is increased even further in women who have elevated plasma levels of bioavailable oestrogens in the presence of normal or even elevated levels of progestogens ('oestrogen-plus-progestogen' hypothesis). The oestrogen-plus-progestogen hypothesis may explain why post-menopausal hormone-replacement therapy with oestrogens plus progestogens appears to increase breast cancer risk more than the use of exogenous oestrogens alone (Ross *et al*. 2000; Schairer *et al*. 2000). In addition, the hypothesis may explain why obese premenopausal women on average may experience a mild reduction in breast cancer risk, as obesity and elevated insulin levels may cause chronic anovulation and reductions in ovarian progesterone production in women with a genetic predisposition towards ovarian hyperandrogenism.

For prostate cancer, the predominant hypothesis on the role of endogenous steroid hormones is that risk is increased in men with high intra-prostatic concentrations of dihydrotestosterone. Dihydrotestosterone is formed from testosterone within the prostate, and binds and activates the androgen receptor with a four times higher affinity than testosterone (Grino *et al*. 1990; Wilson, 1996). One determinant of intra-prostatic dihydrotestosterone formation may be variations in the activity of intraprostatic (type II) 5-α-reductase (SRD5A2), that catalyses the testosterone–dihydrotestosterone conversion. Another possible determinant, which could provide a physiological link between prostate cancer risk and nutritional lifestyle factors, is an increase in circulating levels of bioavailable testosterone unbound to SHBG, that can freely diffuse into the prostatic cells. However, in men, in contrast to post-menopausal women and women with PCOS, obesity and chronic hyperinsulinaemia generally correlates inversely with total plasma testosterone levels, and does not lead to any increase

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in bioavailable testosterone unbound to SHBG (Seidell *et al*. 1990; Pasquali *et al*. 1991; Haffner *et al*. 1993*a*,*b*, 1994; Wu *et al*. 1995; Tibblin *et al*. 1996; Vermeulen, 1996; Ferrini & Barrett-Connor, 1998; Falkner *et al*. 1999; Vermeulen *et al*. 1999). The generally-accepted explanation for this finding is that an increase in bioavailable testosterone causes a compensatory decrease in pituitary luteinising hormone secretion (long-loop feedback inhibition), and hence in testicular androgen production. Levels of bioavailable testosterone are thus kept approximately constant. This feedback mechanism might at least partially explain why prostate cancer risk does not appear to be associated with obesity and chronically-elevated plasma insulin levels, while in addition prostate cancer risk does not appear to be strongly related to circulating levels of total or bioavailable testosterone (Eaton *et al*. 1999).

Discussion

In the present literature review we have evaluated whether current evidence supports the hypothesis that excess energy intake, relative to total energy expenditure, is related to cancer risk and, particularly, whether such a relationship is possibly mediated by alterations in the metabolism of insulin, IGF-I, and IGFBP.

A first conclusion is that chronic hyperinsulinaemia may be a risk factor for cancers of the endometrium, pancreas and colon. For each of these three forms of cancer, however, this conclusion is based largely on indirect evidence, in particular the associations between cancer risk and a previous history of diabetes. Nevertheless, for cancers of the endometrium and colo-rectum, case–control or prospective studies have also related risk directly to measurements of plasma insulin or C-peptide, whereas for cancer of the pancreas one prospective study showed a relationship with plasma glucose levels after an oral glucose tolerance test performed many years earlier. It is of note, at least for cancers of the endometrium and colon, that risk is also related to obesity and sedentariness, two major determinants of insulin resistance and chronic hyperinsulinaemia. For breast cancer, for which risk is also related to lack of physical activity, the association between risk and obesity appears to vary with menopausal status, and one may speculate that failure to account for such differences between pre- and post-menopausal women may have obscured associations between risk and previous diabetes. Interestingly, the results from two case–control studies on plasma measurements of insulin or C-peptide suggest that hyperinsulinaemia may indeed also be related to breast cancer risk. For each of these various cancer sites, further studies, preferably of a prospective cohort design, will be needed to confirm whether chronically-elevated plasma insulin levels are indeed a major risk factor.

A second conclusion from the present review is that, independently of chronic hyperinsulinaemia, elevated plasma IGF-I (as total concentrations or relative to IGFBP-3) may be positively related to risk of cancers of the prostate, breast (possibly only in young women) and colo-rectum. It is an intriguing observation that these associations are for those cancers that apparently have no association with obesity or chronic hyperinsulinaemia, but which do show a relationship with height, a possible marker of total and bioavailable IGF-I levels during the peripubertal growth spurt. Further prospective cohort studies are needed to confirm the associations between cancer risk and IGF-I observed so far, and to examine whether similar relationships also exist for cancers at other organ sites.

A key question with respect to these conclusions is through which mechanisms may chronically-elevated plasma levels of insulin or IGF-I be related to tumour formation.

There is overwhelming evidence from *in vitro* studies and animal experiments that IGF-I may have direct effects on tumour development, by stimulating cell proliferation, and by inhibiting apoptosis (Jones & Clemmons, 1995; Stewart & Rotwein, 1996; Werner & LeRoith, 1996). These effects have been shown for various cell types, for the mammary gland (Dickson & Lippman, 1995; Lee *et al*. 1998), endometrium (Rutanen, 1998), colo-rectum (Singh & Rubin, 1993) and prostate (Culig *et al*. 1996), as well as for other organs. Insulin has been shown to exert similar effects, although it cannot always be established clearly from these *in vitro* studies whether these effects were mediated through insulin receptors, or whether they were mediated through IGF receptors and through hybrid insulin–IGF-I receptors, to which insulin, especially at supraphysiological concentrations, can also bind. Studies on transgenic animals that overexpress the IGF-I gene have shown that these animals have increased rates of spontaneous or induced tumour formation (Bol *et al*. 1997; Wilker *et al*. 1999; DiGiovanni *et al*. 2000*a*,*b*). Conversely, PC-3 (breast) xenograft tumours grow significantly more slowly in IGF-I-deficient hosts compared with IGF-I-intact controls (Yang *et al*. 1996), and tumorigenesis (sarcoma formation) was also found to be inhibited in nude mice with an inactivating mutation in the IGF-I receptor (Prager *et al*. 1994). With respect to the IGFBP, pro-apophtotic and anti-mitogenic effects, as well as reductions in tumour growth, have been demonstrated for IGFBP-3, as mentioned earlier (p. 94). Also IGFBP-1 has been shown to have important growth regulatory (and anti-tumour) effects in a number of cell types (Lee *et al*. 1997; Rutanen, 1998). In addition to their possible direct effects on tumour development through their cognate receptors, it is also possible that insulin and IGF-I affect cancer risk through modifications in endogenous sex steroid metabolism, as discussed on pp. 97–99.

These physiological mechanisms provide an insight into how chronically-elevated levels of insulin or IGF-I may be related to cancer risk. Nevertheless, several crucial questions remain.

A first major question is why, for some cancers (e.g. of the prostate), only increases in total IGF-I or in IGF-I relative to IGFBP-3 appear to be related to risk, whereas increases in IGF-I bioactivity that one would expect to result from reductions in IGFBP-1 and -2 (e.g. due to obesity and hyperinsulinaemia) apparently are not. This question relates to a number of issues. First, it is only partially understood how IGF-I bioactivity within tissues is quantitatively modified by concentrations of various IGFBP, since several of the IGFBP can either inhibit or potentiate binding of IGF-I to its receptor, depending on the relative concentrations of IGF-I and IGFBP. Second, it is not fully

understood how circulating levels of total IGF-I and IGFBP may be quantitatively related to tissue levels, since some of the circulating IGFBP can diffuse more easily through the endothelial barrier than others, whereas in addition the IGFBP can be synthesized locally. Third, it is also possible that, instead of being the predominant determinants of tissue concentrations, levels of circulating IGF-I and IGFBP merely reflect the levels of IGF-I and IGFBP synthesis in other tissues, as the synthesis in the liver (the predominant source of the circulating peptides) and other organs may be regulated to a large extent by the same endocrine factors, including GH, insulin and other hormones.

A second major question is which physiological mechanisms may underlie the increases in circulating total IGF-I, or in IGF-I relative to levels of IGFBP-3, in subjects at increased risk for cancers of the prostate, breast or colorectum. One major paradox, discussed earlier (p. 95), is that chronic energy restriction causes a dramatic drop in circulating IGF-I levels, but that obesity, a reflection of long-term positive energy balance, does not increase total IGF-I levels in comparison with the normally-nourished but non-obese state. Another paradoxical observation is that physical activity, a protective factor against various forms of cancer (and especially those cancers, perhaps, that appear to be related to hyperinsulinaemia) does not generally seem to decrease total circulating IGF-I levels. Thus, it is not clear how elevated levels of total IGF-I, or of IGF-I relative to IGFBP-3, may be related to diet and physical activity.

It is possible that increases in circulating total IGF-I, or in IGF-I relative to IGFBP-3, reflect a relatively elevated pituitary GH secretion. GH provides a key stimulus for the synthesis of IGF-I particularly, but to a lesser extent of IGFBP-3, and conditions of elevated pituitary GH secretion, such as the pubertal growth phase or acromegaly, are generally associated with increases not only in the total concentrations of IGF-I and IGFBP-3, but also in IGF-I : IGFBP-3 (Juul *et al*. 1994, 1996; Jasper *et al*. 1999). An elevated secretion of GH by the pituitary could thus explain the observations of increased risk of breast, prostate or colo-rectal cancers either with increased total IGF-I, or with IGF-I adjusted for IGFBP-3. One behavioural factor that might directly contribute to increasing pituitary GH secretion is a high frequency of consumption of foods or drinks rich in rapidly-digestible carbohydrates. This type of food causes high postprandial glycaemic and insulinaemic peaks, followed by periods of hypoglycaemia. Hypoglycaemia triggers the secretion of hormones that stimulate gluconeogenesis, including cortisol and GH (Casanueva, 1992; Vance *et al*. 1992). Another dietary factor typical of Western societies that might increase GH secretion and IGF-I levels is the relatively high intake of animal protein, rich in essential amino acids. Further research will be needed to clarify how these and other lifestyle factors, in interaction with genetic background factors, may lead to chronically-elevated IGF-I levels.

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