REVIEW

Energy balance and cancers
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Energy balance results from the exact equilibrium between caloric intake and caloric expenditure. A caloric intake larger than caloric expenditure results in overweight, even obesity, but other determinants, like hormonal dysfunction and/or genetic traits may play a part in obesity syndrome. Obesity, and even overweight, have been recognized as risk factors for the development of cancers. Human epidemiological studies, which have tended to establish the nature of the relationship between energy balance and cancer, are summarized first, with the influence of the various factors which act both on obesity and on cancer risk. Among these factors are the macronutrients responsible for the caloric intake, and some lifestyle factors (physical activity, drinking habits and tobacco use). Second, the animal studies help to distinguish between different relevant factors, and to understand some of the underlying mechanisms. However, the insulin-resistance syndrome, which appears to underlie the relationship between obesity and hormone-dependent cancers, and possibly colon cancer, is only relevant to human physiology because hormonal alterations are part of it. Prevention of hyperinsulinemia, insulin resistance and the accompanying visceral obesity appears to be a major public health task for the prevention of cancers.

Key words: Animal studies, cancers, colon cancer, energy balance, epidemiological studies, hormone-dependent cancers, insulin resistance syndrome, obesity, overweight.

Introduction

Energy balance results from the exact coincidence between calorie intake and calorie expenses. Food and alcohol make up the calorie intake, basal metabolism, thermogenesis and physical activities being responsible for the expenses.

A calorie intake larger than calorie expense results in overweight, even obesity, but other determinants, like hormonal dysfunction and/or genetic trait may play a part in obesity syndrome.

In human beings, the relationship between energy balance and cancers is generally evaluated through the analysis of the association between obesity/overweight measured by the body mass index (BMI) and cancer risk. However, obesity determinants (e.g., food intake, physical activity, hormonal imbalance) or lifestyle factors acting on BMI (e.g., tobacco and alcohol) might also independently affect carcinogenesis, complicating the analysis of the relationship between energy balance and cancer, based on BMI.

In animal tumour models, it is possible to feed different experimental groups with isocaloric diets. Thus, the specific effect of some nutrients can be distinguished from the effect of the caloric intake more easily.

We will first summarize the human epidemiological studies, which tended to establish the nature of the relationship between energy balance and cancer, and will describe the influence of the various factors which act both on obesity and on cancer risk. Then, the animal studies will help to distinguish between the different relevant factors, and to understand underlying mechanisms.

Human studies

Obesity has been associated with cancer mortality. Inversely, physical activity showed a negative association with cancer mortality (Pi-Sunyer, 1991; Wannamethee *et al.,* 1993). Müller *et al.* (1994) have shown an increase of 16% of cancer incidence in a cohort of obese men and women compared with normal weight persons in Denmark. In the cohort of the Nurses study (Manson *et al.,* 1995), cancer mortality in-creases with BMI (OR = 2; CI: 1.2-3.0 for a BMI > 32). Contrarily, the Buffalo Health Study (Dorn *et al.,* 1997), does not show an increase in cancer mortality. However, the study was designed to evaluate the effect of obesity on cardiovascular disease mortality, and only 637 women and 611 men have been followed. This sample is too small for a study on cancer mortality; besides, the BMI was recorded only at the base line of the 29-year follow up.

The hormone-dependent cancers are generally responsible for a large part of the association between obesity and cancer risk (Kirschner *et al.,* 1982; Ségala *et al.,* 1991; de Waard, 1975; Wynder *et al.,* 1966), but the association has also been described of other sites. The study of the relationship obesity/ cancer by cancer site discloses specific mechanisms relevant to each cancer, which are described below.

Oesophagus adenocarcinoma
Several case-control studies reported a significant association of obesity with oesophagus adenocarcinoma (Brown *et al.,* 1995; Chow *et al.,* 1998). In this cancer, the relationship between obesity and risk presents the peculiarity to be explained via a physical mechanism: obesity promotes gastroesophageal reflux which, in turn, predisposes to Barrett's oesophagus, a metaplastic precursor state for adenocarcinoma of the oesophagus and of the gastric cardia. However, obesity may also influence cancer risk through other mechanisms.

Hormone-dependent cancers

Breast cancer. A review of the relationship between anthropometric measurements and breast cancer has been recently published (Clavel-Chapelon *et al.,* 1997). Age and time in life at which weight is evaluated, but also at which cancer is diagnosed, appear to influence the type of association between BMI and breast cancer risk.

About two thirds of the studies show a positive association of height with breast cancer risk, either pre- or post-menopausal. The negative studies take place in Latin countries (Ségala *et al.,* 1991; La Vecchia *et al.,* 1990). Height is obviously determined by factors occurring in adolescence, among them food intake, which may be relevant to cultural differences (diet, lifestyle), or modified by other factors occurring later in life (e.g. reproductive factors), which might explain that this association is not consistently found. Knowing the importance currently attributed to IGF-1 in breast cancer development, it is tempting to propose the hypothesis illustrated in Figure 1.
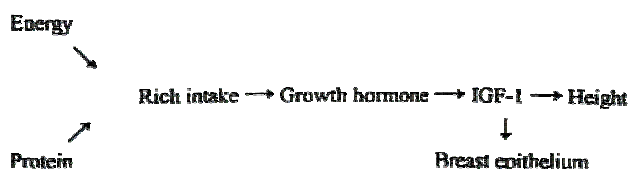

Figure 1. Biological mechanism proposed to explain the relationship
between caloric intake, height and breast cancer risk.

Synthesis of growth hormone is stimulated by a rich caloric and protein intake and results in an increased liver synthesis of IGF-1, of which primary function is the growth of the entire body, but might also be available to the breast epithelium for hyperproliferation.
The analysis of the relationship between obesity and breast cancer risk shows opposite direction for pre- and post-menopausal cancer, requiring a distinct description.

Pre-menopausal cancer. Twenty-seven studies (reviewed in Clavel-Chapelon, 1997 and Müller *et al.,* 1994; Taioli *et al.,* 1995; Swanson *et al.,* 1996; Yong *et al.,* 1996; Huang *et al.,* 1997; Trentham-Dietz *et al.,* 1997; Magnusson *et* al., 1998) have been reported: six show no association between obesity and breast cancer, seven a

non-significant association (3 OR 1), only one study reported that breast cancer risk increased with obesity, and 13 describe a linear relationship between increasing BMI and decreasing breast cancer risk in young women, prior to menopause. A detection bias has been evoked, since it appears to be easier to detect a nodule in a small breast rather than in a large breast. However, markers of hormonal imbalance in lean pre-menopausal women and measurements of hormones in obese pre-menopausal women provide a better explanation of the inverse relationship between obesity and breast cancer in pre-menopausal women.
Women with benign breast diseases (BBD) mammographically (Boyd et al., 1989; Gram et al., 1995) or histologically (Ferraroni et al., 1993; Gerber, 1993) identified, present higher HDL-cholesterol (HDL-C) and lower triglycerides (TG) plasma levels than those in women without BBD. Since there exists a direct correlation between TG plasma levels and BMI (Ferraroni et al., 1993; Saintot et al., 1995), and an inverse one between HDL-C and BMI, it is expected that these women with BBD, a risk factor for breast cancer, (Carter et al., 1988; Ségala et al., 1991; Gerber, 1993) are lean.
All the factors exposed above (BBD, HDL-C, TG, BMI) are related to oestrogen imbalance:
• Boyd et al. (1989) reported that oestrogen levels are higher during the two menstrual cycle phases in women with BBD than in normal controls.
• Low TG and high HDL-C levels may result from an increased activity of the liver lipoprotein lipase, induced by a high oestrogen level (Appelbaum-Bowden et al., 1989).
• HDL-C level vary with physiological oestrogen levels over lifetime (puberty, menarche;" ménô= pause) and also with oestrogen replacement therapy (Boyd and McGuire, 1990):
• Finally, plasma free-oestradiol concentration is negatively correlated with adipose stores in pre-menopausal women (Pedersen et al., 1995). Thus, leanness might be a sign of oestrogen excess, whereas obesity might be the sign of an oestrogen deficit in young women. The study by Potishman et al. (1996) provided direct evidence for this hypothesis, by showing that obese pre-menopausal women (BMI > 27.1) had lower total oestradiol serum concentrations during the folicular phase than lean women (BMI > 23.2).

Post-menopausal cancer. An elevated BMI was reported as a significant risk factor for breast cancer in 20 studies, whereas seven studies showed a non-significantly increased risk, two showed no relation-ship, and one reported a decreased risk (Clavel-Chapelon et al., 1997; Yong et al., 1996; Huang et al., 1997; Trentham-Dietz et al., 1997; Magnusson et al., 1998; Kaaks et al., 1998).
The long-time proposed mechanism underlying this association was based on the extragonadal oestrogen synthesis taking place in adipose stores through the amortisation of androstenedione. Post-menopausal

women (BMI > 27.1) showed higher total oestradiol serum concentration phase than lean women (BMI > 23.1) (Potishman et al., 1996). With regard to breast cancer, Toniolo et al. (1995) reported that post-menopausal overweight women were at higher risk for breast cancer, and that oestrogen levels were highly correlated with BMI in these women. A comparable result is reported by Hankinson et al. (1995).

However, a type of obesity, diversely named (apple type, android, central, abdominal, visceral), appeared to be specifically related to breast cancer risk and called the attention towards another mechanism, not necessarily exclusive (Bruning et al., 1992; Kirschner et al., 1982; Secreto et al., 1991). Schapira et al. (1994) showed precisely that visceral obesity, assessed by computerized tomography, was a risk factor for breast cancer independently from weight and waist/ hip ratio. Abdominal obesity is associated with low sex hormone binding globulin (SHBG) levels (Bruning et al., 1992), and thus with high levels of free oestradiol and androgens. It is also associated with hyperinsulinemia and insulin-resistance. Together these changes complete the picture of the insulin-resistance syndrome. In this syndrome, there is a dysregulation of IGF-1 through an alteration of the binding protein IFG-BP3 (Conover et al., 1992; Stoll, 1994; Kaaks, 1996). ThuS; * IGF-1 could act as a growth factor for mammary epithelium. Whatever the mechanism at work, obesity is a risk factor for post-menopausal women, precisely when obesity starts, at the third decade of age (Kumar et al., 1995). Besides, survival is shorter in overweight breast cancer patients than in leaner patients with a lower lipid intake (Zhang et al., 1995).

Endometrial cancer. Since the first report, more than 30 years ago (Wynder et al., 1966), obesity has been consistently described as a risk factor for endometrial cancer, a post-menopausal cancer. Both -weight and height appear as risk (Tretli and Magnus, 1990). Four large prospective studies (Folsom et al., 1989; Tretli and Magnus, 1990; Tornberg and Carstensen, 1994; Müller et al., 1994) demonstrate increasing risk with increasing BMI. Two of them state that overweight is already a risk factor (Table 1).

	BMI quintiles				
	1	2	3	4	5
Tretli and Magnus N = 570,000, cases = 2208	1.0	1.1	1.2	1.4	2.2
Tornberg and Carstensen N = 47,000, cases = 22	1.0	1.3	1.6	1.7	2.6

Table 1. Correlation of increasing cancer risk with increasing BMI

Tretli and Magnus (1990) also estimated that keeping BMI below 24 in a population would decrease endometrial cancer incidence by 10%. Levi *et al. (1992)* predicted that it was a late-in-life obesity which increased the risk, but that the risk was even higher when obesity was present in the third decade of a woman's life. Obesity appears to act as a promoter. As for breast cancer in post-menopausal women, obesity is the direct cause of extragonadal oestrogen synthesis, and/or obesity as part of the insulin-resistance syndrome, and IGF-1 might be responsible for the promoting effect. However, diabetes does not appear to confer an additional risk of endometrial cancer in women who are not overweight (Shoff and Newcomb, *1998).*

Epithelial ovarian cancer. The association of obesity with ovarian cancer is inconsistent (reviewed in Parazzini *et al., 1997* and Thorling, *1996).* In the study on the obese person's cohort, an increased risk was found only for the age class *50-59* which corresponds with the first years of menopause. The risk decreased over thé remaining life time. Thus, effect of obesity might be critical at the change in hormonal metabolism.

Prostate cancer. All but one prospective study showed that prostate cancer was associated with one or all aspects of body size, weight, BMI, fat or lean body mass. The prospective Japan Hawaii Cancer Study (Chyou *et al., 1994),* reported a positive association of weight with prostate cancer (for a weight > *70* kg: *OR: 1:52, CI: 1.09-2.12;* trend P = 0.008), whereas in a previous analysis of the same cohort, prostate cancer risk was rather associated with muscular mass. The authors compared their results with previous studies on prostate cancer: case--control studies also showed that prostate cancer was associated with obesity, whereas two were negative, and three prospective studies showed that mortality was associated with obesity, whereas one study was negative. A recent study confirmed the significant association of prostate cancer risk with BMI, height and lean body mass in a cohort of *135,006* construction workers in Sweden (Andersson *et al., 1997).*

An hormonal mechanism is likely to explain the possible relationship between obesity and prostate cancer. In this male cancer, the obesity is expected to be `android', that is to say abdominal. Therefore, it is accompanied by low levels of SHBG and high levels of testosterone, possibly also of hyperinsulinemia and insulin-resistance, with a dysregulation of IGF-1. When the muscular mass is specifically involved, it is plausible that it reflects hyperandrogeny with its anabolising effect.

The relationship obesity/prostate cancer is similar to the relationship obesity/breast cancer in post-menopausal women and obesity/endometrial cancer, with a promotional effect of sexual hormones and IGF-1. This is in line with the delayed increase in prostate cancer incidence observed in migrant studies *(Yu et al., 1990).*

A recent study by Giovannucci *et al. (1997)* evokes another similarity between prostate and breast cancers: obese children showed a (ower risk and tall children a higher risk of prostate cancer at adult age than their lean and small counterpart, respectively. This reminds us of what has been described for pre-menopausal breast cancer: in this situation obesity reduces breast cancer risk, and height is a risk factor. A hormonal mechanism with lower level of testosterone in obese children and

high levels of IGF-1 in tall subjects is a plausible mechanism, as for breast cancer.

Role of determinants of obesity in hormone-dependent cancers. Obesity is consistently associated with post-menopausal breast cancer, endometrial, and to a lesser extent with prostate cancer and ovarian cancer. That the association is causal is plausible because of the relationship between total and/or abdominal obesity, and hormones/growth factors. The question remains with regards to determinants of obesity which have been shown as risk factors for these cancers, as to whether energy-rich foods, alcohol, tobacco, and physical exercise are influencing cancer development directly, through obesity, or both.

A caloric intake larger than caloric expenses induces overweight. Thus, it is expected that total caloric intakes, protein-, carbohydrate- and lipid-caloric intake are reported as risk factors. One of these nutrients has been found as a risk factor alternatively in different studies, varying with the age and menopausal status of the women, country, food habits, etc. It is likely that the risk is mediated through overweight.

The case of lipids has been specifically investigated to elucidate whether they represent a risk factor *per se*. As a matter of fact, lipid intake is highly correlated with energy intake, and this colinearity is very difficult to disentangle. Several statistical models have been developed in an attempt to control the caloric effect of lipid (reviewed and discussed in Kipnis et al., 1993). Whereas the residual model (Willett and Stampfer, 1986) does not attribute any role to lipids in breast cancer risk, the partition model (Howe, 1989) attributes a significant effect to lipids. Physiological considerations support this finding. Fats appear as the most efficient macronutrients to make up adipose stores, because they are oxidised after carbohydrates to fuel the energy demand, and tend to accumulate (Astrup et al., 1994; Flatt, 1995). Fat has been irregularly found as a risk factor for breast cancer (Clavel-Chapelon et al., 1997), but more consistently for endometrial cancer (reviewed in Gerber, 1996; Goodman et al., 1997), ovarian (Risch et al., 1994) and prostate cancers (reviewed in Thorling, 1996). Among fats, saturated fatty acids or animal fats, the least oxidisable fatty acids, are most often found as risk factors. This was recently confirmed in a study on breast cancer, using the different statistical models for energy adjustment (Decarli et al., 1997). Monounsaturated fatty acids are also found as a risk factor in countries where meat is the major contributor of oleic acid. It is not clear whether it is a risk factor per se, or a marker of meat intake (Gerber and Richardson, 1995), which is a major source of saturated fatty acids, since in Mediterranean countries where olive oil is the major contributor of oleic acid, monounsaturated fatty acids do not seem to be a risk factor (Martin-Moreno et al., 1994; Trichopoulou et al., 1995). The difficulty in distinguishing between the effect of fat and meat is also shown in two studies on prostate cancer (Giovanucci et al., 1993; Gann et al., 1994), where alpha-linolenic acid was shown to be a risk factor. This fatty acid was a marker of red meat intake (Giovannucci et al., 1993; Gann et al., 1994; Stampfer, personal communication), although it is considered as a vegetal constituent, mainly of soya. However, it is possible that cattle were fed soya-derived products. In animal studies (see below), a specific role has been attributed to polyunsaturated fatty acids in carcino-genesis. This has never been found in human studies. However, lipids could play a role independently from their part in caloric intake and adipose stores constitution: they influence the composition of the gut microflora, and consequently the oestrogen entero-hepatic cycle, in an inverse manner to fibre (Gerber, 1996). They also decrease the density of possibly beneficial nutrients, either through their strong caloric impact, or because of food preference: it was shown that obese people prefer fatty food stuffs and avoid `healthy' foods such as cereals, vegetables and fruit. This results in a low intake in potential protective nutrients such as fibre, vitamins and antioxidants (Miller et al., 1990; Romieu et al., 1988).

Alcohol has been associated with breast cancer risk (reviewed in Clavel-Chapelon, 1997) and less clearly with endometrial cancer risk (Gerber, 1996).

As a free-radical inducer, alcohol might play a role in carcinogenesis initiation (Petrakis et al., 1981). It was shown to interfere with hormone metabolism, independently from obesity: 30 g/day alcohol increases plasma levels of DHEA (dehydro-epiandrosterone), of oestradiol and oestrone (Reichman et al., 1993). A direct correlation between alcohol intake and oestrone sulphate levels was shown in the Nurse's study (Hankinson et al., 1995).

However, alcohol modifies the relationship between food intake and obesity. Generally, a high intake of alcohol is associated with weight loss (Hellerstedt et al., 1990). In moderate drinkers, alcohol calories are additive and not substitutive, resulting in a higher total caloric intake (Liu et al., 1994), and there is a positive correlation between alcohol intake and BMI. Finally, another study showed that alcohol facilitated abdominal obesity, a specific risk factor for breast and possibly other cancers (Troisi et al., 1991). Thus, there is a possible role for alcohol in breast cancer development, both independently from obesity, and through obesity.

Because it regulates energy balance, physical exercise is expected to play a part in the relationship between obesity and hormone-dependent cancers. Physical activity is difficult to evaluate, and many studies were not able to clearly demonstrate a relationship between breast cancer and exercise (Clavel-Chapelon, 1997). However, careful studies showed a decreased risk of breast cancer for women who exercised regularly (Bernstein et al., 1994; Thune et al., 1997), with the

notable exception of the Nurse's study (Rockhill et al., 1998).

In the same line, Levi et al. (1993) reported a beneficial effect of moderate physical activity on endometrial cancer. This result has been recently confirmed (Moradi et al., 1998). For prostate cancer, results are contradictory so far (Le Marchand et al., 1991; Lee et al., 1992).

There are some indications that physical exercise might interfere directly with hormonal metabolism in adolescence. In young sportive women, a delayed menarche (Frisch et al., 1985) and a decreased androstenedione synthesis (Kaye et al., 1991) were observed. Thus, physical exercise might also play a part in the relationship between obesity and hormone-dependent cancers through obesity, and in-dependently from obesity.

We have observed that several factors are related together with obesity and hormone cancers. The complexity of the relationship between these factors, food intake, alcohol, physical exercise, and obesity might interfere with the relationship of these factors with cancers. It is difficult to take into account all of these potential confounding factors; such a complexity might explain the difficult interpretation of some studies.

Figure 2 proposes a model to illustrate the relationship between the various factors acting on obesity, hormone-dependent cancer and hormones.
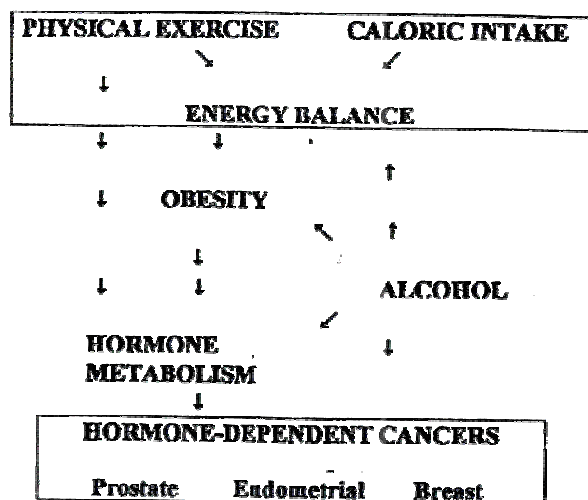

Figure 2. Various factors interacting between energy balance and hormone-dependent cancers.

Colorectal cancer

Obesity is positively associated with colorectal adenoma and cancer risk in most studies (e.g. Nomura et al., 1985; see the review of Chyou et al., 1994; followed by studies of Bayerdorffer et al., 1993; Shinchi et al., 1994; Giovannucci et al., 1995; Bird et al., 1998), whereas some studies do not find a link between obesity and colorectal cancer (e.g., Neugut et al., 1991). In contrast, several determinants of obesity were shown to be related to colorectal cancer risk.

Caloric intake. The effect of caloric intake on colorectal cancer is supported by international ecological studies: countries with high caloric intakes (and high fat intakes) have a high colorectal cancer incidence and/or mortality (Weindurch et al., 1991). By contrast, the prospective studies of Willett et al. (1990) and Giovannucci et al. (1992, 1994) do not show any relationship between caloric intake and colorectal cancer. Moreover, a European prospective study (Goldbohm et al., 1994) and case-control studies (e.g. Little et al., 1993) show a tendency of reduced risk in people with high caloric intake. This paradoxical finding can be explained because the caloric intake may be an indirect measure of caloric expenditures: 'big eaters' may also be 'big spenders' with respect to energy when they practice physical exercise (Riboli and Cummings, 1993). Also, a low caloric diet decreases the proliferation or the rectal mucosa, which is considered as a risk factor for tumour growth (Steinbach et al., 1994). To reconcile the previous observations, that both people with high caloric intake and people with low caloric intake might be at low risk for colorectal cancer, we speculate that the energy balance is more relevant to colon carcinogenesis than the caloric intake itself.

Macronutrients intake. Nutrient contributors to caloric intake were shown to be associated with colorectal cancer. They are strongly correlated to caloric intake and, in spite of statistical models designed to control for energy intake, it is difficult to disentangle their respective effect. Fat was found as a risk factor in the Nurse's Health Study, as well as red meat, but neither poultry nor fish were implicated (Willett et al., 1990).

Besides its caloric effect, dietary fat may modify many colonic parameters, including bile acid and fatty acid concentrations, and gut flora metabolism of bile acids. The possible protective effect of dietary fibres on colorectal cancer might be due to their low caloric content. Moreover, fibre decreases the caloric density of the macronutrients and reduces their digestibility, which leads to a kind of caloric restriction.

It seems that starches and refined cereals are risk factors mainly in European countries where the meat-associated colorectal cancer risk is not consistently found (Faivre et al., 1997; Franceschi et al., 1998). These macronutrients are strong contributors to the caloric intake, and because of industrial processing are devoid of fibre and beneficial micro-nutrients. In any case, high intake of these carbohydrates might favour hyperinsulinemia and insulin resistance, with a possible increased activity of IGF-1.

nutrients (glucose, triglycerides, fatty acids), and of hormones (insulin, IGFI) (McKeown-Eyssen, 1994). These blood factors would, in turn; lead to insulin resistance, and enhance the proliferation of normal and neoplastic cells, as discussed later.

Physical activity. Physical activity is consistently associated with low risk of colorectal cancer. Most case-control and cohort studies show that people with a high level of physical exercise have a lower risk of getting a

colorectal tumour (cancer or polyp) than people with a sedentary lifestyle (Slattery et al., 1988; Fredriksson et al., 1989; Ballard-Berbash et al., 1990; Gerhardsson de Verdier et al., 1990; Arbman et al., 1993; Little et al., 1993; Potter et al., 1993; Giovannucci et al., 1995; Martinez et al., 1997). The protective exercise can be either occupational or recreational (sports), but some, such as jogging, seem more protective than others (Potter et al., 1993; Giovannucci et al., 1995).

A sedentary lifestyle lowers caloric expenditures. It may also lower the gut flow rate, and increase the time of residence of digestive contents (Oetlle, 1991). This would allow a longer contact with gut mucosa, and increase the effect of toxic compounds present in the colonic content, e.g. carcinogens (polycyclic aromatic hydrocarbons, heterocyclic amines), and promoters (bile acids). Dietary fibres may counteract this phenomenon, by accelerating the transit rate. This simple explanation is not supported by carefully controlled studies in volunteers, showing that physical activity does not reduce the mean transit time (Bingham and Cummings, 1989). However, anyone who practices jogging can give evidence of a mechanical effect on the intestinal transit, and since jogging seems more protective than other sports (Potter et al., 1993; Giovannucci et al., 1995), this may be indirect evidence. However, no firm link has yet been established between transit time and colorectal cancer.

Epidemiological studies thus suggest that obesity might be a marker for other associated risk factors: superfluous caloric intake, excess of dietary fat, and sedentary lifestyle resulting in energy imbalance seem to be the key risk factors, because of the consistency of the observations on the risk-reducing effect of physical exercise.

Cellular and molecular mechanisms of this effect were mainly dissected in animal studies, but at the human organism level, it was proposed that the imbalance between caloric intake and expenditure can modify the blood concentration of energetic nutrients (glucose, triglycerides, fatty acids), and of hormones (insulin, IGF1) (McKeown-Eyssen, 1994). These blood factors would, in turn, lead to insulin resistance, and enhance the proliferation of normal and neoplastic cells, as discussed later.

Other cancers
The Danish cohort (Müller et al., 1994) showed a relationship between obesity and cancer for several groups: those generally associated with alcohol consumption (mouth, oropharynx, oesophagus and liver), and also cancer of the pancreas (Silverman et al., 1998), biliary ducts (Saracci, 1990) and kidney in women (Mellemgaard et al., 1991). Also, a high intake of calories was a risk factor for intestinal gastric adenocarcinoma (Harrison et al., 1997). On the contrary, an inverse association is observed for lung cancer, especially in men (Chyou et al., 1994). This might be related to the inverse relationship between tobacco and BMI.

Animal studies

Mammary carcinogenesis
Hormonal metabolism and. factors related to reproductive events are of paramount importance in breast cancer carcinogenesis. Therefore, it is understandable that animal models are difficult to interchange with a human situation.

Caloric restriction. Indeed, it has been shown that caloric restriction decreased mammary carcinogenesis in several murine models, spontaneous, trans-planted or chemically-induced ones (Tannenbaum, 1940; Krichevsky et al., 1989; Sinha et al., 1988; Welsch et al., 1990; Cohen et al., 1988, 1991; Arts et al., 1991). Caloric restriction appeared to counteract the promoting effect of lipids (Welsch et al., 1990), and is effective whatever the proportion of lipids in the diet (Cohen et al., 1988; Kritchevsky et al., 1989; Pariza, 1986).

Calories and fat intake. However, lipid restriction inhibits mammary carcinogenesis in isqcaloric diet, but the tumour-promoting effect of lipids is mainly due to polyunsaturated fatty acids, an effect never observed in epidemiological studies on human breast cancer. The study reported by Singletarry et al. (1991) supports the importance of caloric restriction in mammary carcinogenesis: alcohol facilitates DMBA-induced mammary carcinogenesis in rats when alcohol intake is moderate. When the alcohol intake is such that it decreases the outside-alcohol caloric consumption, the facilitating effect of alcohol is negated.

Caloric expenditures. The studies of the effect of physical exercise on mammary carcinogenesis are very inconsistent, depending upon the type and the extent of physical activity. A recent study (Gillette *et al.,* 1997) conjugates the analysis of the effect of caloric restriction and of physical activity in a F-344 rat model of methyl nitrosurea-induced mammary carcinogenesis. Only caloric restriction inhibited tumour development. Although unrestricted exercised rats lost weight and showed fat-free carcasses, tumour incidence was as high as in sedentary unrestricted rats. Moreover, exercised caloric-restricted animals showed the highest tumour incidence.

Mechanisms. These findings demonstrate that caloric restriction does not play a role in murine mammary carcinogenesis through the avoidance of adipose stores, but more probably through a mechanism comparable to the one effective in colon cancer (see below). With regard to physical exercise, it does not appear to be related to an interaction with the energy balance when it inhibits mammary carcinogenesis and when strenuous, it might enhance tumour development (Thompson, 1992).

Colon carcinogenesis

Caloric restriction. Tannenbaum started experimental carcinogenesis studies in the 1940s. He showed that an intense caloric restriction inhibits the emergence of

spontaneous tumours, and of chemically induced cancers (most studies dealt with mammary and skin cancers). Many facts and mechanisms proposed above for mammary carcinogenesis also stand true for colorectal carcinogenesis (see `mammary carcinogenesis' section above).

Four independent studies have shown that chemically induced adenocarcinoma are strongly inhibited in caloric-restricted rodents, as long as they receive an adequate supply of micronutrients (Kritchevsky, 1993). For example, groups of rats were fed a restricted diet after an azoxymethane initiation. Experimental groups were fed a restricted diet bringing 90%, 80% and 70% calories, compared with a control group fed ad libitum (100% intake). At termination, the tumour incidence was 92%, 66% and 61% respectively, of the tumour incidence observed in the control group (Kumar et al., 1990). According to Clinton et al. (1992), the number of cancers is correlated with the caloric intake, even in ad libitum-fed rats: the incidence of cancer doubled in the group of animals that spontaneously eat more calories (+25%).

Calories and fat intake. A high energy intake thus appears to promote tumour growth. However, it is not easy to separate the promoting effect of calories from the effect of fat, the most caloric nutrient, and the risk of extra calories may be independent from the risk of fat. For example, rats fed a high-fat but caloric-restricted diet by Kumar (23% corn oil, but 80% calories) had less cancers than rats fed ad libitum a low-fat diet (5% corn oil, 100% calories). Indeed, the restricted rats fed the high-fat diet were eating 2.39 g fat per day vs. 0.85 g in control rats, and the number of adenocarcinoma was divided by a factor two by the caloric restriction (Kumar *et al.,* 1990). Moreover, many experimental studies show no promoting effect of high-fat diets when calories are balanced between groups of rats, as long as the low-fat control diet contains enough essential fatty acids (e.g. 3.5% corn :oil) (Newberne and Sahaphong, 1989). Roberfroid showed, for example, that after a dimethylhydrazine initiation, no difference in cancer incidence or tumour burden could be detected between rats fed isocaloric diets with 5%, 10%, 15% or 20% of fats (a mixture of saturated, monounsaturated and polyunsaturated fats in equal proportions) (Roberfroid, 1991): Clinton *et* al: (1992) also could not detect any difference in the incidence or number of intestinal tumours in rats eating the same daily calories, and given diets with 6%, 12% or 24% corn oil after azoxymethane initiation (Clinton *et al.,* 1992).

Many studies, however, show a promoting effect of fats in rodents, specifically in Fischer 344 rats. However, the promoting effect of saturated and monounsaturated fats does not stand after adjustment for the total caloric intake (Zhao *et al.,* 1991), which suggests that these fats have no specific promoting effect. If decreased energy intake or caloric restriction acts to inhibit colon carcinogenesis, then increased energy expenditure should exert a similar inhibitory effect.

Caloric expenditures. Rats exposed to moderate and voluntary exercise are consistently protected against chemically induced colorectal cancers. This protection remains, even when exercising rats eat more food and more calories than controls (Pariza, 1988). For example, after azoxymethane injections, the adenocarcinoma incidence is one third of that of controls in a group of rats that have free access to a running wheel, although the rats are fed *ad libitum* and gain the same body weight as controls (Reddy *et* al., 1988).

Moreover, Thorling *et al.* (1994) showed that rats fed a diet high in polyunsaturated fats (corn oil) were protected by the exercise more than rats fed a high saturated fat diet (palm oil). No cancer was seen in rats fed the corn oil diet and exercised daily, but 16 adenocarcinoma were seen in sedentary controls fed corn oil. In rats fed palm oil, five adenocarcinoma were seen in exercising rats vs. nine in sedentary controls. The protection seems lower with a saturated fat diet, possibly because of high body weight gains. Besides, caloric or protein restrictions increase the spontaneous level of activity of rats, which adds an extra protection to the beneficial effect of dietary restrictions (Youngman *et al.,* 1992).

Mechanisms. A relative shortage in calories, either because of caloric restriction or of exercise, might protect rats or humans against carcinogenesis by many different mechanisms, as reviewed by Kritchevski (1993).
• Caloric restriction reduces cell proliferation (Albanes *et* al., 1990; Malville-Shipan and Flemming, 1992; Steinbach *et al.,* 1993; Ames *et al.,* 1995). Fasting or extreme caloric restriction eliminates preneoplastic foci in the liver of rats: the proliferation of cells in liver foci is reduced, and also the programmed death of cells (apoptosis) increases in the liver of fasting rats (Grasl-Kraupp *et* al., 1994). We could not show the same phenomenon in colonic preneoplastic foci of food-restricted rats (Corpet *et al.,* 1997). Why does caloric restriction reduce cell proliferation? This could be due to three reasons:

> (a) Caloric restriction would lead to a reduction of energetic nutrient in the bloodstream. Thus, plasma triglycerides and blood glucose concentrations are reduced by two-thirds in rats during a dietary restriction (Turturo *et* al., 1993). Cells would lack energy, particularly tumour cells, and the proliferation would be reduced or inhibited (Kritchevsky, personal communication). The hypothesis proposed in human studies that energetic nutrients (glucose, triglycerides) and/or hormones regulating their use (insulin, IGF-1) are associated with colorectal risk (McKeown-Eyssen *et* al., 1994), has recently received experimental support in

rats (Corpet *et al,* 1997) and in a case-control study (MacKeown-Eyssen *et al.,* 1996).

> (b) Caloric restriction may modify other hormones linked to obesity and to some cancers:

insulin but also oestrogen, prolactin and IGF (Turturo *et al.,* 1993).

(c) Caloric restriction is associated with a strong reduction in enzymes that might play important roles in tumour promotion: ornithine decarboxylase and tyrosine kinase (Kumar *et al.,* 1990).

• Caloric restriction might regulate the methylation and reparation of DNA, and the expression of oncogene, although this is rather speculative (Hass *et al.,* 1993).

• Caloric restriction would also lower free radical production via mitochondrial leakage, and increase antioxidant defences. In restricted animals, superoxide dismutase, catalase and glutathione peroxidase would increase and lower the DNA and protein oxidative damages (Simic, 1994; Rao *et al.,* 1990; Turturo *et al.,* 1993; Youngman *et al.,* 1992).

Conclusions

Energy imbalance in the direction of excess appears to increase cancer mortality and cancer incidence, mainly post-menopausal breast, endometrial, prostate and colorectal cancer. As a corollary, caloric restriction and/or physical activity appear as protective factors.

In spite of the complexity of the relationship between energy balance and cancer, given the interaction of multiple factors influencing both energy balance and cancer positively or negatively, one can tentatively propose the following conclusions.

In post-menopausal breast cancer, endometrial and prostate cancer, and to a lesser extent ovarian cancer, all hormone-related cancers, obesity, resulting from energy imbalance, has long been considered as part of the aetiology of cancer, because of the extragonadal oestrogen synthesis which might occur in adipose stores. In this case, obesity is directly implicated in the synthesis of growth factors for mammary tumours. More recently, it was proposed that an excess of caloric intake would trigger a metabolic and hormonal imbalance, known as insulin-resistance syndrome, characterized by insulin resistance, hyperinsulinaemia, and visceral obesity. SHBG is decreased, resulting in high testosterone plasma levels, and to a lesser extent high oestrogen levels, and IGF-1 is increased, after a decrease of IGF-13P3. IGF-1 is a growth factor for mammary epithelium. Considering this hypothesis, it is difficult to determine whether obesity is a cause of hyper-insulineamia or an effect (Lazarus *et al.,* 1998). These mechanisms are not necessarily mutually exclusive, and both might play a role in breast cancer development. Lipids appear to be implicated at first, because they are the best energy-providing macro-nutrients and easily cause adipose store, but excess of refined carbohydrates, mainly in the absence of physical exercise, can result in energy imbalazce, possibly insulin-resistance, and appear as a risk factor for breast cancer (Franceschi *et al.,* 1998). It should also be noted that protein intake, mainly in adolescence, is potentially a risk facfor, since it favours the synthesis of IGF-1. There is inereasing evidence that the prostate cancer relationship with energy balance is symmetrical to that between breast cancer and energy balance.

In colorectal cancer, obesity appears mostly as a marker of a high caloric intake that is not balanced by energy expenditures. All human and all animal studies show that energy expenditures can protect against colorectal carcinogenesis. All the experimen-tal studies in animals show a protection by caloric-restricted diets, even when diets are high in fat. Some epidemiological studies show an increased risk of colorectal cancer associated with high caloric intakes. However, Giovannucci and Goldin (1997) favour other mechanisms, among them the synthesis of IGF-1 through the insulin-resistance syndrome. This is supported by the results of the Italian study (Franceschi *et al.,* 1998), showing the risk associated with refined carbohydrate intake. Whether cause for increased cancer risk, or only marker of a syndrome responsible for the increased cancer risk, obesity and also overweight should be avoided through moderate caloric-rich food intake and regular physical exercise.

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