Energy Restriction for Breast Cancer Prevention

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Abstract Weight gain in adult life is an important risk factor for breast cancer. Observational studies indicate that pre- or postmeno-pausal weight loss is associated with a reduction in risk of postmenopausal breast cancer. Here we summarise lifestyle changes including continuous or intermittent energy restriction and/or exercise which may be beneficial for preventing breast cancer and also potential pharmacological approaches to prevention using energy restriction mimetic agents (ERMAs).

11.1 Introduction

Increased energy balance, either produced by increased energy intake or reduced expenditure (or both), may be responsible for approximately one-third of human mammary tumours (Vainio et al. 2002). Energy excess gives rise to alterations within the mammary cell (in the stroma and systemically) which alter epithelial cell metabolism and proliferation and promote carcinogenesis. Here we summarise the evidence for energy excess being a major factor in the development and progression of breast cancer and how this might be circumvented by the use of dietary or exercise energy restriction measures and the potential use of energy restriction mimetic agents (ERMAs). The future of this approach will depend upon the introduction of methods which make energy restriction acceptable on a population basis or by using simple non-toxic ERMAs.

Hypotheses to explain the beneficial effects of energy restriction have been summarised by Sinclair (2005) who suggested that the mild stress provided by energy restriction provides general protection from breast cancer and other chronic disease (hormesis). A related hypothesis suggests that during times of deprivation the body changes from growth and reproduction to dependence on somatic maintenance and repair (Shanley and Kirkwood 2000). Understanding the mechanism of energy restriction is not only important to develop optimal energy restriction approaches but also to determine targets for ERMAs. In turn, responsiveness to ERMAs can give insights into the key modulators of energy restriction.

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11.2 Risk Factors for Breast Cancer

Whilst survival from breast cancer is improving, the incidence of the disease continues to rise in most countries, indicating the need to determine the cause of the increase and to introduce preventive approaches in women most at risk (Bray et al. 2004). The rate of increase in incidence is illustrated by changes which have occurred in Iceland over the past century (Tryggvadottir et al. 2006). Not only has there been a fourfold increase in sporadic breast cancer, from 1.8% in 1920 to 7.5% in 2002, but there has been a similar increase in the penetrance of the *BRCA2* gene amongst mutation carriers, from 18.6% to 71.9%. Whilst screening and other factors may, in part, be responsible for the increase in incidence, it is likely that other factors such as population changes in reproduction and lifestyle have contributed to the increase. Reproductive changes which are likely to increase breast risk include the increased age of first pregnancy by about 5 years since 1970 (Soerjomataram et al. 2007) and the marked reduction in parity in many developing countries (Chia et al. 2005).

Energy intake above requirements (due to excess food intake) combined with reduced expenditure by exercise is also likely related to increased breast cancer risk (Harvie and Howell 2006). In the United States in 1980, 41.6% of women were estimated to be either overweight or obese, whereas this figure was 66.0% in 2004 (http://www.cdc.gov/nccdphp/dnpa/obesity/trend). In England, rates of overweight and obesity have increased from 31% in 1980 to 57% in 2004 (Zaninotto et al. 2006).

11.3 Effect of Weight and Weight Gain and Exercise Deficiency on Breast Cancer Risk

Body weight, body mass index (BMI), waist circumference and weight gain are risk factors for postmenopausal breast cancer (Reeves 2007; Harvie et al. 2003). Weight gain especially before the menopause is a particularly important risk factor (Eliassen et al. 2006; Han et al. 2006; Lahmann et al. 2005; Trentham-Dietz et al. 2000; Magnusson et al. 1998; Huang et al. 1997; Harvie et al. 2005) in both women with and without a family history of the disease, and mainly amongst women who have not taken postmenopausal hormone replacement therapy (HRT). In the Nurses Health Study, weight gain of 25 kg or more since age 18 increased the relative risk (RR) of postmenopausal breast cancer by 1.98 compared to those with stable weight (Eliassen et al. 2006). In this study estimated population attributable risk of postmenopausal breast cancer in women who have not taken postmenopausal hormone therapy was 16.4% for premenopausal weight gain and 7.6% for weight gain after the menopause. Weight gain in the 30s and 40s appears to be a particularly important risk factor for developing breast cancer after the menopause (Han et al. 2006; Harvie et al. 2005). This is the most common period for gain—it is often not appreciated that, on average, there is little gain in weight after the menopause (Health Survey of England: http://www.dh.gov.uk). The effect of reduced energy expenditure on breast cancer risk may be judged from studies relating risk to exercise. One-third or more risk reduction has been reported amongst women undertaking 4 h of exercise or more per week compared to sedentary counterparts. Risk is reduced amongst women with and without a family history and amongst both users and non-users of HRT (Monninkhof et al. 2007).

Studies estimating the interaction of exercise and weight suggest that the effects may be additive. Chang et al. (2006) estimated that women who were obese and undertook less than 4 h of moderate exercise per week were at double the risk of postmenopausal breast cancer compared with women of normal BMI who exercised more than 4 h per week. Weight gain and exercise may modify risk through different mechanisms, and it appears that weight gain is

associated with oestrogen and/or progesterone receptor-positive tumours, whereas exercise appears to be associated with both positive and negative receptor subtypes (Adams et al. 2006).

11.4 Mechanism of Weight Gain and Exercise Deficiency on Risk

It may be appropriate to view human breast cancer risk in the context of the two-stage initiation and promotion carcinogenesis model of Knudson (Moolgavkar 1986). In this report, Moolgavkar suggested that hormones promoted clonal expansion of cells that had been initiated earlier. This is consistent with the preventive effects of oophorectomy and tamoxifen with respect to premenopausal and postmenopausal breast cancer and tamoxifen, raloxifene and aromatase inhibitors with respect to postmenopausal breast cancer (Howell et al. 2007). It seems likely that energy excess may also have promotional effects and that excess energy and hormonal factors may act in concert to promote initiated mammary epithelial cells. Multiple animal models indicate that initiation can occur in the young mammary gland. In humans this may be in utero or during the teenage period of breast growth as judged by data derived from the follow-up of women exposed to radiation from atomic bomb explosions (Land et al. 2003) or mantle irradiation for Hodgkin's lymphoma (Horwich and Swerdlow 2004). Thus, hormonal stimulation and energy excess after the menarche may promote foetal initiation and during the 30s and 40s may promote initiation that had occurred during the teenage period. Weight gain has been linked to post- not premenopausal breast cancer. The development of postmenopausal breast cancer is known to occur in the premenopausal period, since premalignant lesions have been found in the majority of breasts thoroughly examined in the late premenopausal period (Nielsen et al. 1987; Wellings et al. 1975).

Premalignant and malignant lesions are associated with an increase in proliferation and loss of cell polarity (Liu et al. 2005). Several studies show that energy restriction reduces mammary cell proliferation (Klebanov 2007; Varady et al. 2007a; Stragand 1979; Jiang et al. 2003) and is likely to have a favourable effect on cell polarity. In the latter context it has recently been demonstrated that increased adenosine monophosphate related protein kinase (AMPK) is associated with increased cell polarity (Zheng and Cantley 2007; Hurov and Piwnica-Worms 2007). AMPK is an enzyme which senses the energy state of the cell and increases in activity when energy stores are low, when the ADP/ATP ratio is high. These and other recent studies are the first demonstrations of a relationship between epithelial function/morphology and cellular energy status.

11.5 Chronic Energy Restriction Reduces Cancer Risk

There are no prospective randomised trials of chronic energy restriction (CER) for breast cancer prevention (Harvie and Howell 2006). However, observational studies suggest weight loss reduces breast cancer risk (Harvie et al. 2005; Eliassen et al. 2006). In collaboration with the Iowa Women's Health Study, we assessed the effect of maintained weight loss (≥5% of body weight) from age 30 and also after the menopause in women who had gained weight up until these times (Harvie et al. 2005). Weight loss after age 30 resulted in a 38% reduction in postmenopausal breast cancer (RR 0.62; 95% CI, 0.47–0.82) compared with those who continued to gain weight, and after the menopause, weight loss resulted in a 22% reduction (RR 0.77; 95% CI, 0.65–0.94). In the Nurses Health Study, Eliassen et al. (2006), reported that women who had not taken HRT and lost 10 kg or more since the menopause were at lower risk than those who maintained weight (RR 0.43; 95% CI, 0.21–0.86). A small case control study linked weight loss in

BRCA1/2 mutation carriers to reduced risk (Kotsopoulos et al. 2005). Loss of at least 4.5 kg in the period from age 18 to 30 was associated with a decreased risk of breast cancer between age 30 and 49 (RR 0.47; 95% CI, 0.28–0.79).

Multiple studies have demonstrated that CER in rodents started at any time during life reduces breast cancer risk. Dirx et al. (2003) performed a meta-analysis of the reports of CER experiments in studies of spontaneous tumours in mice. The results of 14 studies showed an overall RR of 0.45 (95% CI, 0.39–0.59) indicating a 55% reduction in the incidence of mammary tumours. The results were similar regardless of the degree of CER, the time CER was initiated, whether there was restriction of fat, carbohydrate or protein or the duration of CER (the shortest period was 38 weeks). These experiments support a number of other experiments performed in carcinogen-induced tumours (Thompson et al. 2003) or xenotransplanted human tumour cell lines into nude deprived mice (Giovanella et al. 1982).

11.6 Intermittent Energy Restriction Also Reduces Breast Cancer Risk

Intermittent energy restriction (IER) to prevent breast cancer was tested in rodents after it was shown in the 1930s that this approach could increase rodent life span (Robertson et al. 1934). IER covers a wide range of experimental protocols from every other day (EOD) fasting (Varady and Hellerstein 2007), complete or partial energy restriction at less frequent intervals (Berrigan et al. 2002), or periods of up to 3 weeks of partial restriction and 3 weeks of ad lib feeding (Cleary et al. 2002; Pape-Ansorge et al. 2002). In general, these approaches reduce the risk of spontaneous and genetically engineered mammary tumours but are largely ineffective in carcinogen-induced tumour models.

For example, Carlson and Hoelzel (1945) studied the development of spontaneous mammary tumours in Wister rats. EOD fasting or fasting 1 day in 3 reduced the number of tumours and increased life span in animals who did develop mammary tumours. Another study used MMTV-TGF-α Lep± and MMTV-neu engineered mice and gave 3 weeks with 50% feeding followed by 3 weeks ad libitum feeding. Interestingly, IER mice had a greater tumour reduction than pair-fed CER mice (Cleary et al. 2002; Pape-Ansorge et al. 2002).

IER has been assessed in other diseases: The first suggestion of IER use in humans was reported by Vallejo (1956) who demonstrated that alternating days of ad lib food or a reduction to an estimated 700 calories for 2.5 years in members of a nursing home resulted in a significant reduction in admissions to the infirmary (123 vs 219 $p<0.001$) and a non-significant reduction in deaths (6 vs 13). Hill et al. (1989) randomised moderately obese women to have CER at 1,200 kcal/day, or an alternating diet providing an average of 1,200 kcal/day alternating between 600 to 1,800 kcal/day. The total weight loss for each regimen was about 8 kg over 3 months. However, the IER group experienced greater reductions in total cholesterol (14% vs 6% $p<0.05$). More recently Williams et al. (1998) compared a CER of 1,500–1,800 kcal/day with 5 days of a very low calorie diet (VLCD) of 400–800 kcal/day followed by a similar VLCD for 1 day in each of 15 weeks. The IER diet was associated with significantly improved glycaemic control. In rodents IER was shown to be superior to CER with respect to glucose tolerance (Anson et al. 2003).

11.7 Mechanism of the Effect of CER and IER

During proliferation of normal cells there is an alteration of metabolism so that glycolysis and lipid synthesis are increased and the tricarboxy-

lic acid (TCA) cycle is used to provide substrates for macromolecules (see DeBerardinis et al. 2008 for discussion). Experimentally progressive transformation of normal cells in vitro is associated with an increase in the cell's dependence on glycolysis and a reduced dependence on mitochondrial energy production (Ramanathan et al. 2005; Wu et al. 2006). Increases in glycolysis and lipid synthesis are seen in tumours (Warburg 1930; Medes et al. 1953) and are maintained by alteration in growth factor and signal transduction pathways. CER is associated with a number of changes within target cells. In general, there is a switch from anabolic processes such as cell division to catabolic processes directed towards cell maintenance. The switch results in inhibition of lipid synthesis and enhanced fatty acid oxidation (FAO) and increased mitochondrial activity. It is becoming clear that these changes are controlled by a number of cellular master regulatory molecules which include silent information regulator (SIRT)1 (Boily et al. 2008), AMPK and a co-factor, peroxisome-proliferator γ co-activator (PGC-1) α (Puigserver and Speigelman 2007) and several nuclear transcription factors including peroxisome proliferator-activated receptor (PPAR)-α, -δ and -γ (Fig. 11.1).

Studies of gene expression arrays in various tissues show that a large number of genes change during short-term CER, and they are also altered in the long-term (Dhahbi et al. 2004). These changes may provide clues with respect to the mechanism of the effectiveness of IER. Nearly all short-term fasting studies (24–48 h) have focussed on tissues other than epithelia and the results need confirmation in this tissue. Studies of the effects of short-term fasting on peripheral blood white cells (Bouwens et al. 2007), liver (Bauer et al. 2004), muscle (Spriet et al. 2004; Pilegaard et al. 2003) and fat (Nakai et al. 2008; Varady et al. 2007a, b) show, amongst many gene changes, a relatively consistent pattern of upregulation of carnitine palmitoyl transferase 1 (CPT1), the rate-limiting enzyme of FAO and PPAR-α and downregulation of the enzymes of fat synthesis and desaturation such as fatty acid synthase and stearoyl CoA desaturase 1 (SCD-1). Many studies also show upregulation of pyruvate dehydrogenase kinase 4 (PDK4), an enzyme that inhibits pyruvate dehydrogenase and thus entry of pyruvate into the TCA cycle, indicating an overall change from cell dependence on glycolysis to fat for energy, a phenomenon associated with increased mitochondrial biogenesis (Civitarese et al. 2007). Curiously, genes for enzymes of the glycolytic pathway in breast epithelial cells do not appear to be downregulated by energy restriction (Zhu et al. 2007).

A consistent feature of studies of CER and IER is the associated improvement in insulin sensitivity and the reduction of serum insulin and often, but not consistently, insulin-like growth factor (IGF)-1. Infusion of IGF-1 into animals with tumours controlled by CER showed reversal of the beneficial effects of CER in one study (Dunn et al. 1997) but not in the other (Zhu et al. 2005a, b).

11.8 Energy Restriction Mimetic Agents

Since CER and IER may prove to be difficult to introduce on a population basis to prevent breast and other cancers, there is interest in developing agents which mimic the potential benefits of energy restriction (ERMAs). In mammary epithelial cells, there are metabolic changes which accompany the development of malignancy which are potential targets for ERMAs (Young and Anderson 2008; Clapham and Arch 2007; Dilova et al. 2007). As outlined above, these targets include relative increases in glycolysis, lactate production and fat synthesis and relative decreases in mitochondrial activity and β oxidation of lipids (Ingram et al. 2006; Moreno-Sanchez et al. 2007). The first demonstration that an ERMA may be effective

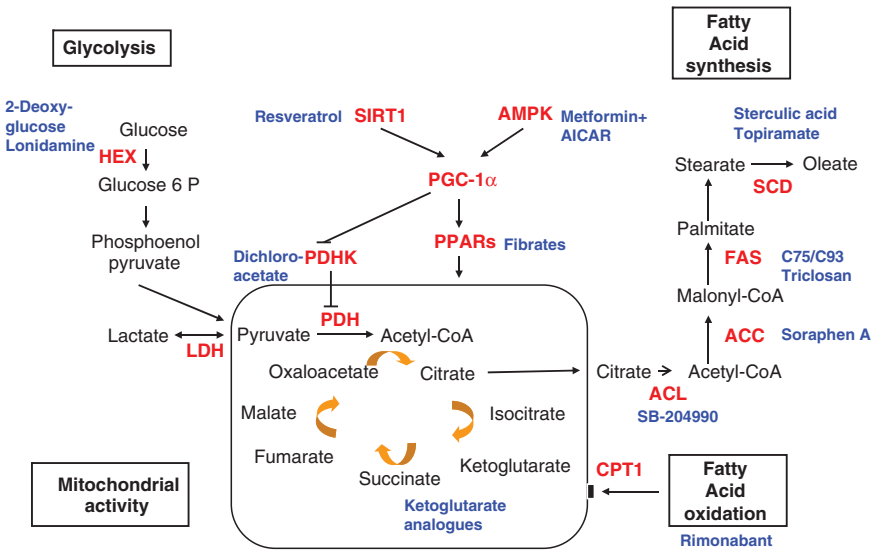

Fig. 11.1 Simplified view of some metabolic pathways which may be affected by CER, IER and ERMAs. In general ERMAs inhibit glycolysis and fatty acid synthesis and stimulate the other pathways shown. Key enzymes and co-factors in *red*. Drugs and processes which may affect the pathways are in *blue*. *HEX*, hexokinase; *LDH*, lactate dehydrogenase; *PDH*, pyruvate dehydrogenase; *PDHK*, pyruvate dehydrogenase kinase; *PGC-1alpha*, peroxisome proliferator receptor γ coactivator-1-α; *SIRT1*, silent information regulator 1; *AMPK*, adenosine monophosphate related kinase; *SCD*, stearoyl CoA reductase; *FAS*, fatty acid synthase; *ACC*, acetyl CoA carboxylase; *ACL*, ATP citrate lyase; *CPT1*, carnitine palmitate transferase 1

was by Lane et al. (1998) who treated rats with 2-deoxyglucose (2DG), which mimicked some of the effects of CER by inhibiting glycolysis. Since that time, 2DG has been shown to inhibit dimethylbenzanthracene (DMBA)-induced carcinomas in rats and the proliferation of tumours produced by the human mammary tumour cell line MCF7 in nude mice (Zhu et al. 2005a, b) and it improves functional and metabolic cardiovascular risk factors in rats (Wan et al. 2003).

In the following sections we examine the mechanism of action and activity of potential ERMAs. Few of these are likely to enter the prevention arena but they are mentioned as agents that indicate "proof-of-principle". We examine inhibitors of glycolysis and lipid synthesis, agents which stimulate activity of mitochondrial function and β oxidation of lipids and which activate the metabolic regulators AMPK, SIRT1 and PGC-1α.

11.9 Inhibitors of Glycolysis

Not only is glycolysis increased in many invasive tumours as first described by Warburg (1930) but there is also evidence of upregulation of enzyme activity in precursor lesions, which makes inhibition of this pathway an attractive approach (Isidoro et al. 2005) for prevention. Whilst there are a large number of molecules which have activity, most of these could not be used for prevention (for review see Chen et al. 2007). 2-Deoxyglucose—which is phosphorylated by hexokinase and cannot be metabolised further or

excreted from the cell, and therefore it, in turn, inhibits hexokinase—inhibits MCF-7 cell growth in vitro and in nude mice and elicits a 'starvation' response intracellularly, resulting in upregulation of AMPK and SIRT1 in MCF-7 cells (Jiang et al. 2008). Lonidamine is also an inhibitor of hexokinase and enhances mitochondrial function by preventing binding of hexokinase to the mitochondrial membrane. Lonidamine has been used to enhance the activity of various chemotherapeutic agents and is in clinical trial for the prevention of benign prostatic hyperplasia (Ditonno et al. 2005).

11.10 Inhibitors of Lipid Synthesis

Increased lipid synthesis in tumours was reported over 50 years ago (Medes et al. 1953). The activity of all four major enzymes of lipid synthesis is increased in tumours, making them targets for prevention and treatment of breast cancer (Swinnen et al. 2006; figure therein). It is likely that increased synthesis is related to the needs of proliferating cells to synthesise membrane lipid and is related to upregulation of lipogenic stimulatory molecules such as sterol regulatory binding protein-1 and SPOT 14 (Kinlaw et al. 2006). Expression of the four major genes for lipid synthesis is downregulated by CER in normal fat tissue in humans (Dahlman et al. 2005).

ATP citrate lyase (ACL) is the first enzyme of lipid synthesis and converts cytosolic citrate (a product of the TCA cycle) to acetyl CoA. The activity of ACL was reported to be 150 times higher in tumours than adjacent normal breast tissue (Szutowicz et al. 1979). RNAi knockdown and use of the ACL inhibitor SB-204990 reduces human tumour cell growth in nude mice (Hatzivassiliou et al. 2005) and decreases cholesterol and triglyceride, concentrations in serum in animal models (Pearce et al. 1998). Newly reported arylbenzenesulphonamide inhibitors of ACL also reduce cholesterol and limit weight gain (Li et al. 2007).

Acetyl-CoA carboxylase (ACC) catalyses the carboxylation of acetyl CoA to malonyl-CoA. There are two isoforms, ACC1 found in liver adipose tissue and the mammary gland and ACC2 in skeletal muscle and heart. *ACC2* knockout mice have a lean phenotype and increased rates of fatty acid and also glucose oxidation (Oh et al. 2005). Specific silencing of *ACC1* by RNAi reduced breast cancer cell survival (MCF7, MDA-MB-231 and HBL 100), but this inhibition was rescued by supplementation of the culture median by palmitate (Chajès et al. 2006). Recently the ACC inhibitor soraphen A was shown to inhibit the proliferation of prostate cancer cells but not cells from benign prostate hyperplasia (Beckers et al. 2007).

Fatty acid synthase (FAS) catalyses the condensation of acetyl-CoA and malonyl-CoA. It is not only expressed in invasive breast tumours but also preneoplastic lesions (Esslimani-Sahla et al. 2006). FAS inhibitors decrease cell proliferation and induce apoptosis in breast cancer cell lines (Pizer et al. 1996) and the FAS inhibitor C75 reduces the growth of MCF-7 xenografts in nude mice (Pizer et al. 2000) and may be particularly active when there is HER2 over-expression (Menendez and Lupu 2007). The antibiotic triclosan is also a FAS inhibitor and reduces nitrosomethylurea (NMU)-induced mammary tumours and preneoplastic lesions in rats (Lu and Archer 2005). Recently Brusselmans et al. (2005) reported that in a series of 18 naturally occurring phenolic compounds reduction of cell proliferation was strongly associated with their FAS inhibitory activity.

SCD-1 is the rate-limiting enzyme in the biosynthesis of monounsaturated fatty acids. It is a key controller in lipid partitioning between lipogenesis and oxidation. High SCD activity is associated with a wide range of disorders including diabetes, obesity and cancer (Dobrzyń and Dobrzyń 2006) *SCD-1* knockout is associated with an increase in FAO, increased AMPK

concentrations and leanness (Dobrzyń et al. 2004). Several inhibitors of SCD—including analogues of conjugated linoleic acid (Choi et al. 2002) and sterculic acid (Khoo et al. 1991)—inhibit the growth of mammary carcinomas in vitro and in vivo. Recently, potent selective orally bioavailable pridazinecarboxamide inhibitors have been reported (Liu G et al. 2007).

11.11 Activation of AMP-Activated Protein Kinase

AMPK is a regulator of the cellular response to low energy. AMPK concentrations increase in response to nutrient deprivation and pathological stresses and is upregulated by 2DG (Jiang et al. 2008), metformin (Zakikhani et al. 2006; Phoenix et al. 2008) and the cell-permeable nucleoside 5-aminoimidazole-4-carboxamide (AICAR) (Swinnen et al. 2005). 2DG and metformin reduce proliferation and growth of human mammary tumour cells in-vitro, tumour formation after carcinogenesis and human tumour cell growth in nude mice. Activation of AMPK results in inhibition of Akt and fat synthesis (by inhibition of acetyl-CoA carboxylase and HMG CoA reductase) and reduction of IGF-1 activity. It is unlikely that AICAR and 2DG can be used for prevention, but metformin treatment for diabetes is associated with reduced breast cancer risk and is being explored as a possible breast cancer preventive agent (Evans et al. 2005).

11.12 Stimulation of Mitochondrial Activity and Fat Oxidation

Tumour cell proliferation is reduced by diversion of pyruvate to the TCA cycle by inhibition of lactic dehydrogenase (LDH) (Fantin et al. 2006) or inhibition of PDK4 (which results in upregulation of pyruvate dehydrogenase) by 2-chloroacetate [in clinical use for the treatment of lactic acidosis (Bonnet et al. 2007)] thus increasing mitochondrial activity and reducing tumour cell proliferation. Several studies indicate that CER increases mitochondrial biogenesis probably related to upregulation of SIRT1 and PGC-1α, which in turn stimulates PPAR-α. PPAR-α agonists (e.g. fenofibrate, WY-14643) have been reported to suppress the growth of tumour cells (Panigrahy et al. 2008; Pozzi et al. 2007). It is of interest that 19% of genes regulated by CER are also regulated by PPAR-α including genes involved in FAO (Corton et al. 2004). FAO is also stimulated by the anti-obesity drug rimonabant, which has also been shown to have anti-tumour activity (Bifulco et al. 2006). Other approaches to mitochondrial stimulation include the use of cell-permeating α-ketoglutarate derivatives (MacKenzie et al. 2007).

11.13 Activation of SIRT1

SIRT1, an NAD+ dependent deacetylase, is known to activate a number of beneficial metabolic pathways including PGC-1α and AMPK and their downstream pathways (Lagouge et al. 2006). In turn, resveratrol and a number of other small molecules are known to activate SIRT1. Their CER mimetic effect upon activation of SIRT1 is demonstrated by improvement in health and survival in mice on a high-calorie diet (Baur et al. 2006) and the treatment of type 2 diabetes (Milne et al. 2007). Numerous studies show that resveratrol has anti-tumour activity. The clinical development of this promising agent has been summarised recently (Howells et al. 2007; Cucciolla et al. 2007).

Summary and Conclusions

The studies outlined above indicate that at least part of the increased incidence of breast cancer is related to energy excess. This conclusion is supported by the reduction of risk of breast cancer in women and in animal models by CER and IER. As yet, in women, the data are observational only, although there is evidence from a randomised trial that IER may be superior to CER (M. Harvie et al., in preparation). We also highlight the well-known phenomenon that carcinogenesis is associated with a change in cell metabolism. Inhibition of the induced anabolic changes or stimulation of the reduced catabolic changes can result in cessation of tumour growth. Some of the cellular metabolic changes seen in tumours are also present in pre-neoplastic lesions, suggesting that some ERMAs could be used for prevention; for example, resveratrol and other activators of SIRT1 and activators of AMPK. It seems likely that at least some of the new PPAR agonists and inhibitors of fat synthesis in development to treat diabetes and cardiovascular disease may ultimately be useful for the treatment and prevention of breast cancer (Harrington et al. 2007).

Although we have focussed on standard CER and IER paradigms, it is of interest that less well known phenomena may regulate energy balance. It appears that certain types of gut bacteria and alterations in biological clock signalling can be associated with leanness possibly acting via PGC-1α (Green et al. 2007; Bäckhed et al. 2007). Potentially, changes in risk related to migration and night shift working might be explained in these ways.

We have focussed on energy balance and risk to the exclusion of diet composition. However, it is important to realise the toxicity of the Western diet. A few weeks of a Western diet causes mammary epithelial proliferation and dysplasia in rodents (Xue et al. 1996) and it seems possible that ingestion of fructose and sucrose may be another mechanism behind increased lipid synthesis particularly via SCD (Miyazaki et al. 2004). Thus, prevention of breast cancer may ultimately be produced by eating a Mediterranean diet with periods of fasting. The question is how often and for what duration? Perhaps the easier alternative is to develop highly specific, non-toxic ERMAs.

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