Endocrine-Related Cancer (2004) **11** 603–622

REVIEW

Nutritional modulation of the cell cycle and breast cancer

L Hilakivi-Clarke, C Wang, M Kalil, R Riggins and R G Pestell

Lombardi Comprehensive Cancer Center, Department of Oncology, 3970 Reservoir Road NW, Box 571468, Washington DC 20057-1468, USA

(Requests for offprints should be addressed to R G Pestell; Email: pestell@georgetown.edu)

Abstract

In the USA, breast cancer accounts for approximately 30% of all cancers diagnosed in women and is the second leading cause of cancer death in women. An understanding of the molecular genetic events governing breast cancer lead to both prevention and intervention strategies in an attempt to reduce mortality and morbidity from breast cancer. The last three decades of medical research examining the molecular pathogenesis of cancers have provided compelling evidence for the universal disruption of the cell cycle in human tumors. The importance of cell cycle control in human cancer was recognized by the recent award of the Nobel Prize to Drs Nurse and Hartwell for their discovery of the cyclins. More recent studies have demonstrated a critical interface between hormonal signaling and the cell cycle. In parallel, epidemiological studies have identified as being associated with breast cancer important dietary and environmental components that regulate hormonal signaling. This review describes the intersection of these two fields of study, which together imply a role for dietary prevention and intervention in human breast cancer perhaps through altering cell cycle components.

Endocrine-Related Cancer (2004) **11** 603–622

Introduction

Breast cancer accounts for approximately 30% of all cancers diagnosed in women in the USA. As the second leading cause of cancer death in women, breast cancer accounts for approximately 15% of all female cancer deaths (Zafonte *et al*. 2000). A comprehensive analysis of cancer mortality and morbidity over the last 25 years has demonstrated a reduction in breast cancer mortality in the 1990s. However, the benefit of reduction in death is greater in white women than in black women. The decline in mortality is likely due to improved screening and early detection, risk factor reduction, and perhaps improved treatment of early stage disease. Risk factors proposed for breast cancer include family history and lifestyle elements, such as diet and lack of exercise.

Over the last two decades, a compelling body of evidence has identified a disruption of cell cycle control mechanisms as a common pathway in human cancer. The importance of the cell cycle to human disease is evidenced by the recent award of the Nobel Prize to Drs Hartwell and Nurse for their discovery of the cyclins in the late 1990s. The dysregulation of cell cycle control in cancer is distilled into a model in which disruption of two parallel pathways is required for the occurrence of cancer (Fig. 1). These two parallel pathways function in such a manner that inactivation of one component of the pathway is sufficient for disruption of the pathway's activity. In this regard, the $p16^{INK4a}$, retinoblastoma protein (pRb), cyclin D1, cdk4 pathway is frequently inactivated in human breast cancer due to overexpression of cyclin D1. In melanoma, loss of $p16^{INK4a}$ is considered a key initiating event. Thus, distinct tumor types are thought to result from inactivation of distinct components of a common signaling pathway.

Breast cancer and the mammalian cell cycle

Cyclin-dependent kinases

The mammalian cell cycle has been divided into a series of sequential phases. The G_1, S, G_2, and M phases are sequentially transitioned in response to growth factor or oncogenic stimulation. The DNA synthetic (S phase) and mitotic (M phase) phases are preceded by gap phases (G_1, G_2). During the transition of the cell cycle, distinct

Endocrine-Related Cancer (2004) **11** 603–622
1351-0088/04/011–603
DOI:10.1677/erc.1.00665
Online version via http://www.endocrinology-journals.org

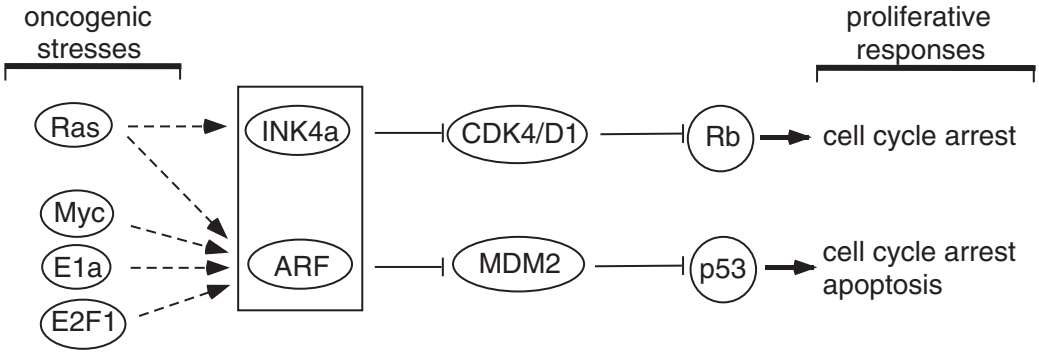

Figure 1 Model for dysregulation of cell cycle proteins (Weinberg 1995, Sherr & Roberts 1999). There are two parallel arms that include either the $p16^{INK4a}$ (INK4a) pathway or the $p19^{ARF}$ pathway, and inactivation of one arm can occur at any point in the respective pathway. Overexpression of cyclin D1 (D1), mutations in CDK4, or mutations in pRB (Rb), for example, will inactivate one arm of the signaling pathway and lead to unchecked cell cycle progression. Inactivation of both arms may therefore be one of the keys to tumorigenesis.

checkpoints are inactivated. These checkpoints provide mechanisms by which the intracellular compartment senses a favorable growth factor environment and continually transduces this information to ensure genetic integrity during cellular replication. The presence of DNA damage and the integrity of mitotic spindles are assessed during transition between these phases of the cell cycle. Cell cycle progression is orchestrated by the relative activity of a family of serine threonine kinases (Fig. 2). The cyclins encode co-regulatory subunits of a holoenzyme that phosphorylates and inactivates a number of substrates including pRb. Cyclin D1 encodes the labile regulatory subunit of the cyclin cdk4/6 holoenzyme. Phosphorylation of the pRb protein is thought to change the confirmation of pRb which, in turn, alters further upon phosphorylation by cyclin E/cdk2 complexes. It is considered that the phosphorylation of the pRb protein by the cyclin D1/cdk4/6 holoenzymes is required for transition through the G_1/S phase of the cell cycle.

The human *cyclin D1* gene was initially cloned at a breakpoint rearrangement within parathyroid adenoma. These arrangements brought the parathyroid hormone promotor upstream of the *cyclin D1* gene. The gene identified at this breakpoint rearrangement, initially referred to as the *PRAD1* gene, was proposed to encode a cyclin based on homology to the yeast *CLN* genes (Motokura *et al*. 1991). Subsequent studies have demonstrated that the *cyclin D1* gene is sufficient for the development of parathyroid adenomas (Imanishi *et al*. 2001). Two decades of subsequent experimentation have confirmed the important role for cyclin D1 in a broad array of human cancers, including human breast cancer.

The *cyclin D1* gene is shown to be overexpressed in 30–50% of human breast cancers. Overexpression of cyclin D1 correlates in several studies with poor prognosis. Indeed, the correlation of cyclin D1 with estrogen receptor (ER)-α-positive tumors is said to convert ERα-positive tumors from good to poor prognosis (Kenny *et al*. 1999). The *cyclin D1* gene is shown to physically associate with the ER and induce ER signaling in a cdk-independent manner (Zwijsen *et al*. 1997). Immuno-neutralizing experiments have shown that cyclin D1 is required for estrogen-induced cellular proliferation (Lukas *et al*. 1996). Cyclin D1 enhances ERα signaling through functioning as a coactivator-like protein, analogous to the p160 steroid receptor coactivator (SRC) of the ERα, in cultured cells.

Subsequent studies have shown the *cyclin D1* gene regulates a number of transcription factors in a cdk-independent manner (Table 1). Two key publications have provided strong evidence for a biological role for two of these molecular targets. In this regard, cyclin D1 was shown to inhibit the activity of two gene products involved in fat metabolism, the CCAAT/enhancer binding protein (CEBP)-β (Lamb *et al*. 2003) and peroxisome proliferator-activated receptor (PPAR)-γ proteins (Wang *et al*. 2003*b*). CEBPβ and PPARγ function in a common molecular pathway of adipocyte differentiation. CEBPβ induces PPARγ and PPARγ in turn, co-ordinates the expression of a number of genes involved in adipocyte differentiation. In these recent studies, cyclin D1 was shown to inhibit the functional activity of either CEBPβ (Lamb *et al*. 2003) or PPARγ (Wang *et al*. 2003*b*).

Lamb *et al*. (2003) overexpressed either cyclin D1 wildtype or a cyclin D1 that was defective in cdk binding in the MCF-7 breast cancer cell line. Although MCF-7 cells express the *cyclin D1* gene, microarray analysis of the cyclin D1-transfected cells showed that cyclin D1 overexpression regulated a subset of genes, some of which were targets of CEBPβ. In turn, a subset of these genes was shown to be dysregulated in human breast cancer. In

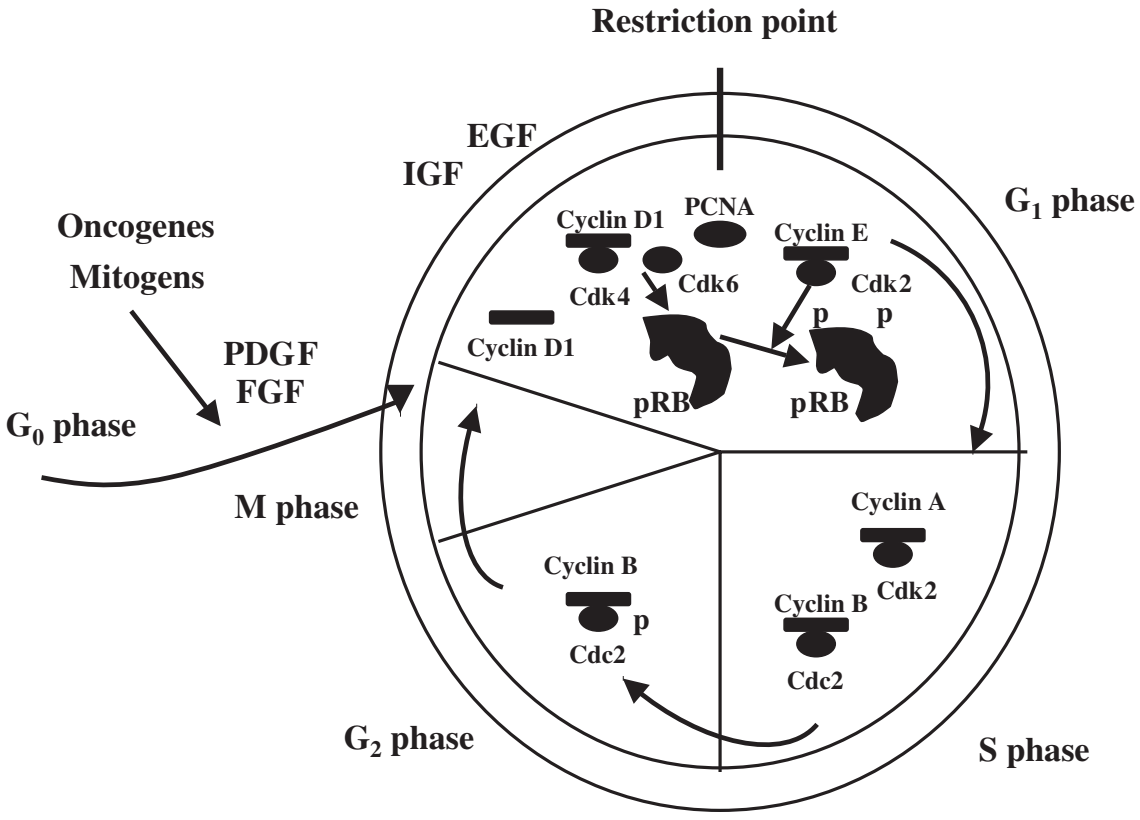

Figure 2 Schematic representation of the mammalian cell cycle. Competence factors such as platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) promote entry into the early G_1 phase. Sequential treatment with progression factors, insulin-like growth factor (IGF) or epidermal growth factor (EGF), promote progression through the G_1 phase restriction point. Competence of the cyclin D1/Cdk4 complex is induced by mitogens. The cyclin D1/Cdk4 complex phosphorylates the pRB protein leading to sequential phosphorylation by cyclin E/Cdk2 and release of free E2F. The phosphorylation (p) of pRB and relief of transcriptional repression by pRB induces genes involved in the induction of S phase entry. Reprinted with permission from Pestell *et al.*1999; The Endocrine Society.

studies by Wang *et al*. (2003*b*), cyclin D1 was found to inhibit the PPARγ protein and its transcriptional activity. Mutagenesis of the *cyclin D1* gene again demonstrated that the repression of PPARγ was cdk independent. Using cyclin D1 knockout mice, Wang *et al*. (2003*b*) have demonstrated that the biological function of cyclin D1 is to inhibit PPARγ function *in vivo*. Consistent with a model in which cyclin D1 repressed PPARγ, analysis of cyclin D1 knockout mice demonstrated the presence of hepatic steatosis, a hallmark of PPARγ overexpression. Furthermore, using cyclin D1 antisense-inducible transgenic mice, Wang *et al*. (2003*b*) showed that cyclin D1 regulated PPARγ-responsive genes in vivo. Together, these studies suggest that an important physiological function of cyclin D1 is to regulate cellular metabolism, in particular, fat metabolism through PPARγ. The relationship between cyclin D1 and cancer through the regulation of fat metabolism remains to be determined.

The cyclin-dependent kinase inhibitors

The cyclin-dependent kinases are inhibited by two families of inhibitors. The cyclin inhibitor protein/kinase inhibitor protein (CIP/KIP) family includes the $p21^{CIF1/WAF1}$, the $p27^{KIP1}$, and the $p57^{KIP2}$ family. The INK4 inhibitor group includes $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$, and $p19^{INK4d}$. The INK4 proteins inhibit the catalytic domains of cdk4 and cdk6. Several additional functions of the $p16^{INK4a}$ protein have been identified, including the regulation of RNA polymerase II (polII) carboxyl terminal kinase domain (CTD) (Nishiwaki *et al*. 2000). The RNA pol II CTD plays an important role in regulating expression of a number of genes suggesting that $p16^{INK4a}$ may play a broad role in co-ordinating gene expression. In addition, $p16^{INK4a}$ regulates cellular motility through an effect on cdk4 at the cell membrane (Fahraeus & Lane 1999). The CIP/KIP family of proteins inhibit the cyclin E/cdk2 kinase family. The role of the

Table 1 Cyclin D1 associated proteins

Proteins	Functional relationship with cyclin D1
Cell cycle machinery	
CDK4/6	Cyclin D1 forms complex with CDK4/6 and facilitates CDK4
p21 (CIP1)	p21 represses cyclin D1/CDK4 kinase activity and promotes cyclin D1 nuclear accumulation
p27	p27 assembles cyclin D1/CDK4 kinase complex and represses cyclin D1/CDK4 kinase activity
p57 (Kip2)	p57 inhibits cyclin D1/CDK4 kinase activity
pRb	Cyclin D1/CDKs phosphorylate pRb and release E2F from an inhibitory complex
PCNA	Forms multiple kinase complexes
Hsc70	Hsc70 promotes cyclin D1 and cyclin D1-dependent kinase maturation
Hsp90	Hsp90 promotes cyclin D1 nuclear accumulation
MCM3/7	Cyclin D1 promotes dissociation of inhibitory pRb/MCM7 complex
GSK-3β	Phosphorylates cyclin D1
CRM1	Promotes cyclin D1 nuclear export
Acetylase/deacetylase	
P300/CBP	Cyclin D1 represses HAT activity
P/CAF	Cyclin D1 represses HAT activity
SRC-1	Cyclin D1 recruits SRC-1 to ERα
HDAC1	Cyclin D1 recruits HDAC1 to AR
HDAC3	Cyclin D1 recruits HDAC3 to TR to form ternary complexes
Transcriptional factor	
ERα	Cyclin D1 recruits SRC-1 to ERα and activates unliganded ERα
AR	Cyclin D1 represses ligand-bound AR activity
PPARγ	Cyclin D1 represses PPARγ-mediated transcription and differentiation
TR	Cyclin D1 represses both the unliganded TR and liganded TR activity
Myb	Cyclin D1 antagonizes B-Myb activity
DMP1	Cyclin D1 antagonizes DMP1 transactivation and overrides DMP1-mediated growth arrest
MyoD	Cyclin D1 represses muscle differentiation and MyoD-mediated transcription
Stat3	Cyclin D1 represses STAT3 activation
Sp1	Cyclin D1 represses Sp1-mediated transactivation
β2/neuroD	Cyclin D1 represses the bHLH transcription factor, β2/neuroD
bHLH	Cyclin D1 inhibits the activity of myogenic bHLH regulator
Others	
TAF(II)250	Cyclin D1 represses Sp1-mediated transcription
DIP1	Repression
BRCA1	Cyclin D1 rescues BRCA1-mediated ERα repression
GCIP	Cyclin D1 inhibits cyclin D1/CDK4 activity

CIP/KIP proteins in cell cycle regulation appears to be dose dependent, inhibiting cyclin-dependent kinase activity in cell cycle progression at higher concentrations but serving as a chaperone or assembly protein enhancing cyclin-dependent kinase activities at lower concentrations (Sherr & Roberts 1999). The functions of the CIP/KIP family are, in turn, co-ordinated by additional proteins that regulate the subcellular distribution of the CIP/KIP proteins including jun-activation binding protein-1 (JAB1).

The $p27^{KIP1}$ protein was characterized as a protein homologous to the $p21^{CIP1}$ tumor suppressor. The abundance of $p27^{KIP1}$ is regulated primarily at the post-translational level through an SCF (composed of SKIP, CUL, and F box proteins) complex. The substrate specificity of the ubiqitin ligase or SCF is determined by the F box protein which binds the substrate. The F box protein that binds $p27^{KIP1}$ is called Skip2. The abundance of Skip2 may therefore contribute to the destruction of $p27^{KIP1}$. Skip2 is frequently overexpressed in tumor cell lines and collaborates with Ras in cellular transformation.

Hormonal control of the cell cycle

Steroid hormones induce cellular proliferation in the breast

A comprehensive analysis of cell cycle control proteins in this process has been reviewed (Pestell *et al*. 1999, Fu *et al*. 2002, Wang *et al*. 2003*a*). Estrogens are known to stimulate cell cycle progression, particularly in early G_1, and the induction of cellular proliferation correlates with the induction of cyclin D1 expression (Lippman & Bolan

1975, Lippman *et al*. 1976, Leung & Potter 1987, Altucci *et al*. 1996, Foster & Wimalasena 1996, Musgrove *et al*. 1996). Estrogen conveys several distinct effects on components of the cell cycle and breast epithelial cells. Cyclin D1 is required for estrogen-induced cellular proliferation in MCF-7 and several other cell types. Two related proteins, ERα and ERβ, function as transcription factors to regulate expression of target genes and modulate the effects of estrogens. Estrogens induce the expression of cyclin D1 through ERα. Conversely, estrogens inhibit cyclin D1 expression through ERβ (Liu *et al*. 2002). ERβ completely inhibits *cyclin D1* gene activation by estrogen and ERα. The opposing action and dominance of the ERβ over ERα in regulating *cyclin D1* gene expression implies a potential role for ERβ as a modulator of the proliferative effects of estrogens (Liu *et al*. 2002).

ERα function determines normal mammary gland duct growth, angiogenesis, and somatogenesis (Davis *et al*. 1994, Eddy *et al*. 1996, Johns *et al*. 1996, Korach *et al*. 1996), together with other hormones and growth factors. Estrogen also functions through membrane tyrosine kinase receptor signaling pathways (Migliaccio *et al*. 1996). Furthermore, peptide growth factors induce ERα activity independently of ligand. Thus, the ERα can be activated through phosphorylation of serine 118 or 167. The Ras/Raf/MAP kinase pathway enhances the recruitment of the ERα coactivators, including amplified in breast cancer-1 (AIB1). As peptide growth factors induce both ERα activity and cyclin D1 abundance, it has been anticipated that ERα and cyclin D1 may be regulated co-ordinately.

Cyclin D1 expression is reduced by estrogen antagonists in T47D human breast cancer cells (Fu *et al*. 2002). Cellular proliferation induced by estrogens in several breast cancer cell lines correlates with induction of cyclin D1 mRNA, protein, and cyclin D1-dependent kinase activity. Cyclin D1 enhances activity of a chimaeric ER, in which the ligand binding domain of the ERα was replaced by the Gal4 DNA binding domain (Neuman *et al*. 1997, Zwijsen *et al*. 1997). It has been proposed that the overexpression of cyclin D1, frequently seen in ERα-positive breast tumors, may function to promote ERα activation of target genes in the presence of low estrogen concentrations. Analysis of murine cyclin $D1^{-/-}$ cells has suggested that cyclin D1 may perform a chaperone function bringing together multi-molecular complexes that in turn regulate the activity of the ERα (R G Pestell & C Wang, unpublished observations).

The cyclin-dependent kinase inhibitors also play an important role in estrogen-induced mitogenesis. $p16^{INK4a}$ inhibits estrogen-induced DNA synthesis in MCF-7 cells (Lukas *et al*. 1996, D'Amico *et al*. 2003), in part through repression of cyclin D1 expression (D'Amico *et al*. 2003). Estrogens also alter subcellular localization of the cyclin-dependent kinase inhibitors. The relative distribution of $p21^{CIP}$ within cyclin E/cdk2 complexes is regulated by estradiol (Planas-Silva & Weinberg 1997). Estrogens can also reduce the amount of $p21^{CIP}$ and $p27^{KIP}$ bound to cyclin E/cdk2 (Prall *et al*. 1997). Estrogen induces both cyclin E/cdk4 and cyclin E/cdk2 activity. As Myc is induced by estrogens and Myc is sufficient for the induction of cyclin E/cdk2 activity, c-Myc may contribute to the enhanced DNA synthesis observed with estrogen treatment. As Myc and cyclin D1 collaborate in several models of oncogenesis, the proliferative activity of estrogens in human breast cancer may be in part regulated by both cyclin D1 and c-Myc.

Nuclear receptors in breast cancer

Estrogen receptor

The important role for ERα activity in breast cancer onset and progression is underscored by the efficacy of ER antagonists as adjuncts for breast cancer prevention in high risk individuals and the efficacy of adjuvant therapy for treatment of patients with ERα-positive breast cancer (Jordan 1998). The ER status thus forms part of the stathmin (TMN) staging classification category 1 (Fitzgibbons *et al*. 1998). Estrogens influence normal proliferation, differentiation, and physiology of breast tissue and the development and progression of breast cancer (Hoskins & Weber 1994, Korach 1994, Eisen & Weber 1998, Gustafsson 1998, Jordan 1998). The presence of ERα immunoreactivity serves as an important prognostic indicator of high survival rates and lower relapse risk (Jordan & Morrow 1999, Brodie 2003). Curiously, approximately 50% of ERα-positive tumors fail to respond to anti-estrogen therapy, suggesting that important additional components play a role in ER antagonist therapies.

Androgen receptor

Androgens induce the expression of endogenous estrogen-responsive target genes and are capable of activating an ERα reporter gene in MCF-7 cells. Androgens induce proliferation of ERα-positive cells (Poulin & Labrie 1986, Najid & Habrioux 1990, Boccuzzi *et al*. 1992, Birrell *et al*. 1995). A subset of cell lines is exquisitely sensitive to the proliferative effects of androgens, including the Shianogi line (Stanley *et al*. 1977). The mechanisms by which androgens induce breast cellular proliferation may include induction of ERα. Thus, the androgens dehydroepiandrosterone, 5α-androstene-3β,17β-diol, testosterone, and dihydrotestosterone activate ERα reporter activity and induce breast cancer cell proliferation (Maggiolini *et al*. 1999). The effectiveness of aromatase inhibitors in blocking

the growth of ERα-positive tumors may be in part due to their ability to block androgen induction of ERα activity.

PPAR

The PPARs are ligand-activated nuclear receptors including PPARα, PPARγ, and PPARδ. Their modular structure resembles other nuclear hormone receptors with an N-terminal activation and DNA binding domain and a C-terminal ligand binding domain (Rosen & Spiegelman 2001*b*). PPARγ was cloned as a transcription factor promoting fat cell differentiation. The PPARγ ligands include eicosanoids such as 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ_2), and synthetic ligands including the thiazolidinedione (TZD) class. It has been estimated that approximately 2 million Americans take anti-diabetic agents which are PPARγ ligands. There is some evidence that breast cancer risk is reduced in individuals taking PPARγ ligands (Michels *et al*. 2003). These epidemiological data suggest that the mechanisms by which PPARγ ligands may function are of broad importance in cancer.

PPARγ is expressed in breast, prostate, and colonic epithelium. Several lines of evidence have implicated PPARγ as a candidate tumor suppressor (Rosen & Spiegelman 2001*a*, Koeffler 2003). Heterozygous mutations of PPARγ were identified in four of 55 patients with colon cancer (Sarraf *et al*. 1999). A translocation between paired box homeotic gene 8 (PAX-8) and PPARγ was also identified in follicular thyroid cancer which appeared to serve as a dominant inhibitor of endogenous PPARγ expression (Kroll *et al*. 2000). Addition of PPARγ ligands to cultured tumor cell lines derived from breast, prostate, or colonic cancer inhibits cellular proliferation (Brockman *et al*. 1998, Elstner *et al*. 1998*a*, Mueller *et al*. 1998, Ricote *et al*. 1998). The role of PPARγ ligands in tumor onset *in vivo* is unresolved. Studies of murine familial adenoma models of adenomatosis polyposis coli using Apc^{min} mice demonstrated that PPARγ ligands may either promote (Saez *et al*. 1998) or inhibit colon polyp formation (Niho *et al*. 2003). As the same murine model of tumor formation was used in both studies, the explanation for these disparate findings warrants further analysis.

The relative importance of PPARγ signaling in breast cancer onset and progression is an area of substantial current interest. PPARγ expression has been observed in a subset of human breast cancers and benign breast disease (Wang *et al*. 2003*b*). In breast cancer cell lines, PPARγ activation by TZDs or 15d-PGJ_2 induced cellular differentiation (Elstner *et al*. 1998*a*, Mueller *et al*. 1998). Both TZDs and 15d-PGJ_2 inhibit cell cycle progression through direct repression of *cyclin D1* gene expression (Wang *et al*. 2001). The relative importance of PPARγ agonists as chemopreventive agents in humans remains to be explored. The presence of β-catenin activation in the subset of breast cancers (Lin *et al*. 2000) and the failure of PPARγ ligands to impact tumor progression in the presence of mutant β-catenin in some studies on colon cancer (Saez *et al*. 1998) suggest that PPARγ ligands may be important adjuncts to prevent rather than treat human breast cancer.

Diet and the cell cycle

Diet has been suggested to contribute to the etiology of 30–50% of newly diagnosed breast cancers (Willett 2001). Animal studies strongly support the ability of dietary components either to increase or reduce breast cancer risk. For example, n-6 polyunsaturated fatty acids (PUFAs) present in vegetable oils pre-initiate (i.e. increase susceptibility to carcinogens and other cancer-initiating factors) and promote carcinogen-induced mammary tumorigenesis (Welsch 1992, Hilakivi-Clarke *et al*. 1997). In contrast, n-3 PUFAs present in fish, flaxseed and canola oil reduce the growth of ER-negative human breast cancer cells implanted in nude mice (Rose 1997). Other dietary components that have been suggested to reduce the risk of breast cancer include the phytoestrogen genistein (Bouker & Hilakivi-Clarke 2000), vitamins (such as A, D, and E), and other components in fruits and vegetables (Smith-Warner *et al*. 2001, Riboli & Norat 2003). Restricted energy intake has also been shown to reduce mammary tumorigenesis in animal models (Zhu *et al*. 2002). Despite the compelling evidence from experimental models, studies in human populations that have attempted to link a particular dietary factor to increased or reduced breast cancer risk have generated contradictory data (Willett 2001).

Most human studies have assessed dietary intakes at the time of breast cancer diagnosis or shortly before. As breast cancer is a multi-step process, and there is likely to be a considerable time-lapse between initiation and diagnosis of this disease, studies which assess diet only at or around the time of diagnosis are limited and may miss or wrongly identify dietary components involved in increasing breast cancer risk. For instance, dietary components that affect tumor cell proliferation (e.g. alcohol, phytoestrogens, some fats) might be identified as affecting cancer risk. Those that affect susceptibility to malignant transformation (e.g. anti-oxidant vitamins) may not be different between the cases and controls at the time of diagnosis, although when breast cancer was initiated the cases theoretically could have been consuming fewer vitamins than the controls. It is not uncommon that, as an adult, individuals adopt a healthier diet that includes more fruits and vegetables compared with childhood dietary preferences. Interestingly, the evidence

in humans linking diet to breast cancer is strongest for alcohol and perhaps phytoestrogens and fats, but weak for vitamins.

Dietary factors have several different mechanisms of action, depending on dose or timing of exposure, that could ultimately affect breast cancer risk. The phytoestrogen genistein, present in soy products, is an example. Genistein is a weak estrogen that binds to both ERα and ERβ, and at physiological concentrations (<1 μM) causes cell proliferation (Wang *et al*. 1996, Zava & Duwe 1997). This genistein-induced increase in proliferation has been observed *in vitro* in human breast cancer cells, *in vivo* in animals, and also in normal human breast epithelium (Bouker & Hilakivi-Clarke 2000). Conversely, pharmacological doses (> 10 μM) of genistein cause changes that are potentially protective, including inhibition of tyrosine kinase activity, angiogenesis, and induction of apoptosis (Kim *et al*. 1998, Messina 1999). It is unlikely that soy consumption produces genistein exposures at pharmacological levels, since Asians who, on average, consume high levels of soy compared with Caucasians have blood concentrations around 1–4 μM (Xu *et al*. 1994). It is not clear whether the concentrations of genistein in the breast tissue reflect those in the circulation, or are lower or higher than in the blood.

Timing of exposure

Timing of hormonal and dietary exposures has important ramifications for breast cancer risk. There are three periods during a female's life-time when her breast epithelium undergoes extensive growth and is highly sensitive to estrogens: fetal life, puberty, and pregnancy. In rodents, maternal exposure during pregnancy to estrogenic compounds, including dietary compounds, increases breast cancer risk among female offspring (Walker 1984, 1990, Hilakivi-Clarke *et al*. 1997, 1999). Thus, some breast cancers may be pre-initiated during fetal life by an exposure to high levels of estrogens that may imprint the mammary gland in a manner that increases later susceptibility to breast cancer (Trichopoulos 1990, Hilakivi-Clarke *et al*. 2002*a*). Persistent changes in the mammary glands of rodents exposed to a high estrogenic environment in utero include increased number of targets for malignant transformation (Hilakivi-Clarke *et al*. 1997) and altered expression of ERα and tumor suppressor genes BRCA1 and p53 (Yu *et al*., unpublished data).

Prepubertal estrogenic exposures paradoxically reduce breast cancer risk (Cabanes *et al*. 2004), perhaps through differentiation of the mammary gland structures (terminal end buds; TEBs) that are known to be the sites for malignant transformation. The gland of an animal exposed to estradiol or genistein during prepuberty has been found to contain fewer TEBs and more lobuloalveolar units (Cabanes *et al*. 2004). These changes are accompanied by long-lasting alterations in the expression of ERα and ERβ (Cabanes *et al*. 2004).

Prepubertal exposure to estradiol or genistein leads to a long-lasting up-regulation of BRCA1 mRNA in the rat mammary gland (Cabanes *et al*. 2004), suggesting an increase in DNA repair capacity. The tumor suppressor BRCA1 interacts with estrogens and the ER, at least in normal mouse mammary gland and in human breast cancer cell lines (Gudas *et al*. 1995, Marquis *et al*. 1995, Spillman & Bowcock 1996, Fan *et al*. 1999, 2000, 2001). Loss of wildtype BRCA1 is linked to inherited breast cancers (Garland *et al*. 1998, Satagopan *et al*. 2001), probably because this gene participates in DNA damage repair and recombination processes related to maintenance of genomic integrity, control of cell proliferation, and regulation of gene transcription (Rosen *et al*. 2001, Welcsh *et al*. 2002). BRCA1 regulates the expression of several genes implicated in breast cancer, including cyclin D1, c-myc, and components of the Jak-Stat pathway (Welcsh *et al*. 2002). In addition, BRCA1 inhibits the signaling of the ligand-activated ERα (Fan *et al*. 1999).

Pregnancy is closely linked to changes in breast cancer risk with early first pregnancy reducing and later first pregnancy increasing the risk (MacMahon *et al*. 1970). Higher estrogen levels during pregnancy increase the mother's breast cancer risk (Richardson *et al*. 1998, Peck *et al*. 2002). The proposed mechanism is that the breast tissue of older first time mothers are more likely to have acquired malignant cells that are stimulated by high pregnancy hormonal environment. Collectively, these findings indicate that although estrogens stimulate the proliferation of ER-positive human breast cancer cells, their effect on the normal breast depends on the timing of exposure.

Dietary components that modify the cell cycle

Several dietary factors have been demonstrated to alter the normal cell cycle of non-malignant and malignant breast cells. Herein, we address the role of body mass index (BMI), energy restriction, dietary fat, soy, and vitamin A in affecting breast cancer risk and cell cycle-related end points.

Body weight

Excess weight and obesity are major problems in the Western world because of their link to several serious health problems, including cardiovascular diseases, diabetes, and cancer. According to the 1999 National Health

and Nutrition Examination Survey, it was estimated that 61% of Americans are overweight (BMI 25–30 kg/m^2) and 25% are obese (BMI> 30 kg/m^2) (Flegal *et al*. 2002). BMI affects breast cancer risk, but the effects depend on the developmental stage of an individual. Further, multiple pathways have been identified that could mediate the effects of obesity on breast cancer risk.

Adrenal androgens are aromatized to estrogens in adipose tissue. Most circulating estrogens present in postmenopausal women originate from adipose cells, and approximately one-third of estrogens in premenopausal women come from these cells. A high fat and/or a high total caloric intake increases the levels of circulating free estrogens (Goldin *et al*. 1982, Rose *et al*. 1987, 1993, Bennett & Ingram 1990) and Wu *et al*. (1999) have reported that women who reduce their total fat consumption lower their circulating estradiol levels. In postmenopausal women, BMI correlates with elevated expression of cyclin D1 and bcl-2 mRNA in the mammary tissue (Suga *et al*. 2001), indicating that high BMI may increase breast cancer risk by increasing serum estrogens, modulating cell cycle, and inhibiting apoptosis.

Besides estrogens, other hormones and growth factors that are altered by BMI include leptin, adiponectin, insulin, and IGFs. Further, PPARγ has a key role in adipocyte differentiation and in mediating high fat-induced obesity (Kadowaki *et al*. 2003). Leptin is expressed by the adipose cells as well as epithelial cells: the levels of this hormone are closely linked to BMI, regardless of a woman's age or reproductive status (Huang & Li 2000). Leptin has been linked to increased breast cancer risk (Marttunen *et al*. 2000, Tessitore *et al*. 2000, Ozet *et al*. 2001, Hu *et al*. 2002). Leptin also alters the rate of cell proliferation, and modifies the expression of genes linked to the cell cycle, such as cyclin D1, PPARγ, and ERα and ERβ (Okumura *et al*. 2002). Adiponectin is secreted exclusively by adipose tissue and it is present at high levels in the serum. However, it is reversely associated with BMI (Arita *et al*. 1999, Stefan *et al*. 2002). Reduced adiponectin levels have recently been linked to increased breast cancer risk (Miyoshi *et al*. 2003), and thus this hormone might act as a tumor suppressor. Extensive literature links IGF-I to breast cancer. In addition to being linked to obesity, all these hormones and growth factors interact with each other.

Birth weight

Body weight at birth may alter later risk of developing breast cancer. Women who had a high birth weight have an elevated breast cancer risk in most (Michels *et al*. 1996, Sanderson *et al*. 1996) (but not all studies, Potischman & Troisi 1999), particularly for premenopausal breast cancer (Michels *et al*. 1996, Sanderson *et al*. 1996). The increase in breast cancer risk by high birth weight is profound in twins (Sparano & Winer 2001), suggesting genetic modifiers of high birth weight on breast cancer risk.

Birth weight has been linked to an elevated estrogenic environment during pregnancy (Gerhard *et al*. 1987). In human populations, size at birth correlates with increased cellular proliferation, as mammary epithelial area/and mammographic density are increased (Ekbom *et al*. 1995). In animal studies (Hilakivi-Clarke *et al*. 1997), the results indicate that maternal exposures to a high fat diet or estradiol during pregnancy increased the density of the offspring's mammary epithelium. Thus, one mechanism by which high birth weight increases later breast cancer risk could be through an increase in epithelial cell proliferation.

Prepubertal BMI

High body mass during childhood is associated with a reduction in breast cancer risk (Le Marchand *et al*. 1988, Magnusson *et al*. 1998, Berkey *et al*. 1999, Hilakivi-Clarke *et al*. 2001, Swerdlow *et al*. 2002). This is puzzling in light of the fact that overweight and obese girls reach puberty earlier than lean girls, and early puberty is associated with increased breast cancer risk. A monozygotic twin that reached puberty first has a fivefold higher breast cancer risk than her twin sister with later puberty onset (Hamilton & Mack 2003), suggesting environmental modifiers affecting puberty onset and breast cancer risk. Since in animal studies *in utero* exposures to estrogenic compounds accelerate puberty onset and increase susceptibility to carcinogen-induced mammary tumors (Hilakivi-Clarke *et al*. 1997), early puberty may be a marker of high *in utero* estrogen exposure rather than directly increasing breast cancer risk.

High body mass during childhood may be linked to increased levels of circulating estrogens. Girls with elevated low-density lipoprotein cholesterol levels exhibited a reduction in serum estradiol levels after their dietary fat intake was reduced and fiber intake increased (Dorgan *et al*. 2003). In heifers, elevated energy consumption during the prepubertal period reduced the growth of mammary parenchyma (Hull & Harvey 2002) and increased breast adipose tissue mass, a predictor of reduced breast cancer risk (Oza & Boyd 1993, Boyd *et al*. 2001). Similarly, women who had high BMI at puberty have a persistently lower mammographic density (McCormack *et al*. 2003).

BMI during reproductive years and postmenopause

Postmenopausal breast cancer risk is elevated in individuals who were obese either during the pre- or postmenopausal years, or both (Kabuto *et al*. 2000).

Paradoxically, obesity reduces premenopausal breast cancer risk (Potischman *et al*. 1996, Cleary & Maihle 1997, Huang *et al*. 1997, Trentham-Dietz *et al*. 1997). We have studied excessive weight gain during pregnancy and found that it increases postmenopausal breast cancer, and the effect is independent from the body weight at the time of diagnosis (Kinnunen *et al*. 2004).

High BMI during the postmenopausal years correlates with increased serum estrogens (Toniolo *et al*. 1995, Hankinson *et al*. 1998), although this may not be true for premenopausal women (Trichopoulos *et al*. 1983). In premenopausal women, estrogens derived from an excessive amount of adipose tissue are likely to inhibit the pituitary–gonadal axis, potentially causing a reduction in estrogens to be released from the ovaries. However, the total estrogen levels are not altered, because the loss of ovarian estrogen production is compensated for by adipose-derived estrogens.

Energy restriction

Dietary caloric restriction in monkeys and rodents extends lifespan, slows the aging process (Roth *et al*. 2000), and reduces mammary tumor risk in rodents (Thompson *et al*. 1999, Jiang *et al*. 2003). Energy restriction reduces oxidative tissue damage and mitochondrial free radical generation in rodents (Merry 2002). Energy restriction reduces mammary tumor cell proliferation via G1 cell cycle arrest, possibly through a reduced expression of cyclin D1, Cdk4 and increased expression of p21 and p27 (Jiang *et al*. 2003) perhaps due to increased adrenocortical steroid secretion (Zhu *et al*. 2003).

It is not known whether the health benefits of energy restriction extend to humans. In Norway (Robsahm & Tretli 2002) and The Netherlands (Dirx *et al*. 1999), reduction in energy intake in adolescents and women during World War II (1940–44) and the Hunger Winter (1944–45), increased breast cancer risk later in life (Robsahm & Tretli 2002). Consistent with recent data are the findings that low childhood BMI increased breast cancer risk (Le Marchand *et al*. 1988, Magnusson *et al*. 1998, Luo & Miller 2000, Hilakivi-Clarke *et al*. 2001, Swerdlow *et al*. 2002).

No studies have directly addressed the role of energy restriction during adult life in affecting breast cancer risk. However, women with anorexia nervosa are at a 20% reduced risk of developing a cancer in general (Mellemkjaer *et al*. 2001). Studies that have assessed longevity in thin individuals have generated conflicting findings (Lee *et al*. 2001), possibly because many severe illnesses cause weight loss.

Polyunsaturated fatty acids

High dietary fat intake has been linked to the promotion of breast cancer in animal models (Freedman *et al*. 1990, Welsch 1992), most case–control studies (Howe *et al*. 1990, Richardson *et al*. 1990, Van't Veer *et al*. 1990), but not in prospective cohort studies (Welsch 1987, Willett *et al*. 1992, van den Brandt *et al*. 1993, Willett & Hunter 1994), with few exceptions (Cho *et al*. 2003*a*).

Diets are composed of several types of dietary fats, including mono-unsaturated fatty acids (olive and canola oils), PUFAs (vegetable oils, n-6 PUFA and fish, n-3 PUFA), and saturated fats (dairy products and meat). Saturated fats may be associated with increased breast cancer risk in women (Willett 1997, Cho *et al*. 2003*a*), but animal studies have generally been inconclusive (Rose 1997). Diets high in n-6 PUFAs are associated with elevated breast cancer risk in animal studies (Freedman *et al*. 1990, Welsch 1992), but not humans (Willett 2001, Cho *et al*. 2003*a*). n-3 PUFAs are protective in some (Eid & Berry 1988, Caygill *et al*. 1996, Klein *et al*. 2001), but not all studies (Holmes *et al*. 2003, Stripp *et al*. 2003). In nude mice, dietary n-3 PUFA reduces growth and metastasis of human breast cancer xenografts (Rose *et al*. 1995) and spontaneous or carcinogen-induced rodent mammary tumors (Karmali *et al*. 1984, Hirose *et al*. 1990, Fay *et al*. 1997).

A diet high in n-6 PUFA corn oil, or a low or high fat n-3 PUFA menhaden oil increases serum estradiol levels in rats and mice when compared with a low fat n-6 PUFA standard AIN93 laboratory diet (Hilakivi-Clarke *et al*. 1996*a*,*b*, 1997, 2002*b*). Consumption of a high fat diet may increase the levels of adipose tissue, and thereby increase aromatization of estrogens. n-6 PUFA consumption may also directly enhance aromatization (Richards & Brueggemeier 2003). It is not clear why n-3 PUFA diet increases serum estrogen levels. PPARγ is either activated (Rubin *et al*. 2000) or inhibited by n-3 PUFAs (Thoennes *et al*. 2000), potentially reducing aromatase activity. However, PPARγ agonists can increase arachidonic acid release from the liver (Levine 2001), which could stimulate aromatization.

n-3 and n-6 fatty acids impact cell proliferation and differentiation; however, some studies report inconsistent data (Finstad *et al*. 1994, Rudolph *et al*. 2001). The effects of these fatty acids on the cell cycle suggest that n-6 PUFAs increase cyclin D1 mRNA in T47D breast cancer cells (Razanamahefa *et al*. 2000), the n-3 PUFA docosahexaenoic acid reduces cyclin D1-, E-, and A-associated kinase activity in HT-29 colon cancer cells (Chen & Istfan 2001), and the n-3 PUFA, eicosapentaenoic acid, reduces cyclin D1 and cyclin E in NIH 3T3 cells (Palakurthi *et al*. 2000).

Prepubertal exposure to PUFAs and breast cancer risk

Maternal exposure to a diet containing high levels of n-3 PUFAs reduces an offspring's risk of mammary tumorigenesis (Hilakivi-Clarke *et al*. 2002*b*). In contrast, prepubertal exposure to a high fat n-3 PUFA diet increases carcinogen-induced mammary tumorigenesis, while a prepubertal low fat n-3 PUFA exposure provides a protection against breast cancer (Olivo *et al*., unpublished data).

Identifying the pathways and timing of exposure by which *in utero* or prepubertal exposures to n-3 PUFAs may decrease breast cancer risk is complicated, because multiple potential mechanisms exist (Welsch 1987). We have found that changes induced by having been exposed to a low fat n-3 PUFA diet during prepuberty include an increase in lipid peroxidation, but also an increase in the expression of oxidative damage repair genes, apoptosis and cyclo-oxygenase 2. Animals fed a high fat n-3 PUFA diet prepubertally which increases their breast cancer risk also exhibit increased lipid peroxidation, but this is accompanied by an increase in DNA damage, cell proliferation, cyclin D1 expression, and phosphorylated Akt, and reduced apoptosis and BRCA1 expression (Olivo *et al*. unpublished data). Thus, high levels of n-3 PUFAs fed in a high fat context before the onset of puberty can cause multiple changes in the mammary gland, including disruption of the cell cycle. In contrast, a prepubertal exposure to a low fat n-3 PUFA diet may be protective because of increased oxidative damage repair and apoptosis.

Genistein

Soybeans contain large amounts of the isoflavones daidzein and genistein (Barnes *et al*. 1994, Adlercreutz 1995). Genistein or equol, a metabolite of daidzein, may play significant roles in the bioactivity of soy (Lampe 2003). It has been proposed that high soy intake contributes to low breast cancer incidence among Asian women (Adlercruetz *et al*. 1996), and our recent meta-analysis showed that a high soy intake reduces risk of developing premenopausal breast cancer (Trock *et al*. 2001).

Timing of exposure to soy plays a key role in determining its effect on the breast with soy exposure during childhood significantly reducing breast cancer risk (Shaag *et al*. 2001, Wu *et al*. 2002). Rats exposed to genistein during prepuberty have a reduced risk of developing carcinogen-induced mammary tumors (Murrill *et al*. 1996, Hilakivi-Clarke *et al*. 1998, Cotroneo *et al*. 2002), yet genistein either via injections or dietary soy during adulthood does not affect mammary tumorigenesis (Constantinou *et al*. 1996, Cohen *et al*. 2000). In ovariectomized animals that mimic postmenopause, genistein promotes the growth of human MCF-7 breast cancer cells (Allred *et al*. 2001, Ju *et al*. 2001).

In vitro, genistein has mitogenic effects at low, physiological doses (0.01–1 μM) and anti-proliferative effects at higher, pharmacological doses (> 10 μM) (Wang *et al*. 1996, Hsieh *et al*. 1998). However, when estradiol is present, genistein may not induce cell proliferation (Trock *et al*. 2001). It is not clear whether genistein inhibits estrogens actions in humans, since exposure to soy induces breast proliferation in premenopausal, but not postmenopausal women (Petrakis *et al*. 1996, McMichael-Phillips *et al*. 1998).

Animal studies have investigated whether an exposure to genistein either *in utero* or during prepuberty alters the expression of nuclear receptors in the mammary gland or other tissues. At the time of genistein administration, ERα expression is reduced (Cotroneo *et al*. 2002), a result that is in accordance with findings obtained *in vitro* in cells treated with estradiol (Saceda *et al*. 1988). Both fetal and prepubertal genistein administration causes an increase in ERα expression in estrogen-responsive tissues (Jefferson *et al*. 2002), and prepubertal genistein exposure also up-regulates ERβ in the mammary gland (Y Zhu, R Clarke, S de Assis, J S Miller & L Hilakivi-Clarke, unpublished data). It is plausible that genistein's ability to bind preferentially to ERβ (Kuiper *et al*. 1997) might be more important than its effect on ERα expression in affecting breast cancer risk.

Genistein can directly bind to PPARγ to either inhibit it at physiological doses (<1 μM) or stimulate at pharmacological (> 5 μM) doses in mesenchymal progenitor cells (Dang *et al*. 2003), in adipose cells (Dang *et al*. 2003), and in murine macrophages (Mezei *et al*. 2003).

Physiological doses of genistein and another phytoestrogen, zearalenone, increased the expression of cyclin D1 and Cdk2 in MCF-7 cells *in vitro* (Dees *et al*. 1997) and *in vivo* (Ju *et al*. 2002), but higher doses (100–200 μM) inhibited cyclin D1 and cyclin E (Agarwal 2000). The effects of genistein on cyclin D1 are consistent with genistein's reported ability to both stimulate and inhibit cell proliferation, depending upon the dose.

Vitamin A and retinoids

Since high dietary intake of fruits and vegetables is consistently linked to reduced breast cancer risk (Smith-Warner *et al*. 2001, Riboli & Norat 2003), it seems reasonable that the vitamins present at high levels in these foods contribute to this effect. These vitamins, including A, C, and E, have several potentially beneficial effects on biological pathways related to preventing oxidative

damage, inhibiting cell proliferation, and inducing differentiation. Surprisingly, the evidence linking each of these vitamins to reduced breast cancer risk is weak.

Retinoid receptor function

Retinoid receptors are members of the nuclear steroid/thyroid hormone receptor family that play a key role in the control of cell growth and differentiation (reviewed in Mangelsdorf *et al*. 1993, Fontana & Rishi 2002, Fu *et al*. 2002). Two distinct classes of retinoid receptors exist: the retinoic acid receptors (RARs α, β, γ) and the retinoid X receptors (RXRs α, β, γ). Like other nuclear receptors, these molecules homo- and heterodimerize in response to ligand binding and function as transcription factors at specific promoter elements or indirectly via other transcriptional regulators. In addition, RXRs can heterodimerize with vitamin D and thyroid hormone receptors as well as PPARγ (Dawson *et al*. 2000).

Activation of retinoid receptors has been shown to be growth inhibitory in breast cancer cells as well as other cell types (see Amos & Lotan 1990, Seewaldt *et al*. 1997, 1999), and consequently retinoids have been explored as potential therapeutic and chemopreventive agents. Retinoid receptor activation inhibits cell cycle progression, delaying the transition between G_0/G_1 and S phases (Seewaldt *et al*. 1997, 1999). RARs and RXRs interact with many different downstream effectors, resulting in cell type-specific mechanisms of growth inhibition and apoptosis. In breast cancer cells, the transcriptional regulator CBP/p300 is up-regulated by *trans* retinoic acid, functions as a coactivator for RARs, and is required for sensitivity to retinoid-mediated growth arrest (Dietze *et al*. 2003). Other transcriptional regulators implicated in retinoid responses include the *Drosophila* hairy and enhancer of split homologue transcriptional repressor and SOX-9 (Muller *et al*. 2002). The anti-apoptotic factor Bcl-2 is down-regulated by retinoic acid in MCF-7 cells, leading to enhanced caspase activation (Pratt *et al*. 2003). IGF signaling also appears to be altered in response to retinoids. Retinoic acid induces down-regulation of insulin receptor substrate-1 and Akt, resulting in growth arrest and apoptosis (del Rincon *et al*. 2003).

Heterodimerization of RXR and PPARγ may contribute to retinoid anti-proliferative signaling in breast cancer. Simultaneous activation of both receptors inhibits breast cancer cell proliferation *in vitro* and *in vivo* (Mukherjee *et al*. 1997, Elstner *et al*. 1998*b*). Inhibition of cyclin D1 expression by both RXR and PPARγ stimulation has been demonstrated in a pancreatic cancer cell line (Suh *et al*. 1999). RXR/PPARγ induce apoptosis by inhibiting nuclear factor-κB-dependent survival pathways (Dubuquoy *et al*. 2002) and repression of the P450 aromatase gene, thereby decreasing estrogen synthesis in some (Rubin *et al*. 2002) but not all studies (Mu *et al*. 2001).

Dietary intake of vitamin A and breast cancer

Most studies, however, have failed to identify a clear association between breast cancer and dietary vitamin A or carotenoid intake (Kushi *et al*. 1996, Jarvinen *et al*. 1997, Verhoeven *et al*. 1997, Michels *et al*. 2001) (reviewed in Fairfield & Fletcher 2002). Recent studies suggest that increased intake of vitamin A or carotenoids may prevent breast cancer (Bohlke *et al*. 1999, Zhang *et al*. 1999, Toniolo *et al*. 2001), particularly in premenopausal but not postmenopausal women, women who consume alcohol or women who are at high inherited risk for this disease. Vitamin A may be protective for premenopausal women who smoke, but not in non-smokers (Cho *et al*. 2003*b*).

In rats, vitamin A-deficient and -supplemented rats develop more carcinogen-induced mammary tumors than animals fed vitamin A-adequate diets (Metz *et al*. 2002).

Confounding epidemiological variables include the failure of serum levels of retinoids and carotenoids to correlate with consumption (reviewed in Cheung *et al*. 2003). There are some 600 carotenoid plant pigments, 50 of which may be converted into vitamin A; whether it is strictly vitamin A or other carotenoid metabolites that function to reduce breast cancer risk has not been determined. Similarly, women who consume high levels of carotenoids and vitamin A are also likely to obtain additional nutrients from other fruits and vegetables, and it may be that these contribute significantly to any observed reduction in breast cancer risk (Fairfield & Fletcher 2002).

Conclusions

Several dietary factors modify the cell cycle. Dietary factors that up-regulate cyclin D1 and ERα and down-regulate PPARγ and BRCA1 might play a role in increasing breast cancer risk (Fig. 3). Dietary factors that have opposing effects on these genes could reduce breast cancer risk. *In utero* exposures to genistein and perhaps n-6 PUFA mediate their effects on the breast partly by affecting these genes and increase breast cancer susceptibility (Ju *et al*. 2002, Dang *et al*. 2003). Prepubertal exposure to genistein or a low fat n-3 PUFA diet up-regulates BRCA1 (Cabanes *et al*. 2004, S Olivo, L Hilakivi-Clarke, Y Zhu, R G Lee, A Cabanes, G Khan, A Zwart, Y Wang & R Clarke, unpublished data) and other genes that lead to increased ability to repair DNA damage, or cause apoptosis and differentiation. Further studies will determine whether the timing of exposure to vitamins, such as vitamin A and E which

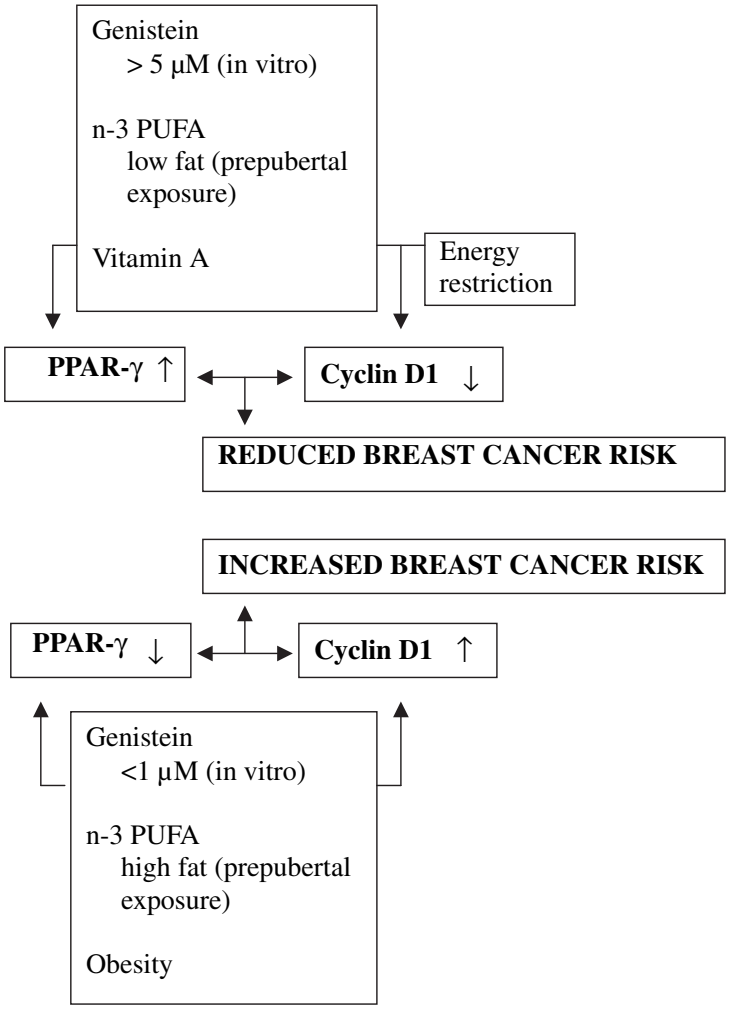

Figure 3 Examples of dietary factors that increase breast cancer risk, perhaps by up-regulating cyclin D1 and down-regulating PPARγ, and dietary factors that reduce breast cancer risk by having the opposite effects on the expression of these two genes.

induce differentiation and have anti-oxidant properties, modifies later breast cancer risk, and whether changes in susceptibility to malignant transformation are related to diet-induced changes in the cell cycle.

References

Adlercreutz H 1995 Phytoestrogens: epidemiology and a possible role in cancer protection. *Environmental Health Perspectives* **103** 103–112.

Adlercruetz CH, Goldin BR, Gorbach SL, Hockerstedt KAV, Watanabe S, Hamalainen E, Markkanen MH, Makela TH, Wahala KT, Hase TA & Fotsis T 1996 Soybean phytoestrogen intake and cancer risk. *Journal of Nutrition* **125** 757S–770S.

Agarwal R 2000 Cell signaling and regulators of cell cycle as molecular targets for prostate cancer prevention by dietary agents. *Biochemical Pharmacology* **60** 1051–1059.

Allred CD, Allred KF, Ju YH, Virant SM & Helferich WG 2001 Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose-dependent manner. *Cancer Research* **61** 5045–5050.

Altucci L, Addeo R, Cicatiello L, Dauvois S, Parker MG, Truss M, Beato M, Sica V, Bresciani F & Weisz A 1996 17beta-Estradiol induces cyclin D1 gene transcription, p36D1-p34cdk4 complex activation and p105Rb phosphorylation during mitogenic stimulation of G(1)-arrested human breast cancer cells. *Oncogene* **12** 2315–2324.

Amos B & Lotan R 1990 Retinoid-sensitive cells and cell lines. *Methods in Enzymology* **190** 217–225.

Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T & Matsuzawa Y 1999 Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochemical and Biophysical Research Communications* **257** 79–83.

Barnes S, Peterson G, Grubbs C & Setchell K 1994 Potential role of dietary isoflavones in the prevention of cancer. In *Diet and Cancer: Markers, Prevention, and Treatment*, pp 135–147. Ed. MM Jacobs. New York: Plenum Press.

Bennett FC & Ingram DM 1990 Diet and female sex hormones concentrations: an intervention study for the type of fat consumed. *American Journal of Clinical Nutrition* **52** 808–812.

Berkey CS, Frazier AL, Gardner JD & Colditz G 1999 Adolescence and breast carcinoma risk. *Cancer* **85** 2400–2409.

Birrell SN, Bentel JM, Hickey TE, Ricciardelli C, Weger MA, Horsfall DJ & Tilley WD 1995 Androgens induce divergent proliferative responses in human breast cancer cell lines. *Journal of Steroid Biochemistry and Molecular Biology* **52** 459–467.

Boccuzzi G, Brignardello E, di Monaco M, Forte C, Leonardi L & Pizzini A 1992 Influence of dehydroepiandrosterone and 5-en-androstene-3 beta,17 beta-diol on the growth of MCF-7 human breast cancer cells induced by 17 beta-estradiol. *Anticancer Research* **12** 799–803.

Bohlke K, Spiegelman D, Trichopoulou A, Katsouyanni K & Trichopoulos D 1999 Vitamins A, C, and E and the risk of breast cancer: results from a case-control study in Greece. *British Journal of Cancer* **79** 23–29.

Bouker KB & Hilakivi-Clarke L 2000 Genistein: does it prevent or promote breast cancer? *Environmental Health Perspectives* **108** 701–708.

Boyd NF, Martin LJ, Stone J, Greenberg C, Minkin S & Yaffe MJ 2001 Mammographic densities as a marker of human breast cancer risk and their use in chemoprevention. *Current Oncology Reports* **3** 314–321.

van den Brandt PA, Van't Veer P, Goldbohm RA, Dorant E, Volovics A, Hermus RJJ & Sturmans F 1993 A prospective cohort study on dietary fat and the risk of postmenopausal breast cancer. *Cancer Research* **53** 75–82.

Brockman JA, Gupta RA & Dubois RN 1998 Activation of PPARgamma leads to inhibition of anchorage-independent growth of human colorectal cancer cells. *Gastroenterology* **115** 1049–1055.

Brodie A 2003 Aromatase inhibitor development and hormone therapy: a perspective. *Seminars in Oncology* **30** 12–22.

Cabanes A, Wang M, Olivo S, de Assis S, Gustafsson JA, Khan G & Hilakivi-Clarke L 2004 Prepubertal estradiol and genistein exposures up-regulate BRCA1 mRNA and reduce mammary tumorigenesis. *Carcinogenesis* **25** 741–748.

Caygill CPJ, Charlett A & Hill MJ 1996 Fat, fish, fish oil, and cancer. *British Journal of Cancer* **74** 159–164.

Chen ZY & Istfan NW 2001 Docosahexaenoic acid, a major constituent of fish oil diets, prevents activation of cyclin-dependent kinases and S-phase entry by serum stimulation in HT-29 cells. *Prostaglandins Leukotrienes and Essential Fatty Acids* **64** 67–73.

Cheung B, Yan J, Smith SA, Nguyen T, Lee M, Kavallaris M, Norris MD, Haber M & Marshall GM 2003 Growth inhibitory retinoid effects after recruitment of retinoid X receptor beta to the retinoic acid receptor beta promoter. *International Journal of Cancer* **105** 856–867.

Cho E, Spiegelman D, Hunter DJ, Chen WY, Stampfer MJ, Colditz GA & Willett WC 2003*a* Premenopausal fat intake and risk of breast cancer. *Journal of the National Cancer Institute* **95** 1079–1085.

Cho E, Spiegelman D, Hunter DJ, Chen WY, Zhang SM, Colditz GA & Willett WC 2003*b* Premenopausal intakes of vitamins A, C, and E, folate, and carotenoids, and risk of breast cancer. *Cancer Epidemiology Biomarkers and Prevention* **12** 713–720.

Cleary ML & Maihle NJ 1997 The role of body mass index in the relative risk of developing premenopausal breast cancer. *Proceedings of the Society for Experimental Biology and Medicine* **216** 28–43.

Cohen LA, Zhao Z & Pittman BSJA 2000 Effect of intact and isoflavone-depleted soy protein on NMU-induced rat mammary tumorigenesis. *Carcinogenesis* **21** 929–935.

Constantinou AI, Mehta RG & Vaughan A 1996 Inhibition of N-methyl-N-nitroisourea-induced mammary tumors in rats by the soybean isoflavones. *Anticancer Research* **16** 3293–3298.

Cotroneo MS, Wang J, Fritz WA, Eltoum IE & Lamartiniere CA 2002 Genistein action in the prepubertal mammary gland in a chemoprevention model. *Carcinogenesis* **23** 1467–1474.

D'Amico M, Wu K, Di Vizio D, Reutens AT, Stahl M, Fu M, Albanese C, Russell RG, Muller WJ, White M, Negassa A, Lee H-W, DePinho RA & Pestell RG 2003 The role of Ink4a/Arf in ErbB2 mammary gland tumorigenesis. *Cancer Research* **63** 3395–3402.

Dang ZC, Audinot V, Papapoulos SE, Boutin JA & Lowik CW 2003 Peroxisome proliferator-activated receptor gamma (PPARgamma) as a molecular target for the soy phytoestrogen genistein. *Journal of Biological Chemistry* **278** 962–967.

Davis VL, Couse JF, Goulding EH, Power SG, Eddy EM & Korach KS 1994 Aberrant reproductive phenotypes evident in transgenic mice expressing the wild-type mouse estrogen receptor. *Endocrinology* **135** 379–386.

Dawson MI, Hobbs PD, Jong L, Xiao D, Chao WR, Pan C & Zhang XK 2000 sp2-bridged diaryl retinoids: effects of bridge-region substitution on retinoid X receptor (RXR) selectivity. *Bioorganic and Medical Chemistry Letters* **10** 1307–1310.

Dees C, Foster JS, Ahamed S & Wimalasena J 1997 Dietary estrogens stimulate human breast cells to enter the cell cycle. *Environmental Health Perspectives* **105** (Suppl 3) 633–636.

Dietze EC, Troch MM, Bowie ML, Yee L, Bean GR & Seewaldt VL 2003 CBP/p300 induction is required for retinoic acid sensitivity in human mammary cells. *Biochemical and Biophysical Research Communications* **302** 841–848.

Dirx MJ, van den Brandt PA, Goldbohm RA & Lumey LH 1999 Diet in adolescence and the risk of breast cancer: results of The Netherlands Cohort Study. *Cancer Causes and Control* **10** 189–199.

Dorgan JF, Hunsberger SA, McMahon RP, Kwiterovich PO Jr, Lauer RM, Van Horn L, Lasser NL, Stevens VJ, Friedman LA, Yanovski JA, Greenhut SF, Chandler DW, Franklin FA, Barton BA, Buckman DW, Snetselaar LG, Patterson BH, Schatzkin A & Taylor PR 2003 Diet and sex hormones in girls: findings from a randomized controlled clinical trial. *Journal of the National Cancer Institute* **95** 132–141.

Dubuquoy L, Dharancy S, Nutten S, Pettersson S, Auwerx J & Desreumaux P 2002 Role of peroxisome proliferator-activated receptor gamma and retinoid X receptor heterodimer in hepatogastroenterological diseases. *Lancet* **360** 1410–1418.

Eddy EM, Washburn TF, Bunch DO, Goulding EH, Gladen BC, Lubahn DB & Korach KS 1996 Targeted disruption of the estrogen receptor gene in male mice causes alteration of spermatogenesis and infertility. *Endocrinology* **137** 4796–4805.

Eid A & Berry EM 1988 The relationship between dietary fat, adipose tissue composition, and neoplasms of the breast. *Nutrition and Cancer* **11** 173–177.

Eisen A & Weber BL 1998 Recent advances in breast cancer biology. *Current Opinion in Oncology* **10** 486–491.

Ekbom A, Thurfjell E, Hsieh CC, Trichopoulos D & Adami HO 1995 Perinatal characteristics and adult mammographic patterns. *International Journal of Cancer* **61** 177–180.

Elstner E, Muller C, Koshizuka K, Williamson EA, Park D, Asou H, Shintaku P, Said JW, Heber D & Koeffler HP 1998*a* Ligands for peroxisome proliferator-activated receptorγ and retinoic acid receptor inhibit growth and induce apoptosis of human breast cancer cells in vitro and in BNX mice. *PNAS* **95** 8806–8811.

Elstner E, Muller C, Koshizuka K, Williamson EA, Park D, Asou H, Shintaku P, Said JW, Heber D & Koeffler HP 1998*b* Ligands for peroxisome proliferator-activated receptorgamma and retinoic acid receptor inhibit growth and induce apoptosis of human breast cancer cells *in vitro* and in BNX mice. *PNAS* **95** 8806–8811.

Fahraeus R & Lane DP 1999 The p16(INK4a) tumour suppressor protein inhibits alphavbeta3 integrin-mediated cell spreading on vitronectin by blocking PKC-dependent localization of alphavbeta3 to focal contacts. *EMBO Journal* **18** 2106–2118.

Fairfield KM & Fletcher RH 2002 Vitamins for chronic disease prevention in adults: scientific review. *Journal of the American Medical Association* **287** 3116–3126.

Fan S, Wang. J-A, Yuan R, Ma Y, Meng Q, Erdos MR, Pestell RG, Yuan F, Auborn KJ, Goldberg ID & Rosen EM 1999 BRCA1 inhibition of estrogen receptor signaling in transfected cells. *Science* **284** 1354–1356.

Fan S, Meng Q, Gao B, Grossman J, Yadegari M, Goldberg ID & Rosen EM 2000 Alcohol stimulates estrogen receptor signaling in human breast cancer cells lines. *Cancer Research* **60** 5635–5639.

Fan S, Ma YX, Wang C, Yuan RQ, Meng Q, Wang JA, Erdos M, Goldberg ID, Webb P, Kushner PJ, Pestell RG & Rosen EM 2001 Role of direct interaction in BRCA1 inhibition of estrogen receptor activity. *Oncogene* **20** 77–87.

Fay MP, Freedman LS, Clifford CK & Midthune DN 1997 Effect of different types and amounts of fat on the development of mammary tumors in rodents: a review. *Cancer Research* **57** 3979–3988.

Finstad HS, Kolset SO, Holme JA, Wiger R, Farrants AK, Blomhoff R & Drevon CA 1994 Effect of n-3 and n-6 fatty acids on proliferation and differentiation of promyelocytic leukemic HL-60 cells. *Blood* **84** 3799–3809.

Fitzgibbons PL, Henson DE & Hutter RVP 1998 Benign breast changes and risk for subsequent breast cancer: an update of the 1985 consensus statement. Cancer Committee of the College of American Pathologists. *Archives of Pathology and Laboratory Medicine* **122** 1053–1055.

Flegal KM, Carroll MD, Ogden CL & Johnson CL 2002 Prevalence and trends in obesity among US adults, 1999–2000. *Journal of the American Medical Association* **288** 1723–1727.

Fontana JA & Rishi AK 2002 Classical and novel retinoids: their targets in cancer therapy. *Leukemia* **16** 463–472.

Foster JS & Wimalasena J 1996 Estrogen regulates activity of cyclin-dependent kinases and retinoblastoma protein phosphorylation in breast cancer cells. *Molecular Endocrinology* **10** 488–498.

Freedman LS, Clifford CK & Messina M 1990 Analysis of dietary fat, calories, body weight, and the development of mammary tumors in rats and mice: a review. *Cancer Research* **50** 5710–5719.

Fu M, Wang C, Wang J, Zafonte B, Lisanti MP & Pestell RG 2002 Acetylation in hormone signaling and the cell-cycle. *Cytokine and Growth Factor Reviews* **13** 259–276.

Garland M, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Spiegelman D, Speizer F & Willett WC 1998 Menstrual cycle characteristics and history of ovulatory infertility in relation to breast cancer risk in a large cohort of US women. *American Journal of Epidemiology* **147** 636–643.

Gerhard I, Vollmar B, Runnebaum B, Klinga K, Haller U & Kubli F 1987 Weight percentile at birth: II prediction by endocrinological and sonographic measurements. *European Journal of Obstetrics, Gynecology and Reproductive Biology* **26** 313–328.

Goldin BR, Adelercreutz H, Gorbach SL & Warram JH 1982 Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. *New England Journal of Medicine* **307** 1452–1547.

Gudas JM, Nguyen H, Li T & Cowan KH 1995 Hormone-dependent regulation of BRCA1 in human breast cancer cells. *Cancer Research* **55** 4561–4565.

Gustafsson JA 1998 Therapeutic potential of selective estrogen receptor modulators. *Current Opinion in Chemical Biology* **2** 508–511.

Hamilton AS & Mack TM 2003 Puberty and genetic susceptibility to breast cancer in a case-control study in twins. *New England Journal of Medicine* **348** 2313–2322.

Hankinson SE, Willett WC, Manson JE, Colditz GA, Hunter DJ, Spiegelman D, Barbieri RL & Speizer FE 1998 Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. *Journal of the National Cancer Institute* **90** 1292–1299.

Hilakivi-Clarke L, Onojafe I & Cho E 1996*a* High-fat diet induces aggressive behavior in male mice and rats. *Life Sciences* **58** 1653–1660.

Hilakivi-Clarke L, Onojafe I, Raygada M, Cho E, Clarke R & Lippman M 1996*b* Breast cancer risk in rats fed a diet high in n-6 polyunsaturated fatty acids during pregnancy. *Journal of the National Cancer Institute* **88** 1821–1827.

Hilakivi-Clarke L, Clarke R, Onojafe I, Raygada M, Cho E & Lippman ME 1997 A maternal diet high in n-6 polyunsaturated fats alters mammary gland development,

puberty onset, and breast cancer risk among female rat offspring. *PNAS* **94** 9372–9377.

Hilakivi-Clarke L, Raygada M, Onojafe I, Cho E, Russo I, Skaar T & Clarke R 1998 Prepubertal exposure to zearalenone or genistein reduces mammary tumorigenesis. *British Journal of Cancer* **80** 1682–1688.

Hilakivi-Clarke LA, Cho E, Onojafe I, Raygada M & Clarke R 1999 Maternal exposure to genistein during pregnancy increases mammary tumorigenesis in female rat offspring. *Oncology Reports* **6** 1089–1095.

Hilakivi-Clarke L, Cabanes A, Olivo S, Kerr L, Bouker KB & Clarke R 2002*a* Do estrogens always increase breast cancer risk? *Journal of Steroid Biochemistry and Molecular Biology* **80** 163–174.

Hilakivi-Clarke L, Cho E, Cabanes A, Olivo S, DeAssis S, Helferich WG, Lippman ME & Clarke R 2002*b* Modulation of pregnancy estrogen levels by maternal dietary exposure to soy isolate or n-3 polyunsaturated fatty acid and breast cancer risk among female rat offspring. *Clinical Cancer Research* **8** 3601–3610.

Hilakivi-Clarke L, Forsen T, Eriksson JG, Luoto R, Tuomilehto J, Osmond C & Barker DJ 2001 Tallness and overweight during childhood have opposing effects on breast cancer risk. *British Journal of Cancer* **85** 1680–1684.

Hirose M, Masuda A, Ito K, Kamano K & Okuyama H 1990 Effects of dietary perilla oil, soybean oil and safflower oil on 7,12-dimethylbenz[a]anthracene (DMBA) and 1,2-dimethylhydrazine (DMH)-induced mammary gland and colon carcinogenesis in female SD rats. *Carcinogenesis* **11** 731–735.

Holmes MD, Colditz GA, Hunter DJ, Hankinson SE, Rosner B, Speizer FE & Willett WC 2003 Meat, fish and egg intake and risk of breast cancer. *International Journal of Cancer* **104** 221–227.

Hoskins K & Weber BL 1994 The biology of breast cancer. *Current Opinion in Oncology* **6** 554–559.

Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan JM, Katsoyanni K, Lubin F, Marubini E, Modan B & Rohan T 1990 Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *Journal of the National Cancer Institute* **82** 561–569.

Hsieh CY, Santell RC, Haslam SZ & Helferich WG 1998 Estrogenic effects of genistein on the growth of estrogen receptor-positive human breast cancer (MCF-7) cells *in vitro* and *in vivo*. *Cancer Research* **58** 3833–3838.

Hu X, Juneja SC, Maihle NJ & Cleary MP 2002 Leptin — a growth factor in normal and malignant breast cells and for normal mammary gland development. *Journal of the National Cancer Institute* **94** 1704–1711.

Huang L & Li C 2000 Leptin: a multifunctional hormone. *Cell Research* **10** 81–92.

Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, Hennekens CH, Rosner B, Speizer FE & Willett WC 1997 Dual effects of weight and weight gain on breast cancer risk. *Journal of the American Medical Association* **278** 1407–1411.

Hull KL & Harvey S 2002 GH as a co-gonadotropin: the relevance of correlative changes in GH secretion and reproductive state. *Journal of Endocrinology* **172** 1–19.

Imanishi Y, Hosokawa Y, Yoshimoto K, Schipani E, Mallya S, Papanikolaou A, Kifor O, Tokura T, Sablosky M, Ledgard F, Gronowicz G, Wang TC, Schmidt EV, Hall C, Brown EM, Bronson R & Arnold A 2001 Primary hyperparathyroidism caused by parathyroid-targeted overexpression of cyclin D1 in transgenic mice. *Journal of Clinical Investigation* **107** 1093–1102.

Jarvinen R, Knekt P, Seppanen R & Teppo L 1997 Diet and breast cancer risk in a cohort of Finnish women. *Cancer Letters* **114** 251–253.

Jefferson WN, Couse JF, Padilla-Banks E, Korach KS & Newbold RR 2002 Neonatal exposure to genistein induces estrogen receptor (ER)alpha expression and multioocyte follicles in the maturing mouse ovary: evidence for ERbeta-mediated and nonestrogenic actions. *Biology of Reproduction* **67** 1285–1296.

Jiang W, Zhu Z & Thompson HJ 2003 Effect of energy restriction on cell cycle machinery in 1-methyl-1-nitrosourea-induced mammary carcinomas in rats. *Cancer Research* **63** 1228–1234.

Johns A, Freay AD, Fraser W, Korach KS & Rubanyi GM 1996 Disruption of estrogen receptor gene prevents 17 beta estradiol-induced angiogenesis in transgenic mice. *Endocrinology* **137** 4511–4513.

Jordan VC 1998 Designer estrogens. *Scientific American* **279** 60–67.

Jordan VC & Morrow M 1999 Tamoxifen, raloxifene, and the prevention of breast cancer. *Endocrine Reviews* **20** 253–278.

Ju YH, Allred CD, Allred KF, Karko KL, Doerge DR & Helferich WG 2001 Physiological concentrations of dietary genistein dose-dependently stimulate growth of estrogen-dependent human breast cancer (MCF-7) tumors implanted in athymic nude mice. *Journal of Nutrition* **131** 2957–2962.

Ju YH, Doerge DR, Allred KF, Allred CD & Helferich WG 2002 Dietary genistein negates the inhibitory effect of tamoxifen on growth of estrogen-dependent human breast cancer (MCF-7) cells implanted in athymic mice. *Cancer Research* **62** 2474–2477.

Kabuto M, Akiba S, Stevens R, Neriishi K & Land CE 2000 A prospective study of estradiol and breast cancer in Japanese women. *Cancer Epidemiology, Biomarkers and Prevention* **9** 575–579.

Kadowaki T, Hara K, Yamauchi T, Terauchi Y, Tobe K & Nagai R 2003 Molecular mechanism of insulin resistance and obesity. *Experimental Biology and Medicine (Maywood)* **228** 1111–1117.

Karmali RA, March J & Fuchs C 1984 Effect of omega-3 fatty acids on growth of a rat mammary tumor. *Journal of the National Cancer Institute* **73** 457–461.

Kenny FS, Hui R, Musgrove EA, Gee JM, Blamey RW, Nicholson RI, Sutherland RL & Robertson JF 1999 Overexpression of cyclin D1 messenger RNA predicts for poor prognosis in estrogen receptor-positive breast cancer. *Clinical Cancer Research* **5** 2069–2076.

Kim H, Peterson TG & Barnes S 1998 Mechanisms of action of the soy isoflavone genistein: emerging role for its effects via transforming growth factor beta signaling pathways. *American Journal of Clinical Nutrition* **68** (Suppl) 1418S–1425S.

Kinnunen T, Luoto R, Hemminki E, Gissler M & Hilakivi-Clarke L 2004 Pregnancy weight gain and breast cancer risk. (In Press).

Klein V, Chajes V, Germain E, Schulgen G, Pinault M, Malvy D, Lefrancq T, Fignon A, Le Floch O, Lhuillery C & Bougnoux P 2001 Low alpha-linolenic acid content of adipose breast tissue is associated with an increased risk of breast cancer. *European Journal of Cancer* **36** 335–340.

Koeffler HP 2003 Peroxisome proliferator-activated receptor gamma and cancers. *Clinical Cancer Research* **9** 1–9.

Korach KS 1994 Insights from the study of animals lacking functional estrogen receptor. *Science* **266** 1524–1527.

Korach KS, Couse JF, Curtis SW, Washburn TF, Lindzy J, Kimbro KS, Eddy EM, Migliaccio S, Snedeker SM, Lubahn DB, Schomberg DW & Smith EP 1996 Estrogen receptor gene disruption: molecular characterization and experimental and clinical phenotypes. *Recent Progress in Hormone Research* **51** 159–186.

Kroll TG, Sarraf P, Pecciarini L, Chen CJ, Mueller E, Spiegelman BM & Fletcher JA 2000 PAX8-PPARgamma1 fusion oncogene in human thyroid carcinoma (corrected). *Science* **289** 1357–1360.

Kuiper GGJM, Carlsson B, Grandien K, Enmark E, Haggblad J, Nilsson S & Gustafsson JA 1997 Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. *Endocrinology* **138** 863–870.

Kushi LH, Fee RM, Sellers TA, Zheng W & Folsom AR 1996 Intake of vitamins A, C, and E and postmenopausal breast cancer. The Iowa Women's Health Study. *American Journal of Epidemiology* **144** 165–174.

Lamb J, Ramaswamy S, Ford HL, Contreras B, Martinez RV, Kittrell FS, Zahnow CA, Patterson N, Golub TR & Ewen ME 2003 A Mechanism of cyclin D1 action encoded in the patterns of gene expression in human cancer. *Cell* **114** 323–334.

Lampe JW 2003 Isofavonoid and lignan phytoestrogens as dietary biomarkers. *Journal of Nutrition* **133** (Suppl 3) 956S–964S.

Lee IM, Blair SN, Allison DB, Folsom AR, Harris TB, Manson JE & Wing RR 2001 Epidemiologic data on the relationships of caloric intake, energy balance, and weight gain over the life span with longevity and morbidity. *Journals of Gerontology* Series A, *Biological Sciences and Medical Sciences* **56** 7–19.

Le Marchand L, Kolonel LN, Earle ME & Ming-Pi MI 1988 Body size at different periods of life and breast cancer risk. *American Journal of Epidemiology* **128** 137–152.

Leung BS & Potter AH 1987 Mode of estrogen action on cell proliferation in CAMA-1 cells: II. Sensitivity of G1 phase population. *Journal of Cellular Biochemistry* **34** 213–225.

Levine L 2001 Stimulated release of arachidonic acid by agonists of the peroxisome proliferator-activated receptor and retinoic acid receptors. *Prostaglandins Leukotrienes and Essential Fatty Acids* **65** 229–232.

Lin S-Y, Xia W, Wang JC, Kwong KY, Spohn B, Wen Y, Pestell RG & Hung M-C 2000 Beta-catenin, a novel prognostic marker for breast cancer: its role in cyclin D1 expression and cancer progression. *PNAS* **97** 4262–4266.

Lippman M & Bolan G 1975 Oestrogen-responsive human breast cancer in long term tissue culture. *Nature* **256** 592–593.

Lippman M, Bolan G & Huff K 1976 The effects of estrogens and antiestrogens on hormone responsive human breast cancer in long term tissue culture. *Cancer Research* **36** 4595–4601.

Liu MM, Albanese C, Anderson CM, Hilty K, Webb P, Uht RM, Price RH Jr, Pestell RG & Kushner PJ 2002 Opposing action of estrogen receptors alpha and beta on cyclin D1 gene expression. *Journal of Biological Chemistry* **277** 24353–24360.

Lukas J, Bartkova J & Bartek J 1996 Convergence of mitogenic signalling cascades from diverse classes of receptors at the cyclin D-cyclin dependent kinase-pRb-controlled G1 checkpoint. *Molecular and Cellular Biology* **16** 6917–6925.

Luo J & Miller MW 2000 Ethanol enhances erbB-mediated migration of human breast cancer cells in culture. *Breast Cancer Research and Treatment* **63** 61–69.

McCormack VA, dos Santos Silva I, De Stavola BL, Perry N, Vinnicombe S, Swerdlow AJ, Hardy R & Kuh D 2003 Life-course body size and perimenopausal mammographic parenchymal patterns in the MRC 1946 British birth cohort. *British Journal of Cancer* **89** 852–859.

MacMahon B, Cole P, Lin TM, Lowe CR, Mirra AP, Ravnihar B, Salber EJ, Valaoras VG & Yuasa S 1970 Age at first birth and breast cancer. *Bulletin of the World Health Organization* **43** 209–221.

McMichael-Phillips DF, Harding C, Morton M, Robert SA, Howell A, Potten CS & Bundred NJ 1998 Effects of soy-protein supplementation on epithelial proliferation in the histologically normal human breast. *American Journal of Clinical Nutrition* **68** 1431S–1436S.

Maggiolini M, Donze O, Jeannin E, Ando S & Picard D 1999 Adrenal androgens stimulate the proliferation of breast cancer cells as direct activators of estrogen receptor alpha. *Cancer Research* **59** 4864–4869.

Magnusson C, Baron J, Persson I, Wolk A, Bergstrom R, Trichopoulos D & Adami HO 1998 Body size in different periods of life and breast cancer risk in post-menopausal women. *International Journal of Cancer* **76** 29–34.

Mangelsdorf DJ, Kliewer SA, Kakizuka A, Umesono K & Evans RM 1993 Retinoid receptors. *Recent Progress in Hormone Research* **48** 99–121.

Marquis ST, Rajan JV, Wynshaw-Boris A, Xu J, Yin GY, Abel KJ, Weber BL & Chodosh LA 1995 The developmental pattern of Brca1 expression implies a role in differentiation of the breast and other tissues. *Nature Genetics* **11** 17–26.

Marttunen MB, Andersson S, Hietanen P, Karonen SL, Koistinen HA, Koivisto VA, Tiitinen A & Ylikorkala O 2000 Antiestrogenic tamoxifen and toremifene increase serum leptin levels in postmenopausal breast cancer patients. *Maturitas* **35** 175–179.

Mellemkjaer L, Emborg C, Gridley G, Munk-Jorgensen P, Johansen C, Tjonneland A, Kjaer SK & Olsen JH 2001 Anorexia nervosa and cancer risk. *Cancer Causes and Control* **12** 173–177.

Merry BJ 2002 Molecular mechanisms linking calorie restriction and longevity. *International Journal of Biochemistry and Cellular Biology* **34** 1340–1354.

Messina M 1999 Soy, soy phytoestrogens (isoflavones), and breast cancer. *American Journal of Clinical Nutrition* **70** 574–575.

Metz RP, Kaeck M, Stacewicz-Sapuntzakis M, Mitrenga T, McCarty H & Schedin P 2002 Adolescent vitamin A intake alters susceptibility to mammary carcinogenesis in the Sprague–Dawley rat. *Nutrition and Cancer* **42** 78–90.

Mezei O, Banz WJ, Steger RW, Peluso MR, Winters TA & Shay N 2003 Soy isoflavones exert antidiabetic and hypolipidemic effects through the PPAR pathways in obese Zucker rats and murine RAW 264.7 cells. *Journal of Nutrition* **133** 1238–1243.

Michels KB, Trichopoulos D, Robins JM, Rosner BA, Manson JE, Hunter D, Colditz GA, Hankinson SE, Speizer FE & Willett WC 1996 Birthweight as a risk factor for breast cancer. *Lancet* **348** 1542–1546.

Michels KB, Holmberg L, Bergkvist L, Ljung H, Bruce A & Wolk A 2001 Dietary antioxidant vitamins, retinol, and breast cancer incidence in a cohort of Swedish women. *International Journal of Cancer* **91** 563–567.

Michels KB, Solomon CG, Hu FB, Rosner BA, Hankinson SE, Colditz GA & Manson JE 2003 Type 2 diabetes and subsequent incidence of breast cancer in the Nurses' Health Study. *Diabetes Care* **26** 1752–1758.

Migliaccio A, DiDomenico M, Castoria G, deFalco A, Bontempo P, Nola E & Auricchio F 1996 Tyrosine kinase/p21ras/MAP-kinase pathway activation by estradiol-receptor complex in MCF-7 cells. *EMBO Journal* **15** 1292–1300.

Miyoshi Y, Funahashi T, Kihara S, Taguchi T, Tamaki Y, Matsuzawa Y & Noguchi S 2003 Association of serum adiponectin levels with breast cancer risk. *Clinical Cancer Research* **9** 5699–5704.

Motokura T, Bloom T, Kim HG, Jüppner H, Ruderman JV, Kronenberg HM & Arnold A 1991 A novel cyclin encoded by a *bcl1*-linked candidate oncogene. *Nature* **350** 512–515.

Mu YM, Yanase T, Nishi Y, Takayanagi R, Goto K & Nawata H 2001 Combined treatment with specific ligands for PPARgamma:RXR nuclear receptor system markedly inhibits the expression of cytochrome P450arom in human granulosa cancer cells. *Molecular and Cellular Endocrinology* **181** 239–248.

Mueller E, Sarraf P, Tontonoz P, Evans RM, Martin KJ, Zhang M, Fletcher C, Singer S & Spiegelman BM 1998 Terminal differentiation of human breast cancer through PPARγ. *Molecular Cell* **1** 465–470.

Mukherjee R, Davies PJ, Crombie DL, Bischoff ED, Cesario RM, Jow L, Hamann LG, Boehm MF, Mondon CE, Nadzan AM, Paterniti JR Jr & Heyman RA 1997 Sensitization of diabetic and obese mice to insulin by retinoid X receptor agonists. *Nature* **386** 407–410.

Muller P, Kietz S, Gustafsson JA & Strom A 2002 The anti-estrogenic effect of all-trans-retinoic acid on the breast cancer cell line MCF-7 is dependent on HES-1 expression. *Journal of Biological Chemistry* **277** 28376–28379.

Murrill WB, Brown NM, Zhang JX, Manzolillo PA, Barnes S & Lamartiniere CA 1996 Prepubertal genistein exposure suppresses mammary cancer and enhances gland differentiation in rats. *Carcinogenesis* **17** 1451–1457.

Musgrove EA, Sarcevic B & Sutherland RL 1996 Inducible expression of cyclin D1 in T-47D human breast cancer cells is sufficient for Cdk2 activation and pRB hyperphosphorylation. *Journal of Cellular Biochemistry* **60** 363–378.

Najid A & Habrioux G 1990 Biological effects of adrenal androgens on MCF-7 and BT-20 human breast cancer cells. *Oncology* **47** 269–274.

Neuman E, Ladha MH, Lin N, Upton TM, Miller SJ, DiRenzo J, Pestell RG, Hinds PW, Dowdy SF, Brown M & Ewen ME 1997 Cyclin D1 stimulation of estrogen receptor transcriptional activity independent of cdk4. *Molecular and Cellular Biology* **17** 5338–5347.

Niho N, Takahashi M, Kitamura T, Shoji Y, Itoh M, Noda T, Sugimura T & Wakabayashi K 2003 Concomitant suppression of hyperlipidemia and intestinal polyp formation in Apc-deficient mice by peroxisome proliferator-activated receptor ligands. *Cancer Research* **63** 6090–6095.

Nishiwaki E, Turner SL, Harju S, Miyazaki S, Kashiwagi M, Koh J & Serizawa H 2000 Regulation of CDK7-carboxyl-terminal domain kinase activity by the tumor suppressor p16(INK4A) contributes to cell cycle regulation. *Molecular and Cellular Biology* **20** 7726–7734.

Okumura M, Yamamoto M, Sakuma H, Kojima T, Maruyama T, Jamali M, Cooper DR & Yasuda K 2002 Leptin and high glucose stimulate cell proliferation in MCF-7 human breast cancer cells: reciprocal involvement of PKC-alpha and PPAR expression. *Biochimica et Biophysica Acta* **1592** 107–116.

Oza AM & Boyd NF 1993 Mammographic parenchymal patterns: a marker of breast cancer risk. *Epidemiological Reviews* **15** 196–208.

Ozet A, Arpaci F, Yilmaz MI, Ayta H, Ozturk B, Komurcu S, Yavuz AA, Tezcan Y & Acikel C 2001 Effects of tamoxifen on the serum leptin level in patients with breast cancer. *Japanese Journal of Clinical Oncology* **31** 424–427.

Palakurthi SS, Fluckiger R, Aktas H, Changolkar AK, Shahsafaei A, Harneit S, Kilic E & Halperin JA 2000 Inhibition of translation initiation mediates the anticancer effect of the n-3 polyunsaturated fatty acid eicosapentaenoic acid. *Cancer Research* **60** 2919–2925.

Peck JD, Hulka BS, Poole C, Savitz DA, Baird D & Richardson BE 2002 Steroid hormone levels during pregnancy and incidence of maternal breast cancer. *Cancer Epidemiology, Biomarkers and Prevention* **11** 361–368.

Pestell RG, Albanese C, Reutens AT, Lee RJ, Segall J & Arnold A 1999 The cyclins and cyclin dependent kinase inhibitors in hormonal regulation of proliferation and differentiation. *Endocrine Reviews* **20** 501–534.

Petrakis NL, Barnes S, King EB, Lowenstein J, Wiencke J, Lee MM, Miike R, Kirk M & Coward L 1996 Stimulatory influence of soy protein isolate on breast secretion in pre- and postmenopausal women. *Cancer Epidemiology, Biomarkers and Prevention* **5** 785–794.

Planas-Silva MD & Weinberg RA 1997 Estrogen-dependent cyclin E-cdk2 activation through p21 redistribution. *Molecular and Cellular Biology* **17** 4059–4069.

Potischman N & Troisi R 1999 *In utero* and early life exposures in relation to risk of breast cancer. *Cancer Causes and Control* **10** 561–573.

Potischman N, Swanson CA, Siiteri P & Hoover RN 1996 Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. *Journal of the National Cancer Institute* **88** 756–758.

Poulin R & Labrie F 1986 Stimulation of cell proliferation and estrogenic response by adrenal C19-delta 5-steroids in the ZR-75-71 human breast cancer cell line. *Cancer Research* **46** 4933–4937.

Prall OWJ, Sarcevic B, Musgrove EA, Watts CKW & Sutherland RL 1997 Estrogen-induced activation of Cdk4 and Cdk2 during G1-S phase progression is accompanied by increased cyclin D1 expression and decreased cyclin-dependent kinase inhibitor association with cyclin E- Cdk2. *Journal of Biological Chemistry* **272** 10882–10894.

Pratt MA, Bishop TE, White D, Yasvinski G, Menard M, Niu MY & Clarke R 2003 Estrogen withdrawal-induced NF-kappaB activity and bcl-3 expression in breast cancer cells: roles in growth and hormone independence. *Molecular and Cellular Biology* **23** 6887–6900.

Razanamahefa L, Prouff S & Bardon S 2000 Stimulatory effect of arachidonic acid on T-47D human breast cancer cell growth is associated with enhancement of cyclin D1 nRNA expression. *Nutrition and Cancer* **38** 274–280.

Riboli E & Norat T 2003 Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *American Journal of Clinical Nutrition* **78** 559S–569S.

Richards JA & Brueggemeier RW 2003 Prostaglandin E2 regulates aromatase activity and expression in human adipose stromal cells via two distinct receptor subtypes. *Journal of Clinical Endocrinology and Metabolism* **88** 2810–2816.

Richardson BE, Hulka BS, Peck JL, Hughes CL, van den Berg BJ, Christianson RE & Calvin JA 1998 Levels of maternal serum alpha-fetoprotein (AFP) in pregnant women and subsequent breast cancer risk. *American Journal of Epidemiology* **48** 719–727.

Richardson S, Gerber M & Cenee S 1990 The role of fat, animal protein and some vitamin consumption in breast cancer: a case control study in southern France. *International Journal of Cancer* **48** 1–9.

Ricote M, Huang J, Fajas L, Li A, Welch J, Najib J, Witztum JL, Auwerx J, Palinski W & Glass CK 1998 Expression of the peroxisome proliferator-activated receptor gamma (PPARgamma) in human atherosclerosis and regulation in macrophages by colony stimulating factors and oxidized low density lipoprotein. *PNAS* **95** 7614–7619.

del Rincon SV, Rousseau C, Samanta R & Miller WH Jr 2003 Retinoic acid-induced growth arrest of MCF-7 cells involves the selective regulation of the IRS-1/PI 3-kinase/AKT pathway. *Oncogene* **22** 3353–3360.

Robsahm TE & Tretli S 2002 Breast cancer incidence in food- vs non-food-producing areas in Norway: possible beneficial effects of World War II. *British Journal of Cancer* **86** 362–366.

Rose DP 1997 Dietary fatty acids and cancer. *American Journal of Clinical Nutrition* **66** 998S–1003S.

Rose DP, Boyar AP, Cohen C & Strong LE 1987 Effect of a low-fat diet on hormone levels in women with cystic breast disease. *Journal of the National Cancer Institute* **78** 623–626.

Rose DP, Connolly JM, Chlebowski RT, Buzzard IM & Wynder EL 1993 The effects of a low-fat dietary intervention and tamoxifen adjuvant therapy on the serum estrogen and sex hormone-binding globulin concentrations of postmenopausal breast cancer patients. *Breast Cancer Research and Treatment* **27** 253–262.

Rose DP, Connolly JM, Rayburn J & Coleman M 1995 Influence of diets containing eicosapentaenoic or docosahexaenoic acid on growth and metastasis of breast cancer cells in nude mice. *Journal of the National Cancer Institute* **87** 587–592.

Rosen ED & Spiegelman BM 2001*a* PPARγ: a nuclear regulator of metabolism, differentiation, and cell growth. *Journal of Biological Chemistry* **276** 37731–37734.

Rosen ED & Spiegelman BM 2001*b* PPARgamma: a nuclear regulator of metabolism, differentiation, and cell growth. *Journal of Biological Chemistry* **276** 37731–37734.

Rosen EM, Fan S & Goldberg ID 2001 BRCA1 and prostate cancer. *Cancer Investigation* **19** 396–412.

Roth GS, Ingram DK, Black A & Lane MA 2000 Effects of reduced energy intake on the biology of aging: the primate model. *European Journal of Clinical Nutrition* **54** (Suppl 3) S15–S20.

Rubin GL, Zhao Y, Kalus AM & Simpson ER 2000 Peroxisome proliferator-activated receptor gamma ligands inhibit estrogen biosynthesis in human breast adipose tissue: possible implications for breast cancer therapy. *Cancer Research* **60** 1604–1608.

Rubin GL, Duong JH, Clyne CD, Speed CJ, Murata Y, Gong C & Simpson ER 2002 Ligands for the peroxisomal proliferator-activated receptor gamma and the retinoid X receptor inhibit aromatase cytochrome P450 (CYP19) expression mediated by promoter II in human breast adipose. *Endocrinology* **143** 2863–2871.

Rudolph IL, Kelley DS, Klasing KC & Erickson KL 2001 Regulation of cellular differentiation and apoptosis by fatty acids and their metabolites. *Nutrition Research* **21** 381–393.

Saceda M, Lippman ME, Chambon P, Lindsey RL, Ponglikitmongkol M, Puente M & Martin MB 1988 Regulation of the estrogen receptor in MCF-7 cells by estradiol. *Molecular Endocrinology* **2** 1157–1162.

Saez E, Tontonoz P, Nelson MC, Alvarez JG, Ming UT, Baird SM, Thomazy VA & Evans RM 1998 Activators of the nuclear receptor PPARgamma enhance colon polyp formation. *Nature Medicine* **4** 1058–1061.

Sanderson M, Williams ML, Malone KE, Stanford JL, Emanuel I, White E & Daling J 1996 Perinatal factors and risk of breast cancer. *Epidemiology* **7** 34–37.

Sarraf P, Mueller E, Smith WM, Wright HM, Kum JB, Aaltonen LA, de la Chapelle A, Spiegelman BM & Eng C 1999 Loss-of-function mutations in PPAR gamma associated with human colon cancer. *Molecular Cell* **3** 799–804.

Satagopan JM, Offit K, Foulkes W, Robson ME, Wacholder S, Eng CM, Karp SE & Begg CB 2001 The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiology, Biomarkers and Prevention* **10** 467–473.

Seewaldt VL, Kim JH, Caldwell LE, Johnson BS, Swisshelm K & Collins SJ 1997 All-trans-retinoic acid mediates G1 arrest but not apoptosis of normal human mammary epithelial cells. *Cell Growth and Differentiation* **8** 631–641.

Seewaldt VL, Dietze EC, Johnson BS, Collins SJ & Parker MB 1999 Retinoic acid-mediated G1-S-phase arrest of normal human mammary epithelial cells is independent of the level of p53 protein expression. *Cell Growth and Differentiation* **10** 49–59.

Shaag Y, Jin F, Dai Q, Wen W, Potter JD, Kushi LH, Ruan Z, Gao YT & Zheng W 2001 Soyfood intake during adolescence and subsequent risk of breast cancer among Chinese women. *Cancer Epidemiology, Biomarkers and Prevention* **10** 483–488.

Sherr CJ & Roberts JM 1999 CDK inhibitors:positive and negative regulators of G1-phase progression. *Genes and Development* **13** 1501–1512.

Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Miller AB, Potter JD, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A & Hunter DJ 2001 Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. *Journal of the American Medical Association* **285** 769–776.

Sparano JA & Winer EP 2001 Liposomal anthracyclines for breast cancer. *Seminars in Oncology* **28** 32–40.

Spillman M & Bowcock A 1996 BRCA1 and BRCA2 nRNA levels are coordinately elevated in human breast cancer cells in response to estrogen. *Oncogene* **13** 1639–1645.

Stanley ER, Palmer RE & Sohn U 1977 Development of methods for the quantitative *in vitro* analysis of androgen-dependent and autonomous Shionogi carcinoma 115 cells. *Cell* **10** 35–44.

Stefan N, Bunt JC, Salbe AD, Funahashi T, Matsuzawa Y & Tataranni PA 2002 Plasma adiponectin concentrations in children: relationships with obesity and insulinemia. *Journal of Clinical Endocrinology and Metabolism* **87** 4652–4656.

Stripp C, Overvad K, Christensen J, Thomsen BL, Olsen A, Moller S & Tjonneland A 2003 Fish intake is positively associated with breast cancer incidence rate. *Journal of Nutrition* **133** 3664–3669.

Suga K, Imai K, Eguchi H, Hayashi S, Higashi Y & Nakachi K 2001 Molecular significance of excess body weight in postmenopausal breast cancer patients, in relation to expression of insulin-like growth factor I receptor and insulin-like growth factor II genes. *Japanese Journal of Cancer Research* **92** 127–134.

Suh N, Wang Y, Williams CR, Risingsong R, Gilmer T, Willson TM & Sporn MB 1999 A new ligand for the peroxisome proliferator-activated receptor-gamma (PPAR-gamma), GW7845, inhibits rat mammary carcinogenesis. *Cancer Research* **59** 5671–5673.

Swerdlow AJ, De Stavola BL, Floderus B, Holm NV, Kaprio J, Verkasalo PK & Mack T 2002 Risk factors for breast cancer at young ages in twins: an international population-based study. *Journal of the National Cancer Institute* **94** 1238–1246.

Tessitore L, Vizio B, Jenkins O, De Stefano I, Ritossa C, Argiles JM, Benedetto C & Mussa A 2000 Leptin expression in colorectal and breast cancer patients. *International Journal of Molecular Medicine* **5** 421–426.

Thoennes SR, Tate PL, Price TM & Kilgore MW 2000 Differential transcriptional activation of peroxisome proliferator-activated receptor gamma by omega-3 and omega-6 fatty acids in MCF-7 cells. *Molecular and Cellular Endocrinology* **160** 67–73.

Thompson HJ, Jiang W & Zhu Z 1999 Mechanisms by which energy restriction inhibits carcinogenesis. *Advances In Experimental Medicine and Biology* **470** 77–84.

Toniolo PG, Levitz M, Zeleniuh-Jacquette A, Banerjee S, Koenig KL & Shore RE 1995 A prospective study of endogenous estrogens and breast cancer in postmenopausal women. *Journal of the National Cancer Institute* **87** 190–197.

Toniolo P, Van Kappel AL, Akhmedkhanov A, Ferrari P, Kato I, Shore RE & Riboli E 2001 Serum carotenoids and breast cancer. *American Journal of Epidemiology* **153** 1142–1147.

Trentham-Dietz A, Newcomb PA, Storer BE, Longnecker MP, Baron J, Greenberg ER & Willett WC 1997 Body size and risk of breast cancer. *American Journal of Epidemiology* **145** 1011–1019.

Trichopoulos D 1990 Hypothesis: does breast cancer originate *in utero*? *Lancet* **355** 939–940.

Trichopoulos D, Polychronopoulou A, Brown J & MacMahon B 1983 Obesity, serum cholesterol, and estrogens in premenopausal women. *Oncology* **40** 227–231.

Trock B, Butler LW, Clarke R & Hilakivi-Clarke L 2001 Meta-analysis of soy intake and breast cancer risk. *Journal of Nutrition* **130** 690–691.

Van't Veer P, Kok FJ, Brants HAM, Ockhuizen T, Stumans F & Hermus RJJ 1990 Dietary fat and the risk of breast cancer. *International Journal of Cancer* **49** 12–18.

Verhoeven DT, Assen N, Goldbohm RA, Dorant E, van' V, Sturmans F, Hermus RJ & van den Brandt PA 1997 Vitamins C and E, retinol, beta-carotene and dietary fibre in relation to breast cancer risk: a prospective cohort study. *British Journal of Cancer* **75** 149–155.

Walker BE 1990 Tumors in female offspring of control and diethylstilbestrol-exposed mice fed high fat diets. *Journal of the National Cancer Institute* **82** 50–54.

Wang C, Fu M, D'Amico M, Albanese C, Zhou JN, Brownlee M, Lisanti MP, Chatterjee VK, Lazar MA & Pestell RG 2001 Inhibition of cellular proliferation through IkappaB kinase-independent and peroxisome proliferator-activated receptor gamma-dependent repression of cyclin D1. *Molecular and Cellular Biology* **21** 3057–3070.

Wang C, Li Z, Fu M, Bouras T & Pestell RG 2003*a* Signal transduction mediated by cyclin D1: from mitogens to cell proliferation: A molecular target with therapeutic potential, edn, pp 217–237 Ed. R Kumar. Dordrecht: Kluwer Academic Publisher.

Wang C, Pattabiraman N, Fu M, Zhou JN, Sakamaki T, Albanese C, Li Z, Wu K, Hulit J, Neumeister P, Novikoff PM, Brownlee M, Scherer P, Jones JG, Whitney KD, Donehower LA, Harris EL, Rohan T, Johns DC & Pestell RG 2003*b* Cyclin D1 repression of peroxisome proliferator-activated receptor gamma (PPARgamma) expression and transactivation. *Molecular and Cellular Biology* **23** 6159–6173.

Wang TT, Sathyamoorthy N & Phang JM 1996 Molecular effects of genistein on estrogen receptor mediated pathways. *Carcinogenesis* **17** 271–275.

Weinberg RA 1995 The retinoblastoma protein and cell cycle control. *Cell* **81** 323–330.

Welsch CW 1987 Enhancement of mammary tumorigenesis by dietary fat: review of potential mechanisms. *American Journal of Clinical Nutrition* **45** 192–202.

Welsch CW 1992 Relationship between dietary fat and experimental mammary tumorigenesis: a review and critique. *Cancer Research* **52** 2040–2048.

Welcsh PL, Lee MK, Gonzalez-Hernandez RM, Black DJ, Mahadevappa M, Swisher EM, Warrington JA & King MC 2002 BRCA1 transcriptionally regulates genes involved in breast tumorigenesis. *PNAS* **99** 7560–7565.

Willett WC 1997 Specific fatty acids and risks of breast and prostate cancer: dietary intake. *American Journal of Clinical Nutrition* **66** 1557S–1563S.

Willett WC 2001 Diet and breast cancer. *Journal of Internal Medicine* **249** 395–411.

Willett WC & Hunter DJ 1994 Prospective studies of diet and breast cancer. *Cancer* **74** 1085–1089.

Willett WC, Hunter DJ, Stampfer MJ, Colditz G, Manson JE, Spiegelman D, Rosner B, Hennekens CH & Speizer FE 1992 Dietary fat and fiber in relation to risk of breast cancer. *Journal of the American Medical Association* **268** 2037–2044.

Wu AH, Pike MC & Stram DO 1999 Meta-analysis: dietary fat intake, serum estrogen levels, and the risk of breast cancer. *Journal of the National Cancer Institute* **91** 529–534.

Wu AH, Wan P, Hankin J, Tseng CC, Yu MC & Pike MC 2002 Adolescent and adult soy intake and risk of breast cancer in Asian-Americans. *Carcinogenesis* **23** 1491–1496.

Xu X, Wang HJ, Murphy PA, Cook L & Hendrich S 1994 Daidzein is a more bioavailable soymilk isoflavone than is genistein in adult women. *Journal of Nutrition* **24** 825–832.

Zafonte BT, Hulit J, Amanatullah DF, Albanese C, Wang C, Rosen E, Reutens A, Sparano JA, Lisanti MP & Pestell RG 2000 Cell-cycle dysregulation in breast cancer: breast cancer therapies targeting the cell cycle. *Frontiers in Bioscience: A Journal and Virtual Library* **5** D938–D961.

Zava DT & Duwe G 1997 Estrogenic and antiproliferative properties of genistein and other flavonoids in human breast cancer cells *in vitro*. *Nutrition and Cancer* **27** 31–40.

Zhang S, Hunter DJ, Forman MR, Rosner BA, Speizer FE, Colditz GA, Manson JE, Hankinson SE & Willett WC 1999 Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. *Journal of the National Cancer Institute* **91** 547–556.

Zhu Z, Jiang W & Thompson HJ 2002 An experimental paradigm for studying the cellular and molecular mechanisms of cancer inhibition by energy restriction. *Molecular Carcinogenesis* **35** 51–56.

Zhu Z, Jiang W & Thompson HJ 2003 Mechanisms by which energy restriction inhibits rat mammary carcinogenesis: *in vivo* effects of corticosterone on cell cycle machinery in mammary carcinomas. *Carcinogenesis* **24** 1225–1231.

Zwijsen RML, Wientjens E, Klompmaker R, van der Sman J, Bernards R & Michalides RJAM 1997 CDK-independent activation of estrogen receptor by cyclin D1. *Cell* **88** 405–415.