

# **Nutrition and Cancer Prevention: Targets, Strategies, and the Importance of Early Life Interventions**

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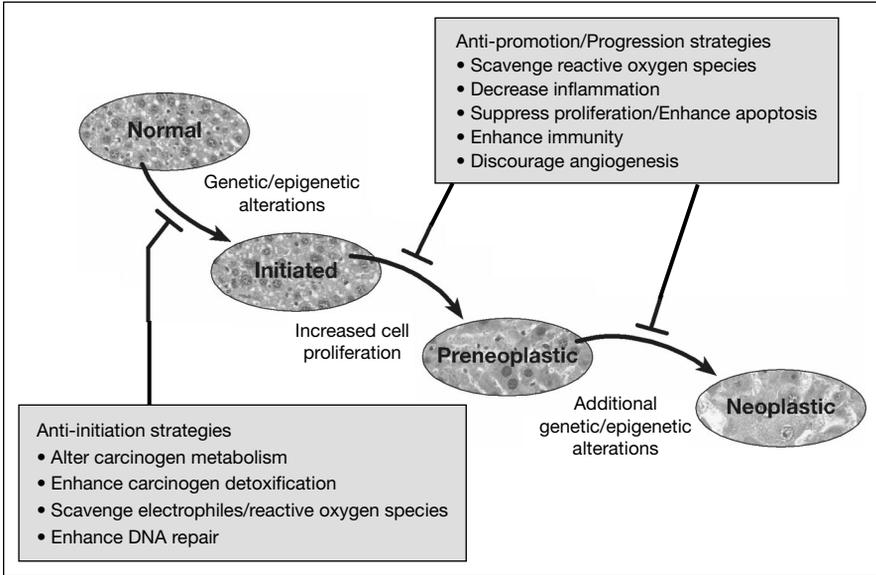
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## **Introduction**

More than one million Americans will be diagnosed with cancer in 2005. This is especially tragic given that many cancers are preventable. Doll and Peto [1] estimated in 1981 that 30% of cancers were due to tobacco use while 35% could be attributed to poor dietary practices, and there is mounting evidence that diet-related conditions, such as obesity, can also greatly influence cancer risk [2]. Some significant progress in tobacco control in the United States has been made since the 1964 Surgeon General's Report on Smoking and Health identified cigarette smoking as the cause of lung cancer [3]. Smoking cessation at the individual level, as well as several effective community-based interventions, including regulations to restrict smoking in public places and tobacco product advertising to adolescents and children, have led to declines in tobacco use and lung cancer rates [4]. However, the development and application of diet-related strategies for cancer prevention remain an ongoing challenge to the medical, scientific and public health communities.

Adding to this challenge is the recent recognition of the role of perinatal and childhood nutritional exposures in cancer development across the life course. The established role of perinatal nutrition in neurological development and the relation of maternal and perinatal nutritional status to birth weight and subsequent risk of hypertension, diabetes and cardiovascular disease identify pregnancy and early childhood as critical windows for nutritional interventions to prevent these diseases. The influence of early life dietary exposures on carcinogenesis has been less studied, but evidence



**Fig. 1.** Multi-step carcinogenesis pathway. A schematic presentation of the multi-stage process of carcinogenesis as well as stage-specific prevention strategies. The initiation stage is characterized by the conversion of a normal cell to an initiated cell in response to genetic or epigenetic changes in the cell's DNA. The conversion of an initiated cell to a preneoplastic population of cells and ultimately to a tumor is determined by additional genetic/epigenetic changes that effect the balance between growth and death in these cells. Strategies to intervene in these processes, using nutritional or other preventive strategies to decrease rates of mutation and epigenetic change and maintain the growth/death balance in cancer cells, are listed.

from human and animal studies suggest that nutrition during early time points along the life course can also have a major impact on cancer risk later in life.

It is beyond the scope of this paper to comprehensively review the field of diet and carcinogenesis. Rather, the objective of this review is to use our current knowledge about carcinogenesis to suggest opportunities for nutritional interventions, including during infancy and childhood. In the following sections, each of the potential targets for the nutritional modulation of cancer depicted in figure 1 will be examined, and examples of how these carcinogenesis-associated processes can be modulated will be presented. In addition, a brief discussion is included of the literature on early life exposures and the risk of breast cancer, the best studied cancer to date regarding nutritional effects across the life course. The information sources for this review

include the MEDLINE (from January 1, 1993 through January 1, 2004) and CANCERLIT (from January 1, 1983 through January 1, 2004) databases, which were searched with the key words 'carcinogenesis'; 'nutrition and neoplasms'; and 'diet and neoplasms'. For the early life nutritional exposure and breast cancer section, subject search terms included breast cancer risk or incidence and the following: 'in utero', fetal, preeclampsia, birth weight, birth length, preterm, breast or infant feeding, infancy, childhood, puberty, adolescence, (catch-up) growth, age at menarche, maternal and paternal age, birth order or parity, intergenerational, and programming. Reviews, editorials and primary journal articles identified by this search, along with chapters from textbooks on cancer etiology and prevention available at the National Institutes of Health Medical Library, were used to summarize our current knowledge of carcinogenesis and the effects of nutritional factors on that process.

### **Multistage Carcinogenesis: Pathways and Targets for Nutritional Intervention**

Humans are exposed to a wide variety of endogenous and exogenous carcinogenic insults, including chemicals, radiation, physical agents, bacteria and viruses. Recent progress in the study of the multi-step process of carcinogenesis, particularly on the mechanisms of chemically and virally induced cancer, has revealed several points along the carcinogenesis pathway that may be amenable to cancer prevention strategies [5]. The classic view of experimental carcinogenesis, in which tumor initiation is followed by tumor promotion and progression in a sequential fashion, has undergone significant revision as our understanding of cancer-related genes and the biosystem has evolved [6–8]. However, the concepts and underlying processes of initiation, promotion, and progression remain theoretically important. Tumor initiation begins in cells with DNA alterations resulting from inherent genetic mutations or, more commonly, from spontaneous or carcinogen-induced genetic or epigenetic changes. Alterations in specific genes modify the responsiveness of the initiated cell to its microenvironment, eventually providing a growth advantage relative to normal cells [6]. The tumor promotion stage is characterized by clonal expansion of initiated cells due to alterations in the expression of genes whose products are associated with hyperproliferation, apoptosis, tissue remodeling and inflammation [7]. During the tumor progression stage, preneoplastic cells develop into invasive tumors through further clonal expansion, usually associated with alterations in gene expression and additional genetic damage due to progressive genomic instability [9].

As depicted in figure 1, possible ways of interfering with tumor initiation events include: (1) modifying carcinogen activation by inhibiting the enzymes responsible for that activation or by directly scavenging DNA-reactive electrophiles and free radicals; (2) enhancing carcinogen detoxification by

altering the activity of detoxifying enzymes, and (3) modulating certain DNA repair processes. Possible ways of blocking the processes involved in the promotion and progression stages of carcinogenesis include: (1) scavenging reactive oxygen species (ROS); (2) altering the expression of genes involved in cell signaling, particularly those regulating cell proliferation, apoptosis, and differentiation; (3) decreasing inflammation; (4) enhancing immune function, or (5) suppressing angiogenesis.

In 1976, Sporn [10] defined the term chemoprevention as the use of natural or synthetic agents to reverse or suppress multistage carcinogenesis. There are numerous examples in the literature demonstrating that bioactive food components or chemopreventive nutrients can influence one or more of these targets and interfere with the carcinogenesis process, and specific examples will be discussed later in this review. We now appreciate that the nature of initiation, promotion and progression events is complex. For instance, we know from the work of Fearon and Vogelstein [11] and Spitz and Bondy [12] that multiple mutational and epigenetic events are involved in the formation of cancers. Furthermore, humans are generally exposed to mixtures of agents that can simultaneously act at different stages of the carcinogenesis process. Thus, rather than three discrete stages occurring in a predictable order, human carcinogenesis is best characterized as an accumulation of alterations in genes regulating cellular growth, death, and malignant properties. These alternations occur through a series of clonal selections influenced by endogenous and exogenous factors. Concomitant epigenetic instabilities often develop in a cancer and may significantly contribute to tumorigenesis [13]. Nonetheless, the processes involved in cancer initiation, promotion and progression described above remain important and relevant targets for cancer prevention. Nutritional interventions that increase or decrease rates of mutation, rates of epigenetic change, or the balance between growth and death in cancer cells can significantly influence the ultimate development of cancer.

## **Targets for Anti-Initiation Strategies**

### *Carcinogen Activation*

Most chemicals are not carcinogenic, but a wide variety of chemicals and chemical classes can cause cancer in animals and humans. Most chemical carcinogens are genotoxic, causing DNA damage by reacting with DNA bases. The carcinogens form covalent adducts with DNA in the nucleus and mitochondria. Endogenous carcinogens, which are often ROS generated as part of normal oxidative metabolism or as a result of xenobiotic metabolism, as well as ultraviolet radiation and gamma radiation, can also cause extensive DNA damage. For instance, proto-oncogenes and tumor suppressor genes are normal cellular genes that can be mutated to cause uncontrolled cell growth or other characteristics that increase the probability of neoplastic transformation [11–16].

Metabolic activation of procarcinogens (i.e., carcinogens requiring enzymatic conversion to DNA-reactive intermediates) is generally catalyzed by cytochrome P450 enzymes through oxidation. More than 100 distinct mammalian P450 enzymes have been identified [17]. In addition, there are other enzyme systems involved in carcinogen activation, such as peroxidases (including the cyclooxygenases, which will be discussed in more detail below) and certain transferases such as N-acetyltransferase and sulfotransferase [18, 19]. Each of these enzymes provides a potential target for modulating carcinogen activation.

One common feature of the metabolic activation of all procarcinogens is that their ultimate DNA-reactive carcinogenic species are electrophilic [20]. In addition, many direct-acting carcinogens damage DNA through electrophilic intermediates [21]. Thus the electrophilicity of the ultimate carcinogenic species serves as a shared intervention target for most chemical carcinogens. The electrophilic metabolites may themselves be ROS and interact as such with DNA [22]. Oxygen free radicals may also be involved in a step required for activation of a procarcinogen, and thus the reactions involved in metabolic activation of carcinogens may release ROS which can in turn attack DNA [22]. Thus, directly scavenging DNA-reactive intermediates with antioxidants or other agents that can scavenge electrophiles constitutes a plausible strategy for modulating this early stage of carcinogenesis.

#### *Carcinogen Detoxification*

In addition to the carcinogen-activating enzymes, a series of enzymes (the so-called phase-II enzymes) detoxify activated carcinogens, thus preventing their binding to DNA. The induction of the glutathione S-transferases (GSTs) is an important response for the detoxification of xenobiotics [23]. This class of enzymes couples a number of diverse substrates to glutathione to excrete them from the body. GSTs are segregated into three classes based on their sequence homology and specificity for substrates [24]. Other detoxification enzymes include uridine diphosphate-glucuronosyl transferase, quinone reductase, and the epoxide hydrolases [25, 26]. The efficiency with which these and other enzymes detoxify carcinogens is a critical factor in determining the carcinogenicity of a particular xenobiotic.

#### *DNA Repair Processes*

The generation of DNA-reactive intermediates by most chemical carcinogens leads to the production of DNA adducts or other types of damage. As reviewed by Mitchell et al. [27], normal mammalian cells can efficiently remove DNA damage induced by carcinogens. Cells use different strategies to repair DNA damage, depending on the structure of the damage and its location in the genome. For example, small lesions, such as alkylated DNA bases, can be repaired by a mechanism termed base excision repair [28]. This process involves removal of the damaged base followed by a 'small cut and

patch' repair involving removal of a few nucleotides. When methylation occurs at either the O<sup>6</sup> or O<sup>4</sup> positions of guanine or thymine, the modified bases can be repaired by the direct transfer of the methyl group to a methyl transferase [29]. Bulky carcinogen-induced DNA adducts and ultraviolet light photodimers can be repaired through a 'large cut and patch' mechanism involving approximately 27–29 nucleotides that include the damaged bases; this is termed nucleotide excision repair [30]. The integrity of the genetic information is threatened not only by various environmental exposures but also by errors produced during normal DNA replication, for example, non-Watson-Crick base-pairing and slippage during DNA replication. Cells have also developed a mismatch repair mechanism to correct the errors resulting from mis-replication [31].

### **Nutritional Modulation of Tumor Initiation Processes: Examples**

#### *Inhibiting Carcinogen Activation*

Fruits, vegetables, herbs and other foodstuffs, as well as non-edible plants, contain numerous bioactive food components known to affect the metabolic activation of chemical carcinogens. Examples of food sources containing agents that decrease carcinogen activation are the cruciferous vegetables, such as cauliflower, broccoli and cabbage. The crucifers are sources of isothiocyanates, which are known to interfere with the metabolism of nitrosamines and other carcinogens. For example, studies by Chung et al. [32], Hecht [33], and Stoner and Mukhtar [34] have shown conclusively that the metabolism and carcinogenicity of the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone are decreased by the administration of phenylisothiocyanate. Extensive structure-activity studies by these investigators have also shown that the carbon chain length of the isothiocyanate moiety correlates with tumor prevention activity, with a longer chain isothiocyanate apparently more suitable for insertion into the cell due to increased lipophilicity [35, 36]. Also, diallyl sulfide, a common volatile in garlic, has been shown to be a potent inhibitor of cytochrome P450 2E1 [37, 38]. This cytochrome P450 metabolizes ethanol, acetone, and several known chemical carcinogens, including several nitrosamines that target the nasal tissues, oral cavity, liver and esophagus, as well as dimethylhydrazine and its metabolites, which induce colon tumors in rodents [39].

Members of several other classes of plant compounds have demonstrated anti-initiation activity, including the flavonoids, isoflavonoids, and coumarins. For example, earlier studies suggested that coumarins, which are widely distributed in nature and are found in all parts of plants [40], could modulate drug-metabolizing enzymes and cytochrome P450s [41]. Cai et al. [42]

showed that several naturally occurring coumarins can block skin tumor initiation by polycyclic aromatic hydrocarbons such as benzo[a]pyrene and 7,12-dimethylbenz[a]anthracene by inhibiting cytochrome P450s involved in the metabolic activation of the carcinogens.

As reviewed by MacLeod and Slaga [20], several compounds have been proposed as scavengers for the ultimate electrophilic metabolites of carcinogens such as benzo[a]pyrene diol epoxide (BPDE), a metabolite of benzo[a]pyrene. Earlier studies showed that several sulfhydryl compounds, including cysteine and 2-mercaptoethanol, were effective as nucleophilic traps for BPDE [43]. In addition, riboflavin has been shown to promote the detoxification of BPDE by enhancing hydrolysis [44]. Also, a group of plant phenols, notably ellagic acid, has been identified which reacts readily with BPDE and thereby blocks the mutagenicity of BPDE in *in vitro* systems [45]. Ellagic acid has been shown to be an anticarcinogen *in vivo*, having protective activity against topically applied BPDE in the mouse skin model [46]. In addition, a major polyphenolic antioxidant found in green tea, epigallocatechin-3-gallate (EGCG), has been shown to have strong anticarcinogenic effects in several models, including the mouse skin, lung, fore stomach, esophagus, duodenum, pancreas, liver, breast, and colon models [47]. EGCG reportedly can trap the activated metabolites of several procarcinogens [34].

#### *Enhancing Carcinogen Detoxification*

As mentioned above, the process by which potentially dangerous xenobiotics are conjugated to an endogenous cellular nucleophile and then excreted from the body is also an important target for the prevention of tumor initiation. Detoxification of chemical carcinogens by enzymes such as GSTs and uridine diphosphate-glucuronyl transferase is enhanced by several constituents of garlic and onions, cruciferous vegetables, and certain spices. For example, in animals phase-II enzymes are induced by oral exposure to diallyl sulfide and *s*-allyl-cysteine which are found in garlic; both compounds enhance GST levels in liver and colon [48]. As previously discussed, these organosulfur compounds are also known to inhibit the activity of several cytochrome P450s [37]. Thus, the tumor-inhibiting effects of diallyl sulfide and related compounds may be due to the dual effect of decreased carcinogen activation and enhanced carcinogen detoxification [49]. The isothiocyanates also play a dual role: they suppress carcinogen activation as well as enhance carcinogen detoxification by increasing GST activity [33]. The antischistosomal drug oltipraz [50] and the antioxidative agent N-acetylcysteine [32] are also highly effective inducers of GSTs and are potent inhibitors of induced colon, lung, and bladder carcinogenesis. The phytoalexin resveratrol, found in grapes and other food products and an inhibitor of the two-stage mouse skin carcinogenesis model, also has been shown to induce phase-II enzymes such as quinone reductase [51].

### *Enhancing DNA Repair*

Although the gene products and general mechanisms of DNA repair in prokaryotes are fairly well characterized, mammalian repair systems have only recently been elucidated, and little is known about the influence of dietary factors on these processes. In animal studies, calorie restriction [52, 53], EGCG [54], and selenium [55] enhance unscheduled DNA synthesis and other measures of repair capacity. Calorie restriction in mice has also been shown to increase apoptotic cell death in heavily damaged cells, thereby accelerating the elimination of cells with irreparable DNA damage [56].

## **Targets for Anti-Promotion and Anti-Progression Strategies**

### *Epigenetic Changes in Cell Signaling*

The tumor promotion phase of multistage carcinogenesis involves the clonal expansion of initiated cells. Tumor-promoting agents are not mutagenic like carcinogens but rather alter the expression of genes whose products are associated with hyperproliferation, apoptosis, tissue remodeling, and inflammation. At some point, the developing tumor constitutively expresses these genes and thus becomes tumor promoter independent. The identification of the mechanisms by which tumor promoters alter gene expression has been a major goal during the past decade, particularly because determining the critical events will reveal targets for the development of new prevention strategies. It has also become clear in the past few years that apoptosis and mitogenesis are equally important in cell number homeostasis, and that the growth advantage manifested by initiated cells during promotion is usually the net effect of increased proliferation and decreased apoptosis. Thus, in addition to cell proliferation, apoptosis has emerged as a critical target for cancer prevention [57].

As described earlier (fig. 1), the mouse skin model of multistage carcinogenesis is an excellent system for studying the molecular alterations associated with the various stages of tumor development and so will be the primary focus of the following discussion on mechanisms involved in tumor promotion. Among the most potent mouse skin tumor promoters are the phorbol esters; tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) has been the prototype for many years [7]. However, a wide variety of compounds are tumor promoters and bring about both biologic and molecular changes similar to those elicited by TPA [58]. Changes in gene expression as a consequence of external tumor promoter stimuli usually activate (but sometimes inactivate) specific signal transduction pathways. The nature of the initial interaction of tumor promoters with the cell depends on the type of promoter used. For example, TPA interacts with specific receptors that are isoforms of protein kinase C (PKC) [59]. The identification of PKC as the major target for phorbol esters and other promoters such as mezerein, indole alkaloids, and polyacetates

suggests that activation of PKC is a critical event in carcinogenesis. By activating PKC, phorbol esters and related tumor promoters appear to bypass the normal cellular mechanisms for regulating cell proliferation. Several oncogenes (particularly *ras*), hormones, growth factors, and cytokines are also known to activate this signaling pathway. Other promoters such as okadaic acid are potent inhibitors of phosphatases and increase the level of phosphorylated proteins, which often has an activating effect similar to the activation of kinases [60]. However, regardless of the disparity in the tumor promoters' initial signaling events, the key biologic and molecular changes they elicit, such as increased DNA synthesis, induction of ornithine decarboxylase, induction of growth factors and cytokines, and increased production of eicosanoids, are all similar. This overall alteration in signal transduction and gene expression contributes significantly to the selection and growth of the initiated cell population.

As discussed by Fischer and DiGiovanni [60], not all tumor promoters work through receptor-mediated mechanisms. Organic peroxides such as benzoyl peroxide and hydroperoxides are examples. Unlike the phorbol esters, the peroxides require metabolic activation. The molecular targets of benzoyl peroxide have not been elucidated, although it has been shown to produce macromolecular damage, particularly covalent adducts with proteins [22]. Altering signaling by non-receptor-mediated mechanisms would require considerably higher doses of promoter than required by receptor-dependent modulators, e.g., a 20-mg dose of benzoyl peroxide is needed for tumor promotion, whereas only microgram amounts of TPA are required [60].

Despite its importance, activation of PKC alone does not appear to be sufficient for mediating phorbol ester-induced hyperproliferation *in vivo*, in part because a major consequence of PKC activation in keratinocytes is the induction of terminal differentiation. The regulation of keratinocyte proliferation and differentiation is a complex process and probably involves interaction of different cell types in the epidermis and dermis as well as multiple signaling pathways within the keratinocytes themselves. Several receptor tyrosine kinases and their ligands appear to be linked to keratinocyte proliferation. The four main receptors are the epidermal growth factor receptor (EGFR), insulin-like growth factor-1 (IGF-1) receptor, basic fibroblast growth factor receptor, and hepatocyte growth factor receptor [60]. All four of these receptors are expressed on the surfaces of keratinocytes; however, with the exception of transforming growth factor- $\alpha$  (TGF- $\alpha$ ), which is the ligand for EGFR, the ligands for the receptors are produced by dermal fibroblasts or inflammatory cells and act in a paracrine manner.

Several lines of evidence suggest that tumor promoters generally increase the expression of a number of growth factors and cytokines. TPA induces TGF- $\alpha$ , TGF- $\beta$ , tumor necrosis factor- $\alpha$ , granulocyte-macrophage stimulating factor, and interleukins (IL)-1 and 6 [61]. The profile of growth factor induction is different for promoters with different initial mechanisms of action, although most seem to induce TGF- $\alpha$  mRNA expression. TPA treatment also

increases expression of EGFR, possibly as a consequence of activating c-Ha-ras. Alternatively, high TGF- $\alpha$  levels may lead to autoinduction of EGFR [60]. Regardless of how it occurs, elevated levels of EGFR and its principal ligand, TGF- $\alpha$ , are strongly correlated with the development of neoplasias.

### *Inflammation*

In addition to inducing changes in gene expression by activating specific signaling pathways, tumor promoters can elicit the production of protein factors such as IL-1 and several non-protein factors through intracellular activation mechanisms [60]. Of critical importance to the promotion process is the release of arachidonic acid and its metabolism to eicosanoids [62]. Eicosanoids, which include the prostaglandins and hydroperoxy forms of arachidonic acid, are involved in such processes as inflammation, the immune response, tissue repair, and cell proliferation.

Prostaglandin synthesis is regulated by cyclooxygenase (COX) gene expression. Two separate gene products, COX-1 and 2, have similar COX and peroxidase activities, although they are differentially regulated [62, 63]. While a variety of factors, including serum, growth factors, and phorbol esters, can upregulate the mRNA levels of both COXs, the COX-2 gene generally responds in a much more dramatic fashion and thus has been referred to as a phorbol ester-inducible immediate early gene product [64].

In the mouse two-stage skin carcinogenesis model, tumor promotion is a distinct, rate-limiting step that determines the formation of premalignant tumors. As discussed above, the role of tumor promoters in human cancer is more complex because human exposure tends to involve sporadic low doses of complex mixtures of carcinogens, co-carcinogens, and tumor-promoting agents. Nonetheless, studies of rodent tumor models of liver, bladder, colon and mammary cancer and analyses of human tumor formation suggest that processes analogous to tumor promotion by TPA on the mouse skin, including COX-2 overexpression, prostaglandin release and other aspects of inflammation, are a common feature of carcinogenesis [6]. Thus, epigenetic changes in cell signaling such as altered growth factor production and receptor expression, and elevated synthesis of inflammatory and mitogenic factors such as cytokines and eicosanoids, are key targets for inhibiting tumor promotion.

### *Tumor Progression*

As noted earlier, tumor progression involves the accumulation of additional genetic and/or epigenetic alterations in an initiated cell clone, and generally gives a growth advantage to the progressing clone. In progression a focal lesion consisting of a population of initiated and promoted cells ultimately becomes an invasive malignant tumor mass. One frequently observed genetic alteration that appears to contribute to malignant progression is mutation in the p53 tumor-suppressor gene [65]. The p53 gene product is a transcription

factor that regulates the expression of a number of DNA-damage and cell cycle-regulatory genes, and genes regulating apoptosis. By enhancing transcription of these critical genes, p53 regulates the cellular response to DNA damage [66]. p53 also plays a role in maintaining genomic stability [67]. Genomic instability, a hallmark of spontaneous malignant progression, is characterized by sequential chromosomal aberrations such as duplications, deletions, and loss of heterozygosity, which lead to rapid accumulation of unfavorable genetic alterations and eventually to malignant cell growth. Cell numbers, normally maintained by a balance of genes regulating cell proliferation and apoptosis, are altered. DNA hypomethylation, frequently observed in malignant tumors, may also contribute to malignant progression [68]. Thus, p53, other cell cycle and apoptosis regulators, and other genes regulating genomic instability and DNA methylation are critical targets for cancer prevention at later stages (i.e. progression) of carcinogenesis.

### **Nutritional Modulation of Tumor Promotion and Progression: Examples**

#### *Scavenging ROS*

ROS play an important role in a variety of normal processes within the body, including the immune response against pathogens, intracellular signaling, and vascular permeability. However, the accumulation of ROS as byproducts of normal energy metabolism and in response to inflammatory conditions or ROS-generating environmental exposures (i.e. to particulates in tobacco smoke), has been associated with the pathogenesis of cancer in rodents and humans [22, 69]. Experimental studies have shown that ROS can act as both initiators and promoters of tumors by damaging critical cellular macromolecules such as DNA, proteins, and lipids and by acting as cell-signaling molecules, as nitric oxide does [22, 69]. Antioxidants, including ascorbic acid,  $\alpha$ -tocopherol, selenium, and several polyphenolic compounds found in green tea, spices, fruits, and vegetables have been shown to effectively inhibit TPA promotion in mouse skin [19]. Calorie restriction, which is one of the best documented and most effective experimental manipulations for decreasing rodent tumor development [70], including TPA-induced skin carcinogenesis [71], may exert its antitumor effects largely by decreasing ROS production and enhancing antioxidant defenses. Calorie restriction decreases the rate of accumulation of oxidized DNA and protein that accompanies aging in rodents [72]. In addition, a number of intracellular antioxidant defense systems, including superoxide dismutase, catalase, and glutathione peroxidase, are reportedly enhanced by calorie restriction [73]. Thus, evidence is mounting that calorie restriction may decrease oxidative stress by decreasing oxidant production and enhancing antioxidant capacity, although the exact mechanisms involved have yet to be fully established. On the other hand, obesity increases

the risk of many types of cancer [2], probably at least in part by increasing ROS production and inflammation.

*Altering the Expression of Genes Regulating Cell Proliferation, Apoptosis, and Differentiation*

Many studies using the two-stage carcinogenesis model in mouse skin have identified dietary components that act through diverse mechanisms to alter tumor promotion and progression. A number of retinoids, particularly all-*trans* retinoic acid, are specific inhibitors of TPA-induced tumor promotion in the mouse skin [74, 75]. Although the retinoids' mechanism of action is not fully understood, data indicate that they affect epithelial differentiation and also reduce elevated polyamine levels by inhibiting the induction of epidermal ornithine decarboxylase [76]. Several reports indicate that polyamines are involved in regulating cellular differentiation and growth [76, 77]. Retinoids bring about many of their effects by interacting with nuclear receptors. These nuclear receptors are *trans*-activating factors that can regulate the expression of specific genes involved in differentiation, proliferation, and apoptosis [78, 79]. The synthetic retinoid fenretinide, which has shown promising chemopreventive activity against several cancers, appears to exert its antitumor effects primarily by inducing apoptosis in damaged cells [80]. As mentioned earlier, it has become clear in the past few years that apoptosis and mitogenesis are equally important in maintaining cell number homeostasis; thus, in addition to cell proliferation, apoptosis has emerged as a critical target for prevention.

Perhaps the clearest example of dietary modulation of skin carcinogenesis through alteration of the PKC pathway comes from the laboratory of Birt et al. [71] showing that calorie restriction, which inhibits skin tumor promotion by TPA, inhibits PKC activity and decreases the concentrations of different PKC isoforms (particularly PKC $\alpha$  and PKC $\zeta$ ). Birt et al. [81] have also shown that feeding diets high in corn oil increases PKC activity in epidermal cells, apparently by influencing intracellular lipid metabolism rather than altering the distribution of PKC isoforms.

*Decreasing Inflammation*

A number of prostaglandin synthesis inhibitors are effective in counteracting skin tumor promotion and carcinogenesis. Compounds such as anti-inflammatory steroids (i.e. glucocorticoids) are potent inhibitors of mouse skin tumor promotion by phorbol esters [61]. These compounds are effective phospholipase A2 inhibitors, which may explain their ability to decrease the amount of arachidonic acid available for metabolism to important proinflammatory end-products. Inhibitors of the COX pathway, such as indomethacin and flurbiprofen, have been best studied as colon cancer chemopreventives [82] and also inhibit skin tumor promotion in most mouse strains [83]. The COX pathway is a major prevention target, primarily because these enzymes (particularly COX-2) play a role in inflammation as well as in apoptosis and

cellular adhesion in some cells [84]. Recent findings have raised questions about the possible increased risk of myocardial infarction with the class of agents termed selective COX-2 inhibitors, such as rofecoxib [85]. However, several safe, effective, and inexpensive agents that can perturb the COX pathway, such as the nonsteroidal anti-inflammatory drugs, are readily available. In addition, numerous dietary factors, such as several organosulfur compounds in garlic and onions, and resveratrol in grapes, can also safely target the COX pathway [86, 87].

### **Early Life Nutritional Exposures and Childhood Cancer Risk**

The impact of early life nutritional exposures on childhood cancer has not been well studied. The primary focus of research on the relationship between childhood diet and childhood cancer risk has focused on N-nitroso compound exposure in cured meats and brain cancers. No clear picture of a link between early-life consumption of these meats, such as hot dogs, and brain cancer development has emerged [88, 89]. The leading cause of cancer morbidity under age 5 is childhood leukemia, and four studies have now been published assessing the link between early life exposures and leukemia risk [90–93]. Two of these [90, 91] focused on consumption of N-nitroso compounds, again without conclusive findings that cured meat intake is an important risk factor. A recent report [92] suggests that consumption of fruits or fruit juices that contain vitamin C and potassium (particularly oranges and bananas) may reduce the risk of childhood leukemias, but these findings need to be confirmed. Breast cancer in adulthood is the best studied cancer regarding early life nutritional exposures as a risk factor [94], and this will be the focus of the remainder of the review.

### **Early Life Nutritional Exposures and Adult Breast Cancer Risk**

In this section, we describe: (1) animal experimental studies of dietary modulations in pregnancy and cancer risk; (2) certain concepts and underlying processes of human pregnancy, highlighting growth factors, hormones, and hypoxic states in pregnancy, and (3) explore hormonal and nutritional exposures during pregnancy, infancy and childhood to determine the extent of their association with breast cancer risk.

#### *Animal Experimental Studies*

Adult female offspring of alcohol-exposed dams in pregnancy developed significantly more 7,12-dimethylbenz[a]anthracene-induced mammary tumors, compared to adult offspring of non-exposed dams in pregnancy [95]. In addition, compared to the mammary gland structure in the offspring of non-exposed

dams, the mammary epithelial tree of the alcohol-exposed offspring was denser and contained more structures, illustrated by elevated levels of estrogen receptor- $\alpha$ , that are susceptible to DNA damage and other initiation events that begin the breast carcinogenesis process.

Maternal diet during pregnancy affects estrogen levels and leads to reproductive system tumors in the offspring. Specifically, pregnant rats fed a high-fat diet have higher estradiol levels than controls. Female offspring of mice fed a high-fat diet during pregnancy developed more reproductive system tumors and metastases than offspring of pregnant mice fed a low-fat diet [96]. But in a subsequent study, female mice who were exposed in utero to low-fat diets and then nursed from dams who were fed high-fat diets during their pregnancy had a higher frequency of mammary tumors than mice exposed in utero to high-fat diets but nursed from dams who were fed low-fat diets in pregnancy [97]. Thus diet during the early postnatal life of rodents appears to have its greatest effect when the hypothalamus matures in females. Indeed, this model may be appropriate for women who were very preterm births and as newborns had immature hypothalamic-pituitary feedback systems.

Nutritional perturbation of epigenetic gene regulation is a likely link between early nutrition and later metabolism and risk of cancer in Agouti mice [98]. Specifically, dietary methyl supplementation of *a/a* dams with extra folic acid, vitamin B<sub>12</sub>, choline, and betaine altered the phenotype (fur color) of their *A<sup>vy</sup>/a* offspring via increased C<sub>p</sub>G methylation at the *A<sup>vy</sup>* locus [99]. Thus, maternal supplementation in pregnancy permanently affected the offspring's DNA methylation at epigenetically susceptible loci. Further studies in the role of epigenetic mechanisms in pregnancy and cancer risk are needed to address the implications for mothers and children.

### *Human Pregnancy*

Pregnancy is a set of dynamic interactions between the mother, placenta, and the fetus. Endogenous hormonal and metabolic exposures in utero are modulated by maternal energy expenditure, her diet, pre-pregnancy body mass, weight gain and physical activity in pregnancy, and by fetal growth and development.

During the first trimester of a normal, healthy pregnancy, the placenta is undergoing angiogenesis under hypoxic conditions [100]. Vasculogenesis, whereby blood vessels arise from blood islands and angiogenesis from existing vessels, is initiated around 3 weeks of gestation [101]. Blood islands arising from the mesoderm are induced by fibroblast growth factor-2 (FGF-2) to form hemangioblasts, precursors for vessels and blood cell formation. Hemangioblasts in the center of the blood islands form hematopoietic stem cells, the precursors of all blood vessels.

Growth factors such as the placental growth factors, vascular endothelial growth factors, and others well-known in carcinogenesis are upregulated by the placenta as are leptin and other hormones required for growth [102]. The

trophoblasts differentiate into the layers associated with the maternal contact, the syncytiotrophoblasts, and the layers proximal to the fetus, choriotrophoblasts. By 5–7 weeks of gestation, hypoxia-inducing factor-1 (HIF-1) and TGF- $\beta$  are also upregulated, leading to an increase in oxygen tension by 9 weeks of gestation. By 11–14 weeks of gestation, the Von Hippel-Lindau tumor-suppressor gene has downregulated certain growth factors and HIF-1 $\alpha$  and 1 $\beta$  with the advent of low-resistance channels that have developed across the placenta to increase the flow of nutrients and hormones from the mother to the fetus and the outflow of waste from the fetus. Maternal hormonal trajectories reveal patterns of decreasing levels of IGF-binding protein-1 (IGFBP-1), and increasing levels of IGF-1 and 2, progesterone, estrogens, and insulin; while glucose is the fuel that drives the fetal engine [103, 104]. This is the dynamic state of a well-tuned clavier, in which angiogenesis is arrested once the placenta has penetrated the spiral arteries and is capable of sustaining the fetus until birth, and hyperinsulinemia is a characteristic maternal state.

During the remaining two trimesters, the fetus will be exposed to many other factors which may influence the risk of cancer for which gestational age at birth is a marker. Compared to the preterm (<38 weeks gestation), the full-term newborn has undergone the androgen surge late in the third trimester, while the post-term ( $\geq$ 42 weeks gestation) newborn will have higher exposures to estrogens and insulin beyond the levels of the full-term neonate. These elevated hormonal exposures have been hypothesized to lead to large-for-gestational age (LGA) or high birth weight (>4,000 g) neonates and in turn risk of breast cancer [105]. Yet the high birth weight is a heterogeneous group, including offspring of gestational diabetics, an intergenerational component, as well as gender- and ethnic-group specificity. More males than females are higher birth weight, which is reflected in the gender-specific distribution of childhood acute lymphoblastic leukemia [106]. More Hispanic and non-Hispanic whites have LGA than African-Americans, an ethnic group specificity reflected in childhood acute lymphoblastic leukemia. In an analysis of the 1958 British Birth Cohort, Hennessey and Alberman [107] identified the following determinants of birth weight-for-gestational age: maternal birth weight, height, smoking, age at menarche, and weight gain in pregnancy plus gender of the offspring.

### *The Fetal Period: Birth Weight*

#### *Rationale*

A woman's life-time hormonal exposure from endogenous metabolism and exogenous preparations is associated with breast cancer risk [108, 109]. Hormonal exposure begins in utero when estrogen levels are as high as in puberty [105]. One indicator of intrauterine hormonal exposure is birth weight, which varies directly with: levels of maternal estrogen in pregnancy

[110–112]; peak placental growth hormone at 37 weeks gestation [113], and umbilical-cord blood IGF-1 [114–117] and leptin levels [118]. IGF-1 promotes postnatal somatic growth [119] and is a potent mitogen and anti-apoptotic agent in vivo [120], and stimulates aromatization of estrone to the more biologically active estradiol in breast cancer cells in vitro [121]. Adult IGF-1 levels are positively associated with breast cancer risk in premenopausal women [122]. Leptin increases breast cancer cell growth in vitro [123]. Body mass index (BMI) varies directly with serum leptin concentrations and is positively associated with a risk of postmenopausal breast cancer [124].

Birth weight reflects intrauterine nutritional exposures, and correlates directly with maternal weight gain in pregnancy [125, 126], parental birth weight [127], and maternal pre-pregnancy BMI [128, 129]. An estimated 40% of the variance in birth weight can be explained by genetic contributions [130, 131] or by a form of transgenerational epigenetic inheritance [132]. The proportion of macrosomic ( $\geq 4,000$  g) newborns peaked in the United States in the 1980s at 11% and declined to 9.2% in 2002; this percentage varies by ethnic group [133]. African-American and non-Hispanic white women from families where previous generations delivered neonates of low or high birth weight have a twofold increased risk of delivering a low or high birth weight neonate, respectively [134, 135].

#### *Birth Weight-Breast Cancer Association*

Table 1a shows the risk estimates from four cohort studies [135–139] and 12 case-control studies [140–151], three of which were nested within cohort studies [140, 142, 143]. Compared to normal birth weight neonates (2.5–2.99 kg), the high birth weight ( $\geq 4,000$  g) experienced a 20% to fivefold increased risk of premenopausal breast cancer, except for a study in young women where a U-shaped relation of birth weight and breast cancer was observed [150]. In studies analyzing pre- and postmenopausal women in the same model, four of ten reported a significantly increased risk in the category with the highest birth weight [139, 146, 148] or reduced risk in those weighing  $< 4,000$  g at birth compared to those weighing  $\geq 4,000$  g [142]. Research on birth weight and postmenopausal breast cancer is also inconsistent. Therefore, the literature is most suggestive of an association of high birth weight neonates and risk of premenopausal breast cancer after adjustment for adult risk factors (in the comments to table 1a). Of note, the research has largely been conducted in non-Hispanic white women. Two studies in Asians [144, 151] report no association between birth weight and breast cancer. Asians have a more peaked birth weight distribution and a smaller proportion of low and high birth weight neonates than Caucasians [152] to detect an association in the extremes of the distribution.

Three linked birth-cancer registry studies examine the relation of birth length and breast cancer risk [136, 140, 148] (table 1b). All three studies demonstrate a positive trend of higher breast cancer risk in premenopausal or

**Table 1a.** Adjusted relative risk of breast cancer by study design, birth year, ethnic group, menopausal status and birth weight

Reference	Birth year	Ethnic group	Cases <sup>a</sup>	Birth weight, kg					p trend	Comments
				<2.5	2.5–2.9	3.0–3.4	3.5–3.9	≥4.0		
<b>Cohort studies</b>										
McCormack et al. [136], 2003	1915–1929	NHW	63 <sup>1</sup>	1.0	1.6	2.4*	3.5*	0.01	B-ca registry, proxy indicators of adult risk	
		NHW	296 <sup>2</sup>	(ref)	0.8	1.0	0.9	NS		
dos Santos Silva et al. [137], 2004	1946	NHW	21 <sup>0</sup>	1.0	1.4	2.2	5.0*	0.03	Adjusted for childhood and adult risk factors	
		NHW	59 <sup>3</sup>	(ref)	1.0	1.4	1.6			NS
				<hr/>						
				<2.0	2.0–2.9	>3.0				
				<hr/>						
Kaijser et al. [138], 2003	1925–1949	NHW	19 <sup>1</sup>	1.5	0.7	2.5				Std incidence ratio reported; B-ca registry, sampled neonates <35 weeks gestation or 2,000 g and >35 weeks gestation, no adjustment for adult risk factors; standardized incidence ratios shown
		NHW	39 <sup>3</sup>	1.1	0.7	2.6*				
				<hr/>						
				2.5 <sup>c</sup>	3.0	3.4	3.6	4.0		
				<hr/>						
Ahlgren et al. [139], 2004	1930–1975	NHW	2,74 <sup>3</sup>	1.0 (ref)	1.0	1.1	1.1	1.2*	– <sup>d</sup>	Adjusted for childhood and adult risk factors

**Table 1a.** (continued)

Reference	Birth year	Ethnic group	Cases <sup>a</sup>	Birth weight, kg						p trend	Comments
				<2.5	2.5–2.9	3.0–3.4	3.5–3.9	≥4.0	>4.5		
<b>Case-control studies</b>											
Ekblom et al. [140] <sup>e</sup> , 1997	1874–1961	NHW	1,068 <sup>30.8</sup>	1.0 (ref)	1.0	1.0	1.0			NS	B-ca registry, no adult risk factors; nested within cohort
Titus-Ernstoff et al. [141], 2002	1911–1945	NHW	1,716 <sup>2</sup>	1.1	0.9	1.0 (ref)	1.1	0.9	1.2	NS	Self-reported data after diagnosis; nested within a cohort
Michels et al. [142], 1996	1921–1965	NHW	550 <sup>3</sup>	0.6	0.7*	0.7*	0.9	1.0 (ref)		<0.01	Self-reported after diagnosis; adjusted for adult risk factors; nested within cohort
Lahmann et al. [143], 2004	1924–1950	NHW	88 <sup>2</sup>		1.0 (ref)	1.9	2.3	2.7		– <sup>d</sup>	Birth records; adjusted for adult risk factors; nested within cohort
Sanderson et al. [144], 2002	1932–1973	Asian	288 <sup>3</sup>	0.9	1.0 (ref)	1.1	0.8	0.7		NS	Maternal recall after diagnosis; adjusted for adult risk factors
Sanderson et al. [146], 1996	1944–1969	NHW	746 <sup>3</sup>	1.3	1.0 (ref)	1.3*	1.2	1.7*		0.06	Self-reported after diagnosis; no adjustment for adult risk factors
	1924–1940	NHW	401 <sup>3</sup>	0.9	1.0 (ref)	1.1	0.8	0.6		0.06	
Sanderson et al. [145], 1998	1945–1947	NHW	510 <sup>1</sup>	1.2	1.0 (ref)	1.0	1.0	1.3		NS	Maternal recall after diagnosis; adjusted for adult risk factors

Mellemkjaer et al. [147], 2003	1935–1966	NHW	881 <sup>1</sup>	1.6	0.8	1.0 (ref)	1.0	1.3		B-ca registry, no adult risk factors
				<hr/>						
				<3.1	3.1–3.4	3.5–3.7	>3.7			
				<hr/>						
Vatten et al. [148], 2002	1910–1970	NHW	373 <sup>3</sup>	1.0 (ref)	1.1	1.2	1.4*		0.02	B-ca registry, adjusted for adult risk factors
Hodgson et al. [149], 2004	1949–1978	AA NHW	83 <sup>3</sup> 108 <sup>3</sup>	1.1 0.9	1.0 (ref) 1.0 (ref)	0.4 0.9			NS NS	Birth hospital record data
				<hr/>						
				<1.5	1.5–2.4	2.5–3.4	3.5–4.4	≥4.5		
				<hr/>						
Innes et al. [150], 2000	1958–1981	AA, NHW	484 <sup>1</sup>	3.0*	1.5*	1.0 (ref)	1.1	3.1*		B-ca registry, no adjustment for adult risk factors
				<hr/>						
				1.16–2.94	2.95–3.34	3.341–4.45				
				<hr/>						
Le Marchand et al. [151], 1988	1946 on	Asian, NHW	71 <sup>1</sup>	1.0 (ref)	0.7	0.8			NS	B-ca registry, no adjustment for adult risk factors

NHW = Non-Hispanic white; AA = African American; B-ca registry = birth-cancer registry; NS = non-significant.

\*95% Confidence interval excludes one.

<sup>a</sup>Menopausal status: <sup>0</sup>premenopausal; <sup>1</sup>premenopausal based on age <50 years; <sup>2</sup>postmenopausal based on age >50 years; <sup>3</sup>both.

<sup>b</sup>Includes case from De Stavola (2000).

<sup>c</sup>Median of each quintile.

<sup>d</sup>Ahlgren et al. [139] OR per kg increase 1.1 (95% CI 1.01–1.20); Lahmann et al. [143] OR per 100 g increase 1.1 (95% CI 1.00–1.12).

<sup>e</sup>Includes cases from Ekblom (1992).

**Table 1b.** Adjusted relative risk of breast cancer by study design, birth year, ethnic group, menopausal status and birth length

Reference	Birth year	Ethnic group	Cases <sup>a</sup>	Birth length, cm					p trend	Comments
				<49.0	49.5–50.0	50.5–51.0	51.5–52.0	>52.5		
<b>Cohort study</b>										
McCormack et al. [136], 2003	1915–1929	NHW	65 <sup>1</sup> 294 <sup>2</sup>	1.0	2.1	2.9*	3.5*	3.4*	0.001	B-ca registry, proxy indicators for adult risk
				1.0 (ref)	1.0	1.1	0.8	1.3	NS	
<b>Case-control studies</b>										
Vatten et al. [148], 2002	1910–1970	NHW	373 <sup>3</sup>	<50.0	50.0	51.0	>51.5		0.02	B-ca registry, adjusted for adult risk factors
				1.0 (ref)	1.2	1.5*	1.3			
Ekblom et al. [140] <sup>a</sup> , 1997	1874–1961	NHW	1,068 <sup>3</sup>	Quartile 1	Quartile 2	Quartile 3	Quartile 4		NS	B-ca registry, no adult risk factors; nested within a cohort
				1.0 (ref)	1.1	1.2	1.1			

NHW = Non-Hispanic white; B-ca registry = birth-cancer registry; NS = non-significant.  
\*95% Confidence interval includes one.  
<sup>a</sup>Menopausal status: <sup>1</sup>premenopausal based on age <50 years; <sup>2</sup>postmenopausal based on age >50 years; <sup>3</sup>both.

pre- and postmenopausal patients who were 51 cm or more in length at birth. Two report significant trends after adjustment for gestational age and adult risk factors. The risk is larger than the risk for birth weight alone, indicating that growth factors specific to linear bone growth may play an important role in breast cancer etiology [136, 148].

### *The Fetal Period: Preterm Births*

#### *Rationale*

Women who deliver preterm have higher estradiol levels than those who deliver full-term [114]. Preterm neonates (<37 weeks gestation) have higher levels of gonadotrophins than full-term neonates in early infancy. Gonadotrophins stimulate the ovary to produce excessive amounts of estradiol, which are associated with an increased risk of ovarian cysts in adolescence. And since estrogens may have a direct mutagenic potential [153], exposure to higher levels of estrogens in early postnatal life may lead to an increased risk of breast cancer.

#### *Preterm Birth-Breast Cancer Association*

Based on linked birth-cancer registry data, there appears to be a significant trend of increasing risk (or SIR) of breast cancer with decreasing gestation age of the neonate [138, 154, 155] and a significantly higher risk of breast cancer in newborns of gestation ages <33 or 30–38 weeks [136, 140]. In contrast, no association is observed in the case-control studies [142, 145] (table 2). Several caveats should be noted: (1) the cutoff for preterm births and therefore the referent group varies by study; (2) research is based on small numbers, and (3) women who deliver early may incorrectly recall gestational age of the index child because they never reached the landmark 'due date' [156]. Misclassification of preterm births based on maternal-reported gestational age might attenuate the relation of preterm births to breast cancer. Of note, in birth cohorts before the 1980s, neonatal intensive care units were not in existence to support survival of the preterm; therefore survivors might be LGA (>90th percentile of birth weight for newborns delivered each week of gestation) babies who had a high growth rate in utero (during a short pregnancy). Factors that stimulated intrauterine growth and a higher rate of mitotic division in the LGA neonate might have eventually led to an increased risk of breast cancer [109].

### *The Fetal Period: Maternal Age and Preeclampsia*

#### *Rationale*

Maternal age-specific hormone levels in pregnancy have not been examined extensively. Pregnancy estriol levels do not vary by maternal age in one

**Table 2.** Adjusted relative risk (RR) of breast cancer by study design, birth year, ethnic group and preterm birth

Reference	Birth year	Ethnic group	Cases <sup>a</sup>	Gestational age, weeks	RR	Comments
<b>Birth cancer registry studies</b>						
Ekbohm et al. [140]	1874–1961	NHW	10 <sup>3</sup>	<33	4.0*	Referent: >33 weeks
Le Marchand et al. [151]	1946 on	Asian, NHW	9 <sup>0</sup>	<36	1.2	Referent: 36–40 weeks
Vatten et al. [148]	1910–1970	NHW	77 <sup>3</sup> 291 <sup>3</sup>	<32 32–36	1.2 1.1	Referent: >40 weeks; p for trend = 0.02
McCormack et al. [136]	1915–1929	NHW	63 <sup>1</sup>	30–38	2.1*	Referent: >41 weeks; p for trend = 0.03
					Std incidence ratio	
Kajiser et al. [138]	1925–1949	NHW	19 <sup>1</sup>	≤32 33–34	1.4 0.9	Referent: birth weight <2,000 g and gestation >35 weeks
		NHW	39 <sup>3</sup>	≤32 33–34	1.1 0.9	
Ekbohm et al. [155]	1925–1934	NHW	12 <sup>3</sup>	<31 31–32 33–34 ≥35	6.7* 2.3 0.7 0.2	Referent: birth weight <2,000 g and gestation >35 weeks
<b>Case-control studies</b>					RR	
Michels et al. [142]	1921–1965	NHW	8 <sup>3</sup>	Preterm	1.0	Referent: not preterm
Sanderson et al. [145]	1945–1947	NHW	18 <sup>1</sup>	<37	0.9	Referent: 37–42 weeks; crude OR provided

NHW = Non-Hispanic white.

\*95% Confidence interval excludes one.

<sup>a</sup>Menopausal status: <sup>0</sup>premenopausal; <sup>1</sup>premenopausal based on age <50 years; <sup>2</sup>postmenopausal based on age >50 years; <sup>3</sup>both.

study [111], but total estrogen (TE) and estradiol (E<sub>2</sub>) levels are highest in women aged 20–24 years, lowest in teenagers and intermediate in women aged 25+ years in another study [157]. Maternal age co-varies with parity, which exhibits a consistent hormonal pattern across three studies. Specifically, TE and E<sub>2</sub> levels (at 16 and 27 weeks gestation in one study or at 26 and 31 weeks gestation in another study) are higher among women in their

first than those in their second full-term pregnancy and higher in the same woman in her first than in her second pregnancy [112, 158]. Maternal age is associated with a risk of poor pregnancy outcomes. Compared to women aged 20–24 years, women aged 35+ are at increased risk of delivering a newborn with birth defects, a marker of chromosomal aberrations and in turn cancer risk [159]. Compared to primiparous women aged 20–24 years, primiparous women aged 30+ are at increased risk of delivering low birth weight neonates [160]. Compared to women aged 20–24 years, teenagers have fewer pregnancies and higher rates of small-for-gestational age (SGA; <10th percentile of birth weight for newborns delivered each week of gestation) and preterm births, thus, women aged 20–24 years are considered the referent group in maternal and child health research. In sum, if maternal age at the birth of the index case is related to breast cancer risk in the offspring, then the association may be via parity (and hormone levels), birth weight and/or adverse pregnancy outcomes.

#### *Maternal Age-Breast Cancer Association*

Because the maternal age-breast cancer association has breast cancer rates of offspring of teenage mothers as the referent group, the relative risks (RRs) are re-calculated using cancer rates of daughters of women aged 20–24 years as the referent group (for the reasons mentioned above; table 3). Data are presented from 10 case-control studies [141, 146, 147, 150, 151, 161–165], one of which is a birth-cancer registry study, and two cohort studies [166, 167]. The RR of breast cancer increases with increasing maternal age to 35–39 years in five studies and is slightly higher in the offspring of teenagers in four. The RR for the maternal age-breast cancer association remains the same after stratification by reproductive risk factors in the patient [163, 164, 166], while a J-shaped relation was observed after adjustment for her birth weight [150]. Thus maternal age is probably not a marker for hormonal exposures in utero, because the RR of breast cancer in the offspring of the 20- to 24-year-olds, who have reportedly the highest hormone levels in pregnancy, are not higher than those in the offspring of other mothers.

#### *Rationale for Preeclampsia*

Preeclampsia, a condition characterized by pregnancy-induced hypertension, edema, and proteinuria, is diagnosed in 2–10% of pregnant women. Preeclampsia, known as the ‘disease of theories’, may be more than one disease of heterogeneous origin with early and late onset patients who vary by severity of disease [168–170] and who deliver neonates at risk of being SGA or LGA [171, 172]. Increased cardiac output of late onset preeclamptics may enhance uteroplacental perfusion, which increases the risk of delivering LGA neonates, while severe, early onset patients may experience reduced uteroplacental perfusion, which increases the risk of delivering a SGA [171]. The levels of dehydroepiandrosterone sulfate (DHEAS) in the cord blood of

**Table 3.** Revised relative risk (RR) of breast cancer by maternal age at birth of the index case, stratified by study design, year of study, ethnic group and number of cases

Reference	Birth year	Ethnic group	Cases <sup>a</sup>	Maternal age by year <sup>b</sup>						Comments
				<20	20–24	25–29	30–34	35–39	40+	
<b>Cohort studies</b>										
Colditz et al. [166]	1921–1946	NHW	1,799 <sup>3</sup>	1.0	1.0 (ref)	1.1	1.1	1.1	1.0	p for trend: NS
					<25	25–29	30–35	>35		
Zhang et al. [167]	1886–1919	NHW	149 <sup>3</sup>		1.0 (ref)	1.2	1.3	1.1		
<b>Case-control studies</b>										
				<20	20–24	25–29	30–34	35–39	40+	
Rothman et al. [161]	NR	AA, NHW, Asian	4,339 <sup>3</sup>	0.9	1.0 (ref)	1.2	1.1	1.2	1.1	
Thompson and Janerich [162]	1926–1962	AA, NHW	2,492 <sup>3</sup> – parous	1.1	1.0 (ref)	1.2	1.2	1.5*	1.3	
		AA, NHW	499 <sup>3</sup> – nulliparous	1.3	1.0 (ref)	1.1	1.2	1.6	0.7	
Janerich et al. [163]	1875–1947	NHW	2,414 <sup>3</sup>	1.0	1.0 (ref)	1.1	1.1	1.0	1.0	
Newcomb et al. [164]	1913 on	NHW	1,253 <sup>3</sup>	1.2	1.0 (ref)	1.2	1.1	1.4	1.1	Subject report after diagnosis; p for trend: NS
Sanderson et al. [146]	1944–1969	NHW	746 <sup>3</sup>		1.0 (ref)	1.0	1.2	1.0		
Mellemkjaer et al. [147]	1935–1966	AA, NHW	881 <sup>1</sup>		1.0 (ref)	1.1	1.1			B-ca registry; p for trend: NS
Titus-Ernstoff et al. [141]	1911–1945	NHW	1,555 <sup>2</sup>	1.0	1.0 (ref)	1.0	1.2	1.2	1.3	p for trend = 0.04

Innes et al. [185]	1958– 1981	AA, NHW	484 <sup>1</sup>	1.2	1.0 (ref)	1.4*	1.5*	2.0*	p for trend = 0.01
Weiss et al. [165]	1948 on	AA, NHW	2,106 <sup>3</sup>	1.0	1.0 (ref)	1.0	1.0	1.0	p for trend: NS
				15–22	23–26	27–30	31–46		
Le Marchand et al. [151]	1946 on	Asian, NHW	153 <sup>1</sup>	1.2	1.0 (ref)	1.2	1.7		

NHW = Non-Hispanic white; AA = African American; NR = not reported; NS = non-significant.

\*95% Confidence interval excludes one.

<sup>a</sup>Menopausal status: <sup>0</sup>premenopausal; <sup>1</sup>premenopausal based on age <50 years; <sup>2</sup>postmenopausal based on age >50 years; <sup>3</sup>both.

<sup>b</sup>When a column is left blank the reader assumes that the OR includes all age categories older or younger.

neonates are highest in severe hypertensives in pregnancy, intermediate in the moderate hypertensives, and lowest in mild hypertensives who have comparable levels to the neonates of normotensive women [173, 174]. Within strata of birth weight-for-gestational age, cord blood levels of IGF-1 are lower, but levels of IGFBP-1 and leptin are higher in the offspring of severe preeclampsics than normotensive controls [175, 176]. Estrogen and androgen concentrations do not differ in the cord blood of preeclamptic compared to normotensive offspring in another study [177].

#### *Preeclampsia Exposure in Utero and Breast Cancer Risk*

In several studies, the daughters of preeclampsics have a 10–60% lower risk of breast cancer than the daughters of normotensives [140, 145, 150] (table 4). Although so far breast cancer risk in the offspring of preeclampsics has been discussed, preeclampsia also influences the risk of breast cancer in the mothers. Compared to normotensive pregnant women, preeclampsics have higher levels of progesterone, androgen precursors of estrogen (e.g. DHEAS), cortisol, insulin, and human chorionic and other gonadotropins in pregnancy, but lower levels of estrogen and of IGF-1 [173, 174, 178, 179]. Twenty-two women with prior preeclampsia and a similar number of normotensive control women, matched on age and BMI, were studied on average 17 years postpartum [180]. Compared to the normotensives, women with a history of preeclampsia had elevated levels of free testosterone, free androgen, and free testosterone to estradiol ratios in serum.

#### *Preeclampsia-Maternal Breast Cancer Association*

Women who report a diagnosis of preeclampsia (eclampsia, toxemia, or pregnancy-induced hypertension) have a 10–70% lower risk of breast cancer [181–185], except in one cohort study [186] that describes a 40% higher risk in prior preeclampsics (table 4). All but the cohort study of Middle Eastern women in Jerusalem, Israel, by Paltiel et al. [186] were conducted in European/non-Hispanic white populations. RRs vary by criteria for diagnosis and by parity, as illustrated by the RR of 0.3 in nulliparous preeclamptic women [181]; the RR of 0.7 in all women diagnosed with pregnancy-induced hypertension in contrast with a RR of 1.1 in nulliparous women in the same study [182]. Thus the criteria for diagnosis of preeclampsia may alter the magnitude of breast cancer risk; while the as yet unknown underlying disease etiology may be protective or conducive to breast cancer. Potential mechanisms underlying the lower risk of breast cancer in preeclampsics include: the index pregnancy may lower estrogen and/or IGF-1 levels postpartum and in turn lower breast cancer risk; or complex mechanisms related to programming from life-long androgenic exposures and genetic variants associated with preeclampsia may influence breast cancer risk.

**Table 4.** Adjusted relative risk (RR) of breast cancer in the mother or daughter by maternal preeclampsia (yes vs. no), birth year and ethnic group

Reference	Birth year	Ethnic group	Number of cases <sup>a</sup> /Total number of cases <sup>b</sup>	Diagnosis criteria	RR	Comments
<b>Daughter's risk</b>						
Ekbom et al. [140]	1874–1961	NHW	14/1,068 <sup>3</sup>	Toxemia	0.4*	B-ca registry; no adult risk factors
Sanderson et al. [145]	1944–1947	NHW	20/509 <sup>3</sup>	Preeclampsia or eclampsia	0.8	Maternal recall, adjusted for adult risk factors
Innes et al. [150]	1957–1981	AA, NHW	6/462 <sup>1</sup>	Toxemia	0.9	B-ca registry; no adult risk factors
<b>Maternal risk</b>						
Polednak and Janerich [181]	1926 on	NHW	2/314 <sup>1</sup>	Toxemia	0.3*	Case-control; hospital record data
Thompson et al. [182]	1926–1962	AA, NHW	139/3,897 <sup>3</sup>	Hypertension	0.7*	Diagnosed with hypertension before the end of the most recent term pregnancy; case recall
Troisi et al. [183]	1946–1972	AA, NHW	97/1,236 <sup>3</sup>	Toxemia	0.8	Case-control; case recall
Vatten et al. [184]	NR	NHW	280/5,474 <sup>3</sup>	Preeclampsia or hypertension	0.8*	B-ca registry; analysis restricted to primiparous women
Innes and Byers [185]	NR	AA, NHW, Hispanic	95/2,404 <sup>3</sup>	Preeclampsia	0.9	B-ca registry, case-control; analysis restricted to primiparous women

**Table 4.** (continued)

Reference	Birth year	Ethnic group	Number of cases <sup>a</sup> /Total number of cases <sup>b</sup>	Diagnosis criteria	RR	Comments
					Delivery	
					preterm	term
				Normotensive	1.0	1.0 NS
				Preeclampsia or hypertension	0.9	0.8*
					RR	
Paltiel et al. [186]	NR	Includes Israel, WA and NA	40/91 <sup>3</sup>	Preeclampsia	1.4*	Cohort of births 1964–1976; linked to cancer registry

NHW = Non-Hispanic white; AA = African American; WA = West Africa; NA = North Africa; NR = not reported ; NS = non-significant.  
\*95% Confidence interval excludes one.  
<sup>a</sup>Number of breast cancer cases diagnosed with toxemia, preeclampsia or hypertension in pregnancy.  
<sup>b</sup>Menopausal status: <sup>0</sup>premenopausal; <sup>1</sup>premenopausal based on age <50 years; <sup>2</sup>postmenopausal based on age >50 years; <sup>3</sup>both.

*Infancy: Breast and Bottle Feeding**Rationale*

Human breast milk and infant formula from cow's milk or soy are the major sources of nutrition in infancy. Breast milk composition reflects maternal diet, nutritional status, hormone levels, and environmental exposures. Hormones such as IGF-1 in breast milk vary in concentration by age of the infant as well as by phase of the menstrual cycle in the mother [187]. The major hypothesis relating breast milk intake to breast cancer risk arises from the animal work done by Bittner [188] in the 1930s wherein a factor (later identified as a retrovirus) present in mouse milk was essential for the development of breast cancer [189]. The evidence that a similar virus appeared in human breast milk has not been consistently documented [189–192]. Breastfeeding has undergone a dramatic secular trend in the United States, from a low frequency of breastfeeding in 29% of infants aged 1 week old in 1955 [193] to a high proportion of breastfeeding in 67.5% of infants aged 1 week in 1998 [194, 195]. Birth weight of the neonate, ethnic group, and socioeconomic status influence the proportion of infants who are breastfed and the duration of breastfeeding [196]. Since the 1960s, approximately 10% of infants are exclusively fed by soy formula, and breastfed infants may be supplemented with soy formula [197].

*Breast Feeding-Breast Cancer Association*

Epidemiologic research, primarily designed as case-control studies, has demonstrated a modest, but not significant, lower risk of premenopausal breast cancer in those who reported having been breastfed [145, 165, 198–201] with two exceptions [202, 203] (table 5). Of the three studies in postmenopausal breast cancer, the RRs vary above [202, 203] and below the null value [198], but none are significant. Having been breastfed is not associated with risk of breast cancer in women whose mothers later developed breast cancer [198]. In two studies, the duration of breastfeeding is not associated with breast cancer risk [145, 203].

Breastfeeding has also been shown to influence weight status and has been extensively reviewed by Butte [204]. Breastfeeding was associated with a reduced risk of being overweight as a child in four of the 16 studies discussed. However, several factors make interpretation of these results difficult including small sample sizes, and different definitions of the exclusivity and duration of breastfeeding. The evidence to date suggests that breastfeeding reduces the risk of being overweight as a child to a moderate extent. Gillman et al. [205] for example reported that adolescents (9–14 years) who were breastfed for at least 7 months were 20% less likely to be overweight (OR 0.80; 95% CI 0.67–0.96) than those breastfed for 3 months or less. The duration of breastfeeding was also inversely related to the risk of being overweight at adolescence. Specifically, compared to those who were never breastfed or

**Table 5.** Adjusted relative risk (RR) of breast cancer by study design, birth year, ever breastfed (bottle-fed) as well as duration of breastfeeding

Reference	Birth year	Ethnic group	Breastfeeding, %		RR	Comments		
			cases <sup>a</sup>	controls				
<b>Cohort studies</b>								
Michels et al. [142]	1921–1964	NHW	36.3 <sup>0</sup>		Ever	1.0 <sup>b</sup>	Referent: never breastfed	
					Duration		RR	
					<3	0.7 <sup>b</sup>	Referent: never breastfed; adjusted for multiple covariates; p for trend: NS	
		4–8	1.0 <sup>b</sup>					
		>9	0.9 <sup>b</sup>					
		NHW	73.5 <sup>2</sup>		Ever	1.1	Referent: never breastfed	
Duration					RR			
<3	1.3 <sup>b</sup>				Referent: never breastfed; adjusted for multiple covariates; p for trend: NS			
4–8	0.9 <sup>b</sup>							
>9	1.3 <sup>b</sup>							
<b>Case-control studies</b>								
Brinton et al. [199]	NR	NHW	73.7 <sup>3</sup>	74.3	Ever	0.9 <sup>b</sup>	Referent: never breastfed	
Ekbom et al. [200]	1874–1954	NHW	88.9 <sup>3</sup>	88.1	Ever	1.0	Referent: never breastfed	
Freudenheim et al. [198]	1901–1951	NHW	48.9 <sup>0</sup>	58.5	Ever	0.7	Referent: never breastfed; adjusted for age and education	
			80.6 <sup>2</sup>	85.7	Ever	0.7	Referent: never breastfed	
Weiss et al. [165]	1936–1972	NHW	41.7 <sup>1</sup>	49.5	Ever	0.7 <sup>b</sup>	Referent: never breastfed	
Titus-Ernstoff et al. [202]	1942–1945	NHW	42.0 <sup>0</sup>	48.1	Ever	0.7	Referent: never breastfed	
Sanderson et al. [156]	1944 on	NHW	44.5 <sup>1</sup>	44.6	Ever	1.0	Referent: never breastfed	
					Duration		RR	
					<3	1.0	Referent: never breastfed	
					3–5.9	1.1		
					>6	1.0		

NHW = Non-Hispanic white; NS = non-significant.

<sup>a</sup>Menopausal status: <sup>0</sup>premenopausal; <sup>1</sup>premenopausal based on age <50 years; <sup>2</sup>postmenopausal based on age >50 years; <sup>3</sup>both.

<sup>b</sup>Relative risk.

breastfed for <1 month, an 8% reduction in the risk was demonstrated for every increment of 3 months of breastfeeding (adjusted OR 0.92; 95% CI 0.87–98) or breastfed for <1 month. It has been suggested that this may be due to the latent effect of the infant feeding mode and not solely to lower fatness during the first 2 years of life [206]. This is of biological interest as obesity during and after adolescence is highly predictive of adult obesity [207, 208] and increased risk of postmenopausal breast cancer [209].

Several possible mechanisms have been put forward to explain how breastfeeding could be related to lower rates of overweight in children including behavioral and hormonal pathways. Birch and Fisher [210] have shown that children who are breastfed are better able to adjust intake at a meal in response to a high calorie pre-load and concluded that breastfed children may learn to self-regulate caloric intake better than non-breastfed infants. In addition, infant formula feeding compared with breastfeeding evokes a higher and more prolonged insulin response and therefore earlier fat deposition [211]. The effect may also be due to different metabolic programming of breastfed from formula-fed infants due to variations in milk composition, protein intake, fatness and/or rate of weight gain in early life and residual confounding by variables such as child feeding practices and physical activity.

Research has shown that mothers' child feeding practices are directly related to children's energy intake, food preferences, the ability to regulate food intake and body weight [212–214]. In addition to the association between infant feeding and the risk of being overweight in childhood or adolescence, infant feeding may alter dietary intake during childhood. This could be due to demographic and physiologic differences between mothers who breastfeed versus those who bottle-feed. Indeed it may be possible that food preferences subsequent to breastfeeding are affected by the mode of infant feeding. Of note, very little information is currently known regarding differences in the age at introduction of solid foods and the type of solid food given in breastfed versus bottle-fed infants by ethnic group, energy expenditure and other metabolic markers of body size.

### *Linear Growth and Body Size from Infancy Through Adolescence*

#### *Rationale*

Infancy and childhood are periods of rapid growth in weight, height, and brain size. Recent analyses of birth weight, childhood growth, and breast cancer risk have led to the exploration of factors influencing catch-up or -down growth in early childhood. In the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC), Ong et al. [215] describe how thinner, shorter newborns with tall fathers experience the greatest catch-up in weight compared with those who show no change from birth to 2 years. Moreover, ALSPAC children with early catch-up growth have higher serum IGF-1 levels at 5 years

**Table 6.** Growth patterns and relative risk (RR) of breast cancer by birth year, ethnic group and menopausal status

Reference	Birth year	Ethnic group	Cases	Ages at which measurements were taken	RR	Comment
<b>Cohort studies</b>						
De Stavola et al. [223]	1946	NHW	51	2-4	0.9	Linear velocity (cm/year), adjusted for age at menarche, age at first birth, parity and social class
			53	4-7	1.3*	
			49	7-11	1.0	
			43	11-15	1.1	
			37	15-adulthood	0.9	
				7 years	Hazard ratio	
Hilakivi-Clarke et al. [95]	1924-1933	NHW	22	<114.5 cm	1.0 (ref)	p for trend in linear growth = 0.01; adjusted for birth weight and birth length
			32	117.5	1.3	
			39	120	1.7*	
			41	123	1.7*	
			43	>123	1.9*	
				15 years		
		NHW	23	<153	1.0 (ref)	
	34		157	1.3		
	33		160	1.3		
	38		163	1.8*		
	49		>163	1.9		
<b>Case-control studies</b>						
Herrinton and Husson [254]	1934-1963	NHW,	77	12-14	1.7*	Tall vs. short height-at-age, controls matched on birth year, age at entry, marital status, alcohol use, race, parity, age at first birth and menopausal status
		AA				
		NHW,	59	15-18	2.2*	
		AA				
					RR	
Ahlgren et al. [139]	1930-1975	NHW	3,340	7-8 years	1.1*	Adjusted RR per 5-cm increase; p for trend = 0.01
		NHW		8-14 years	1.2*	

NHW = Non-Hispanic white; AA = African American.  
 \*95% Confidence interval excludes one.

than those remaining on trajectory or experiencing catch-down, after adjustment for current size [216]. A similar pattern of higher IGF-1 concentrations appear at 4 and 9 years of age in children who are thinner and smaller newborns, experience catch-up in linear growth, and have tall fathers [217, 218]. Thus, in utero effects may be modulated by childhood growth velocity, by genetic factors, and may correlate with IGF-1 concentrations in childhood.

In addition, adult height is known to be positively associated with breast cancer risk [219, 220]. Furthermore, there was a trend of decreasing risk of breast cancer with increasing age at attainment of height and women had a 30% reduction (OR = 0.7; 95% CI 0.5–1.0) in risk of breast cancer for pre- and postmenopausal women who reached their maximum height at 18 years or older compared with women who reached their maximum height at age 13 or younger [221, 222]. De Stavola et al. [223] suggested that women who grow faster in childhood and reached adult height above the average for their menarche category are at particularly increased risk of breast cancer. For example for each 1-standard deviation increase in height velocity at age 4–7 years, the breast cancer risk increased by 54% (OR 1.54; 95% CI 1.13–2.09).

Alberman et al. [224] stated that factors in early life which contributed to a significant increase in adult height included gender and parental height, birth weight and maternal pre-pregnant weight, while increasing gestational age had a negative effect. In addition, a woman's final adult height can also be influenced by the onset of ovarian function during adolescence. However, other early life exposures which could potentially affect age at final height and adult height, such as infant feeding practices have not been extensively studied. One study by Zadik et al. [225] showed that despite their slower growth rate, breastfed children reach the same final height as bottle-fed children. The American Dietetic Association advocates exclusive breastfeeding for 4–6 months and breastfeeding with weaning foods for at least 12 months [226]. It is therefore of interest to assess the effect of infant feeding (type and duration) on age at final height and actual adult height.

### *Diabetes and Breast Cancer Risk*

Epidemiologic studies suggest that type-2 diabetes is associated with a 10–20% increased risk of breast cancer [227–230]. Although this association has been observed in both premenopausal and postmenopausal women, most reports only observed a significant increase in risk among postmenopausal women and many did not have the statistical power or data to investigate the association by menopausal status [227–230]. Furthermore, hyperinsulinemia with insulin resistance may promote breast cancer through several mechanisms including: activation of the insulin pathway, activation of the IGF pathway, and impaired regulation of endogenous sex hormones [228]. The proposed carcinogenic effects of insulin in relation to increased breast cancer

**Table 7.** Summary of literature on early life exposures and breast cancer

Exposure	Number of studies with significant findings*/total number of studies	Range RR
High birth weight		
Premenopausal	3/7	3.1–5.0
Postmenopausal	0/3	–
Both	5/11	1.2–2.6
Birth length	2/4	1.5–3.5
Preterm	3/8	2.1–6.7
Preeclampsia	6/9	0.3–1.4
Maternal age	2/12	1.5–2.0
Infant feeding	0/7	0.7–1.3
Linear growth	4/4	1.1 <sup>a</sup> –1.9

\*95% Confidence interval excludes one.  
<sup>a</sup>Adjusted RR per 5-cm increase.

risk may result from insulin's ability to directly target breast cells or the related IGF-1 polypeptide [228]. IGF-1 is synthesized in the liver, but is also present in breast cells and functions as an autocrine growth factor [231]. Circulating IGF-1 is bound with high affinity to IGFBP-3 and evidence suggests that IGFBP-3 plays a regulatory role in the proliferation of breast cancer cells as a result of its inhibition of IGF-1, the binding protein for cellular integration [231]. High circulating concentrations of IGF-1 and IGFBP-3 are associated with an increased risk of breast cancer and IGF-1 appears to be an important link between obesity and increased risk of breast cancer [228].

Type-2 diabetes is characterized as a high insulin state caused by insulin resistance in fat and muscle tissues and leads to an increased production of insulin, whereas type-1 diabetes is a state of absolute deficiency of insulin caused by autoimmune destruction of pancreatic  $\beta$  cells. The main risk factors for type-2 diabetes include: older age, obesity, and genetic predisposition. The etiology of type-1 diabetes is much less understood than that of type-2, but evidence suggests that both genetics and environmental exposures early in life, including nutrition, could play a role in the disease process. Early infant feeding patterns, such as reduced duration of exclusive breastfeeding, early age at introduction to dairy products, or early age at introduction to gluten-containing solid foods, have been associated with a risk of type-1 diabetes. Furthermore, it is possible that the aforementioned infant feeding patterns are associated with a risk of type-2 diabetes later in life, or that particular infant feeding patterns could modify exposures later in child- or adulthood that in turn increases one's risk for type-2 diabetes, hyperinsulinemia, and the subsequent risk of breast cancer. To date, most studies investigating the association between early infant feeding patterns and risk of

diabetes focused solely on the association between ever-breastfeeding and the duration of overall breastfeeding and the risk of type-1 diabetes. To our knowledge, very few studies have investigated the association between early life feeding patterns other than ever-breastfeeding, or have extensively investigated the association between early infant feeding patterns and the risk of type-2 diabetes in the US.

### *Breastfeeding and Risk of Diabetes*

Reported findings on the association between the duration of breastfeeding (total and exclusive breastfeeding), age at introduction of supplementary milk products or solid foods and the risk of type-1 diabetes are mixed. Several older studies have observed an increase in the incidence of type-1 diabetes in individuals who have not been breastfed or who were breastfed for <4 months [232]. Data from more recent studies investigating this hypothesis are mixed. Perez-Bravo et al. [233] observed a statistically significant difference in the reported duration of breastfeeding (5.4 vs. 7.6 months,  $p < 0.02$ ) among children with type-1 diabetes compared to controls, while Couper et al. [234] did not observe an association between the total duration of breastfeeding and the risk of diabetes-associated autoantibodies. Furthermore, a study of German children with a first-degree family history of type-1 diabetes reported that breastfeeding duration, either exclusive or partial, was not associated with an increased islet autoantibody risk by 8 years of age [235]. Recent data suggest that there may be an association between the duration of exclusive breastfeeding and the risk of diabetes. A study of Finnish children found no difference in the duration of any breastfeeding or in the age at introduction of solid food and the risk of type-1 diabetes; however, they did observe a statistically significant decrease in the risk of type-1 diabetes among children who were exclusively breastfed for at least 2 (OR 0.60, 95% CI 0.41, 0.89) or 3 months (OR 0.63; 95% CI 0.43, 0.95) [236]. Adjustment for mother's age and education, child's birth weight, or birth order did not affect the results [236]. In addition, a recent study of Finnish children with a family history of diabetes reported that those infants who were breastfed exclusively for at least 4 months had a lower risk of seroconversion to all autoantibodies, including IA-2A, ICA, GADA, and insulin (IAA) [237]. There was no association between the duration of any breastfeeding and the presence of diabetes-associated autoantibodies, or any of the antibodies [237]. It is possible that exclusive breastfeeding itself is not associated with an increased risk of type-1 diabetes, and that the observed association between breastfeeding and diabetes may be completely explained by the correlation of duration breastfed and timing of exposure to cow's milk, cereal, or other solid foods. Finally, the association between breastfeeding and diabetes may be biased due to residual confounding by the sociodemographic and other characteristics of the women who chose to exclusively breastfeed for 4 months or longer.

The relationship between early infant diet and the risk of type-2 diabetes has not been well documented compared to the association with risk of type-1 diabetes. Furthermore, the etiology of type-2 diabetes remains unclear, which hampers our ability to target specific exposures and time periods that may play a role in the risk of type-2 diabetes. Three studies to date indicate that there may be a link between early infant feeding and the risk of type-2 diabetes later in life. One investigation of breastfeeding and the incidence of type-2 diabetes among the Pima Indians reported that exclusive breastfeeding for the first 2 months of life was associated with a significantly lower rate of type-2 diabetes [238]. Another study investigated the association between early life exposures and the risk of insulin resistance and type-2 diabetes among middle-aged men living in rural and urban areas near Bangladesh, India [239]. The researchers observed that men living in urban compared to rural areas and those with increased adult weight gain over the 10 years of follow-up compared to those men without adult weight gain were at significant higher risk for insulin resistance and type-2 diabetes [239]. Canadian children who were breastfed for at least 12 months had a lower risk of developing type-2 diabetes compared to children breastfed for less than 12 months (OR = 0.24; 95% CI 0.13, 0.99) [240]. The estimate remained protective, but non-significant (OR = 0.27; 95% CI 0.06, 1.26), after adjustment for maternal smoking, maternal alcohol use, birth weight, maternal BMI, and maternal diet [240]. Finally, a study in Holland observed that men and women aged 48–53 years who were exclusively breastfed had lower fasting insulin and post-challenge glucose levels compared to those who were bottle-fed [241]. It is possible that susceptibility to type-2 diabetes may be a function of the interaction between genetic factors, intrauterine exposures, infant and childhood diet, as well as lifestyle across the lifespan.

#### *Age at Introduction of Milk Supplementation and Risk of Diabetes*

Ecologic studies provide evidence to support an association between diabetes incidence and cow's milk consumption based upon their observations of a positive correlation between the regional incidence of type-1 diabetes and per capita milk consumption [232, 242]. These observations lead to investigations into the association between cow's milk-based infant formula consumption early in life and later development of insulin-dependent diabetes [232, 242]. Two meta-analyses showed a moderate increase in the risk for type-1 diabetes in children exposed to cow's milk before 3 months of age. The first meta-analysis by Gerstein et al. [243] of 13 studies found a 1.5 times higher risk of developing diabetes for people who were exposed to milk-based products before 4 months of age compared to those exposed at or after 4 months of age. In addition, the second meta-analysis of early infant diet and the risk of type-1 diabetes found a similar relationship between exposure to cow's milk (OR = 1.61; 95% CI 1.31, 1.98) and exposure to breast-milk substitutes (OR = 1.38; 95% CI 1.18, 1.61) before the age of 3 months [244]. In contrast,

no association was observed in prospective studies of diabetes-related autoantibodies and the age when cow's milk or cow's milk-based formulas were introduced. A small study of Australian children with a first-degree family history of type-1 diabetes found no association between age at introduction of cow's milk and the development of islet autoantibody [234]. Another similar study of children with a first-degree family history of type-1 diabetes in Germany also reported no association between early age at milk supplementation and risk of increased islet autoantibodies in the children by 8 years of age [235].

*Intrauterine Exposures, Age at Introduction of Gluten-Containing Foods, and Risk of Diabetes*

Among infants with a first-degree family history of type-1 diabetes, those who received food supplementation with gluten-containing foods before 3 months of age were at an increased risk of islet autoantibodies (HR = 4.0; 95% CI 1.4–11.5) compared to children who were exclusively breastfed until 3 months of age [235]. In addition to these findings, American children with a family history of type-1 diabetes were at an increased risk of islet autoimmunity if they were exposed to cereals at 3 months of age or younger or at 7 months of age or older, compared to those exposed from 4–6 months of age [245].

It is possible that there is a window of exposure to cereals outside which the risk of autoimmunity is increased, however further investigation into the association between timing and type of cereal supplementation and risk of autoimmunity or type-1 diabetes is needed. Additional studies may elucidate whether the observed risk from the aforementioned study is due to exposure to specific antigens or to other components of cereals or possibly the combination of the ingredients (i.e. type of milk or type of cereal).

In addition to the proposed association between early childhood diet and risk of islet autoimmunity and type-1 diabetes, it is possible that intrauterine nutritional or other exposures may play a role in the subsequent risk of diabetes in the offspring. In a study of the association between intrauterine nutritional exposure and the risk of islet autoimmunity in children with a family history of type-1 diabetes, an inverse association was observed between maternal dietary intake of vitamin D during pregnancy and the risk of islet autoimmunity in offspring [246]. Thus the offspring of women who consumed higher levels of vitamin D from food were at a decreased risk of islet autoimmunity compared to the offspring of mothers who reported lower vitamin D intake (HR = 0.49; 95% CI 0.26, 0.94) [20]. A significant association remained, even after adjustment for HLA genotype, family history of type-1 diabetes, presence of gestational diabetes mellitus, and ethnicity (HR = 0.37; 95% CI 0.17, 0.78) [246]. The researchers did not observe any association between maternal fatty acid intake and the risk of islet autoimmunity in the offspring. These results suggest that maternal intake of vitamin D through foods may

have a protective effect on the appearance of islet autoimmunity and the risk of type-1 diabetes in their offspring.

*Biological Mechanism of Infant Feeding Patterns and Risk of Diabetes*

The biological mechanisms responsible for the association between early infant feeding patterns and the risk of diabetes remain unclear and further research is necessary before any conclusions can be drawn. It is possible that differences in feeding methods may play a role in both intrauterine and post-natal development of metabolic disorders either directly or indirectly through immune responses to maternal nutritional intake, cow's milk proteins, and/or accelerated childhood growth and adiposity. There are several proposed mechanisms by which infant feeding may affect childhood overweight and obesity, including altered plasma insulin and leptin levels [247].

Endocrine responses to dietary intake in infancy may play a direct role in later risk of diabetes through increased weight gain associated with infant feeding patterns. In one study of endocrine responses of breastfed and bottle-fed infants, bottle-fed infants had significantly higher plasma concentrations of insulin after feeding compared to infants who were exclusively breastfed [248]. Infant feeding patterns may also play a role in the infant's response to insulin and in the fat deposition of the infant. Higher insulin levels stimulate greater adipose tissue deposition and have been associated with a subsequent increase in weight gain and obesity [247]. Since insulin enhances cell glucose uptake and inhibits lipolysis, bottle-fed infants may have a different composition of body fat or increased BMI compared to breastfed infants, that in turn may play a role in the later risk of diabetes. Several studies have documented that infant-feeding practices are associated with differences in weight and body mass during infancy, early childhood, and in adolescence. In six studies of individuals between 3 and 26 years, all but one showed a significant association between ever-breastfeeding and reduced risk of child overweight [247]. Significant associations remained after controlling for several covariates including: paternal BMI and education level, maternal smoking, child birth weight, number of siblings, physical activity of the index, and dietary factors [247]. Another mechanism by which infant feeding may play a role in adult risk of increased body mass and diabetes is through the effects of leptin, a key regulator of appetite and body fatness. Early infant diet has been associated with leptin levels in adolescents. Specifically, adolescents who were born prematurely and randomized at birth to receive a high-protein preterm formula had a significantly greater ratio of leptin to fat mass compared to children who received banked donated breast milk [249]. Human milk intake was significantly associated with lower leptin concentrations relative to fat mass in adolescence, independent of potential confounders [249].

As mentioned previously, the association between short-term breastfeeding and the risk of diabetes could be due in part to early age at introduction of

cow's milk. Breast milk protects the infant against infections by maternally transmitted immunity and this could also influence the child's resistance to other potential triggers of diabetes-associated autoimmunity, including exposure to autoantibodies in cow's milk [232, 237, 242]. Proteins present in cow's milk have been proposed to activate the immune system in a destructive process in some individuals leading to type-1 diabetes; this process may be mediated by exposure to and/or duration of breastfeeding as well as the age at introduction to cow's milk [237]. Thus short-term exclusive breastfeeding and early introduction of cow's milk could predispose individuals to autoimmunity or diabetes.

Large-scale studies are needed to disentangle the association between intrauterine, infant, childhood, and adult risk factors and the risk of type-2 diabetes and insulin resistance as well as determine the association between exclusive breastfeeding, age at introduction to breast milk substitutes and gluten-containing solid foods, as well as other childhood dietary exposures and risk of breast cancer.

## **Conclusions**

Carcinogenesis is a multi-step process, and the cellular and molecular pathways associated with each step provide targets for cancer prevention via nutritional interventions throughout the life course. This includes early life nutritional exposures, an area which has been understudied but has tremendous promise for impacting cancer risk. In fact, preventing or reversing the genetic and epigenetic changes associated with initiation and promotion processes early in life can be expected to have far greater preventive activity than late-in-life interventions that primarily act at the progression stage of carcinogenesis, when multiple genetic and epigenetic alterations have accumulated.

In the above case series describing early life nutritional exposures and breast cancer, over 20 studies of birth weight, birth length, and preterm births were examined, but no consistent association between a birth parameter and breast cancer risk appeared. The strongest effects on breast cancer can be seen in birth length, albeit research is limited, and linear growth velocity in childhood and adolescence, for which the most consistent associations appear.

What will we need to identify nutrition interventions in pregnancy and in early life that could reduce adult cancer risk? Future etiologic research needs to focus on measurement of the newborn's length of the trunk and limbs to explore the source of variation in birth length. Care should be taken in linear growth measurements from birth through infancy and childhood, because anthropometrics are riddled with error from inadequate standardization and training of anthropometrists, improper calibration of equipment, and lack of

growth reference data. Finally, cord blood analysis of immunologic parameters, such as CD19 and macrophages, and hormone levels of insulin, IGF-1, IGFBP-3, and leptin could be correlated with the birth size (length of limb vs. trunk) of the neonate to identify underlying hormonal-nutritional mechanisms related to those who have longer birth length than the average birth length for gestational age.

Maternal height and pre-pregnancy BMI along with weight gain in pregnancy, dietary intake and physical activity in pregnancy are important elements of the picture puzzle related to the birth size of the offspring and later breast cancer risk. More detailed information about the duration of exclusive and partial breastfeeding, the ages at introduction of breast milk supplements and substitutes as well as solid foods are needed in tandem with the anthropometric data. Access to anthropometric data collected at multiple points in infancy, childhood and adolescence along with parental anthropometry would enhance the opportunity to examine the factors influencing linear growth velocity, body fat distribution, and insulin resistance, all three endpoints of which are currently being investigated in relation to breast cancer research.

Methodological research in physical activity assessment has led to the development of the International Physical Activity Questionnaire, a version of which has been validated for children and one for adults (IPAQ website). This tool in tandem with the use of pedometers, accelerometers or another mode of calibration of actual physical activity will advance our understanding of the interplay of energy balance from diet and physical activity. Along this line, considerable research in energy expenditure (assessed by whole room indirect calorimetry, by  $VO_{2max}$  or another vehicle utilized during exertion) in children aged 5–17 years has revealed ethnic group differences in expenditure. In particular, African-American children have a consistently lower average resting, and basal energy expenditure than non-Hispanic white children, after taking into consideration pubertal stage, diet, and age [250]. These findings follow along with the secular trend in obesity [251] and in age at onset of puberty and menarche, where the African-American girls and boys enter puberty earlier than the non-Hispanic whites [252], and the average age at menarche is several months earlier in African-American than non-Hispanic white girls [253]. No data have been reported on energy expenditure in Hispanic children by ethnic subgroup. Moreover, gaps in energy expenditure research during pregnancy and lactation preclude the development of nutritional programs in early life.

Another area for future research examines the effect of weight loss from dieting and/or physical activity on risk factors for breast cancer. Neither animal nor human studies have reportedly examined whether weight loss during different phases of the life course will reduce cancer risk. While dieting in pregnancy and early childhood is not advocated for most individuals, extremely obese children have been placed on weight loss plans and enhanced physical activity. The components of the diet in the weight loss

plans have not been elucidated nor have the children been followed after intervention to assess any long-term effects. Key areas for consideration include the identification of biomarkers other than hormones for breast cancer prevention research. Thus the area of energy balance, weight loss and physical activity in relation to cancer prevention will be greatly enhanced by multidisciplinary research combining animal experimentation and human exploration.

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