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The maternal womb: a novel target for cancer prevention in the era of the obesity pandemic?

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Abstract

The dramatic rise in worldwide prevalence of obesity has necessitated the search for more efficacious anti-obesity strategies to counter the increased cancer risks in overweight and obese individuals. The mechanistic pathways linking obesity status with adult chronic diseases such as cancer remain incompletely understood. A growing body of evidence suggests that novel approaches and interventional agents to disrupt the feed-forward cycle of maternal to offspring obesity transfer that is initiated *in utero*, will be important for stemming both the obesity pandemic and the associated increase in cancer incidence. The convergence of multiple research areas including those encompassing the insulin and insulin-like growth factor (IGF) systems, epigenetics, and stem cell biology is providing insights into the potential for cancer prevention in adult offspring previously exposed to the intrauterine environment of overweight/obese mothers. Here, we review the current state of this nascent research field, with a focus on three major cancers namely breast, colorectal and liver, and suggest some possible future directions to optimize its impact for the health of future generations.

Keywords

fetus; obesity; cancers; programming; interventions

Obesity pandemic and cancer risks

Obesity has become a global problem (http://apps.nccd.cdc.gov/dcpcglobalatlas/DietNutrition.aspx#WorldMap). The last three decades have seen a huge rise in the number of individuals who are overweight (body-mass index [BMI] 25-29.9 kg/m^2) or obese (BMI ≥30 kg/m^2). In the United States alone, the age-adjusted prevalence of adult obesity during 2007-2008 reached 33.8% while that for obesity and overweight combined rose to 68.0% of the population (1). Importantly, nearly 50% of American women of childbearing age are overweight or obese. Among children and adolescents, 31.7% were at or above the 85th percentile of BMI for age within the same period (2). These statistics are alarming, as children who are overweight or obese tend to remain so later in life. The presumed foremost cause of the obesity pandemic is the imbalance between caloric intake and physical activity, although environmental,

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developmental (fetal, postnatal and trans-generational), and genetic factors are contributors as well. The excess burden of bodyweight in both the young and adult brings with it significant health complications including increased rates of: cancer, cardiovascular disease, type 2 diabetes, hypertension, metabolic syndrome, and non-alcoholic fatty liver disease.

Numerous studies have documented the positive associations of cancer incidence with high BMI. In one recent report (3), increased risks of multiple cancers were found to be commensurate with a 5 kg/m^2 increase in BMI; this corresponds to weight gains of only 15 kg and 13 kg, respectively in men and women with an average BMI of 23 kg/m^2. In men, these cancers included those of the esophagus, thyroid gland, colon, kidney, and rectum as well as malignant melanoma, multiple myeloma, leukemia and non-Hodgkin's lymphoma. In women, cancers whose risk is positively associated with obesity were those of the endometrium, gallbladder, kidney, esophagus, thyroid gland, (post-menopausal) breast, pancreas, and colon in addition to leukemia and non-Hodgkin's lymphoma (3, 4). The magnitude of association of high BMI with colon and rectal cancers was stronger for men than women, whereas that for renal cancer was stronger for women than men, reflecting the complex interactions of obesity and gender with cancer risk (3).

Several recent trends in cancer incidence noted for the US population suggest associations with obesity. For example, whereas the age-adjusted colorectal cancer incidence rates for 1997-2006 declined among both men and women of age 50 years or greater, these rates increased among those younger than 50 years of age (5) and for which obesity rates have also greatly increased. In men, incidence of kidney, liver and esophageal cancers as well as leukemia, myeloma and melanoma have increased between 2002 and 2006 (5). An upward trend in incidence rates of lung, thyroid, pancreas, bladder and kidney cancers and non-Hodgkin's lymphoma, melanoma and leukemia were similarly noted for women of the (5).

Birth weight and birth length as surrogates of fetal growth and nutrition: links with later obesity and cancer incidence

Birth weight and length for infants of normal gestation period has important predictive value for later adult BMI as well as propensity for chronic diseases. High birth weight has been associated with an increased tendency for obesity in later life (6). Low birth weight is associated with increased risk for heart disease, hypertension, type 2 diabetes and glucose intolerance in adulthood (7). Importantly, birth weight and birth length are positively associated with risk for certain cancers (8, 9). Among childhood cancers, birth weight is positively associated with increased risk for neuroblastoma (10) and leukemia (11-13). Further, the risk of prostate (14, 15) and testicular (16, 17) cancers in men is positively associated with birth weight. In contrast, increased risk for colorectal cancers is linked to lower birth length for men, but not women (18).

The influence of birth weight on breast cancer risk is not as straightforward, although several recent reports show a modest positive correlation of birth weight (and length) with occurrence of this cancer in adulthood (19-22). Women who had lower birth weight but had increased adipose tissue deposition while young had lower breast cancer risk (23). In this regard, the apparent positive associations of birth weight and length with a pre-menopausal woman's circulating estradiol levels (considered a major risk factor for breast cancer) are intriguing (24). However, in another study, pre-menopausal women with lower than average birth weights who then gained excess weight as adults tended to have elevated serum estrogen concentrations than did women with higher birth weights and excess weight gain as adults (25). While it is apparent that birth indices can have long lasting effects on circulating estradiol levels, the relative contributions of the ovaries, adrenals and adipose depots to

these programmed changes in estradiol synthesis and secretion, with potential impact on breast cancer risk, remain unexplored.

Maternal BMI and progeny's adiposity

Maternal BMI is positively associated with increased birth weight and neonatal adiposity (26). A high pre-pregnancy BMI and/or excessive weight gain during pregnancy confer a propensity for greater adiposity of children born from these mothers (27-30). Children with high BMI often become obese adults (31-33). The effect of pre-pregnancy obesity on adiposity status of progeny may be amplified by concurrent gestational diabetes (and insulin resistance) in pregnant mothers (30, 34). Thus, a positive feed-forward cycle of adiposity transferred from mother to child will in all likelihood, increase relative risk for cancers in the latter during adulthood and maybe even earlier (Figure 1).

Obesity and insulin/IGF systems

The insulin and IGF systems are likely important functional links between obesity and increased cancer risk. Of particular note, obesity leads to enhanced circulating levels of insulin, IGF-I, IGF-II and IGFBP-3, while reducing levels of the low molecular weight IGF-binding proteins (IGFBP-1, IGFBP-2) (Table 1). The net effect of these changes is increased signaling through the insulin and IGF-I receptors, with resultant increased mitogenesis and decreased apoptosis, in many if not all tissue sites. An elevated circulating level of insulin is a major risk factor for colon, breast and liver cancers (Table 2). Similarly, an elevated circulating level of IGF-I and reduced circulating levels of IGFBP-1 and IGFBP-2 are known risk factors for colon cancer (Table 2). The circulating IGF system, as well as pancreatic insulin secretion and tissue insulin sensitivity, are influenced by dietary or obesity effects *in utero* and/or during lactation (35-38).

Maternal obesity and breast cancer

Pregnancy weight gain may influence risk for breast cancer in mothers and their daughters. For post-menopausal women, excessive weight gain during their prior pregnancies was found to increase risk for development of breast cancer (39). By contrast, a comparable gain in weight may confer short-term protection against pre-menopausal breast cancer (40). Interestingly, BMI, pregnancy weight gain and dietary fat intake do not appear to significantly affect maternal steroid hormone levels during pregnancy (41-43). In animal models of mammary carcinogenesis, consumption of a high fat diet resulted in enhanced pregnancy weight gain and an increase in subsequent mammary cancer incidence (44). Effects of obesity (and of excessive weight gain) during pregnancy on breast cancer risk of daughter(s) has also been examined, albeit only in limited fashion. Pre-pregnancy BMI was not associated with breast cancer risk of daughters, whereas a pregnancy weight gain of 25-34 pounds was associated with a slightly increased risk for breast cancer (OR=1.5; CI 1.1, 2.0) in daughters (45). Paradoxically, women whose mothers gained 35 pounds or more during pregnancy were not at increased risk. While these associations were based on a limited number of subjects (510 case mothers, 436 control mothers), have not been replicated, and the mechanism(s) underlying this association at the molecular level remains unexplored, the potential consequences of these associations if confirmed, are highly relevant to the current global obesity pandemic.

The uterine milieu has been shown to affect offspring's risk for adult breast cancer. For example, the condition of preeclampsia has been associated with protection against breast cancer risk in both mothers and their female offspring (19, 46, 47). Pelvic intercristal width in pregnant mothers, which was used as a surrogate for maternal circulating sex steroid hormones, was positively associated with risk of breast cancers in adult offspring (48).

Further, a linkage between higher maternal BMI and elevated cord blood C-peptide levels (26), a stable biomarker of insulin secretion, has been reported. The latter provides a possible route by which maternal BMI may adversely influence the fetus.

Exposure of rats or mice during pregnancy and/or lactation to diets rich in energy, fats and/or sugars has detrimental health effects in their offspring. These include: increased adiposity; hyperglycemia; hyperinsulinemia; triglyceridemia; depressed immune function; altered neural and satiety regulatory pathways; hypertension; reduced plasma antioxidant status; and lower bone mineral density (36, 49-56). Pregnant rats fed a high fat diet delivered pups with increased birth weight and their female offspring exhibited shortened mammary tumor latency and increased tumor growth when given a mammary carcinogen as young adults (57). In a similar model of mammary carcinogenesis, offspring of dams fed diets containing a large amount of corn oil as fat source prior to and during pregnancy/lactation, showed increased mammary tumor incidence (58). In contrast, feeding an equivalent amount of olive oil (considered a healthy source of dietary fats) to dams was inhibitory to tumor formation in their progeny. These latter studies highlight the value of dietary lipid composition (good *vs.* bad fats) in the *in utero* programming of breast cancer.

Maternal obesity and colo-rectal cancers

Overweight and obesity are positively associated with increased colo-rectal cancer risk in men and to a lesser degree in women (59-63). The positive linkage between colon cancer mortality and obesity is also more evident in men than in women (64). Similar findings were observed in rat (65-67) and mouse (68, 69) models. In obese animals, colon tumor genesis was correlated with elevations in serum insulin, leptin, glucose, triglycerides, and cholesterol. However, proof of causality for any of these factors, individually or together, remains lacking.

Several studies have probed the developmental influences of underweight, overweight and obesity in children on their subsequent risk for colo-rectal cancer. Exposure to energy restriction during childhood and adolescence (Dutch famine years of WW II) was associated with reduced risk of colo-rectal cancer later in life (70), presumably reflecting metabolic programming and/or an epigenetic phenomenon. High BMI (i.e., above the 85th percentile of a US reference population) at adolescence (i.e., 14-19 years of age) was positively associated with increased risk of death (relative risk of 2.1 and 2.0 for males and females, respectively) from colorectal cancers at later life (71). Interestingly, a recent study showed that colon cancer risk in men is highly influenced by less drastic weight gains (63). In their study, Thysegen and colleagues reported that a cumulative mean BMI above 22.5 conferred increased colon cancer risk. Weight gain (1 lb/year) beginning at age 21 was associated with increased cancer risk (63). Short-term (2-4 years prior) weight gain of 10 lbs was positively associated with cancer risk in the proximal half of the colon (63). The rise in propensity for colon cancer with long-term weight gains was demonstrated in a study of African-American women (72). In this case, a ≥30 kg weight gain beginning at age 18 was positively associated with risk for colorectal polyps. Animal studies also support the influence of early postnatal weight gain on colon cancer incidence. Early over-feeding of pre-weanling rats enhanced colon tumorigenic capability later in life (65). In a rat model of intestinal carcinogenesis, switching of pregnant rat dams from a non-obesogenic diet to a more obesogenic diet at parturition accelerated early neonatal body weight accretion, increased colon tumor multiplicity and altered circulating levels of IGF system components in male progeny as later adults (35). However, no studies (using human populations or animals) have yet evaluated the role of maternal obesity on progeny's colon cancer risk at later adulthood.

Maternal obesity and hepatocellular carcinoma

Obesity leads to an increased propensity for liver cancers in humans (73-76). Feeding a 'Western' or 'cafeteria' diet rich in fats and sugars to pregnant and lactating rats promoted hepatic steatosis and liver oxidative stress response in their progeny (53). Steatosis and oxidative stress are well-known promoters of the liver pathology that precedes hepatocellular carcinoma (77). Thus, it is tempting to speculate that the rising incidence of liver cancer in the US and other western societies (associated with increased rates of hepatitis virus infection) is further fueled, in part, by maternal obesity. However, to the best of our knowledge, no studies have directly examined this possibility.

Maternal obesity and the fetal/neonatal epigenome

Effects of diet and nutrition can be trans-generational. Chronic consumption of high fat diets by young female rats conferred glucose intolerance, hyperinsulinemia, triglyceridemia, and increased adiposity to their male progeny, indicating long-term, programmed and heritable alterations in metabolism, gene expression, and tissue phenotype (78). Feeding a high carbohydrate diet to female rat pups around weaning led to hyperinsulinemia and increased adiposity later in life; effects they transmitted to their progeny (79). Similarly, consumption of a high fat diet for four weeks by dams from pre-pregnancy through to weaning induced a heritable increase in body length and a decrease in insulin sensitivity in first and second-generation rat offspring (80). Most interestingly, these trans-generational effects were propagated via maternal and paternal lineages, indeed supporting an epigenetic basis (80).

The long-term contributions of maternal diet to adult offspring health have been postulated to also involve altered stem cell numbers and/or rates of stem cell renewal (81, 82). To date, only a few known links between nutrition, the insulin and IGF systems, and stem cell renewal have been defined (83-85). While the relevance of insulin as an essential factor for *in vitro* sphere-forming ability (a measure of cancer stem cell renewal) of multiple cancer stem cell types is compelling, given this factor's mitogenic action, further studies are required to mechanistically explain these connections.

With increased interest in the role that epigenetics plays in disease evolution, studies seeking to understand if, and how, maternal obesity (and maternal diet) affects the epigenome of the fetus and neonate and in so doing, modifies disease susceptibility at later adulthood have grown in numbers within the last several years. Initial studies have focused on rat liver metabolic and metabolism-regulatory genes to model dietary influences involving the epigenome in the impairment of developmental processes in progeny. Dietary protein restriction and folic acid supplementation in pregnant rats were found to elicit specific changes in DNA methylation of liver glucocorticoid receptor and peroxisomal proliferator-activated receptor-α genes in progeny, correlating with respective levels of expression (86-88). Importantly, both of these nuclear receptors are key players in metabolic regulation by the liver. In a study of intrauterine growth-restricted rat fetuses, altered histone methylation status of the liver IGF-I gene was associated with corresponding modifications in hepatic IGF-I expression and deregulated metabolic status (38). Remarkably, a high fat diet fed to male rats programmed pancreas β-cell dysfunction, as well as hypomethylation of a specific pancreatic islet gene in their female progeny (89). Neonatal overfeeding, via litter size restriction, led to increased methylation of the insulin receptor gene promoter in adult rat hypothalamus (90). Such phenomena are not restricted to rodents. A recent study of pregnant women found that maternal folic acid supplementation during pregnancy correlated with increased DNA methylation of the IGF-II gene differentially methylated region (DMR) in their children at age 1½ years (37). Most significantly, an inverse association between extent of IGF-II gene DMR methylation and birth weight was documented. While none of

the above studies specifically examined for effects of maternal obesity or overweight on epigenetic phenomena in progeny, they do provide impetus for further investigations in this direction.

In order to comprehensively address the contribution of the maternal environment, fetal stem cells and the fetal epigenome to the etiology of breast cancer, the epigenetic program of mammary gland development and functional differentiation was recently elucidated (91). This information will provide an initial roadmap into understanding how the *in utero* and immediate postnatal environments (and interactions with maternal obesity phenotype) modify the mammary gland epigenome as well as this organ's predisposition to or protection from, tumorigenesis in adult progeny. Similar strategies will invariably prove useful for other tissues subject to fetal programming and high cancer incidence such as the liver, colon and uterus. The ultimate goal of such studies is to enable reversal of *in utero*-instigated epigenetic events (i.e., silencing of tumor suppressive genes and pathways) that contribute to tumor initiation and progression (92-95).

Need for new metabolism-based screening paradigms for cancer pre-disposition

It is now recognized that a greater than average weight gain during the first years of postnatal life is positively associated with obesity and insulin resistance later in life (6, 27, 31, 96), thereby also leading to increased cancer risk. Weight gains from 0 to 3 months of age were negatively associated with serum ghrelin and adiponectin when corrected for body fat at age 17 years (96). Children born from mothers with type 1 diabetes exhibit increased frequency of overweight/obesity and the BMI of their children were found to be positively correlated with cord blood leptin, albeit not with insulin levels (97). Moreover, daughters born from mothers who had gestational diabetes mellitus and impaired glucose tolerance during pregnancy had increased waist circumference and increased insulin resistance at 15 years of age (98). These findings point to the utility of screening paradigms for children born from overweight, obese, or gestational diabetic mothers to estimate pre-disposition for adiposity and associated co-morbidities. Such screens could include indices of rates of weight gain, adiposity, adipose-related serum hormones, and insulin sensitivity/resistance during early childhood. Screening could be coupled with nutritional or other preventive interventions such as changes in lifestyle and increased physical activity.

Interventions prior to and during pregnancy

Dietary interventions prior to and during pregnancy may confer some degree of protection against the programming effects of maternal obesity status (99). Indeed, an increased understanding of the maternal influence on health status of progeny has led to current goals to reduce weight gain prior to and during pregnancy for obese/overweight women and to control hyperglycemia in mother and fetus. The newly revised Institute of Medicine guidelines (http://www.iom.edu/Reports/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines.aspx) call for less overall body weight gain during gestation for those women who begin pregnancy already overweight or obese. Nonetheless, there is a dearth of understanding, borne from a lack of science, for how children's cancer risk is influenced by the mother's BMI at peri-conception and pregnancy. Additionally, the relative contribution, if any, of paternal overweight and obesity status during the peri-conceptual period to an offspring's cancer risk is unknown. These are important questions, ripe for elucidation using new high-throughput methodologies.

Several hypoglycemic agents that potentially are useful (in combination with diet) during preconception and pregnancy to mitigate the negative effects of maternal obesity include metformin, glyburides and glucagon-like peptide (GLP-1) analogs (100-105). Metformin, in particular, has recently been associated with reduced cancer incidence of multiple tissue sites (including breast, colon and liver) in diabetic individuals (106-111). While actively investigated as a treatment for gestational diabetes, to our knowledge, no studies have examined the efficacy of metformin during pregnancy to prevent cancers in progeny (either animal or human studies). The 'promise' of metformin in prevention of cancer programming is highlighted by its ability to traverse the placenta and its lack of teratogenic activity for the human fetus (112).

Maternal obesity and high fat/high calorie maternal diets impose a pro-inflammatory state on the fetus (113, 114). In a study of pregnant rat dams, supplementation of a high-fat diet with the anti-oxidant (and dietary factor) quercetin partially reversed the metabolic syndrome phenotype in progeny (51). This remarkable result raises the possibility that anti-oxidant-enriched maternal diets could be used to favorably affect an offspring's cancer risk. While there are only few pre-clinical studies that directly address this potential, there are many dietary phytochemicals with known anti-oxidant properties and which also exhibit *in vivo* bioavailability and *in vitro* or *in vivo* cancer-inhibiting actions; examples include quercetin, lycopene, resveratrol, anthocyanin(s), curcumin, silymarin, and catechins (115). Diets enriched for these factors, and perhaps used in combination with metformin, may provide benefits to expectant mothers who are obese. Since some of these same bioactive factors appear to be modifiers of the epigenome, the elucidation of their influence on the expression and activity of chromatin-modifying enzymes may provide insights into their potential cancer-inhibitory actions in offspring (116, 117). The feasibility of this approach for minimizing susceptibility to cancer and other adult-onset chronic diseases clearly necessitates pre-clinical studies in rodent models of maternal obesity.

Cancer risk, both in the immediate and longer term, is potentially modifiable by nutritional means (118). A striking example of this is the observation that soyfood consumption during childhood and adolescence lowers breast cancer risk in females during later adulthood (119, 120). Indeed, a soy protein-based diet fed only during gestation delayed the first appearance of tumor, decreased tumor multiplicity, and inhibited tumor grade in female rat progeny given a mammary carcinogen, when compared to control animals (121). Similarly, a maternal (gestation/lactation) diet containing a soy protein isolate resulted in significant reductions in body weight, mammary terminal end bud number, and abdominal fat pad weight, and enhanced mammary gland differentiation in female weanling rats, compared to a control maternal diet (122). A maternal (gestation plus lactation periods) diet containing blueberry powder (a rich source of anthocyanins and polyphenols with demonstrated anti-oxidant activities) enhanced mammary epithelial differentiation in weanling rats, an effect that may indicate tumor-protective actions in later life (123). Lastly, a recent report demonstrated significant improvement in glucose tolerance for 6-month-old mice, whose dams received a soy protein-based diet from preconception and throughout pregnancy (124). These studies provide strong rationale for further development of specific dietary formulations for pregnant obese/overweight mothers with the goal of reducing the potential for cancers in offspring as adults (125). Lastly, given the reports that breast-feeding may confer a lower risk of overweight/obesity for children borne of obese mothers (126), the question of whether the risk of adult disease in progeny may differ with maternal BMI status during pregnancy and lactation in breast-feeding mothers warrants further scrutiny.

Perspectives

Emerging data predict a positive impact of anti-obesity strategies for children on decreasing their long-term cancer risk (127). However, most current strategies do not consider targeting obesity risk beginning in the womb for the dual-prevention of obesity and cancer. Data summarized above demonstrate the maternal contributions to determining an offspring's relative risks for obesity and attendant cancer risk (Figure 1). Intervening in the feed-forward cycle of maternal to offspring adiposity/obesity with new strategies and approaches will be required to stem the obesity pandemic. Given the increasingly acknowledged link between obesity and many cancers, such approaches may also counter the expected rise in occurrence of cancers in children and adults borne from overweight or obese mothers. The fields of epigenetics and stem cells will undoubtedly be important in addressing the large gaps in our understanding of the mechanistic aspects of fetal programming of adult cancers and specifically as influenced by maternal obesity and/or maternal diet. Mature fields such as epidemiology, the study of bioactive dietary factors, and the molecular endocrinology of insulin and IGFs also will find application to the above challenges. Since many aspects of embryo-maternal interaction, placentation, fetal organ system development, and pregnancy are species-specific, it will be important to study multiple animal models, as well as primates and the human where appropriate, to elucidate the generalities of maternal obesity effects on a fetus/neonate's later cancer risk and how this may be countered by targeting the pregnant uterus.

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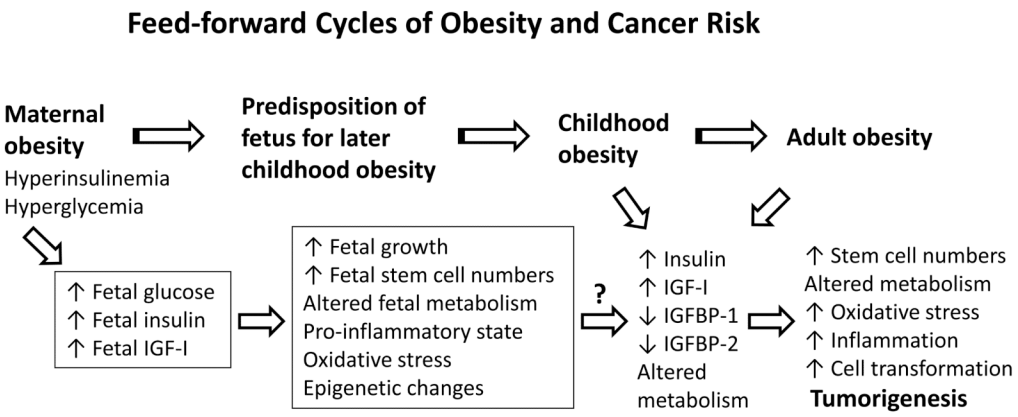

Fig. 1.

Model for maternal to offspring transmission of obesity and cancer risk. IGF-I, insulin-like growth factor-I, (mitogen, cell survival factor); IGFBP-1, insulin-like growth factor-binding protein-1, (an IGF-I binding protein present in sera and tissues and which regulates IGF-I bio-availability); IGFBP-2, insulin-like growth factor-binding protein-2, (an IGF-I binding protein present in sera and tissues and which also regulates IGF-I bio-availability). The experimental data supporting this model are discussed in the text. The model predicts the efficacy of early intervention (i.e., in overweight/obese mothers, prior to or during pregnancy) in lowering risks for both obesity and cancer in their offspring.

Table 1

Associations of obesity or body mass index (BMI) with blood levels of insulin and insulin-like growth factor system components in adults and children

Obesity (men)	↑ insulin ↑ free IGF-I	↓ IGFBP-1 ↓ IGFBP-2	Ref. 128
Overweight/obesity (women)	↑ insulin	↓ IGFBP-1 ↓ IGFBP-2	Ref. 129
BMI (men)	↑ IGFBP-3	↓ IGFBP-2	Ref. 130
BMI (men and women)	↑ IGF-II	↓ IGFBP-2	Ref. 131
BMI (women)	↑ IGF-II ↑ IGFBP-3		Ref. 132
	↑ bioactive/total IGF-I	↓ total IGF-I ↓ IGFBP-1	Ref. 133
Obesity (children)	↑ insulin ↑ IGF-II ↑ IGFBP-3 ↑ IGFs/IGFBPs	↓ IGFBP-1 ↓ IGFBP-2	Ref. 134
	↑ insulin	↓ IGFBP-2	Ref. 135
	↑ insulin ↑ IGF-I ↑ IGFBP-3		Ref. 136
	↑ insulin ↑ IGFBP-3		Ref. 137

Only those factors that exhibited a statistically significant association with obesity or BMI within a given study are listed. IGF-I, insulin-like growth factor-I; IGFBP-1, insulin-like growth factor-binding protein-1; IGFBP-2, insulin-like growth factor-binding protein-2; IGFBP-3, insulin-like growth factor-binding protein-3; IGF-II, insulin-like growth factor-II.

Table 2

Associations of insulin and insulin-like growth factor system components (in serum or plasma) with risk for three major cancers

Elevated insulin	↑ Colon cancer risk Refs. 138-143	↑ Breast cancer risk (pre-menopausal) Ref. 144	↑ Breast cancer risk (post-menopausal) Refs. 4, 138, 145	↑ Hepatocellular carcinoma risk Refs. 107, 146-148
Elevated IGF-I	↑ Colon cancer risk Refs. 139, 141, 149, 150			
IGFBP-1	↓ Colon cancer risk Refs. 139, 141, 142			
IGFBP-2	↓ Colon cancer risk Refs. 139, 142			

Only those endocrine factors that exhibited a statistically significant and consistent (i.e., over multiple studies) association with specific cancer risk are shown. Some studies reported significant associations of serum IGF-I, IGFBP-1, IGFBP-2 and/or IGFBP-3 with pre-menopausal or post-menopausal breast cancer risk, however a comparable number of other studies reported a lack of such associations.

The liver is the major tissue source of circulating IGF-I and IGFBPs. The relationships of serum IGF-I and IGFBPs with hepatocellular carcinoma risk (and status) are complex, due to the dys-regulated expression of these genes in pre-neoplastic, transformed or cancerous liver cells.