

Review Article

Obesity, metabolism and the microenvironment: Links to cancer

Sneha Sundaram¹, Amy R. Johnson¹, Liza Makowski^{1,2*}

Departments of ¹Nutrition, and ²Medicine, Nutrition Obesity Research Center, and Lineberger Comprehensive Cancer Center, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, 135 Dauer Drive, CB #7461, Chapel Hill, NC, 27599, USA

E-mail: liza.makowski@unc.edu

*Corresponding author

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Abstract

Historically, cancer research has focused on identifying mutations or amplification of genes within the tumor, which informed the development of targeted therapies against affected pathways. This work often considers tumor cells in isolation; however, it is becoming increasingly apparent that the microenvironment surrounding tumor cells strongly influences tumor onset and progression. This is the so-called “seed and soil” hypothesis wherein the seed (cancer cell) is fed and molded by the metabolites, growth factors, modifications of the extracellular matrix or angiogenic factors provided by the soil (or stroma). Currently, 65% of the US population is obese or overweight; similarly staggering figures are reported in US children and globally. Obesity mediates and can exacerbate, both normal and tumor microenvironment dysfunction. Many obesity-associated endocrine, metabolic and inflammatory mediators are suspected to play a role in oncogenesis by modifying systemic nutrient metabolism and the nutrient substrates available locally in the stroma. It is vitally important to understand the biological processes linking obesity and cancer to develop better intervention strategies aimed at curbing the carcinogenic events associated with obesity. In this review, obesity-driven changes in both the normal and tumor microenvironment, alterations in metabolism, and release of signaling molecules such as endocrine, growth, and inflammatory mediators will be highlighted. In addition, we will discuss the effects of the timing of obesity onset or particular “windows of susceptibility,” with a focus on breast cancer etiology.

Keywords: Basal-like breast cancer, health disparities, inflammation, macrophage, tumor subtype, window of susceptibility

INTRODUCTION

Cancer is the second leading cause of death in the developed world, surpassed only by heart disease^[1] and obesity is increasingly recognized as an oncogenic factor.^[2] The World

Health Organization estimates that 500 million adults and almost 43 million children under the age of five are obese worldwide.^[3] In the US, the incidence of obesity may be plateauing, but the prevalence of obesity (body mass index [BMI] >30) remains at 30%. Individuals who are overweight (BMI > 25 and < 30) represent a staggering 65% of the population.^[4] Childhood obesity is of particular concern^[5] as healthcare professionals are increasingly treating children for chronic diseases and endocrine disorders such as early menarche that are linked to cancer predisposition.^[6,7] In 2003, the results of large US and UK cohort studies first reported the striking association between obesity and cancer.^[2,8-10] Since then, it is now estimated

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that being overweight or obese contributes to 20% of US cancer deaths by influencing cancer onset.^[11] For a review of common cancers associated with an increased BMI refer to.^[12]

This review will discuss obesity-mediated mechanisms leading to tumor progression. Specific foods or nutrients such as saturated fats, processed foods, or charred meat that can act as carcinogens have been reviewed elsewhere and are beyond the scope of this review.^[7,13-17] Metabolic alterations associated with obesity have been reviewed in detail by Johnson *et al.*^[18] and will be briefly discussed herein. It is now widely accepted that obesity may promote cancer through several mechanisms and the effects of obesity on cancer risk is the primary topic covered in this review, with a focus on a specific breast cancer (BC) subtype called basal-like breast cancer (BBC).

OBESITY, BREAST CANCER AND WINDOWS OF SUSCEPTIBILITY

BC represents the highest incidence of cancers affecting women. It is the second most fatal cancer type.^[19,20] It is likely that it is likely that throughout the lifespan particular “windows of susceptibility” exist during which during which obesity plays a disproportionately greater role in promoting BC onset. Obesity, which disturbs tissue homeostasis, is one of the few modifiable BC risk factors; therefore, in order to develop more effective therapeutic strategies aimed at combating obesity-associated BC, it is critical to first understand the molecular mechanisms orchestrating the effects of obesity on BC. Our work has focused on specific periods of heightened susceptibility to BC due to the presence of an obese environment, such as the post-partum period.^[21] In addition, we have studied the normal breast microenvironment in both preclinical and human models to understand the role that obesity plays in cell-cell crosstalk and to delineate the underlying factors contributing to increased BC risk.^[21-23]

With the advent of high-throughput gene sequencing and expression analysis and the construction of The Cancer Genome Atlas, the classification of tumor subtypes with defined risks and clinical outcomes has opened the door to consider subtype-specific mechanisms.^[24,25] Considering that BC is a heterogeneous disease with many identified intrinsic subtypes (including luminal A and B, basal-like, claudin-low, and other subtypes),^[26] it is not surprising that intricate relationships exist between modifiable and non-modifiable risk factors in each subtype. Considering BCs overall, the relationship between obesity and risk is complex having no (or even protective) effects on premenopausal BC risk, yet obesity is associated with an increased risk of postmenopausal BC.^[27] With the ability to stratify BCs according to subtype,

epidemiologic studies have demonstrated that obesity is strongly associated with an increased risk of BBC in both pre- and postmenopausal women,^[27] whereas luminal BCs are associated with obesity solely during the postmenopausal period. BBCs are aggressive cancers, typically estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 negative (so-called “triple-negative BCs”) and as such, targeted therapies for BBCs are currently unavailable.^[28] These tumors are highly proliferative, patients have poor overall survival and are diagnosed predominantly in young African-American women, particularly obese women.^[4,26,27] Millikan *et al.* estimated that up to 68% of BBCs could be prevented by encouraging more women to breastfeed and by reducing obesity^[26,27] suggesting that this aggressive subtype of BC may be preventable through lifestyle modifications. Determining mechanistic risk factors could help address the need to reduce BBC risk as well as observed health disparities. Studies in preclinical models of other BC subtypes demonstrate that diet-induced obesity is associated with shortened mammary tumor latency^[29,30] and our findings demonstrate that this is also true for obesity-linked BBC.^[21]

Mechanisms of obesity related cancer

Growth factors and hormones

The mechanism(s) by which obesity induces carcinogenesis is likely to vary by cancer site, although several obesity-related systemic alterations may contribute to cancer onset globally through nutrient sensitive signaling cascades, such as the insulin/insulin-like growth factor (IGF-1) and PI3K/Akt/mammalian target of rapamycin (mTOR) pathways thus driving cell proliferation, angiogenesis, glycolysis and anti-apoptosis pathways leading to tumorigenesis and increased metastasis^[31-35] [Figure 1]. The connection between hyperinsulinemia and oncogenesis, known as the insulin-cancer hypothesis, was first proposed in the early 1990s.^[36,37] Obesity leads to insulin resistance, hyperinsulinemia and greater bioavailability of IGF-1.^[12,18,38] IGF-1 exhibits effects similar to insulin because of their shared downstream signaling pathways and studies suggest that IGF-1 may be the more relevant obesity-mediated growth factor.^[39] In the Women’s Health Initiative observational study, BC incidence was increased 2.4-fold in women in the highest quartile of fasting insulin concentrations compared with women in the lowest quartile. Ultimately, insulin/IGF-1 signaling may explain the relationship between BMI and BC risk, independent of estradiol levels.^[40] Furthermore, the alterations in IGF-1 signaling and inflammation observed in animals that over-express insulin-like growth factor receptor (IGF-1R) result in the formation of mammary tumors that share features with BBC.^[41] Conversely, genetic ablation of IGF-1R delays tumor onset as does treatment with

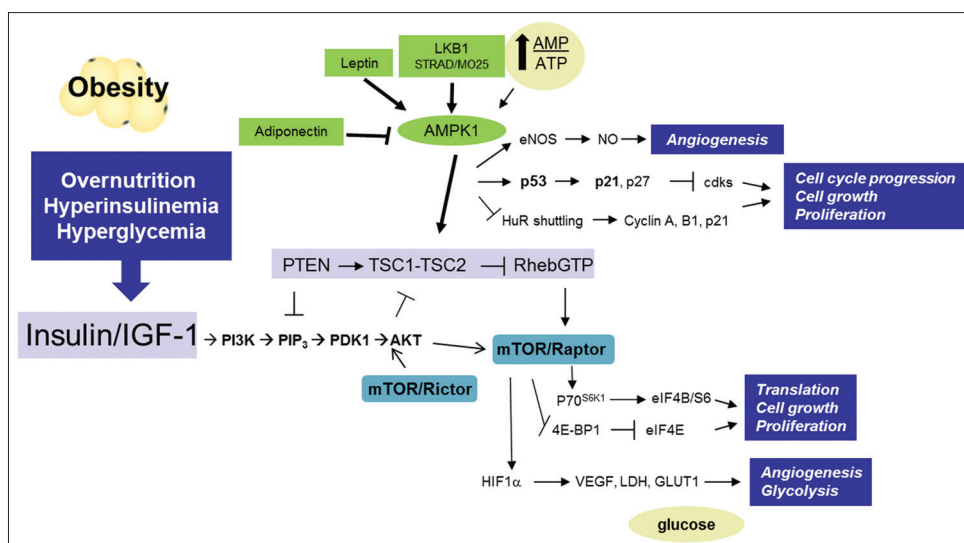


Figure 1: Obesity mediated alterations in nutrient sensitive pathways. Overnutrition in obesity leads to an increase in insulin and glucose. Insulin, insulin-like growth factor-I and downstream pathways are activated increasing fuel metabolism and cell growth through Akt-dependent pathways. Energy sensing pathways such as AMP-activated protein kinase and mammalian target of rapamycin are potential targets to blunt cell growth either through caloric restriction or pharmacologically.

an IGF-1R inhibitor.^[42] Three classes of inhibitors targeting the IGF-1R pathway are currently in clinical trials including anti-receptor antibodies, anti-ligand antibodies and small molecule tyrosine kinase inhibitors.^[38] First, anti-receptor antibodies are specific to IGF-1R and spare insulin receptors.^[43] Their mechanism of action is through inhibition of the binding of ligands to the IGF-1R.^[43] However, these antibodies are associated with severe side-effects including hyperglycemia and hyperinsulinemia.^[43] Although, phase II clinical trials with these antibodies showed promise, early phase III clinical trials have demonstrated lack of efficacy and metabolic toxicity (hyperglycemia).^[43] Second, anti-ligand antibodies are specific to IGF-1 and IGF-2 and do not cross react with insulin.^[44] However, the concern regarding high levels of free insulin-like growth factor binding protein that normally bind to the IGFs is still being addressed. Third, tyrosine kinase inhibitors were developed to be specific to IGF-1R but tend to inhibit all members of the pathway including insulin.^[45] Interestingly, these agents are proving to be safer than previously expected and may be of therapeutic advantage due to their broader range of inhibition.^[45] In sum, although there was a strong rationale for targeting the IGF-1R pathway based on preclinical studies, clinical trials have so far not been proven to be useful in the treatment of cancer.

Nutrient sensitive pathways, metabolism and cancer

There is great interest in controlling tumor growth through metabolic reprogramming.^[46,47] Glucose metabolism and growth control are tightly linked in proliferating cells and involve signaling pathways including the PI3K/Akt/mTOR pathway^[48] [Figure 1]. The “Warburg effect” describes cells exhibiting a metabolic shift toward glycolysis, supporting

increased production of biomass, especially amino acids and nucleic acids.^[49] We found that BC subtypes could be characterized as more or less aggressive using metabolomics analysis, which measure Warburg-like changes within tumors.^[50] Furthermore, fibroblasts isolated from patient BBC tumors and co-cultured with BBC-like epithelial cells drove glucose transporter-1 expression and glucose metabolism in BBC-like epithelial cells, which correlated with metabolic phenotypes in patient samples,^[50] thus denoting integrated cross-talk between the stromal and epithelial phenotypes on tumor metabolism. In experimental animal models, diet-induced obesity leads to activation of Akt and mTOR in a variety of epithelial tissues.^[31,32] Conversely, calorie restriction represses signaling through the PI3K/Akt/mTOR pathway.^[31,32]

Recent evidence suggests that metformin, an anti-diabetic biguanide medication, lowers cancer risk and reduces cancer incidence and deaths among diabetic patients, hence clinical trials are underway, some focusing on BC,^[51-54] and reviewed in.^[38] Metformin inhibits complex 1 of the mitochondrial electron transport chain and therefore, oxidative phosphorylation (i.e., adenosine triphosphate production). The subsequent low energy state drives 5' Adenosine monophosphate (AMP)-activated protein kinase (AMPK) activity [Figure 1], a master metabolic regulator that modulates multiple anabolic and proliferation pathways, including the PI3K/Akt/mTOR pathway and glucose uptake.^[47,55,56] Cancer incidence in diabetic patients on metformin was 7.3% compared with 11.6% in non-metformin users.^[53] However, it remains unclear whether metformin's

potential anti-neoplastic effects relates to the systemic action of this drug, (e.g., by reducing circulating glucose and insulin levels) and/or some direct action on cancer cells. Preclinical data suggests that the anti-tumorigenic efficacy of metformin is dependent on the obese and insulin resistant state.^[57,58] Metformin-mediated AMPK activation decreases cell growth *in vitro* and in xenograft models through inhibition of mTOR.^[59,60] Thus, metformin may have dual interrelated anti-tumorigenic functions – inhibition of the mTOR pathway and disruption of glucose uptake by cancer cells. Taken together, obesity is a high-energy condition that promotes increased growth factor signaling through the insulin/IGF-1 axis and is a nutrient-rich environment ultimately driving excessive stimulation of the PI3K/Akt/mTOR pathway [Figure 1].^[34,35,61,62]

Estrogens

Obesity can drive carcinogenesis by increasing estrogen concentrations. Obese adipose tissues up-regulate the conversion of androstenedione to estrone and testosterone to estradiol,^[63,64] while at the same time reducing sex hormone-binding globulin capacity which leads to increased levels of free, biologically active estrogens.^[64,65] In postmenopausal women, aromatization of androgens in the adipose tissue by aromatase elevates local and circulating levels of estrogen, although this is not true in some murine models (data not shown). Obesity-associated cytokines including interleukin-6 and tumor necrosis factor alpha (TNF- α), and adipokines, such as leptin, stimulate aromatase activity leading to an increase in estrogen synthesis, while weight loss has been shown to blunt estrogen levels.^[64,66] The role of obesity in regulation of estrogen and progesterone are reviewed in detail.^[67,68]

Adipokines

The adipose tissue secretes several growth factors and cytokines, known as the adipokines, involved in energy homeostasis, immunity, angiogenesis, and endocrine signaling.^[18] Leptin is produced mainly by expanding white adipose tissue, and is involved in the regulation of energy homeostasis.^[18] Leptin activates the Janus kinase (JAK)/signal transducer and activator of transcription (STAT), mitogen activated protein kinase (MAPK) –extracellular signal-regulated kinases (ERK1/2), PI3K/Akt, AMPK, and insulin receptor substrates pathways [Figure 1]. Leptin is mitogenic, anti-apoptotic, pro-angiogenic, and pro-inflammatory, and thus, is implicated in the stimulation, migration, and invasion of tumor cells, as well as in the production of cytokines by macrophages.^[69] Leptin also induces activation of the ERBB-2 pathway which interacts with IGF-1 to promote migration and metastasis of tumor cells.^[70,71]

Adiponectin is inversely correlated with obesity and leptin concentrations. Adiponectin regulates energy intake and expenditure, and plays an anti-inflammatory, anti-atherogenic, and insulin sensitizing role in metabolism. In cancer, adiponectin acts as anti-angiogenic, antiproliferative, pro-apoptotic, and anti-inflammatory mediator through AMPK and peroxisome proliferator-activated receptor signaling^[72] [Figure 1]. Adiponectin blocks induction of angiogenic vascular endothelial growth factor (VEGF) by suppressing TNF- α , inducing apoptosis and inhibiting migration in the vascular endothelial cells.^[73,74] Decreased adiponectin level correlates with increased BC risk in postmenopausal women^[75,76] and conversely high levels of adiponectin are associated with an increased BC survival.^[77] The leptin: adiponectin ratio may be the most relevant indicator of cancer risk as reviewed in detail.^[12,78] VEGF, basic fibroblast growth factor, and hepatocyte growth factor are other growth factors involved in BC-related angiogenesis under investigation.^[50,79,80]

Normal microenvironment

While basic science research has traditionally focused on understanding the contribution of genomic mutations within the cancerous epithelial cells, the characteristics of the tissue microenvironment are proposed to play an integral role in supporting the proliferation of cancer cells.^[81] In order to proliferate and escape apoptotic control mechanisms, transformed epithelial cells must adapt to – and take advantage of the conditions within the microenvironment in which they reside.^[82,83] In the breast, stromal cells including, adipocytes, fibroblasts and macrophages and other immune cells play fundamental roles in normal mammary development as well as carcinogenesis.^[84] Macrophage, eosinophil, and mast cell influx typify different developmental stages and aid in mammary gland formation and involution (remodeling) in the post-natal period, during puberty, after pregnancy and lactation.^[22,84-87] Work by our group and others has increasingly linked obesity and inflammation in various adipose depots.^[22,88,89] In non-breast tissue, macrophages infiltrate adipose tissue at the onset of weight gain and directly contribute to and perpetuate the chronic inflammation characteristic of obese adipose, which is a major causal factor of insulin resistance.^[18,90,91] Our findings^[22], corroborated by those of Dr. Dannenberg's research group have demonstrated that both obese women and murine models also have elevated macrophage infiltration in normal breast tissue.^[92,93]

Tumor microenvironment

Macrophage infiltration in the tumor microenvironment is also a well-established phenomenon; tumor associated macrophages (TAMs) correlate with increased tumor angiogenesis, positive lymph node status and reduced

survival of BC patients.^[94-96] Furthermore, macrophage influx during ductal involution is proposed to create the pro-inflammatory microenvironment that promotes pregnancy associated BC.^[84] Macrophage infiltration in the microenvironment of ductal carcinoma *in situ* is associated with high-grade, ER- and PR-negative BCs.^[97] Indeed, BBC is characterized by unique epithelial-stromal interactions,^[50,98] relative to other BC subtypes,^[98] which likely play a role in its etiology. TAM production of tumor-promoting factors, such as epidermal growth factor (EGF)^[96] and VEGF,^[94] are recognized as particularly important in BBC,^[99,100] and are microenvironment-mediated mechanisms of BBC onset. Other stromal cells also contribute to alterations in the tumor microenvironment. Dr. Lisanti's research group have shown that stroma plays a vital role in the metabolism of the tumor, termed the "reverse Warburg effect," via fibroblast-mediated metabolism.^[101-104] Cancer associated fibroblasts react to oxidative stress emitted from tumor cells by driving the production of inflammatory mediators and up-regulating glycolysis in a hypoxia-inducible factor α /Nuclear Factor- κ B-dependent manner to generate metabolites for energy and proliferation of neighboring epithelial tumor cells.^[101,105] This cross-talk allows for tumor progression that is intricately linked to stromal metabolism. Finally, Stewart *et al.* have demonstrated that basal-like epithelial cells foster a pro-inflammatory milieu that drives differentiation and polarization of monocytes to macrophages^[23,98] and is established by direct interactions between primary BBC patient-derived fibroblasts and mammary epithelial cells in culture.^[50] Recent studies

have also identified a role for neutrophils and mast cells in promoting a pro-tumorigenic breast microenvironment by promoting the release of cytokines and chemokines, reactive oxygen and proteases.^[106]

Anti-inflammatory approaches

Will addressing inflammation cure cancer? Although a tantalizing hypothesis, this is not a simple question to answer due to the complicated nature of macrophage polarization. Macrophages polarized toward the M1-like or the classical phenotype, tend to be pro-tumoricidal while M2-like or alternatively activated macrophages, may be protective of tumor cell growth^[107] [Figure 2]. In BC, T-helper 2 cell-derived IL-4 mediates M2 polarization and promotes metastasis.^[108] B cells in the microenvironment can also skew macrophage function and promote tumor progression via IL-10 induction.^[108,109] Animal models of BC have demonstrated that inflammatory processes contribute to tumor proliferation and metastasis while anti-inflammatory drugs are chemopreventive.^[87,94,96,110-115] Epidemiological studies indicate that anti-inflammatory drugs reduce the risk of both receptor-positive and -negative BC.^[29,116,117] Interactions between the stromal and metabolic microenvironment likely regulate the immune cell population, TAM infiltration and polarization and microenvironment-mediated plasticity; all which are currently under investigation. Understanding how metabolic pathways are altered in tumors and how cancer cells benefit from tumor-specific metabolic changes may contribute to the identification of novel therapeutic targets and the development of more effective cancer therapies.

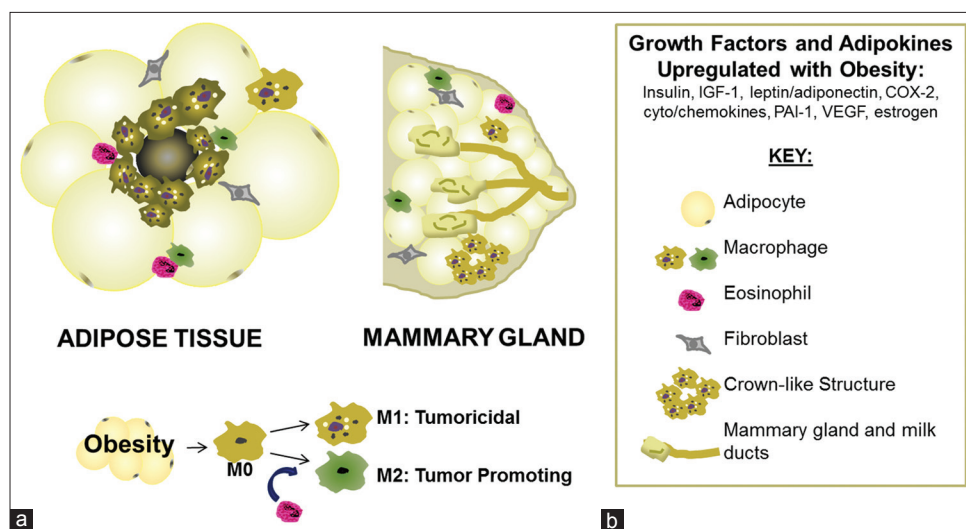


Figure 2: Recruitment of inflammatory cells in the tumor microenvironment mediated by obesity. (a) Obese adipose tissue is characterized by hypertrophy and hyperplasia of adipocytes, apoptosis and a shift in the stroma from less inflammatory eosinophils and M2-polarized cells (promoting insulin sensitivity), to an environment rich in pro-inflammatory M1-polarized macrophages, crown-like structures and activated fibroblasts. The mammary gland displays many of the same phenotypic changes with obesity. This low-level chronic inflammation in the tissue is known to induce oncogenesis, with an interesting shift in polarized macrophages from less M1 tumoricidal macrophages to more M2 tumor-promoting macrophages (b).

CONCLUSION

While some epidemiologic studies fail to find evidence supporting diet-mediated risk on BC,^[118-120] lifestyle factors such as geographic differences and immigrant studies as well as rodent models, suggest that diet-induced obesity may play a role in oncogenesis. The underlying causes of obesity represent a complex web of interactions including inherited genetic traits, low physical activity levels, environmental factors such as toxins and access to affordable, healthy food, cultural identity, socioeconomic status and others.^[121] Despite all of the work aimed at ameliorating obesity, recent projections have estimated that 51% of the US population will be obese by 2030.^[122] Because obesity rates continue to increase worldwide, understanding the role of obesity in carcinogenesis is a question with high public health impact, with the added potential of reducing health disparities associated with certain cancers. Prevention of BC via reduction of obesity offers an important and unique opportunity for intervention. Nearly 90,000 cancer related deaths in the US could be avoided if adults maintained a BMI < 25 for life.^[123]

Effective and targeted prevention of cancer among obese individuals depends upon understanding the molecular underpinnings of obesity-associated BC risk. Specifically, researchers need to elucidate the effects of aberrant systemic metabolism on the characteristics of tissue microenvironments and the promotion of cancer. Highlighting the relationship between nutritional state and disease, populations that suffered from severe caloric restriction, such as during World War II WWII and other famines, exhibit lower death rates from a broad spectrum of cancers.^[124,125] Epidemiologic associations suggest that caloric restriction may be protective against BBC,^[27] but this needs to be validated in additional animal studies and clinical trials. Caloric restriction or drugs that mimic it (like mTOR inhibitors) are approaches currently under study in primate models^[126-128] and rodents (reviewed in detail^[125]). In addition, the glucose lowering agent metformin has been effective in reducing overall cancer incidence and mortality.^[129,130] Ideally, integration of tumor characteristics and the microenvironment using physiologic, immunohistologic, metabolomic, and transcriptomic data should be used to construct a complete picture of the role of obesity-mediated alterations in the etiology of cancer. Furthermore, focusing on a specific window of susceptibility to cancer onset or metabolic state may be the most direct approach to understand links between obesity and oncogenesis.

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AUTHOR'S PROFILE

Dr. Sneha Sundaram: Department of Nutrition, Gillings School of Global Public Health and School of Medicine, UNC Chapel Hill, Chapel Hill, NC.

Dr. Amy R Johnson: Department of Nutrition, Gillings School of Global Public Health and School of Medicine, UNC Chapel Hill, Chapel Hill, NC.

Dr. Liza Makowski: Department of Nutrition, Gillings School of Global Public Health and School of Medicine, UNC Chapel Hill, Chapel Hill, NC.



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