SPECIAL REPORT

Breast Cancer: Lifestyle, the Human Gut Microbiota/Microbiome, and Survivorship

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ABSTRACT

Patients with a current diagnosis of breast cancer are enjoying dramatic cure rates and survivorship secondary to an increase in awareness, earlier detection, and more effective therapies. Although strategies such as Breast Cancer Awareness Month in October focus on early detection, lifestyle changes are seldom discussed other than dietary concerns and physical activity. Lifestyle modifications centered on diet and exercise have been demonstrated to affect overall disease-free survival in breast cancer. Since the early 2000s, the role of the human gut microbiota and its relation to breast cancer has become a major area of interest in the scientific and medical community. We live and survive owing to the symbiotic relationship with the microorganisms within us: the human microbiota. Scientific advances have identified a subset of the gut microbiota: the estrobolome, those bacteria that have the genetic capability to metabolize estrogen, which plays a key role in most breast cancers. Recent research provides evidence that the gut microbiome plays a substantial role in estrogen regulation. Gut microbiota diversity appears to be an essential component of overall health, including breast health. Future research attention should include a more extensive focus on the role of the human gut microbiota in breast cancer.

INTRODUCTION

In 2020, nearly 260,000 women in the US will receive a diagnosis of breast cancer, and more than 40,000 will die due to the disease.[1,2] Breast cancer is the most common malignancy among women, affecting 2.4 million women and responsible for more than 500,000 deaths worldwide.[3] In 2015, there were an estimated 3.4 million breast cancer survivors in the US.[4] This number increases yearly. Most breast cancer patients survive disease free for many years, making survivorship a major health issue. The American College of Surgeons has mandated that survivorship care plans become an integral component of their accreditation. This has prompted the appearance of a plethora of articles addressing lifestyle issues that positively affect many chronic comorbidities, a decrease in recurrence, and an increase in overall survival.[4,5] Lifestyle recommendations, although inadequately addressed, also contribute to prolonged survival.[5,7] Such recommendations are generally focused on diet and exercise, but the developing awareness of the influence of the human gut microbiota on survival and overall health creates the need to expand that focus to encompass diet, exercise, and the microbiome.

GUT MICROBIOTA AND HEALTH

The human microbiome is composed of trillions of microorganisms living inside and outside the human body. Often used interchangeably, the terms *microbiome* and *microbiota* are, in fact, distinctive. The microbiome defines the collection of the genomes that the microbiota (the bacterial population) possess. The microbiota are now considered an "essential organ" and have been associated with overall health and chronic disease.[5,8,9] Bacteria, fungi, protozoa, yeast, and viruses comprise up to 90% of the human cellular population.[10] These organisms, until recently, were the unrecognized "organ system" responsible for most of our immunity. The microbiota rely on us, and in turn, we rely on them, representing a truly symbiotic relationship. An imbalance of healthy and derogatory bacteria can lead to uncontrolled processes resulting in the development of chronic conditions, including cancer.[5,11,12] Results of recent investigations have suggested that specific hormones, particularly estrogen, and the gut microbiome might act synergistically in the development of obesity, type 2 diabetes mellitus (T2DM), and cancer.[5,12]

Metabolic syndrome is characterized by central obesity, T2DM, hypercholesterolemia, insulin resistance/hyperinsulinemia, and hypertension (Table 1). Metabolic syndrome is the result of lifestyle choices that are modifiable by healthy changes.[13-17] Recommendations addressing lifestyle adjustments that influence breast cancer survivorship are evidence based.[5,7] The underlying reasons for their effectiveness are multifactorial, poorly understood, and often vague. In this report, we address potential factors that play a major role in breast cancer survival, particularly those that are influenced by the gut microbiota. The potential ability to manipulate our gut microbiota through lifestyle recommendations may positively affect survival.

Table 1. Characteristics of the Metabolic Syndrome
• Obesity (central)
• Hypertension
• T2DM (often related to obesity)
• Hypercholesterolemia (↓HDL, ↑Triglycerides)
• Hyperinsulinemia (insulin resistance)

Table 1. Characteristics of metabolic syndrome

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Since 2010, the recognition of the gut microbiota on human health has been monumental, as demonstrated by the number of medical publications in well-respected, peer-reviewed journals.[18] We are beginning to understand that a large portion of our immunity resides in the human gut microbiota and that this ecologic system, in and of itself, is a unique "organ." The roughly 37 trillion cells in an average human are far surpassed by the nearly 100 trillion bacterial cells, which account for an estimated 2.25 to 2.7 kg (5-6 lb) of an average human's weight.[19] Furthermore, a human's DNA is outnumbered by the DNA of these microbes by a factor of 100 to 800.[20] The role of the gut microbiota and their effect on dysbiosis (alterations in gut diversity) needs further investigation and may identify potential links in the development of cancer.[21,22] The recently discovered estrobolome—those bacteria that are the subset of the microbiota possessing genetic traits responsible for estrogen metabolism and degradation—plays an important role in the development and/or progression of breast cancer.[23]

There is little literature addressing the influence of the human gut microbiota on long-term breast cancer survivorship. We address how lifestyle and the gut microbiota influence these concerns here and in Appendix 1.

DISCUSSION

Breast cancer survivorship is on the rise.[24,25] Nearly 90% of patients survive at least 5 years after diagnosis. Breast cancer is no longer considered an acute disease; rather, it is now a chronic condition.[7,26] This creates an opportunity to improve the lives of survivors through lifestyle choices. The Western lifestyle (a diet high in sugar and fat, low in fiber, and minimal activity), however, puts one at risk of breast cancer. What has been referred to as the standard American diet results in obesity, insulin resistance, dysbiosis, and inflammation.[5] Insulin also stimulates the synthesis of insulin growth factor-1 (IGF-1), linked to tumor growth and metastasis. Both estrogen and IGF-1-mediated signaling are increased in obese postmenopausal women.[27] "Cross-talk" between such pathways represents an important link to tumor progression. Obesity leads to a pathway of subclinical inflammation; adipose tissues contribute to insulin resistance as well as cancer development and progression. Activated macrophages in adipose tissues in obese individuals produce proinflammatory mediators. Obesity leads to insulin resistance, an increased level of insulin, IGF-1, a decrease in adiponectin (the fat-burning hormone), and an increase in leptin (the satiety hormone).[27,28] Leptin promotes angiogenesis, whereas adiponectin inhibits the same.[28] Obesity has been associated with an increased risk of postmenopausal breast cancer in addition to multiple metabolic disorders.[5] Several biologic mechanisms may contribute to a worsened prognosis of obese patients with breast cancer. This is at least in part the result of the presence of comorbidities in patients with breast cancer (Figure 1).[17,29,30]

Metabolic syndrome is a cluster of conditions that predict an increased risk of cardiovascular disease and T2DM.[30] Although major attention regarding this syndrome has focused on cardiovascular disease risks, results of recent studies suggest that the metabolic syndrome also plays an independent role in increasing the risk factors for breast cancer.[31] Yet, the conditions that define this syndrome are modifiable by lifestyle changes. A well-recognized risk factor for breast cancer and recurrence, obesity

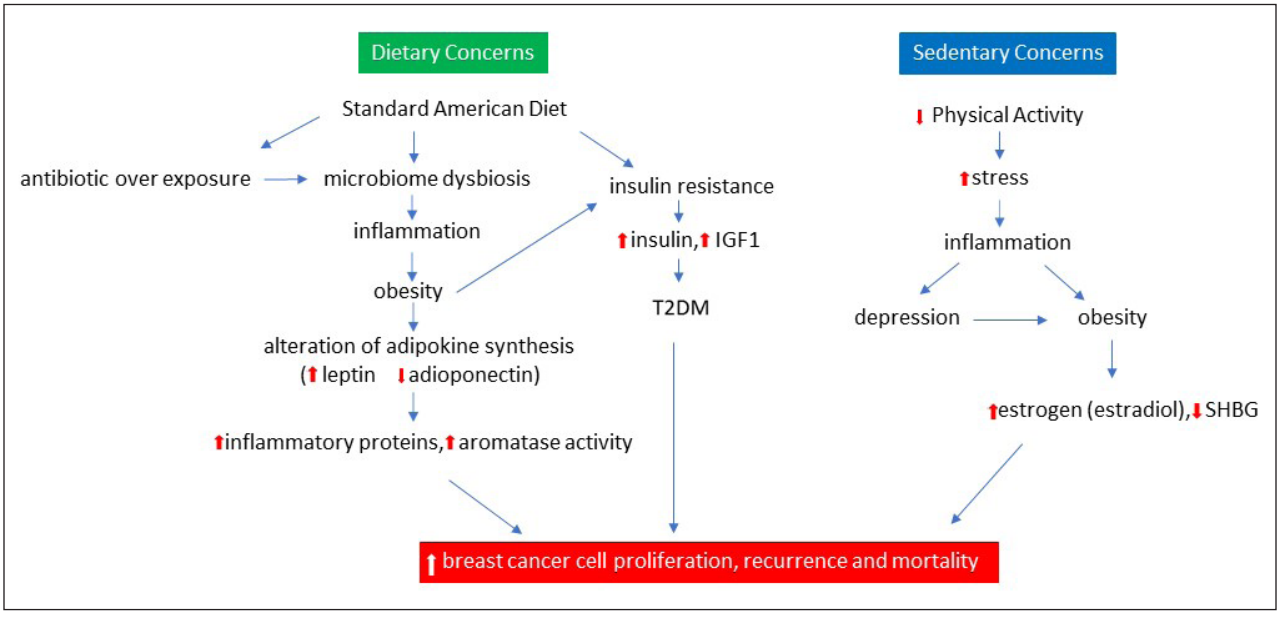

Figure 1. Impact of lifestyle on breast cancer.

Although the diagram separates diet and inactivity, they are intimately connected, leading to an increase in obesity, T2DM, and ultimately an increase in inflammation.

IGF1 = insulin growth factor 1; SHGB = steroid hormone-binding globulin; T2DM = type 2 diabetes mellitus.

may also be substantially influenced by our gut microbiome.[32] In addition to its capacity to store lipid, adipose tissue should be viewed as an active endocrine and metabolic organ. The human gut microbiome is intimately associated with obesity.[19]

A major factor underlying the increased risk of hormone receptor-positive breast cancers in obese women is an elevated estrogen level, which is related to increased adipose tissue mass and the production/storage of multiple inflammatory mediators.[5] Such proinflammatory molecules have been linked to tumor progression and the upregulation of aromatase (the enzyme responsible for the conversion of testosterone to estrogenic compounds and unwanted byproducts of cholesterol metabolism).[27] Obesity also leads to insulin resistance, hyperinsulinemia, and impaired glucose tolerance. High levels of fasting insulin in patients with breast cancer have been associated with distant recurrence, metastases, and increased mortality. Insulin has been implicated in cancer progression by virtue of its mitogenic, antiapoptotic, and proangiogenic properties.

Physical inactivity promotes stress, inflammation, and psychological issues such as depression, which are influenced by the gut microbiome. Obesity and self-image concerns may further contribute to depression. Physical activity after breast cancer decreases cancer recurrence by 24%, decreases the risk of breast cancer-related death by 34%, and decreases all-cause mortality by 41%.[33] Observational evidence suggests a primary reduction in breast cancer between 30% to 50% with regular physical activity.[34] Even exercise such as walking for 30 minutes a day, 5 times per week, may appreciably affect overall health. Physical activity guidelines for health in the US have recently been updated and have concluded that a sedentary lifestyle may be responsible for up to 10% of premature deaths.[35-37] Although the "Physical Activity Guidelines for Americans" report is noteworthy and applauded, there was absolutely *no* mention of the role of lifestyle or its promotion as an interventional strategy in the article by Giroir and Wright.[35] The article did not specifically address cancer survivorship or issues regarding the composition of the gut microbiota, which have been identified as playing a major role in fitness and survival.[38] However, it did note the importance of physical activity for overall health. Additional studies have demonstrated that the adoption of a healthy lifestyle after a breast cancer diagnosis may decrease mortality rates by up to 50%. This can be accomplished if patients adhere to the adoption of a high fruit/vegetable diet (4-5 servings per day) coupled with regular physical activity (30 minutes/5 times per week).[39]

Lifestyle medicine, as it relates to breast cancer survivorship, relies on 3 major pillars: diet, physical activity, and stress management. Stress management is outside the scope of this article; it is extensively discussed elsewhere.[5,7,40,41] There remains considerable debate regarding the association of diet, physical activity, and cancer prevention.[42] Medical advances in treating chronic conditions have seen a revolution since the turn of the 21st century. Perhaps 2 of the most important advances have been 1) the identification of epigenetics (turning genes on and off) and the modification of gene expression as opposed to the alteration of the genetic code itself, which can be influenced by lifestyle,[5,7,43-45] and 2) the recognition that the human gut microbiome plays a major role in overall health.[46-48] We believe the identification of the human gut microbiome equals the importance of the discovery of aspirin, antibiotics, and vaccines. Our bodies are inhabited by trillions of microorganisms that are vital to our survival, the majority of which reside in the gastrointestinal tract, particularly in the large intestine.[18,49,50] The exact number/ratio of human cells vs gut microorganisms and the ratio of their DNA has been debated.[51] Further investigation is needed to resolve these figures. One fact is indisputable: the role of the gut microbiota is indeed important and regulates our well-being.[52]

The human microbiota represent the constellation of microorganisms that inhabit our bodies. The complex interactions of the gut microbiota remain beyond our understanding, regardless of numerous advances in genomic profiling.[53,54] More than 50% of our gut microbiota refuses to be cultured or identified outside the body using current technologies.[8,53,55]

Nearly 90% of our gut bacteria are composed of 2 major phyla: *Bacteroidetes* and *Firmicutes*.[46,53,56] These phyla and their ratios have been extensively studied; however, our understanding of them and their interactions remains elusive.[32,47,57] Improper ratios of thousands of species have been linked to the development of multiple chronic conditions and account for more than 80% of all chronic maladies.[5-7,44,53,58,59] When the ratios are optimal, these gut microbiota provide valuable services (energy production through the fermentation of foods, synthesis of vitamins, the building of amino acids, and a general oversight of the immune system halting infections), keeping chronic conditions at bay and preventing disease.

Diet plays an integral role in the complex interrelationship between the human gut microbiota, estrogen metabolism, and its influence on breast cancer recurrence as well as metastatic potential. The standard American diet results in the increased propagation of unhealthy bacteria, which contain high levels of β-glucuronidase. This enzyme is responsible for deconjugating estrogen and returning it to the circulatory system, thus raising its availability to further fuel estrogen-responsive cancers. This diet results in a decrease in the production of short-chain fatty acids (SCFA; butyrate, propionate, and acetate), which play a major role in the prevention of "leaky gut syndrome." This syndrome is responsible for the flow of harmful inflammatory products into the circulatory system, influencing the development and recurrence of breast cancer. Inflammatory proteins promote insulin resistance and support leptin, which influences carcinogenesis.[60] Insulin binds steroid hormone-binding globulin (SHBG), increasing estrogen availability, promoting higher estrogen levels, and contributing to breast carcinogenesis.[27,61] Adiponectin levels are decreased, resulting in insulin resistance and increased levels of IGF-1, which promote cell proliferation.[27]

In contrast, a whole-food, plant-based diet (especially one high in fiber) results in the promotion of "healthy" microbiota. By decreasing the activity of β-glucuronidase, circulating estrogen levels are minimized, and SGBH is increased along with the fecal excretion of estrogen. As SCFAs are increased, they protect the colonic mucosa from developing leaky gut syndrome, decrease inflammation, and potentially lower the risk of breast cancer.[5,27,48,62-65] Estrogen is conjugated in the liver and excreted

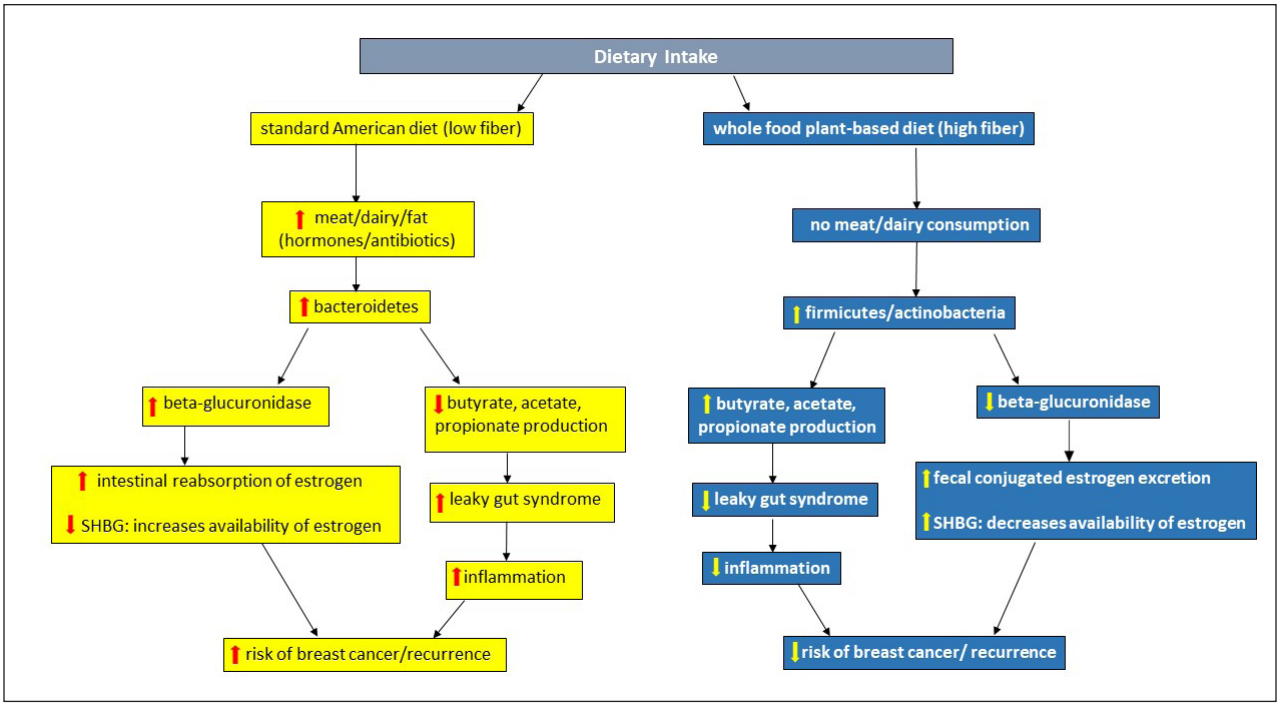

Figure 2. Dietary influence on gut microbiota/microbiome and estrogen metabolism.

SHBG = steroid hormone-binding globulin.

into the gastrointestinal tract; estrogen is deconjugated by bacterial glucuronidase and is reabsorbed as free estrogen into the bloodstream. Multiple bacteria are involved in this process; however, which bacteria are high producers of β-glucuronidase remain controversial (Figure 2).[66,67]

The current literature regarding the gut microbiota is confusing and contradictory as a result of 2 factors. First, only recently have we acquired technologies that effectively identify an important, albeit small, portion of the microbiota. Second, there appears to be a disconnect that surrounds the interaction or interactions of these bacteria. What is currently understood are the major bacteria and their phyla, which are summarized as follows. The phylum *Firmicutes* includes the genera *Lactobacillus* and *Clostridium* (various subtypes), the phylum *Bacteroidetes* includes the genera *Prevetella* and *Bacteroides*, and the phylum *Actinobacteria* includes the genus *Bifidobacterium*. These are believed to be the major producers of SCFAs that result in a decreased breast cancer risk, recurrence, and mortality. There is evidence that 1 or another of the phyla in the gastrointestinal tract may be responsible for the majority of SCFA production. It appears that the primary producers of butyrate (the major colonic epithelial protector) are *Firmicutes*.[68] *Bacteroidetes* may increase propionate, another beneficial SCFA, although this has been less extensively studied.[69]

Firmicutes and *Bacteroidetes* are the major colonic phyla responsible for the metabolism of fiber and polyphenols. Multiple studies have reached different conclusions on the impact of these phyla, particularly as they relate to obesity (a major risk factor for breast cancer).[19,49,50,67,70] Leaky gut syndrome and the inflammation associated with it may well be minimized by the consumption of a high-fiber diet, leading to the production of SCFAs and intestinal alkaline phosphatase.[71] Intestinal alkaline phosphatase is a protein of the intestinal epithelium that plays a major role in gut endothelial integrity. Along with SCFAs, intestinal alkaline phosphatase strengthens the tight junctions of the colonic mucosa, decreasing the leakage of harmful pathogens and their carcinogenic potential.[5,20,72-74] Chronic inflammation may be promoted by the gut microbiota through its influence on self-proliferation and apoptosis.[5,66,74-76]

Nonalcoholic fatty liver disease (NAFLD) affects nearly one-fourth of the global population.[77,78] This presence of fat in the liver (hepatic steatosis) is a diagnosis based on exclusion of other causes such as excessive alcohol consumption. Regardless of our poor understanding of its etiology, NAFLD is of great importance and a major cause of mortality, not only owing to the condition itself but also as a harbinger of malignancies, including breast cancer.[77] This association results from the fact that NAFLD is associated with metabolic syndrome.[79,80] Components of metabolic syndrome and its association with breast cancer have been described and documented in numerous publications.[81-83] The influence of NALFD on extrahepatic carcinogenesis and mortality has also been noted.[84] The association is poorly understood; however, multiple hypotheses to explain a carcinogenic link have been put forth.[85] The common link appears to be an inflammatory state, fueled by hyperinsulinemia and resulting in tumor proliferation.[60]

Inflammation, obesity, T2DM, and chronic conditions such as cancer share common pathways, which are influenced by the human gut microbiota.[57,86-90] This complex and intricate system affects numerous distant organ systems.[91] The idea that our

microbial "friends" aid and participate in the promotion of our health is hardly a new concept; in fact, such recognition dates to the 20th century.[18] Similarly, the association of inflammation and cancer has long been recognized owing to the work of Virchow.[92-94] Inflammation plays a role in most chronic conditions and, if uncontrolled, leads to chronic processes that promote tumorigenesis, from initiation to metastasis.[95]

In the diverse human gut microbiota exists a subset of bacteria that possess the genetic capability to metabolize estrogen: the estrobolome. These microbes favor fiber as their primary source of energy. When a high-fiber diet is consumed, the estrobolome increases the metabolism of estrogen and thus its elimination from the body. Because nearly 70% of breast cancers are estrogen fueled, a high-fiber diet contributes to estrogen elimination, robbing breast cancer cells of a major fuel source. The "commonsense" recommendation to increase dietary fiber in the setting of breast cancer decreases inflammation. The increased consumption of fiber and polyphenols, readily available from a whole-food, plant-based diet, contributes to an overall increase in breast cancer survival.[5,7,96-98] The benefits of lifestyle recommendations in the setting of breast cancer are summarized in Figure 3.

Our gut microbiota are not only subject to our dietary intake but also are influenced by multiple prescription drugs and over-the-counter medications. The Western population seeks a cure for multiple conditions with a drug prescription. This has led to a nation that relies on a "pill for every ill," and such an ideology may affect the gut microbiome (Appendix 2).

The Western world lives in a state of chronic inflammation largely due to the standard American diet and low physical activity, both of which are modifiable. The gut microbiota are a major conduit in the inflammatory process. Our immune system can only be challenged to a certain degree. When overcome by oxidative stressors and chronic inflammation, we may no longer be capable of responding to immunosuppressive conditions; the development of malignancies is the result.[99]

Our sedentary lifestyle, the link between the gut microbiota and obesity, is well known.[5,100] Overweight has now become a pandemic with serious psychosocial ramifications.[101] Obesity is also an inflammatory state that promotes immune responses and carcinogenesis.[5,102,103] Carcinogenesis is fueled by the development of obesity because fatty tissues (particularly in the midsection) are largely responsible for the promotion and storage of numerous proteins that promote inflammation and estrogen production/storage, fueling most breast cancers.[5,52]

Diabetes, now a pandemic, is recognized not just as a metabolic condition but an inflammatory process as well.[91,104,105] The interaction of diabetes, obesity, and carcinogenesis is well known.[91,92] Understanding the role of the human gut microbiome in breast cancer survival, obesity, and the comorbidity of diabetes should be a focus of further research. Interventional strategies need to be identified starting with the promotion of a healthy lifestyle.

Emotional resilience (our response and recovery from a considerable life-altering event) and the ability to deal with such stressful issues (acute and chronic) are also influenced by the gut microbiota. In particular, depression is an underaddressed concern in women with a diagnosis of breast cancer.[106-110] The gut microbiota play an important role in our ability to deal with emotional concerns because they are responsible for the production

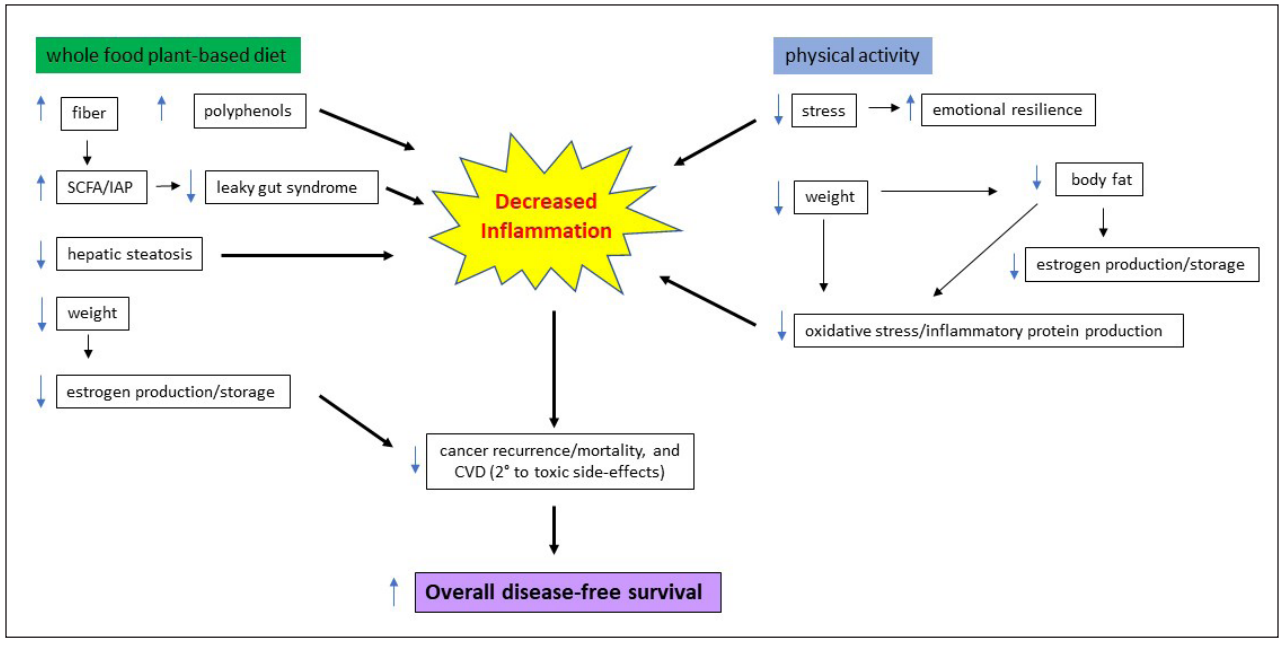

Figure 3. Benefits of lifestyle recommendations for overall disease-free survival in breast cancer.

CVD = cardiovascular disease; IAP = intestinal alkaline phosphatase; SCFA = short-chain fatty acids.

of multiple neurotransmitters, including γ-aminobutyric acid, norepinephrine, serotonin, and dopamine.[111-113] The human gut is responsible for the production of nearly 90% of the neurologic regulators of chemicals that affect our emotions.

A whole-food, plant-based diet contributes to the favorable ratio of *Firmicutes/Bacteroidetes*. Fat and dairy consumption increases *Bacteroidetes*, whereas plant and fiber consumption increases *Prevotella*, *Akkermansia*, and other favorable bacteria.[114-117] Most research to date has addressed only the bacterial population of the gut, and the investigation of the other microorganisms has received little attention. The complex interactions of these inhabitants have yet to be discovered but are certain to exist. The gut microbiota may be our most powerful endocrine regulator, because it affects nearly all distant organs and their appropriate functions.[118,119] There exists a cross-talk between our immune system and the microbiota with the constant exchange of signals, serving as an alarm for immune system activation. The population of our bacterial occupants is affected by dietary choices. Our gut microbiota represent an individual genetic "fingerprint" of each of us, as unique individuals, with no 2 being alike (Sidebar 1: The Lifecycle of the Gut Microbiota).

CONCLUSION

Breast cancer is now a chronic condition and is no longer an acute disease with the mediocre cure rates of decades ago. As such, there is time to intervene and provide healthy lifestyle recommendations that affect long-term, disease-free survival. Dietary recommendations are of major importance as they influence the gut microbiota, a major factor in increasing immunologic strength. Additionally, management of breast cancer survivors is now recognized as a new subspecialty. More health care programs are emerging that address long-term issues related to this ever-expanding population. Most individuals with breast cancer far exceed a 5-year disease-free survival. Dietary and lifestyle

Sidebar 1: The Lifecycle of the Gut Microbiota

The gut microbiota is established at birth as the infant passes through the birth canal and becomes exposed to the vaginal flora. In those born by cesarean section, such an early exposure to the human microbiota is forfeited. Long-term consequences on the future health of such individuals is influenced by their microbiota habitants.[1] Additionally, the breast-fed child is also exposed to additional bacteria, especially from colostrum, which is rich in bifidobacteria and further adds to the colonization of the newborn gut. Lack of early colonization of the young gut has been documented to result in a number of future chronic conditions.[2] The inhabitants of the young gut microbiota appear to play a significant role in the establishment of early onset immunity.[3,4] As the impact of the gut microbiota becomes further unraveled, we are starting to realize that as we age our microbiota "ages" as well; a concept not previously recognized. Each human cell has a natural life cycle with apoptosis (cell death) as their final destination. Currently, we hardly possess a full understanding of the complete life cycle of the nearly 100 trillion gut microorganisms that occupy our gastrointestinal tract. Despite lack of such information, we do understand that the gut microbiota is also subject to an aging process.[5,6] Telomere length, which decreases with age, has been recognized as a bio-marker of aging and its association with the development of malignancies has been noted.[5-9] Bacterial DNA also possess telomeres, which decrease in length with aging, resulting in a reduced lifespan.

Because of our newly acquired understanding of the importance of the gut microbiota, recent attention has also been directed to the importance of educating health care practitioners and patients regarding a healthy lifestyle. This must begin with a focus on nutrition education—the food sources that feed and promote a healthy gut microbiota.[7] As with all living organisms, the health of the microbiota is determined by the quality of the nutrients consumed. There exists a significant lack of nutritional education in medical schools and post-graduate training. As such we are ill-prepared to provide basic and much needed nutritional advice for the prevention and reversal of chronic conditions. Recent publications have called attention to this important matter.[7,10-12] Ultimately a healthy, high-fiber, whole food plant-based diet, combined with an active lifestyle, reduces the risks of comorbidities, improves health, and improves breast cancer survivorship.

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interventions can play a major role in furthering this success. Interventions include alterations that reshape the human gut microbiota through dietary recommendations and increasing the microbial diversity, which can substantially affect long-term health, particularly in breast cancer.

Much of the information published about the microbiome in well-respected, peer-reviewed journals reports contradictory conclusions, strengthening the need for further research. Regardless, there is evidence that the gut microbiome plays an important role in breast cancer survival. We remain in a place of ignorance regarding our understanding of not only the gut microbiota but also their complex interactions. A deeper understanding of the microbiota will result in the development of biomarkers for breast cancer and other cancers, perhaps allowing for even earlier diagnosis and a further increase in survival. It is time to implement changes in our lifestyle to further avert a fast-approaching disastrous course.

The composition of our microbiota depends on our lifestyle and may possibly become the most important factor in health maintenance. It is obvious that lifestyle patterns, both dietary and activity concerns, influence the gut microbiota's flora in complex ways. Consumption of a poor diet and a sedentary lifestyle have a substantial impact on our gut microbiota. As physicians, it is our duty to promote and educate ourselves and our patients regarding the dramatic impact of lifestyle on overall health. Providing such guidance could well replace numerous future surgeries and prescriptions. ❖

Disclosure Statement

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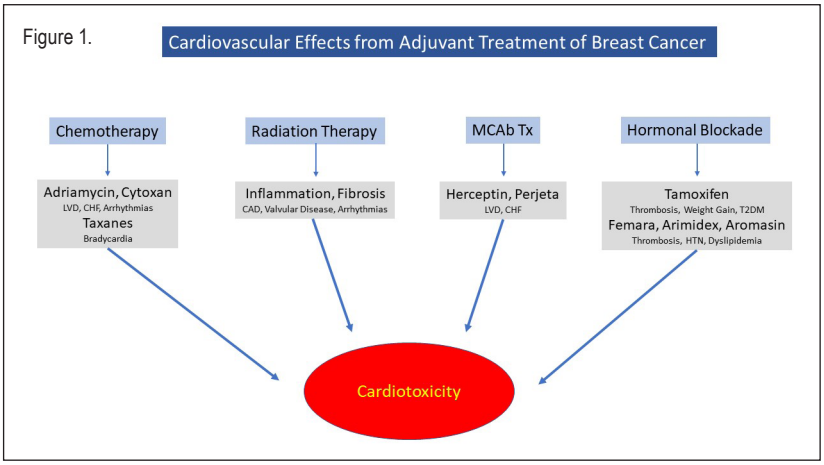
Appendix 1: Adverse effects of currents treatments for breast cancer and the gut microbiome

Cardiovascular Concerns

Cardiovascular disease (CVD) is the current leading cause of mortality in women in the United States.[1-3] Although mortality rates for CVD have declined in recent years, this decline has waned.[4] Recent information appears conflicting regarding long-term toxicities of current regimens employed to treat breast cancer.[5] Survival following breast cancer has increased in the past decades, and as such, increase the risk of death from cardiovascular events simply due to aging. Cardiac events exceed the risk of death from breast cancer or its recurrence.[1,2,6-8] Currently employed chemotherapeutic agents may result in future chronic cardiovascular complications.[3,9,10] Targeted biologic therapies have assumed a prominent role in the treatment of breast cancer portend short- and long-term cardiotoxic effects.[11-13] Radiation therapy, as an adjunctive treatment in breast conserving therapy (BCT), has been proven equally effective compared with modified radical mastectomy, and results in reduced recurrence and mortality.[14-20] As radiotherapy is undergoing a rapid evolution, (i.e. alterations in schedules of administration, radiation exposure, dosage, length of therapy, etc), we anticipate potential cardiovascular effects will diminish. However, many current survivors had been subjected to more intensive and invasive radiotherapies years ago and, thus their cardiovascular adverse effects may only be peaking at 10-20 years post exposure. As such, cardiovascular adverse effects are more likely to occur in this aging population.[21-26] (Figure 1)

Cardiovascular health is influenced by the bacteria that reside in our gastrointestinal tract.[27] The Standard American Diet may promote the development of CVD by influencing the growth and altering the ratios of good/bad bacteria.[28] A major concern is the recognition that the consumption of red and processed meats results in an increase in all-cause mortality. Such foods

Figure 1. Cardiovascular Effects from Adjuvant Treatment of Breast Cancer



are high in L-carnitine and lead to elevated serum levels of trimethylamine which are hepatically converted to trimethylamine oxide (TMAO) through the action of the gut microbiota. Red meat intake reduction may decrease TMAO formation, inhibiting atherogenesis by the down-regulation of the macrophagic uptake of oxidized endothelial cells. Additionally, this may minimize damage to the colonic endothelial barrier decreasing the development of the "leaky gut" syndrome.[29,30] The association of TMAO production appears to be gut-microbiota dependent.[27,31,32]

Bone Health Concerns

Breast cancer survivors are at an increased risk of developing osteoporosis, as an adverse effect of current therapies, as well as increased longevity. As nearly 75% of breast cancers are estrogen driven, the use of aromatase inhibitors (AIs; anastrozole, letrozole and aromasin) in estrogen receptor positive breast cancers have been markedly effective in decreasing recurrence,[6,33] however AIs can result in a substantial and often rapid decrease in bone mineral density and contribute to an increased risk of fracture.[34,35] Osteoporosis, the destruction of the bony matrix, is a condition often unrecognized until a fracture event. Risk factors for the development of osteoporosis have been identified and aggressive interventions for prevention are needed.[36-41] Multiple prescription drugs, especially for minimal indications such as gastrointestinal symptoms related to acid reflux and psychotropic drugs for depression also promote the development of osteoporosis. These, among other frequently prescribed medications, account for more than 100 million prescriptions annually.[42-49] Recent studies have established an association between the human gut microbiota and bone metabolism.[50-52] The exact mechanism of bone metabolism regulation by the gut microbiota is unclear, however multiple pathways have been proposed. These include influencing the immune and endocrine systems as well as potential interference with the absorption of calcium.[50,53-55] A healthier microbiota could be beneficial in maintaining bone health of breast cancer survivors.

Hormonal Blockade Concerns

The majority of breast cancers are endogenous estrogen driven,[56-62] a favorable characteristic associated with less aggressive disease. More than 30 years of data demonstrate the effect of hormonal blockade in decreasing death rates.[9,63,64] Strong evidence suggests overall disease-free survival in patients adhering to long-term hormonal blockade. Unfortunately, a substantial number of patients who would benefit from such therapeutic interventions do not avail themselves of this proven recommendation. Rates of compliance to a 5-year regimen only approach 30% to 70%.[65-67] Previous studies have demonstrated a higher recurrence rate and an increase in mortality in those discontinuing the recommended 5-year regimen.[68,69] More recent studies suggest that a 10-year protocol may result in a further increase in overall disease-free survival.[70-72] Adherence to a five-year regimen appears to be beyond many patient's capabilities; asking them to adhere to twice that number of years, as previously recommended, presents an even further challenge.[6] Lifestyle recommendations, particularly dietary changes, may be beneficial for patients who cannot tolerate the adverse-effects nor adhere to such long-term anti-estrogenic therapies.

The gut microbiome is intricately involved in the regulation of estrogen levels. A dysbiotic environment plays a crucial role in circulating estrogens. Within the nearly 100 trillion microbes that inhabit us, there exists a subset of these colonizers known to possess the genetic capability to influence estrogen metabolism, the "estrobolome."[73,74] Although systemic estrogen modulation is beyond the scope of this article, the reader is directed to several comprehensive reviews of this issue.[6,74,75]

Thromboembolic Concerns

Cancer, regardless of tissue origin, is a prothrombotic state,[76-79] well recognized since the German physician Virchow originally identified the association of cancer and inflammation in 1863.[80-82] The second leading cause of death in patients diagnosed with a malignancy is, in fact, a thromboembolic event.[78,83] Patients with a cancer diagnosis have a 4- to7-fold increased risk of a thromboembolic event compared with those without cancer.[84,85] An important adverse effect of anti-estrogenic therapy is an increase in the risk of thromboembolic events. Tamoxifen, the earliest and most frequently prescribed hormonal blocker increases the risk of such an episode by1% to 2%.[86-90] The human gut microbiome directly increases the potential of a thromboembolic event through its role in the generation of trimethylamine and in the up-regulation of platelet production, increasing the risk of thrombosis. The association between TMAO (oxidized trimethylamine) production and the consumption of foods high in L-carnitine (red meat), and choline (poultry, fish and dairy) is well known. TMAO production is easily influenced by modifying our diet decreasing thrombogenesis.[6,30,33,91,92]

Emotional Concerns

Depression and anxiety, so prevalent in the modern world, are major risk factors affecting health. Depression is projected to be the second-largest health care burden within the next few years.[93] Depression is particularly relevant in the setting of breast cancer as it is often unrecognized, under addressed, and inadequately treated.[6,30,94,95] Depression has also been associated with an increase in CVD.[96] Undiagnosed, depression can diminish treatment adherence, resulting in inferior outcomes.[97] Intensified screening, earlier interventions, and "cancer-specific depression"counseling has become available.[98,99] The role of the gut microbiome is now recognized as a contributor to depression and to overall mental health.[100] This is the result of the gut microbiota's influences on the levels of circulating chemicals that directly influence mood and affect. The role of diet, as it affects depression and anxiety is an area of intense research as current evidence supports such an association.[101-103]

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Appendix 2: The impact of common pharmacologic interventions on the gut microbiota and breast cancer

Antibiotics

Recent concerns have been raised that the ongoing, indiscriminate use of antibiotics may result in an increase in the incidence and fatality of breast cancer.[1] Lifesaving antibiotics are one of the most effective therapeutics since their initial identification by Ehrlich and Fleming in the early 20th century.[2] Undoubtedly, saving countless lives, these drugs may also have become a significant threat to our future. Overprescribing, a common daily practice, disrupts the normal flora of the gut microbiota and may contribute to disease.[1,3] In 2015 nearly 300 million antibiotic prescriptions were dispensed in the US; nearly one-third lacked a proper indication.[4,5] Antibiotics, by destroying pathogens also disrupt healthy bacteria and contribute to a state of dysbiosis.[6] Furthermore, resistance to antibiotics develops as bacterial genes evolve and the growth of multidrug resistant pathogens emerge.[7] In addition to overprescribing, antibiotics enter our diet through meat and dairy products that contain high levels of antibiotics used prophylactically in animals. In fact, most antibiotics produced in the US (18.4 million pounds) are utilized by the agricultural industry.[8] Antibiotics, given in early childhood, also have a profound influence on the development of future obesity.[9] Antibiotics have a definitive impact on the gut microbiota, although their exact interference requires further investigation.[10,11] Antibiotic use and its relation to breast cancer development has been postulated, as these drugs may disrupt the phytochemical metabolic pathways that influence the development and progression of breast cancer.[1]

Proton-Pump Inhibitors

Nearly 150 million prescriptions for proton-pump inhibitors are written annually in the US to treat gastrointestinal complaints, in particular, reflux.[12,13] The majority of such prescriptions are proton pump inhibitors, which inhibit the gastric delivery of acids.[14] Anti-reflux medications, first introduced in the 1980s, contribute to decreasing the diversity of the gut microbiota. Many of these medications are "over the counter" and are used for prolonged periods, without demonstrable benefit, and beyond professional control.[13] Bacteria originating in the oral cavity may be altered by these medications and contribute to dysbiosis in the distal gastrointestinal tract.[14-16] Such drugs also interfere with breast cancer survival as they affect bone metabolism leading to the development of osteoporosis and fragility.[17,18] As our understanding of the gut microbiome expands, the influence of commonly prescribed medications and the role they play in the development of disease progression deserves attention.[19,20]

Antidepressants

Antidepressants are yet another overprescribed medication in the US. Nearly 10% of our population consume such drugs on a regular basis.[17,21,22] These prescriptions have increased nearly 65% since 2010 and women are twice as likely to be prescribed such medications.[23] Each year millions of prescriptions are written; more than one-third are inappropriately dispensed, without evidence of efficacy. Mental health issues, beyond depression, and their relationship to the gut microbiome, are receiving increased attention.[24] Evidence is accumulating that the gut microbiota communicates with the central nervous system influencing human behavior. The gut microbiota not only synthesizes, but also respond to neurotransmitters that affect our mental health.[25,26]

Polypharmacy

Consideration must also be given to the issue of polypharmacy—the simultaneous prescription of multiple drugs which is increasing in the aging population.[27] It has long been known that as the number of drugs prescribed rises, so do potential interactions, often negating or potentiating effects of one on the other or even resulting in adverse events. Polypharmacy needs to be recognized as a growing problem as many malignancies are also age related.[27-29] As the gut microbiota becomes further characterized, newer targeted therapies may be developed that affect overall disease-free breast cancer survival and long-term cure.[30] Multiple other drugs affect the microbiotic ecology which are beyond the scope of the current manuscript but are reviewed in-depth and are available.[31,32]

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