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Role of Microbiome in Breast Carcinogenesis

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BY

YAHAYA ALIYU

In Partial Fulfillment of the Requirements for the Degree of Master of Science in Medical Biology and Genetics

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APPROVAL PAGE

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DECLARATION

I Yahaya hereby declare that all information in this document has been obtain and presented in accordance with academic rules and ethical conduct. I also declared that, as required by these rules and conduct, I have fully cited and referenced all materials and results that are not original to this work.

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DEDICATION

To my parents…

ABSTRACT

Breast cancer has a complex etiology with environmental factors currently having more affinity than genetic factor considering the high incidence rate of the malignancy within both immigrants and local compatriots of the Western World population relative to other parts of the world. Gut microbiota should be on the radar of scientist as an etiological factor of cancer malignancy. Previously, most of the research focuses on viral entities and other specific bacteria [e.g. *Helicobacter pylori*] as microbial agents that can initiate breast malignancy and colon cancer respectively. However, the influential ability of the microbiome to manipulate host' systemic immunity and other downstream pathways is suggestive that the entire microbiome may be of importance toward the development of cancer both in the intestine and extra-intestinal tissues. Nevertheless, ways by which gut microbiome used to modulate cancer risk for its host includes breakdown of double-faced xenobiotics [beneficial and detrimental substances], upsetting the immune system activity, increasing the level of estrogen in the system, and damaging the integrity of the mucosal membrane. Dietary patterns should be appreciated in the study of role microbiome in breast carcinogenesis, because it mediates most of the changes in functional characteristics observed in the microbial communities. It is evident that dietary pattern is among the factors that causes high risk of breast cancer in developed country compared to developing countries. Understanding this multifaceted relationship between the gut microbiome and the type of diet consumed will help to clarify mechanisms behind carcinogenesis and treatment strategies.

Keywords: Breast Cancer, Microbiome, Diets, Dysbiosis

ÖZET

Meme kanseri kompleks bir etiyolojiye sahip, batıdaki lokal popülasyon ve göçmenlerdeki görece yüksek insidans göz önünde bulundurulduğunda çevresel faktörlerin genetik faktörlerden daha önemli göründüpü bir hastalıktır. Bağırsak mikrobiotası kanser malignansisi etiyolojik faktörü için araştırmacıların radarında olması gerekli. Daha önceleri, çoğu araştırma microbial ajanların meme kanseri malignansisi ve kolon kanseri başlatma potansiyelleri olduğundan viral entitiler ve spesifik bakteriler [ör. *Helicobacter pylori*] üzerine yoğunlaşmaktaydı. Fakat, mikrobiomun host sistemik immunitesini etkileme kapasitesi ve diğer bağlı yolaklar da göz önünde bulundurulduğunda, tüm mikrobiomun kanser gelişimde önemli bir rolü olabilir. Bağırsak mikrobiomu, kanser riskini module ederken xenobiotiklerin yıkımı (yararlı ve zararlı), immün system değişimi, sistemdeki östrojen seviyelerinin artırılışı ve mukozal membranın bütünlüğünün bozulması gibi yollar kullanabilir. Diyet alışkanlıkları, her meme kanserinde mikrobiom etkisini ölçen araştırmada dikkat edilmesi gereken bir konudur çünkü microbial yapıdaki fonksiyonel karakteristik değişikliklerin olmasına aracılık eder. Gelişmiş ülkerdeki beslenme alışkanlıklarının gelişen ülkelerdekine oranla kanser riskini artırdığı gösterilmiştir. Bağırsak mikrobiotası ve beslenme alışkanlığının çok yüzeyli ilişkisini anlamak, karsinogenez ve tedavi mekanizmalarını anlamada yardımcı olacaktır.

Anahtar kelimeler: Meme kanseri, Mikrobiyomlari, Diyetler, Dysbiosis.

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ABBREVIATIONS

Abbreviations	Meanings
ATM	Ataxia-telangiectasia mutated
BC	Breast cancer
BRCA	Breast Cancer gene
CCL5	Chemokine (C-C motif) Ligand 5
CD	Cluster of Differentiation
CDK	Cyclin-dependent kinase
CDT	Cytolethal distending toxin
CIF	Cycle inhibiting factor
CSC	Cancer Stem Cell
CXCL12	Chemokine (C-X-C motif) ligand 12
CXCR1	C-X-C chemokine receptor 1
CYP	Cytochrome P450
DCA	Deoxycholic acid
DDR	DNA Damage Response
DSB	Double strand break
E1	Estrone
E2	Estradiol
E3	Estriol
EBV	Epstein-Bar Virus
EMT	Epithelial mesenchymal transition
END	Enterodiol
ENL	Enterolactone
EPEC	Enteropathogenic
ER	Estrogen Receptor
ERK	Extracellular signal-regulated kinases
FA-BRCA	Fanconi Anaemia/BRCA
GI	Gastrointestinal

H_2S	Hydrogen Sulfide
HER2	Human epidermal growth factor receptor
HPV	Human Papilloma Virus
IECs	Intestinal epithelial cells
IL	Interleukin
iNKT	Invariant Natural Killer T cells
LCA	Lithocholic acid
MAPK	Mitogen-activated protein kinase
M-cells	Microfold cells
MDSC	Myeloid derived suppressor cell
miRNA	Micro-RNA
MRE11	Double-strand break repair protein
MSCs	Mesenchymal Stem Cells
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NGS	Next Generation Sequencing
NKC	Natural Killer Cell
NLR	Neutrophils-to-Lymphocytes rate
NOC	N-nitroso Compound
NOD	Nucleotide-binding Oligomerization Domain
NOS2	Nitrogen Oxide Synthase 2
NSAIDs	Non-Steroid Anti-Inflammatory Drugs
O-DMA	0-desmethylangolensin
RAD50	DNA repair protein
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SCFA	Short Chain Fatty Acid
SFB	Segmented filamentous bacteria
SRB	Sulfate-Reducing Bacteria
TGF-β	Tumor growth factor β

TLR	Toll-Like Receptor
TNF	Tumor Necrotic Factor
TREG	Regulatory T cells
VEGF	Vascular Endothelial Growth Factor

1.0 INTRODUCTION

Breast cancer is one of the most prevalent cancers in women [Ahmedin *et al.*, 2004]. The risk and incidence rate of breast cancer is much higher in the western world compared to other parts of the world [Siegel *et al.,* 2015]. Adoption of western lifestyle such as changes in diet contribute to the rise in the incidence of breast cancer [Hiatt *et al.,* 2009], which is been observed in developing countries both in the western world and other part of the world [ACS 2016]. Despite this high incidence rate and numerous researches in the field of breast cancer, scientists are yet to understand the etiopathogenic factors leading to breast tumor [Mazhar *et al.*, 2006]. Researches has shown that among breast cancer patient only a certain proportions are genetically predisposed or exposed to carcinogenic substances, indicating the need for more research. In the quest to determine etiopathogenic factors leading to breast cancer, scientists are focusing on the human-microbiome, considering the role played by some bacteria in the development of colon cancers. It has been indicated that antibiotics and some anti-inflammatory drugs such as aspirin, reduced the risk of breast cancer in women [Ness and Cauley 2004; Harris *et al.,* 2005]. Gastrointestinal [GI] tract bacteria not only trigger colonic tumors but also elicit the formation of mammary and prostate gland tumors in a susceptible mouse models [Poutahidis *et al.,* 2013; Rao *et al*., 2006]. Recently, a study by Lakritz and colleagues showed that human milk-borne microbes were found to inhibit mammary neoplasm in predisposed mice model [Lakritz *et al*., 2013], and the effect is transferred to subsequent generations [Poutahidis *et al.,* 2015]. The effect of the host-microbiome could range from protection against cancer to promoting its initiation and progression [Sun and Kato 2016]. The host-microbiome interaction should be an interesting factor in the study of cancer. It is evident that a rich and dynamic individual-specific microbial interaction involves microbial signaling of host cells that affect metabolic, inflammatory, neurological, immunogenic, and host-defense functions [Sun and Kato 2016: Tlaskalová-Hogenová *et al.,* 2011]. Host-microbiome interactions could be direct and local on mucosal surface, e.g. gastrointestinal tract lumen. Alternatively, these interactions could be indirect and distant, involving immunological factors like cytokines, hormonal or other metabolites [Thomas *et al.,* 2017]. Therefore, human cancers should be ideally considered against a background of host-microbiome interaction.

Specifically for breast cancer, there is convincing evidence that some gut bacteria modulate the level of circulating estrogens in the human body system [Flores *et al.,* 2012]. Estrogen and its metabolites are good mediators of breast cancer. These data put forth that the inter-individual variation in microbial-aid-metabolism may have implications on mammary cancer development. Furthermore, a study by Flores *et al*., [2012] support the proposition that breast cancer risk in postmenopausal women could be modulated by systemic estrogens levels that correlate with variation in fecal microbiota diversity. Therefore, we hypothesized that a dysbiotic microbiome can be an etiologic factor that can lead to breast tumor formation and that microbiome interplays with many of the previously familiar risk factors like age, alcohol, diet, obesity, and physical activity.

1.1 AIM OF THE THESIS

This study aimed to extend the scope of gut microbiome-diet's role outside the gastrointestinal domain, specifically investigating pathways by which the microbiome modulates breast cancer.

1.2 SIGNIFICANCE OF STUDY

This work summarizes the role of host's gut microbiome in relation with diet in modulating the risk of breast cancer development.

1.3 METHODOLOGY

Specific criteria were defined in order to collect articles on the subject matter from Pubmed query using the search criteria (MeSH Terms: gastrointestinal microbiome; breast neoplasms), with this query, a wide range of articles were collected with care. The search was restricted to effect of gut microbiome on breast carcinogenesis that were published from 2000 to 2017 and divided into articles from western world and other parts of the world (Others).

Epidemiological studies of breast cancer risk and dietary patterns were selected from Pubmed query to gather articles related to the subject on was built (MeSH Terms: diet; breast neoplasms) with this query, a wide range of articles were collected from year 2000 to 2017. A total of 43 articles were collected, 22 from Western world and 21 from other parts of the world.

2.0 THE HUMAN MICROBIOME

Human body is born consisting of virtually only its own eukaryotic human cells and a few bacterial cells originating from the mother's vagina during birth, with *lactobacilli* dominating the environment, resembling that of the mother's vagina [Palmer *et al.,* 2007]. However, over the first several years of life our oral cavity, skin surface, gut and other parts of the body are colonized by tremendous diversity of microorganisms. This microbial community is called the human-microbiome. It contains ten times as many cells as our own indigenous cells which also account for several pounds of body weight and magnitude. The microbiome encodes more genes in the body than the human genome, encoding functions that are not evolved in human genes [Human microbiome project consortium 2012; Xu *et al.,* 2007]. These microbial cells are regarded as commensal, having a symbiotic relationship with the human host, helping in digestion of food, nutrient reclamation, absorption of minerals, breakdown of dietary toxins [Shapira *et al.,* 2013], and maintaining the host immune system [Qin *et al.,* 2010]. In turn, the human provides optimal habitat, supplying the microbial cells with nutrients and protection from predators like nematodes and roundworms [Bultman 2014; Ley *et al.,* 2006; Gill *et al.,* 2006], and are mostly found within the lumen of gastrointestinal tract, while others are found within the extra-intestinal sites of the body [Bultman 2014]. Difference among host individuals regarding this symbiotic relationship with microbiota is postulated to alter susceptibility to many malignancies through several pathways: detoxification, nutrition, homeostasis, immune tolerance, metabolism, and especially inflammation [Zhu *et al.,* 2013; Sheflin *et al.,* 2014]. Host microbiome has long been known to play a role in human health [Qin *et al.,* 2010].

2.0.1 HOST INFLUENCES ON THE MICROBIOME

In addition to colonization of pathogenic organisms in the gut, aging, environmental factor and life style like smoking, antibiotics, xenobiotics, hormones and diets disrupt the normal composition of the human microbiome community, leading to disturbed microbiome ecology [dysbiosis] [Cho and Blaser 2012]. This can leads to abnormalities in the host's

immune system, inflammation, and vulnerability to more pathogenic organisms [Sheflin *et al*., 2014]. Aging not only affect the activity of cells in the body but it alters the proportion of *Firmicutes* to *Bacteroidetes,* the two dominant bacterial phyla in the guts microbiome [Human microbiome project consortium 2012]. The intestinal microbiome of newborns and infants is dominated by *Bacteroidetes* unlike in adult individuals where *Firmicutes* were the dominant species. An increased population of *Bacteroides* and *Proteobacteria* phylum is seen in elderly individuals [Stewart and Wild 2015; Mariat *et al*., 2009]. These concepts are relevant to oncogenesis, which is generally age-related [Bultman 2014]. A multi-step hypothesis of oncogenesis by Nordling [1953] proposed that 4-6 somatic cell mutations are required for cancer development. Cho and Blaser [2012] proposed that age-related microbiota shifts can contribute to the aforementioned multi-step process. Microbes inhabiting the biological system can contribute to somatic mutagenesis by secreting genotoxic substances, increasing cell proliferation, synthesizing pro-mutagenic metabolites [Vanhoutvin *et al*., 2009].

2.0.2 MICROBIOME AND CANCER

Dysbiotic state in the microbiome can be as a result of different factors as mentioned earlier, which are also well established factors that help in the development of intestinal and extra-intestinal disease like cancer. Genetic defects that affect the immune system of the intestinal epithelia, favors the formation of dysbiotic state and inflammatory diseases such as Crohn's diseases that increases risk of tumor formation [Dzutsev *et al.,* 2015]. Thus, most of the carcinogenic risk factors are shown to favor the development of dysbiosis [Dzutsev *et al.,* 2015]. The association between dysbiosis and carcinogenesis has gain more interest considering the effect of chronic antibiotics use with an increased in colorectal cancer incidence [Ou *et al.,* 2014]. Several gut microbiota metabolites directly target the epithelial cells of the intestine in mediating oncogenic effects as in the case of hydrogen sulfide and genotoxins. Some microbial metabolites, such as short chain fatty acids [SCFA] aid in suppressing tumorigenesis [Louis *et al*., 2014]. Intestinal-microbiota-effect on carcinogenesis goes beyond the intestinal environment. Altering the intestinal microbiome

shows to influence the incidence and progression of extra-intestinal cancers, including the liver cancer and breast cancer in rat models [Yoshimoto *et al.,* 2013; Dapito *et al.,* 2012]. Studies aiming to find a correlation between gastrointestinal [GI] microbiome and breast cancer are quite limited [Yang *et al.,* 2017]. These findings are reflections of distribution of bacteria and their by-products towards influencing neoplasm [Yoshimoto *et al*., 2013], and also in accordance with epidemiological findings revealing the use of antibiotics, and dysbiosis in increasing the risk of extra-colonic cancer incidence, like the breast cancer [Xuan *et al*., 2014; Velicer *et al.,* 2004]. Diet-microbiome relationship could play acts a double-edged sword role in the modulation of breast carcinogenesis [Hullar *et al.*, 2014]. Gut microbiome can influences breast carcinogenesis indirectly by metabolizing host diet into either toxic substances or beneficial substance that can lead to or prevent the development of breast cancer respectively, most of the effects of diet on breast carcinogenesis occurs only with the intervention of gut microbiome through metabolism [Shapira *et al.,* 2013]. In a dysbiotic state pathogenic microbes can contributes to the formation of cancers directly by secreting genotoxic substances in the body [Nougayrède *et al.,* 2006].

2.0.3 BREAST CANCER

Analysis has shown that breast cancer [BC] is ranked as the second deadliest cancer disease in women [Pevsner-Fischer *et al.,* 2016]: estimating to about one in every eight women can develop this malignancy during their life time. Breast cancer in women claims the life of about half a million women annually in the world [Siegal *et al*., 2015; Stewart & Wild 2014]. There are five different subtypes of breast cancer cells which develop from different cell lines viz: luminal A, luminal B, normal-like, HER2-enriched, and basal-like [Liu *et al.,* 2014]. Not all breast cancer patients are genetically pre-disposed to genetic aberrations; this draws our attention to the role of environmental factor in the pathology of the disease. Breast cancer has several risk factors which are modifiable, this includes: use of menopausal hormone therapy, cigarette smoking, parity, body mass index, physical activity, breastfeeding, oral contraceptive use, and consumption of alcohol [Bardowell *et al*., 2013; Nickels *et al.,* 2013], and now host microbiome is gaining more attention as an

additional risk factor. These known factors may have the ability to modify an individual's susceptibility to cancer by decreasing the genetic expression at the epigenome level [Hieken *et al.,* 2016; Liu *et al.,* 2014].

2.0.4 BREAST CANCER AND MICROBIOME

Research by Urbaniak *et al.* indicates the presence of microbiota in the breast tissue, but the relationship between this microbiota with breast carcinogenesis is yet to be concluded [Urbaniak *et al*., 2016; Xuan *et al.,* 2014; Antonsson *et al*., 2011]. Significant epidemiological studies have shown the presence of human papilloma virus [HPV] and epstein-bar virus [EBV] which were believed to be involved in breast malignancy formation [Khan *et al*., 2008; Kroupis *et al*., 2006; Frega *et al*.,2012], while other researches failed to have such correlation [Lindel *et al*.,2007]. Role of bacteria in breast carcinogenesis have been overlooked in the past years until after the discovery of the effect of gut bacteria in colon cancer. The link or association between cancer disease and intestinal microbiome was first suggested in a research after a germ free mouse model were injected with a carcinogenetic substances 2-2-dimethyl-4-aminobiphenyl [DMAB] in various part of their body. These germ free mouse models show a significantly reduced breast and colon cancer burden compared with the conventional mouse. This study failed to indicate which organ’s microbiota is linked with the breast carcinogenesis modulations.

Using next generation sequencing [NGS] techniques, Xuan and his colleagues analyzed the microbiota in tumors and normal adjacent tissues from estrogen receptor positive [ER+] BC patients and tissues from healthy donors. Similar compositions of microbial cells were detected in the breast tissues with an increased proportion of *Methylobacterium radiotolerans* in tumor tissues while a higher proportion of *Sphingomonas yanoikuyae* is detected in healthy breast tissues. Decrease in microbial load is observed in the mammary tumor tissue with a decrease in the strength of antibacterial response mechanisms against tumor tissue; these include TLR and NOD receptors which are as a result of decline in numbers of *S. yanoikuyae* in tumor tissue, suggesting that this organism may have probiotic functions [Xuan *et al.,* 2014]. Microbial studies describe *Sphingomonas yanoikuyae* as gram-negative bacterium that is able to express glycosphingolipid, a compound that can

activate cells that mediate innate immunity such as natural killer cells [NKCs], macrophages and dendritic cells. NKCs are important mediators of cancer immune-surveillance with a central role in controlling breast cancer metastasis. NKCs kill tumor cells in an *in-vitro* and *in-vivo* models, and inhibits active tumor growth in mice that lack endogenous protective lymphocytes [Bassiri *et al*., 2013; Kubota *et al.,* 2009; Antonsson *et al*., 2011]. The roles of breast microbiota in shaping the local immune response, providing protective function or promoting tumorigenesis in the microenvironment needs further investigation. The primary bacterial phylum found in breast tissue of women who have no clinical signs, symptoms or history of breast infection were *Proteobacteriacaea* and *Firmicutes*- a composition that is significantly different from that of the GI tract and other body organs where members of this phylum make a small proportion [Lagier *et al.*,2012]. Chan *et al.*, [2016] suggest that Proteobacteria colonize the breast tissue due to their affinity to fatty acid which is found in abundant in breast tissue. Other pathogenic bacteria able to metabolize fat such as *Enterobacteriaceae, Psuedomonas,* and *Streptococcus agalactiae,* were also found in breast tissues.

In another research by Urbaniak *et al.,* [2016], *Bacillus, Enterobacteriacaea, Staphylococcus, E.coli, Strep.epidermidis* are found in abundance in breast tumor tissue compared to the healthy breast tissue, while there is a decrease in the amount of lactic acid bacteria within the tumor tissues which are known for their beneficial effects. The bacteria found in the tumor tissue with the exception of *Bacilli,* are known to induce DNA double-strand breaks in Hela cells using the γH2AX phosphorylation assay [Mariat *et al.,* 2009]. *Bacillus* on the other hand is known to metabolize the hormone progesterone into a compound; that is relatively in abundant within breast tumor environment and is believed to promote tumor development, known as 5-alpha-pregnane-3, 20-dione [5αp] [Ojanotko-Harri *et al.,* 1990; Wiebe *et al.,* 2000; Wiebe 2007]. *Sphingomonadaceae* family though present in both women with no breast cancer history and women with breast cancer history, is found in abundance in women who have no history of breast cancer. Bacteria of the genus *Alistipes* on the other hand are found in abundant in women with history of breast cancer from human ductal fluid samples [Xuan *et al.*,2014], which have an enzymatic activity of beta-glucuronidase that may promote cancer [Humblot *et al.,* 2007; de Moreno

de LeBlanc and Perdigon 2005]. Several studies show that prolonged use of antibiotic increases the risk of breast cancer both in human [Boursi *et al.,* 2015; Velicer *et al.,* 2004], and in transgenic mice [Rossini *et al.,* 2006]. This is indicative that microbiome dysbiosis can leads into the development of breast tumor.

In the future bacterial load in the breast can be used as a diagnostic tool for breast cancer.

POSSIBLE MECHANISMS USED BY MICROBIOME IN MODULATING BREAST CARCINOGENESIS

Metabolism of endogenous and exogenous substances, immune regulation and obese status, are all potential related factors of breast cancer development which are all related to microbiome.

2.1.0 ESTROGEN METABOLISM BY GUT MICROBIOME

Diet intake can alter the function of microbiome pool in a host's body system. As mentioned earlier, microorganisms contain genes that codes for enzymes used for certain metabolisms that cannot be conducted by host digestive enzymes. Production of protective and/or harmful metabolites by microbes in the guts depends on dietary intake [Richards *et al.,* 2016]. This indicates that dietary intake and commensal bacteria in the gut can influence malignancy like cancer within and outside the gut. Gut microbiome has a unique metabolic role that can support the mechanisms by which gut microbiome 1) - alter the level of circulating endogenous compounds e.g. steroid hormones that influences breast tumorigenesis, 2) - synthesize metabolites from diets that can be harmful to the host.

Apart from the well known risk factors for BC; circulating estrogens increase breast cancer risk in postmenopausal women [Key *et al*., 2011; Fuhrman *et al*., 2012; Eliassen *et al.,* 2011; Dallal *et al*., 2013]. Estrogens are C-18 steroid hormones derived from the stepwise reduction of C-27 cholesterol. The main forms of endogenous estrogens are estradiol [E2, predominant in non-pregnant premenopausal women], estrone [E1, predominant in women at menopausal stage], and estriol [E3, predominant during pregnancy stage] [Gruber *et al.,* 2002]. Free or protein-bound estrogens exert different biological effects as they circulate in the blood [Kwa *et al.,* 2016]. Parent estrogen [E2, E1] undergo hepatic metabolism where a hydroxylation process occurs at C-2, C-4, or C-16 positions of the steroid ring. This results into the synthesis of estrogenic metabolites that vary from the parent estrogen in terms of their hormonal potency and half-life [Zhu *et al.,* 2006]. Estrogens are conjugated in the

liver to make them less potent through glucuronidation or sulfonation by hydroxylation before undergoing excretion through the bile [Zhu *et al.*, 1998], urine and feces [Raftogianis *et al.*, 2000]. It has been hypothesized that systemic estrogens can be modulated by gastrointestinal microbiome [Plottel *et al.*, 2011]. Conjugated estrogen excreted from the liver through the bile are deconjugated by gut bacteria that posses β-glucuronidase activity, leading to the reabsorption of estrogen back to the circulatory system [Gloux *et al*., 2011; McIntosh *et al*., 2012] (Figure 1).

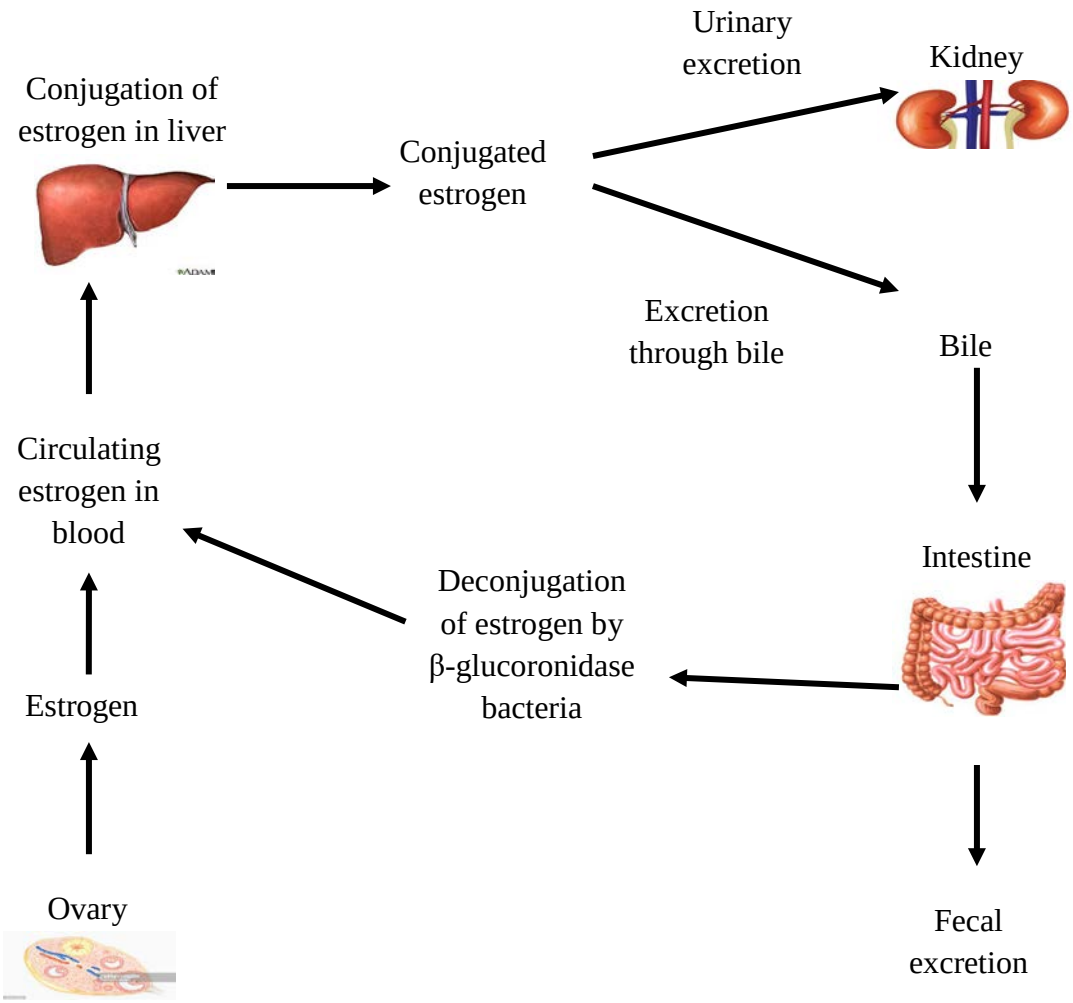

Figure 1. The estrobolome and enterohepatic circulation of estrogens. [Adopted from Kwa *et al.*, 2016]

Microbial β-glucuronidases has been known to catalyze the hydrolysis of endogenous β-glucuronides produced in the liver and exogenous β-glucuronides found in the diet [Blaut & Clavel 2007]. After hepatic glucurinidation, many metabolites, steroid hormones, and xenobiotics are excreted into the intestine through the bile. The effect of gut bacteria on these substances promotes reabsorption of their previous respective aglycones into the enterohepatic circulation. Bacteria possess different β-glucuronidase genes that are used in estrogen deconjugation. GUS gene a well characterized β-glucuronidase gene is found in bacteria colonizing human GI tract [Gloux *et al.,* 2011; Beaud *et al.,* 2005], whereas, BG gene has more recently been described using metagenomic analysis. BG gene is expressed in *Bacteroidetes* while, gus gene is mostly in *Firmicutes* phyla of the GI microbiota [McIntosh *et al*., 2012]. Diet intake can modulate the activity of bacterial β-glucuronidase in the gut. Several researches show an increase in fecal β-glucuronidase activity in healthy humans consuming diets high in fat or protein while a decreased activity is observed in fiber diet consumption [McIntosh *et al.,* 2012; Wallace *et al*., 2010]. Bacterial population density control the β-glucoronidase activity as shown from a culture of *E.coli*, suggesting the effect of quorum sensing in enzyme activity expressions [Al-Hussaini *et al*., 2011].

Approximately 80% of breast cancer cells express the estrogen-receptor [ER], making ER+ breast cancer the most prevalent breast cancer type [Al-Hussaini *et al.,* 2011]. A study by Fuhrman *et al*., [2012] showed that breast cancer in postmenopausal women is correlated with high level of estradiol, estrone and estrone sulfate circulating in their body. Relationships between circulating levels of estrogen, breast cancer risk, and intestinal microbial activity have been described [Plottel *et al.,* 2011].

2.1.1 MOLECULAR MECHANISMS LINKING MICROBIAL-DERIVED ESTROGEN METABOLITES AND BREAST CARCINOGENESIS

Estrogens and their metabolites are able to form DNA adducts on breast cells, which eventually cause damages to the DNA and lead to breast cancer [Eliassen *et al.*, 2012]. The most common estrogen metabolite in the breast tissue is E2, which can initiate breast cancer using two pathways. The first involves the release of DNA-estrogen [estradiol-adenine-guanine] adducts from the DNA backbone which subsequently leaves the de-

purinated sites error-prone in DNA repair mechanisms. The second pathway involves generation of reactive oxygen species [ROS] such as superoxide anion. This occur from redox cycling of 4-OH to 3-4 estradiol quinine, which causes oxidative DNA damage. CYP1A1 and CYP1B1 hydroxylate endogenous estrogen E2 to catechol estrogens, 2-hydroxyestradiol [2-OHE2] and 4-hydroxyestradiol [4-OHE2] respectively. The latter, is been oxidized to form 3,4-quinone [E2-3,4-Q]. E2-3,4-Q can destabilizes the glycosylated bond of DNA by covalently binding to the adenine and/or guanine producing unstable adducts of 4-OHE2-1-N3- adenine and 4-OHE2-1-N7-guanine creating mutagenic apurinic [AP] sites due to the depurination of the glycosidic bond [Li *et al*., 2004]. Studies show that accumulation of 4-OHE2 and catechol-O-methyltransferase [COMT] inhibitors can induce ataxia-telangiectasia mutated [ATM]-dependent γH2AX in MCF-7 cells [Van Duursen *et al*., 2004]. Estrogen metabolites can also undergo redox cycling generating oxygen free radicals in the form of superoxide. The superoxide generated damage DNA-bound guanine to form 8-oxo-guanine. The unstable quinine adducts [4-OHE2] and 8-oxo-guanine bases are deleted from the affected DNA segments through depurination [Yue *et al*., 2010]. These depurinated sites are susceptible to mutations in an error-prone DNA repair mechanism. Subsequent increase in estrogen metabolites through the effect of gut microbiome activity can lead to accumulation of mutations which will then contribute to breast cancer development [Yager *et al*., 2006]. Another mechanism used by estrogen is the activation of estrogen receptor α [ERα]. ERα plays a vital role in regulating/altering DNA repair and DNA damage response [DDR] by regulating key effector proteins ATM, ATR, CHK1, BRCA, and p53 [Caldon, 2014].

2.2.0 OXIDATION OF ETHANOL TO PRODUCE ACETALDEHYDE

Excess consumption of alcoholic beverages is considered as an important factor that can increase the rate of many cancer incidences. Qian *et al.,* [2014], performed a case control study in the Sub-Saharan Africa among 2139 women with invasive breast cancer and 2590 controls. They found that alcohol consumption contributes to the development of breast cancer. The relationship between incidence of breast cancer and alcohol consumption is

irrespective of BRCA mutation predisposition [Bissonauth *et al.,* 2009; Dennis *et al.,* 2011]. Chronic alcohol consumption triggers the overgrowth of gut bacteria and also increases the level of bile acids in the biological system. Ethanol does not exert a carcinogenic effect but its immediate oxidative product acetaldehyde is carcinogenic on cells. Microorganisms in the guts contribute to the carcinogenic effect of ethanol consumption by oxidizing it to yield acetaldehyde. Antibiotic such as ciprofloxacin have been used to examine the effect of colonic bacteria in the oxidation of ethanol to acetaldehyde. Ciprofloxacin reduce the amount of aerobic bacteria in the gut which also shows a decrease in the elimination rate of ethanol by about 10% in rat models [Tillonen *et al.,* 1999]. Overgrowth of gut microorganisms due to excessive ethanol/alcohol consumption contributes to the production and accumulation of acetaldehyde from ethanol, leading to increased concentration of acetaldehyde in the intestinal lumen as well as in the blood [Zhong and Zhou 2014]. Accumulation of acetaldehyde reduces the amount of *Bacteroidetes* while increasing the population of *Proteobacteria,* leading to a dysbiotic state in gastrointestinal microbiome. *E.coli,* a *Proteobacteria,* metabolizes alcohol to acetaldehyde via alcohol dehydrogenase. Accumulation of acetaldehyde subsequently induces DNA damage and inactivates Fanconi Anaemia/BRCA [FA-BRCA] network in liver and breast cells [Abraham *et al*., 2011]. Acetaldehyde has an electrophilic nature enabling it to bind to a cellular proteins and DNA causing a morphological and functional impairment such as inactivation of the cellular protein 06-methylguanine transferase which affect DNA repair mechanism [Huycke and Gaskins 2004]. Alcohol exposure causes a disturbed gut microbiota homeostasis which result in intestinal barrier dysfunction [Zhong *et al.,* 2015]. Translocation of bacteria and/or its metabolites from the intestine to other organs occur only if there is intestinal barrier dysfunction. Substances like peptidoglycans escape to other tissue when there is intestinal barrier dysfunction. Study by Xie *et al*., found the expression of Toll-like receptor 2 [TLR2] in breast cancer cell line MDA-MB-231 with high metastatic characteristic. They found that peptidoglycans of infectious bacterium *Staphylococcus aureus* are responsible for the metastasis of the MDA-MB-231 cancer cells in vitro. Peptidoglycans induced the phosphorylation of TAK1 and IκB in the TLR2-NF-κB pathway and also stimulate IL-6 and TGF-β secretion in the cancer cells. [Figure 2].

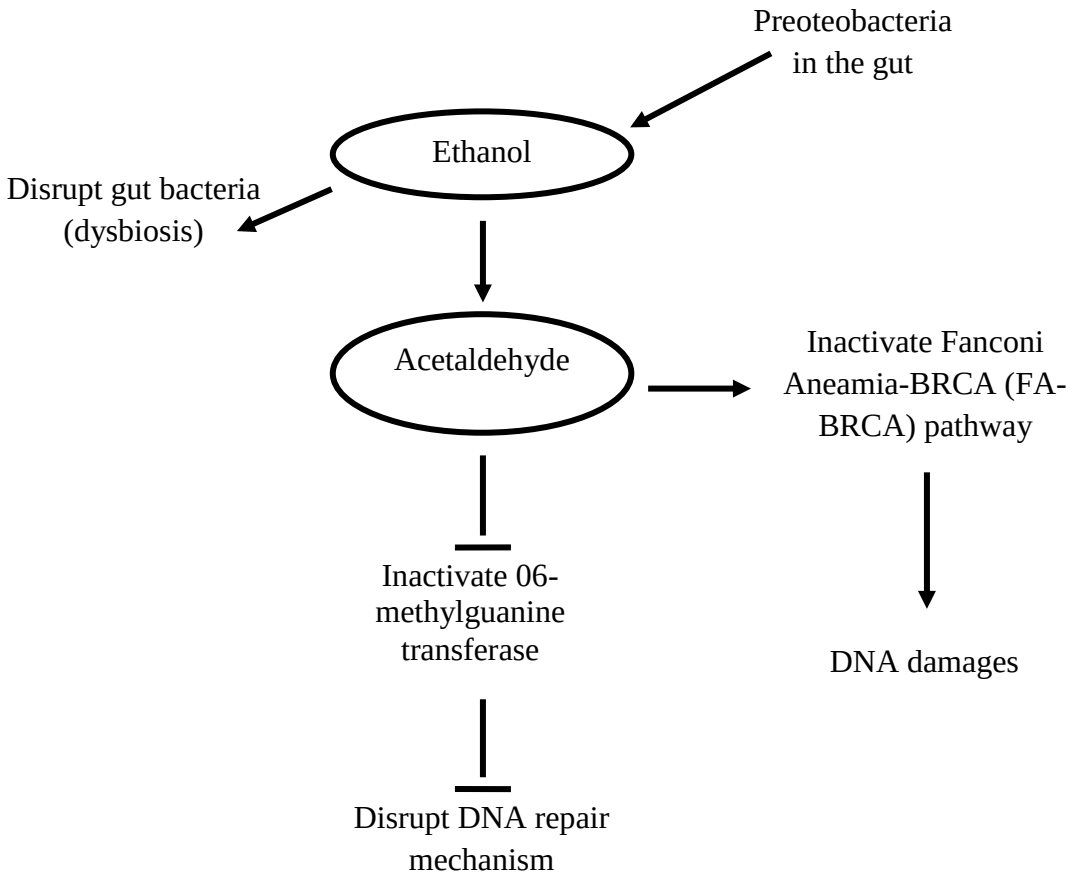

Figure 2. How gut bacteria affect metabolism of ethanol leading to breast carcinogenesis. [Adopted from Huycke and Gaskins 2004]

2.3.0 METABOLISM OF NITROGENOUS SUBSTRATES

High intake of protein can increase the level of diet-derived protein compounds such as branched chain fatty acids, phenylacetic acids, N-nitroso compounds [NOCs], ammonia and polyamines in the colon [Windey *et al*., 2012; *Ou et al*., 2013]. Gut bacteria mostly the *Bacteroides* spp. and few from *Firmicutes* phylum, ferments aromatic amino acids to produce bioactive products, including phenylacetic acid, p-cresol, indoles, and phenols. N-nitroso compounds [NOCs], a nitrogenous product, cause DNA alkylation which can lead to mutation in affected cell [Louis *et al.,* 2014]. A positive significant correlation between

dietary N-nitroso compounds and colorectal cancer in western world populations has been observed [Loh *et al*., 2011]. N-nitroso compounds can be formed endogenously via nitrosation of amine derived from fermentation of proteins by microbes in the large intestine. *Proteobacteria* are probably the major contributors of nitrosation reactions in the gut that reduces amine to N-nitroso compounds. Nitric oxide synthase 2 [NOS2], an example of nitroso compounds have the ability to induce Akt phosphorylation in breast tissue by activating the P13/Akt/BAD pro-survival pathway in a breast tumor [Ridnour *et al*., 2012]. Disruption of intestinal barrier leads to penetration of nitroso compound into other organs such as breast tissue. Nitric oxide compounds may have a genotoxic or angiogenesis properties in breast tissue. Presence of nitric oxide in tumor cells induces vascular endothelial growth factor [VEGF] on tumors. Nitric oxides metabolites e.g. nitrite genotoxic effects by nitrosative deamination and DNA strand breakage [XU *et al*., 2002][Figure.3].

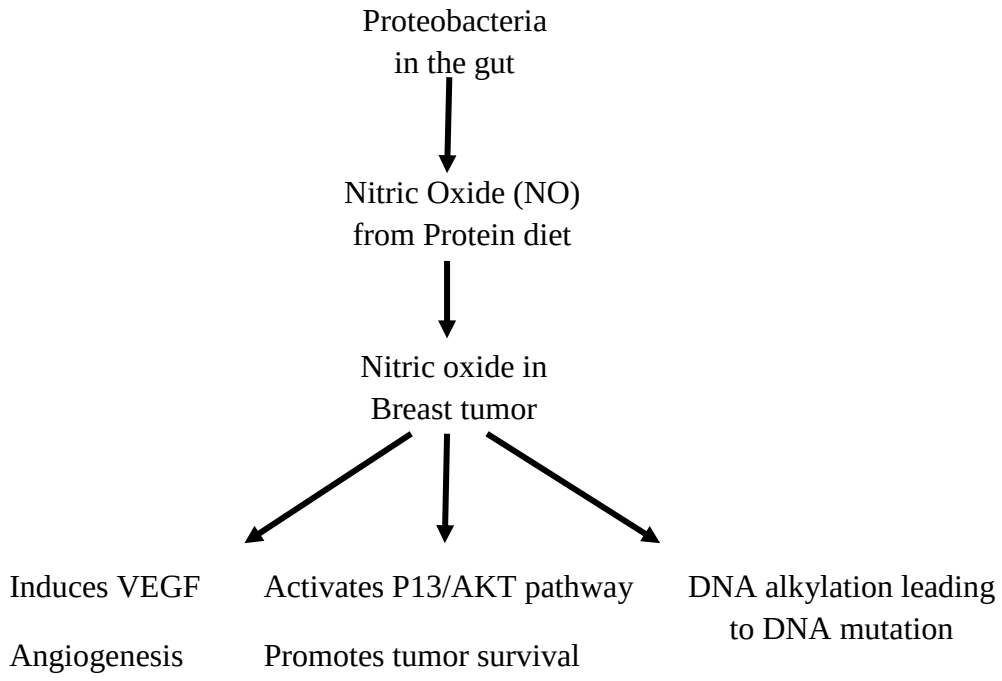

Figure 3. How microbial-metabolized nitric oxide modulates the molecular pathways of breast carcinogenesis. [Adopted from Ridnour *et al.*, 2012]

2.4.0 BACTERIAL GENOTOXINS

Bacteria can indirectly modulate carcinogenic processes in a host by modulation og toxic metabolites, induction of chronic inflammation as well as activation of non-classical oncogenes NF-κB. Several gram-negative bacteria effectors may contribute to tumor initiation and progression. There are some substances secrete by gram-negative bacteria that can directly modulate carcinogenesis, these are known as cyclomodulins [Nougayrède *et al*., 2006]. These cyclomodulins can either promote cell proliferation by blocking apoptosis [e.g. cytotoxic necrotizing factor (CNF) produced by *E.coli*] or can induce DNA damage by contributing to acquisition of genomic instability. Bacterial substances able to promote genomic instability are regarded as genotoxins. The three widely known genotoxins are: Typhoid toxin, cytolethal distending toxin [CDT], and colibactin produced by *salmonella typhi*, gram-negative bacteria, and strains of phylogenetic group B2 of *E.coli* respectively [Nougayrède *et al*., 2006]. Cytolethal distending toxin [CDT] was first isolated from gram-negative bacteria *E.coli*, and *Campylobacter* spp. These toxins were found to induce cytotoxicity and DNA damage in cultures of mammalian cells [Heywood *et al*., 2005]. CDT is a product of three-operon viz: cdtA, cdtB and cdtC that synthesize proteins of 25.5-29.9kDa. CdtB is the active subunit which presents a canonical four layered-fold structure of the DNase I family, and it have the ability to cleave naked DNA and promote single and double strand breaks in cells [Fedor *et al*., 2013]. Binding of CdtB catalytic domain with Mg^{2+} impairs the CDT intoxication activity.

2.4.1 MOLECULAR MECHANISMS OF ACTION OF CDT ON CELL-CYCLE KINETICS

CDT has homology to type 1 DNA and is able to cause DNA degradation [Grasso *et al.*, 2015]. After the production of double strand break [DSB] on DNA by CDT, ATM pathway respond by initiating DNA damage checkpoints and phosphorylation of γH2AX, around DSB site. Double strand repair protein MRE11 and DNA repair protein RAD50 are recruited to the lesion. This leads to the phosphorylation of p53, CHK2 and CDC25 to activate checkpoints and initiate cell cycle arrest at G1/S and G2/M [Alaoui-El-Azher *et al*., 2010]. These checkpoints help to provoke cell cycle arrests, in order for DNA repair to

occur. CDT synergistically cooperates with cycle inhibiting factor [CIF] to cause cell cycle arrest. CIF are found in some gram negative bacteria like enteropathogenic [EPEC] *E.coli*. The bacteria inject this toxin into the infected epithelial cells, Cif arrest the cells at G2/M phase [Marches *et al*., 2003] causing a unique alterations in the host cell that lead to attachment of cytoskeleton to the affected host' cell. Attachment of the cytoskeleton prevents mitosis. DNA synthesis can be initiated afterward, but nuclear division does not occur [Mager 2006] [Figure. 4].

Western diet and alcoholic beverages disrupt the microbiome pool of the guts promoting the proliferation of gram negative *Proteobacteria* such as *E.coli* and *Compylobacter* spp. *E.coli* releases endotoxins CDT and CIF which have the ability to cause DNA damage on epithelial tissues and also compromise the immune system of the body by inhibiting mitosis in the lymphocytes. Low count of lymphocytes is related with increase in the risk of breast cancer [Dejea *et al.*, 2013].

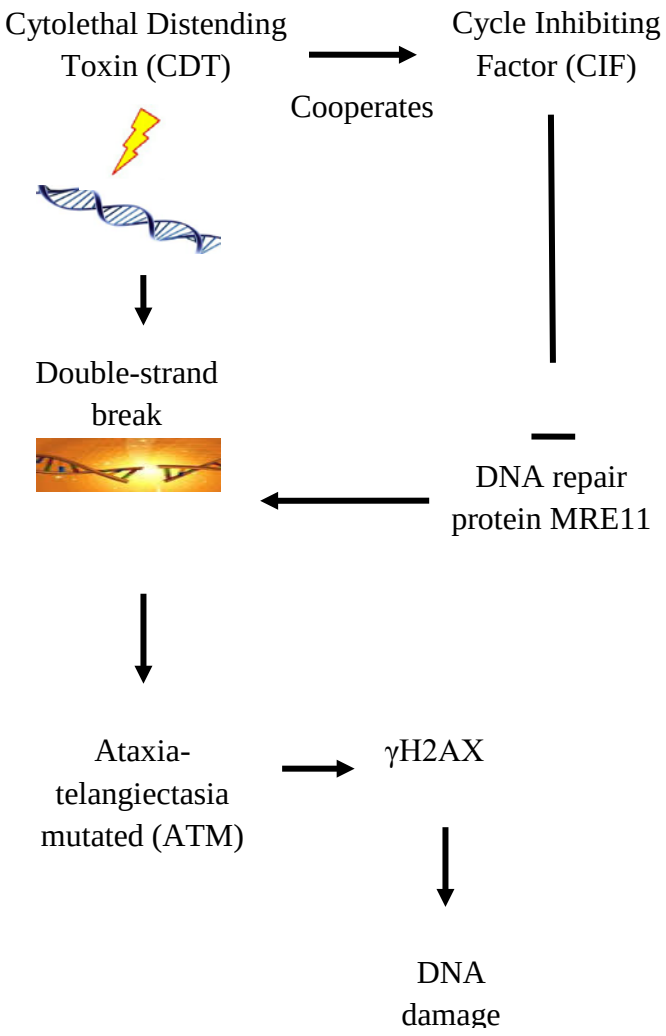

Figure 4. How CDT induces DNA damage and cooperates with CIF to prevent DNA repair as well as disruption of cell cycle. [Adopted from Levi *et al.,* 2015]

2.5.0 MICROBIOME' ROLE IN IMMUNE MODULATION AND BREAST CARCINOGENESIS

Modulation of host immune system by microbiome is a contributing factor towards tumorigenesis, metastasis, chronic inflammation, maintenance of gut epithelial cells, and regulating the amount of circulating neutrophils. These effects hold a prominent potential for cancer prevention and treatment strategies [Shapira *et al*., 2013]. The gastrointestinal

tract covers the largest surface of the human body where microbial products interact with the immune system. It has become clear that equilibrium of systemic health is routinely enforced by activities of CD4+ T-regulatory [TREG] cells along mucosal surfaces [Belkaid and Hand 2014]. These lymphocytes play a complex role by modulating host immune system during an acute inflammatory response, and subsequently regaining suppressive roles that limit deleterious pathological sequela of chronic smoldering inflammation [Wing and Sakaguchi, 2010; Bollrath and Powrie 2013; Round and Mazmanian, 2010]. Experiment using preclinical models shows that intestinal bacteria modulates TREG activity in restoring homeostasis in the body following environmental insults [Levkovich *et al*., 2014; Smith *et al*., 2013; Brisson *et al.*, 2015]. These studies on TREG cells solidify a pivotal role for gut microbiota in shaping systemic immune tone and responses.

Poor diets and life style like chronic alcohol consumption can promote the development of pathogenic bacteria in the gut disrupting the epithelial barrier and increasing the risk for developing inflammatory diseases and cancer. A compromised gut epithelial barrier allow the translocation of pathogenic bacteria and its metabolites thereby affecting systemic immunity and inflammatory index which can lead to cancer in distant sites e.g. breast tissue [Iida *et al*., 2013]. Immuno-competent hosts have efficient T-regulatory [Treg] cell responses in respond to microbial challenges. This helps restore gut epithelial homeostasis. Disruptive events on the epithelia of GI tract increase risk for microbial translocations together with systemic immune cell trafficking [Varada *et al*., 2007]. Translocation of harmful bacteria metabolites into distant organs like breast can increase their systemic inflammatory index which can leads to formation of cancer cells in the tissues [Varada *et al*., 2007]. One of the ways that bacteria can modulate cancer development is by providing a healthy immune system. This alone can provide an explanation for perplexing increase in the incidence of cancers arising from epithelia of colon and breast in countries with stringent hygienic practices [Ness and Cauley, 2004]. Chronic antibiotic use disrupts the constructive bacterial-immune enhancement in the body process leading to higher rates of breast malignancy in women [Velicer *et al*., 2004; Rossini *et al*., 2006]. Therefore, ways in which gut microbiota stimulate inherent host homeostatic properties are an attractive target for systemic good health approaches using probiotic bacteria or microbial product vaccines.

Efforts in understanding the relationship between the intestinal microbiome and systemic immune system comes from studies using gnotobiotic rodents. A decrease in the size of the intestinal Peyer's patches of the spleen is observed in gnotobiotic models which help in modulating distant organs immune system [Jung *et al.,* 2010]. The size of the pancreas and the number of beta-cells are also abridged [Sudo *et al.,* 2004]. Due to the decrease in the microbiota-derived peptidoglycans in gnotobiotic animals, number and functions of neutrophils in serum and bone marrow also decrease. The effects of human microbiome on the immune system is determine through colonization, and observing subsequent changes in gnotobiotic rodents. *Lactobacillus reuteri*: a gut microbiota, triggered host immune system CD4+, CD25+ lymphocytes to inhibit breast cancer progression [Lakritz *et al.,* 2014]. Natural killer T-lymphocytes cell which are capable of eliminating breast tumor cells are activated after exposure to glycosphingolipids of *Sphingomonas*'s [of Proteobacteria phylum] antigen [Hix *et al*., 2011]. Invariant Natural Killer T [iNKT] cells play an integral role in controlling the metastasis of breast tumor which is properly developed in the presence of *Sphingomonas* bacteria in the biological system [Wei *et al*., 2010; Franchi *et al*., 2009]. Presence of *Sphingomonas* activates Nucleotide-binding Oligomerization Domain [NOD 1] stimulating the formation of effector CD8+ antitumor cytotoxic T-cells that helps in combating breast tumor progression [Franchi *et al*., 2009; Mercier *et al.,* 2012; Gritzapis *et al*., 2008]. Inflammation decreases the proportion of *Sphingomonas* and prevents proper development of CD8+ antitumor cytotoxic T cells [Gritzapis *et al*., 2008]. CD8+Tcells are the most potent immune cells capable of eliminating foreign antigens and breast tumor cells. From the 12^{th} week of gestation, differentiation of T-cells begins in the thymus until 9 months of age when the thymus regresses through involution [Gui *et al.,* 2012]. This is replaced in part by the interactions between multiple organisms in the microbiome and cells of the immune system [Maynard *et al.,* 2012; Chung *et al*., 2012]. Such interactions occur with the help of multi-fenestrated Microfold cell [M-cells] lining the Peyer's patches.

Dendritic cells in the Peyer's patches sample have direct contact with the microbial contents mostly segmented filamentous bacteria [SFB] of the intestines and adapt the immune responses to the antigenic load, these microbial organisms are required for an effective

maturation of CD4+ helper cells and CD8+ effector cytotoxic T cells [Nanno *et al.,* 1986]. [Table 1]. There is a correlation between the number of CD8+ effector T-cells infiltrating breast tumors with patients survival [Mahmoud *et al*., 2011]. Diet rich in fats cause a dysbiotic state in the gut microbiome favoring the colonization of *Fusobacterium nucleatum* capable of killing immature lymphocytes in the Peyer's patches [Kaplan *et al*., 2010]. This causes an overall decrease in the amount of circulating systemic lymphocytes. Studies show that high neutrophils-to-lymphocytes rate [NLR] is associated with poor survival in patients diagnosed with several types of cancer [Chua *et al*., 2011; Kaneko *et al.,* 2012; Guthrie *et al.,* 2013; Margolis *et al*., 2007]. Loi *et al*., [2013] examined 2000 node positive breast cancer patients and found a significant reduction in the risk of breast cancer relapse and death due to infiltration of tumor stroma with lymphocytes. Risk of cancer relapse reduces by 17% with a 10% increase in the amount of lymphocytes independent of stage at diagnosis and patients' age [$p< 0.0001$] [Loi *et al.,* 2013]. In another study, over 170 triple negative breast cancer patients followed up over 8 years after the diagnosis, patients with more lymphocytes infiltrating their tumors [approx. $36/mm^2$] were associated with 60% recurrence-free survival whilst patients with fewer lymphocytes [approx. $20/mm^2$] having less than 20% recurrence-free survival [West *et al*., 2013]. These indicate that NLR ratio is associated with survival of patients with breast cancer.

Table 1 Roles of microbiome on the host immune system and carcinogenesis

Microbial species	Effect on immune system	Role in carcinogenesis	References
Firmicutes phylum: *Lactobacillus reuteri*	Triggers CD4+ and CD25+	Inhibit progression of breast cancer	Lakritz *et al.*, 2014
Proteobacteria phylum: *Sphingomonas* species	activates CD8+ T-cells	Eliminate breast tumor	Mahmoud *et al*., 2011
Fusobacteria: *Fusobacterium nucleatum*	Directly kills immature lymphocytes	Lower systemic lymphocytes promotes growth and metastasis of breast tumor	Kaplan *et al*., 2010
Actnobacterium phylum: *Bifidobacterium*	Type 1 T-helper Th1 non-inflammatory cells	Protects against inflammation and cancer	Sun and Kato 2016

2.6.0 MODULATION OF INFLAMMATION BY MICROBIOME

A great awareness was experienced in the last decade on the role of chronic inflammation in inducing immune-suppression and cancer. Rudolf Virchow in the nineteenth century hypothesized that inflammation could have a role in the development and progression of cancer, identifying the occurrence of this disease in the sites prone to chronic inflammation [Botta *et al.*, 2014].

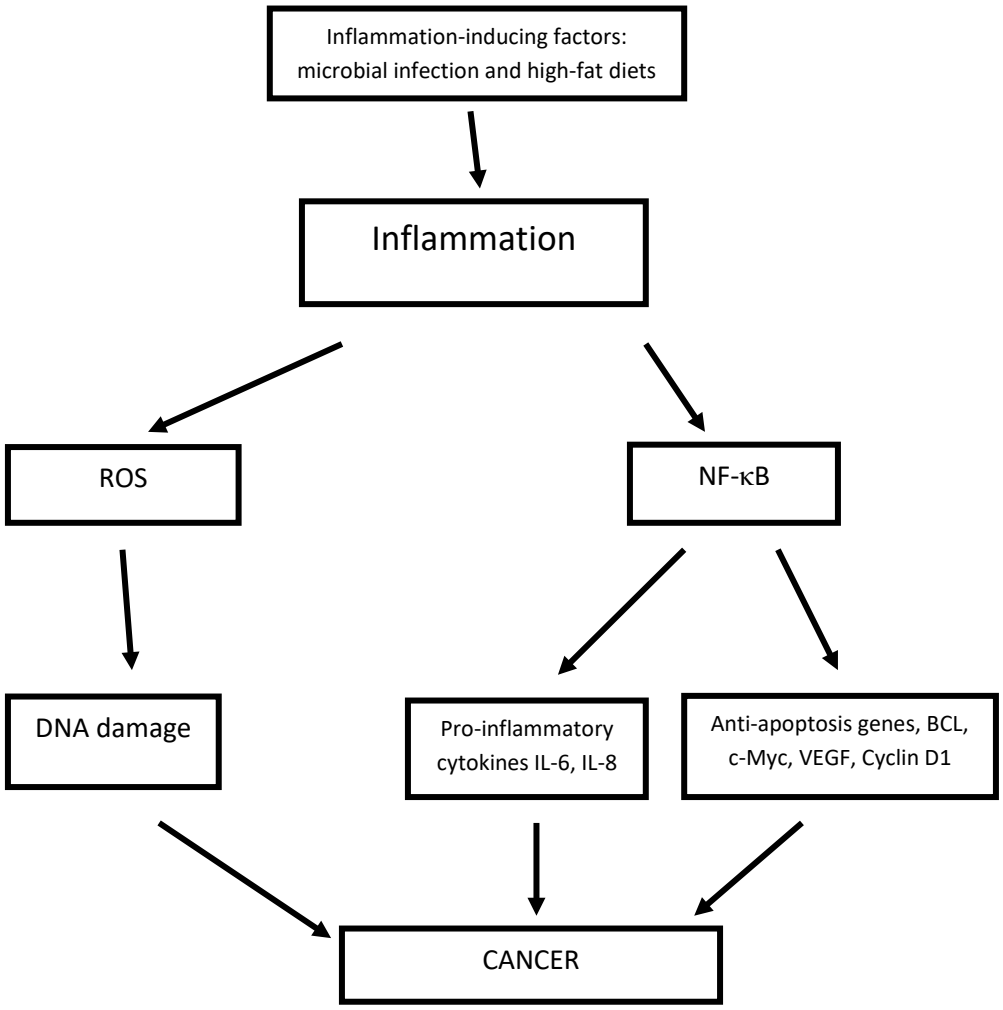

Figure 5. Schematic overview of how inflammation contributes to cancer. [Adopted from Zhang 2011].

The purpose of inflammation in the body is to protect by confining a damage region, thereby attracting immune cells to the region to eliminate the invading pathogens. This will subsequently promotes wound healing of affected tissues. An unexpected event can occur in some cases, where the body can sustain a long-term inflammatory state in response to a

lingering, low-grade infection or due to cross of boundary by commensal bacteria as seen in inflammatory bowel diseases [IBD] [Strober *et al*., 2013] (figure 5). Hanahan and Weinberg [2010] proposed a six cornerstone hallmarks of cancer, which are almost entirely cancer cell autonomous characteristics. These characteristics are: resistance to cell death; resistance to tumor suppression; increased proliferation; replicative immortality; angiogenesis; induction of invasion. Inflammation is now regarded as a new hallmark of cancer due to the fact that almost all cancer cells have a characteristic of inflammation during tumor formation [Hanahan and Weinberg, 2011]. Non-Steroidal anti-Inflammatory drugs [NSAIDs] show a protective role against different tumors and this also confirmed the role of inflammation in carcinogenesis [Farraye *et al.*, 2010; Ullman & Itzkowitz 2011]. It is widely accepted that inflammation contributes to breast malignancy. Furthermore, a number of reports indicate that inflammation can enhance the effects of all other hallmarks of cancer, using different mechanisms [Hanahan and Weinberg 2011]. For instance, cytokines can serve as growth factors and as anti-apoptotic factor to cancer cells, thereby enabling cancer cells with uncontrolled proliferations [Kalimuthu and Se-Kwon 2013]. Synergistic effect of chemokines and cytokines that are produced by intra-tumoral immune cells can activate angiogenesis; cause oncogenic mutations and loss of tumor suppressor proteins by activating epigenetic and miRNA-based pathways of gene silencing [Grivennikov *et al.*, 2010]. The immune cells can promote cancer cell invasion and metastasis by forming a cell-to-cell junction [Grivennikov *et al*., 2010; Grivennikov 2013]. Microbial cells like bacteria are important factors in the development of cancers that develop from the epithelium surface such as breast cancer. Several findings, from epidemiological studies of patients down to molecular studies of modified mice models have led to acceptance that cancer and microbial driven inflammation are linked [Trinchieri 2012; Ben-Neriah and Karim 2011]. As discussed above, chronic inflammation can increase the risk of developing cancer and this can be triggered by microbial infection, microbial derived autoimmune disease and other inflammatory conditions with unknown origin.

Host-microbiome interaction is a constant relationship which is very important for maintaining an array of indispensable biological functions. This relationship presents the

host with difficult problems such as how to eliminate harmful pathogen without disrupting commensal microbes. Different mechanism are tried to solve this problem, but in one way or the other, the commensal microbes are disrupt and disease follows. It still also not cleared whether it is the altered microbiome that leads to a disease or is the altered microbiome a product of the disease. This likely depends on the circumstances of the disease in question [Francescone *et al*., 2014; Candela *et al*., 2014]. However, microbiome exerts a deleterious effect on host cells using three distinct mechanisms: direct interaction with intestinal epithelial cell [IECs]; stimulation of pro-inflammatory immune response cascades; production of immune and epithelial-modulatory metabolites. Pro-inflammatory cytokines and chemokines such as IL-1, IL-6, IL-8, TNF-α, MCP-1, CCL5 and CXCL12 play vital role in breast carcinogenesis [Goldberg and Schwertfeger 2010]. Inter-leukine-6 [IL-6] is transiently induced by monocyte-derived MCP-1 which drive a feed-forward inflammatory signaling pathway [or cascade] that leads to production of IL-6 [Rokavec *et al*., 2012], showing a relationship between IL-6 and breast carcinogenesis. Breast cancer stem cells are characterized by treatment resistance and relapse after therapy [Kakarala and Wicha 2008]. IL-6 enhances the recruitment of bone marrow derived mesenchymal stem cells [MSCs] to the site of developing breast tumor and also helps in the production of CXCL7 in MSCs. This effect encourages the proliferation of breast cancer stem cell population [Liu *et al*., 2012]. IL-6 also promotes the expansion of breast cancer stem cells by driving an inflammatory loop, and provides resistance to Trastuzumab in HER2+ breast cancer [Korkava *et al.,* 2012]. The above studies suggest that IL-6 is one of the most important cytokines associated with breast cancer progression and treatment. Breast cancer stem cell population and systemic metastasis is reduced following the blockage of IL-8/CXCR1 signaling pathway. This indicates that inhibiting this pathway may improve the therapeutic effect of traditional chemotherapy targeting cancer stem cell population [Ginestier *et al*., 2010]. Hence, chemokines and inflammatory cytokines promote breast cancer development and metastasis by acting on the cancer stem cell [CSC] population, and blocking relevant signaling pathways in CSC may represent attractive therapeutic targets [Korkava *et al*., 2011].

Presence of cytokine and chemokine profiles in tumor microenvironment indicates that

cancer chemotherapy induces the production of TNF-α in endothelial cells. This enhances tumor cell's CXCL1/2 production through NF-κB activation, which, in turn, aids in recruitment of CD11b+Gr1+ MDSCs. These cells release S100A8/9, an inflammatory modulator that activates the p70S6K and ERK1/2 signaling pathways and subsequently provides a survival advantage for both primary and metastatic tumor cells. Interrupting the CXCL1/2-S100A8/9 axis by CXCR2 inhibition increases the effectiveness of chemotherapy [Acharyya *et al*., 2012]. TNF-α can also promote breast cancer metastasis by inducing the epithelial-mesenchymal transition [EMT] through the NK-κB-mediated transcriptional activation of Twist1 [Li *et al.,* 2012]. Additionally, the microRNA miR-520/373 family acts as a tumor-suppressor in ER negative breast cancers by reducing the production of IL-6 and 8 through negatively regulating NF-κB-mediated transcription and TGF-β-activated signaling pathway [Keklikoglou *et al*., 2012]. A study shows that IL-18 recently identified as a cytokine that contributes to Doxorubicin resistance in breast cancer treatment [Yao *et al*., 2011].

2.6.1 MECHANISMS RELATING HOST MICROBIOME, INFLAMMATION AND BREAST CARCINOGENESIS

Significant microbial associated effects on tumor inflammation progress are supported from a study by Rutkowski *et al.,* [2015] in TLR5-responsive mice. In these oncogenic K-ras activated and p53 ablated models, there is a fast progression of mammary tumor tissues. Absence of TLR5 signaling in same model is resulted in a different microbial cell composition with a slow mammary tumor progression. Microbial signaling through TLR5, leads to increased secretion of IL-6 and tumor growth. This is suggesting that microbiome is able to promote tumor progression via inflammation in a TLR5 dependent manner. In the quest to determine effect of microbial-derived inflammation on tumor tissues, Lakritz focused on specific bacterium [*H. hepaticus*] on mice that are predisposed to breast cancer. They found that mice infected with *H. hepaticus* showed an increase in breast tumor load compared to the non-infected control models. This increased tumor load is characterized by broad neutrophil infiltration into the tumor. Reduction of neutrophils from the tumor slows down the tumor development [Lakritz *et al*., 2015]. Findings in mouse models suggested

that certain gut bacteria trigger systemic events that lap over primary pro-carcinogenic signaling by reducing the quantity of systemic inflammatory index of pro-inflammatory cytokine and inflammatory cells [Erdman and Poutahidis 2015]. Gut microbiome also stimulates the expression of cytokines that can affect systemic immunity response. This is evident from a study in which germ free mice colonized with gut microbiota is used and an upregulation of cytokines that are known to influence adaptive and innate immunity such as IL-1, IL-8, IL-10, TNF, and IFN-γ, components is shown [Larsson *et al.*, 2012]. The above studies reveal that individual or whole microbiome can promote mammary tumor progression via inflammation using multiple mechanisms. In contrast, gut microbiota are shown in some circumstances to prevent carcinogenic process in epithelial cells distal from the intestine such as breast tissue [Belkaid and Hand 2014]. This indicates the possibility of using microbial models as novel targets for therapeutic and preventive ways for breast carcinogenesis.

2.7.0 DIETARY FIBER METABOLISM BY GUT MICROBIOME

As stated early, host microbiome aid in the digestion of foods that are indigestible by the human digestive enzymes e.g. dietary fibers. Fibers are part of plants cell wall that is classified as soluble and insoluble dietary fibers. Human intestinal microbiota are able to ferment soluble dietary fibers such as arabinoxylans, inulin, lignans, beta-glucans, amylase resistance starches, fructans and pectins into short chain fatty acids [SCFA], while they are not able to ferment insoluble fibers like cellulose, dextrins, waxes, lignins and chitins [Topping and Clifton 2001]. Lignan is a very important soluble dietary fiber which is found mostly in soy, fruits, whole grains and vegetables. While banana and onion contains arabinoxylans fibers, other fruits contain large quantity of fructans and pectins [Saarinen *et al.,* 2010]. Presence of high concentrations of soluble fiber in the distal ileum and colon increases the growth and maintenance of beneficial *Bifidobacterium* [member of the Actinobacteria phylum], commensal species from *Bacteroidetes* and anti-inflammatory *Faecalibacterium prausnitzii* [a *Firmicute*] [Hippe *et al.*, 2011]. Using 16S ribosomal tagged probes by fluorescent In Situ hybridization [FISH], Benus *et al.*, [2010] shows 80% reduction in *Roseburia intestinalis*, *Faecalibacterium prausnitzii*, and short chain fatty acid

[SCFA] in 14 healthy volunteers after consuming fiber-free diets for 2 weeks, followed by 2 weeks of a low fiber diet [<5 grams/day]. *Firmicutes* and *Bacteroidetes* within the intestinal microbiota are able to metabolize dietary lignans into potent phytoestrogens enterodiol [END] and its oxidative product enterolactone [ENL] that are readily absorbed into the bloodstream thereby, modulating the effect of estrogen in breast carcinogenesis [Wang *et al*., 2010]. SCFA, a product of bacterial fermentation, is shown to affect mucosal immune system through G-protein coupled receptors by inducing the production and increased function of Treg and IL-18 [Singh *et al.,* 2014]. Phytoestrogens are plant estrogens having similar structure as estrogens in human with weak estrogenic actions. Several major classes of plants estrogens exist all having different dietary sources, but the most intensively investigated phytoestrogens are the isoflavones. Figure 6 shows the effects of phytoestrogens.

It is found that Asian populations who consume high concentration of dietary soy products with isoflavanone have lower incidence rate of breast cancer. This led to further research on protective effect of soy food consumption on breast cancer and other hormone dependent cancers with phytoestrogen the prime target [Miller and Snyder 2012]. Gut bacteria and glucosidase breaks down phytoestrogens into their respective aglycones leading to more efficient absorption [Bilal *et al*., 2014]. Two immediate aglycones of phytoestrogen: genistein and deidzein, are further metabolized by intestinal bacteria to 0-desmethylangolensin [O-DMA] and equol, respectively. Less than 50% of the world population can produce equol while about 90% are able to produce 0-DMA [Patisaul and Jefferson, 2010]. Genetic and microbiome pool are contributing factors that determine the amount of phytoestrogens metabolized and absorbed [Snedeker and Hay 2012]. Absorbed phytoestrogen aglycones are conjugated to glucuronic acids in hepatic circulation which are subsequently, de-conjugated prior to excretion with urinary concentrations increasing in parallel to consumption [Karr *et al*., 1997].

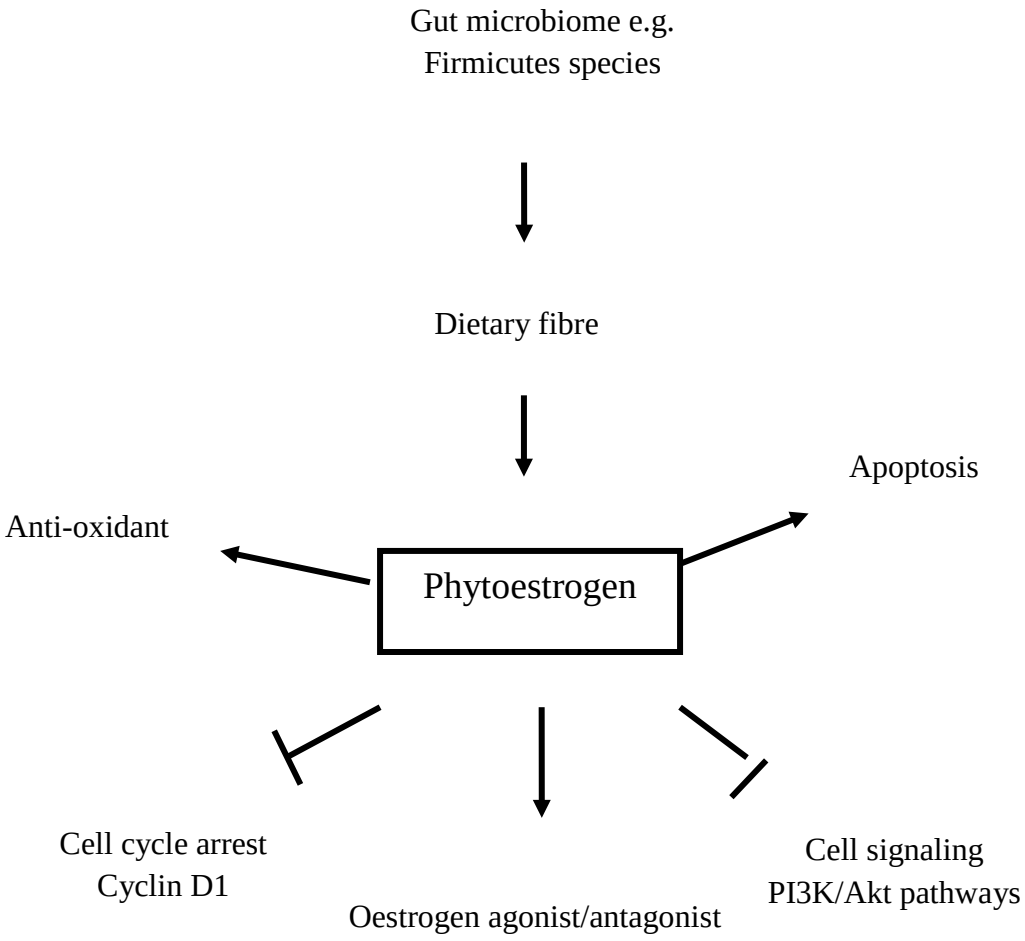

Figure 6. Multiple targets for the action of phytoestrogens. [Adopted from Martin *et al.*, 2007]

The two major hormonal receptors in the breast tissue estrogen receptors α and β are encoded by different genes with different role in gene regulations and tissue distributions [Thomas and Gustafsson 2011]. They also have differential effects in estrogen-sensitive tissue and in breast tissue, ERα activation can stimulate proliferation whilst ERβ activation antagonized the effect of ERα. This is believed to be mediated by dimerization of ERβ with ERα [Thomas and Gustafsson 2011; Saji *et al*., 2005]. In breast tumour the ratio of ERα to ERβ is raised and there is increased tumor aggressiveness in those that are ERβ negative [Saji *et al*., 2005]. Phytoestrogen has a weak relative binding affinity [RBA] to ERs

compare to hormonal estradiol. Aglycones of phytoestrogen such as daidzein and genistein posses a 9-10 fold increase in the affinity for ERβ than ERα [Kuiper *et al.,* 1998]. A study shows that concentration of total genistein and diadzein were 20-40 folds higher than oestradiol equivalents in breast adipose/ glandular tissue after dietary intake supplement [Bolca *et al.,* 2010]. The ability of phytoestrogens to accumulate and activate ERβ in the breast tissue may have some clinical significance. Over-saturating dose of phytoestrogens [≥10 μmol/L] is required to induce apoptosis or at least inhibit cell growth in breast tissue [Leclercq and Jacquot 2014]. Nevertheless, phytoestrogens can also act on cell surface estrogen receptors or interact with cytokine signaling pathways and growth factor. Therefore, it is shown that phytoestrogens can modulate the responses to growth factors or activate/ inhibit kinases which may alter ligand-independent transcriptional activity of oestrogen receptors, NF-κB and AP-1 [Heldring *et al.,* 2007]. Genistein acts as a tyrosine kinase inhibitor and has been shown to alter the expression of PI3/Akt pathway and extracellular regulated kinase [ERK] [Barnes 2010]. Long-term treatment of breast cancer cells with dietary genistein [8-10 mol/L] down-regulate the expression of Akt [Anastasius *et al.,* 2009]. Regarding growth-repressing effect of ERβ and cell signaling, Cotrim *et al.,* [2013] showed that activation of the MEK 1/2 and PI3K/Akt pathways inhibited the ERβ growth-mediated repression in breast cancer cells.

Recently researchers focused on the action of phytoestrogens in modulating the expression of proteins regulating the cell cycle and apoptosis. Cyclins are a group of proteins that regulate transition of the cell cycle through the G1, S, G2 and M phases, and through uniting with cyclin-dependent kinases [CDKs], they initiate gene transcription that regulates the cell cycle. Cyclin D1 is regarded as an oncogene and is over-expressed in more than 50% of breast cancer. It regulates G1 to S phase of the cell cycle [Tobin and Bergh 2012]. High concentration of phytoestrogens [≥10 μmol/L range] inhibits expression of Cyclin D1 [Chen and Sun 2012; Rahal and Simmen 2010]. In some studies it has no effect on Cyclin D1 [Waite *et al.,* 2005; Seo *et al.,* 2011]. CDK [CDIs] are able to regulate the activity of Cyclin/CDK complex [Chu 2008]. The two most extensively investigated CDI's are p21 [CIP1/WAF1] and p27 [Kip1] and the expression of p21 is controlled by p53 [a tumor suppressor gene] [May & May 1999] which has many other actions including

inducing apoptosis [Haupt *et al.,* 2003]. An *in-vitro* study shows that high doses of phytoestrogen are shown to increase the expressional activity of p21, p27 and p53 [Seo *et al*., 2011; Sakamoto *et al*., 2010; Hsieh *et al*., 2011], with parallel changes in the reduction of cyclin D1. Both *in vivo* [Liu *et al.,* 2012] and *in vitro* studies [Sakamoto *et al*., 2010, and Rajah *et al*., 2012] have shown that phytoestrogens increase the Bax/Bcl-2 ratio and stimulate apoptosis.

2.7.1 GUT BACTERIA LIGNAN METABOLISM

In an experiment by Mabrok *et al.,* [2011] gnotobiotic rat models with mammary tumor are infected with some strains of gut bacteria. The microorganisms in the rat models convert plants lignans into enterolignans which shows anticancer effects. Notable decrease in mammary tumor was observed by increasing tumor apoptosis. This is in conjunction with an epidemiological study that shows inverse relationship between high blood level of phytoestrogens and risk of breast cancer [Ward and Kuhnle 2010]. A case study involving over 6,000 women with estimated lignans consumption to 3 times per week shows a 50% reduction in breast cancer among premenopausal women irrespective of their weight [Cotterchio *et al*., 2008]. Similar study was taken by the UK Women's Cohort Study 35,000 women to analyze the effect of whole grain fiber and fruit fibre consumption on risk of breast cancer. It shows that premenopausal women with ≥13 grams of whole grain fiber and 30 grams of total fiber consumption per day had a 50% reduction in risk of breast cancer. However, a lower reduction was observed in women whose total daily fibre came mostly from fruits which accounts to only 35% lower risk [Cade *et al.,* 2007]. Effect of high fiber diets on the risk of breast cancer occurrence extends also to postmenopausal women even though there is compositional change in the ratio of *Firmicutes* to *Bacteroidetes* in the gut microbiome with age [Mariat *et al*., 2009]. In effort to check the effect of fibre on postmenopausal women, 51,000 volunteers are examined over the course of 8 years. The result shows that women with ≥30 grams of fiber intake from fruit and whole grains had 34% decrease in breast cancer risk compare to those with lesser consumption quantity. This indicates that lignan fibre is more protective than fruit and

vegetable fiber [Cade *et al.,* 2010]. In another study of premenopausal women with benign breast disease who are at risk of having breast cancer were asked to undergo a baseline periareolar fine needle aspiration [RPFNA] and were then monitored on a diet which included daily plant lignans [intervention] for one year. Serum enterolactone was measured before and after the intervention. There is a nine-fold increase in serum enterolactone from the baseline after intervention. After one year, a repeated RPFNA showed atypia in only half of the women with nine-fold increase in serum enterolactones from baseline levels, treated with diets rich in lignans [Fabian *et al.,* 2012]. Serum enterolactone, a product of microbiome fermentation of dietary lignans, appear to have protective as well as preventive effects in breast cancer. Equol, which is synthesized from deidzein by human intestinal flora, is biologically more active than any other isoflavone aglycone.

2.8.0 CUES ON FUTURE MANAGEMENT STRATEGIES OF BREAST CANCER

Previous and recent studies indicates that chronic or frequent use of antibiotics either for medication of certain infections or for hygiene purposes increases the risk for breast carcinogenesis [Ness and Cauley 2004; Velicer *et al.,* 2003]. As discussed earlier, microbial cells in a human host is 10 fold the number of host cells and exert some genes and enzymes that helps in the metabolism of certain food substances that cannot be digest by the host's enzymes, therefore, antibiotics can disrupt the metabolizing effect of gut bacteria from food to cancer-protective metabolites. Chronic antibiotics used in some instances disrupt the commensal microbiota that are known to perform protective role in the host, while making the environment friendly to pathogenic microbes to proliferate and induce bacterial genotoxins or metabolize harmful metabolites that can act as pro-carcinogenic for both intestinal and extra-intestinal environments [Table 2]. Velicer *et al*., [2004] indicates that antibiotic-use, disturb gut microbial community leading modulation of the expression of factors such as T-lymphocytes, cytokines and prostaglandins that are known as inflammatory mechanisms in the host. Other factors include disruption of immune mechanism, estrogen and phytochemical substance metabolism through gut microbiome. Rao *et al*., [2007] hypothesized that the quest for a stringent hygiene life style and frequent use of antibiotics as practiced by western populace, weakens the interleukin 10

[IL-10], exposing individuals toward developing inflammation associate cancers such as breast cancer [Ness and Cauley 2004; Schwabe and Jobin 2013].

Apart from the scenarios discussed above, host's dietary habits [such as high fat diet, red meat diet and excessive alcohol consumption] can influences dysbiosis and bacterial translocation in the host's microbiome and subsequent production of detrimental metabolites such as hydrogen peroxide, estrogen, bile acid nitric oxide, acetaldehyde etc which increases risk of breast carcinogenesis. High fiber diets can influence gut microbiome to produce or metabolize substances such as butyrate and phytoestrogens that can reduce the risk of developing breast cancer. Dietary interventions by consuming high lignan and probiotic rich food, and avoiding junk diets is a possible mechanism that can be used to curtail the rate of breast cancer incidence and death tolls.

Table 2. Impact of some substrates metabolized by gut microbiome on breast carcinogenesis. [Adopted from Blaut and Clavel 2007]

Substrates	Substrate metabolism	Microbial species	Impact on host
Endogenous estrogen	Estrogen to Estradiol (E2) and Estrone (E1)	Bacterial species containing β-glucoronidase activity, mostly *Bacteroides*	Increases systemic level of circulating estrogen aglycones which is associated with breast cancer risk.
Ethanol	Oxidation of ethanol to acetaldehyde	*Proteobacteria* that contains alcohol dehydrogenase enzymes e.g. *E.coli*	Disrupt intestinal barrier integrity, induces DNA damage, and activates FA-BRCA in liver and breast tissue
Nitrate in red meat	Reduction of nitrate to N-nitroso compounds [NOC] e.g. Nitric oxide synthase 2 [NOS2].	Multiple gut bacteria including *Bacteroides* and *Proteobacteria* species.	Induces Akt phosphorylation and promotes angiogenesis in breast tumor
Phytoestrogen from dietary fibres	Phytoestrogen deidzein and genistein are converted to equol and 0-desmethylangolensin [O-DMA] respectively	Multiple *Firmicutes* species in the gut e.g. *Lactobacillus*	Antagonize the effect of hormonal estrogen, increases tumor apoptosis in breast tissue, down regulate the expression of Akt in breast tissue etc.

3.0 RESULT

Twenty-three (23) original articles studied the role of gut microbiome in breast cancer including both human and animal studies. Different heterogeneous methods were used and different microbial organisms were considered. However, some bacteria are augmented such as *Closteridia*; *E.coli* and *Blautia* while beneficial bacterial species are diminished in breast cancer such as *Lactobacillus* species. The augmented species were found to increase systemic level of estrogen while *Lactobacillus* species helps in promoting systemic immunity. A significant increase in the number of researches conducted in other part of the world showing a positive effect of prudent diet in the risk of breast carcinogenesis (P=0.0452). This could be a factor that promotes the reduction in the risk of breast cancer in developing country compare with Western developed countries. Host microbiome plays a vital role in modulating diets to affect breast cancer risk.

Number of articles showing effects of diets on breast carcinogenesis from 2000-2017

Total number of articles sourced = 23

Total number of articles from Western world = 14

Total number of articles from other parts of the world (others) = 09

Table 3(a) studies showing effect of gut microbiome in breast carcinogenesis from Western world (2000-2017)

Authors	**Location**	**Type of study**	**Conclusion**
Attraplsi *et al.*, 2014	California and Illinois	Cross sectional study	Composition of gastrointestinal microbiome is unalike between BC patients and abnormal-mammography controls.
Bard *et al.*, 2015	USA	Cross sectional study	Significant differences were observed for absolute numbers of total bacteria as well as absolute numbers and/or proportions for some studied bacterial groups according to clinical stages of BC. Suggesting the role of GI microbiome in the development of BC.
De Spiegeleer *et al.*, 2015	USA	Experimental study	Shows how microbiome promotes angiogenesis in breast tumor using quorum sensing peptides.
Flores *et al.*, 2012	USA	Cross sectional study	Intestinal microbial richness and functions influence levels of non-ovarian estrogens
Fuhrman *et al.*, 2012	USA	Case control study	Estrogen metabolites that are metabolized by gut bacteria increase risk of breast cancer.
Fuhrman *et al.*, 2014	USA	Cross sectional study	Women with a more diverse gut microbiome exhibit an elevated urinary ratio of hydroxylated estrogen metabolites to parent estrogen
Geodart *et al.*, 2015	USA	Population based case-control study	Postmenopausal women with breast cancer have altered composition and estrogen-dependent low diversity of their gut microbiota

Lakritz *et al.*, 2014	UK	Experimental study	Gut bacteria *Lactibacillus reuteri* ATCC-PTA-6475 trigger CD4+; CD8+ lymphocytes and inhibits mammary neoplasia.
Mabrok *et al.*, 2012	Germany	Experimental study	Gut bacterial conversion of plant lignans to enterolignans beneficially influences their anticancer effects.
Moore *et al.*, 2016	USA	Case control study	Lower urinary bacterial-metabolized estrogen level is associated with reduced postmenopausal BC risk Shanghai women than in Asian American women with higher risk of BC.
Rao *et al.*,., 2006	USA	Experimental study	The study shows that gut pathogen *Helicobacter hepaticus* significantly promotes mammary tumor in mouse model.
Rutkowski *et al.*,., 2015	USA	Experimental study	TLR5-dependent commensal bacterial promotes malignant progression at extra-mucosal locations like breast by increasing systemic IL-6.
Trang *et al.*,., 2016	France	Case control study	The feacal bacteria composition of the patients is similar but higher percentage of *C. leptum, F. prausnitzii*, and *Blautia* species
Xuan *et al.*,., 2014	USA	Experimental study	Microbial dysbiosis is associated with formation of BC with a reduction in the number of microbes in BC patients

Fourteen 14 studies from Western world all signifying that gut microbiome in relation with diet modulates breast carcinogenesis

Table 3(b) studies showing effect of gut microbiome on breast carcinogenesis in other parts of the world (2000-2017).

Author	Location	Type of study	Conclusion
Aragon *et al.*,., 2014	Argentina	Experimental study	Breast tumor growth is avoided or delayed after stimulation of immune response against it, due to the presence of gut microbiota *Lactobacillus casei* CRL431.
Dallal *et al.*,., 2012	Iran	Experimental study	*Lactobacillus casei* increases the production of IFN-γ; IL-12 and natural killer (NK) cells decreasing the growth rate of mammary tumor in mice model.
Fooladi *et al.*,., 2015	Iran	Experimental study	*Lactobacillus acidophilus* can promote immune response and increases antitumor response by increasing the production of IFN-γ.
Maroof *et al.*, 2012	Iran	Experimental study	*Lactobacillus acidophilus* causes a significant decrease in tumor growth and an increase in the number of IFN-γ; IL-4; TGF-β; and lymphocytes
Miyoshi *et al.*, 2003	Japan	Case control study	High serum estrone conjugated by gut bacteria is responsible for significant increase breast cancer risk
Poojary *et al.*, 2017	India	Experimental study	*Corynebacterium* species should be considered as on eof the causative agents of breast abscess.
Rachid *et al.*, 2005	Argentina	Experimental study	*Lactobacillus helveticus* decrease growth rate of mammary tumors by increasing apoptosis in tumor and decreasing the production of pro-inflammatory cytokines IL-6.
Wang *et al.*, 2010	China	Experimental study	Gut bacterial-biotransformation of dietary flaxseed into enterodiol which is protective against BC.
Yazdi *et al.*, 2010	Iran	Experimental study	Immunomodulatory cytokine IL-12 production is upgraded in the presence of *Lactobacillus acidophilus*, which helps in restraining the growth of breast tumor.

Nine (9) studies from other parts of the world showing how commensal gut microbiome influences the risk of breast carcinogenesis by up-regulating systemic host immunity.

Number of articles showing effects of diets on breast carcinogenesis from 2000-2017

Total number of articles sourced = 43

Total number of articles from Western world = 22

Total number of articles from other parts of the world (others) = 21

Diet-breast carcinogenesis (DBC) relationship

Table 4(a). Articles from Western world showing Diet-Breast carcinogenesis (DBC) relationship from 2000-2017

Authors	Location	Conclusion	Yes	No
Adebamowo *et al* 2005	USA	This finding suggests that there is no association between diet pattern and BC risk.		+
Agurs-collins *et al* 2009	USA	The study indicates that prudent diet pattern may protect against BC in some black women.	+	
Bessaoud *et al* 2012	France	BC risk is associated with type of diet.		+
Buck *et al* 2011	Germany	No association between healthy and unhealthy diet with BC risk		+
Cade *et al* 2011	UK	Consumption of Mediterranean-type diet does not show any strong association with BC risk.		+
Castello *et al* 2014	Spain	Thus study shows the harmful effect of Western diet on BC risk.	+	
Catsburg *et al* 2015	USA	Plant-based diet with limited red meat intake may be associated with a reduced risk in BC in postmenopausal women.	+	
Cottet *et al* 2009	France	Avoidance of Western-type diet with high intake of diet comprising of fruits and vegetables may contribute to substantial reduction in BC risk.	+	
Demetriou *et al* 2012	Cyprus	Diet rich in fish, vegetables, legumes and olive oil may favorably influences the risk of BC.	+	
Edefonti *et al* 2008	Italy	Vitamins, animal products and fiber food pattern may be associated with a reduced risk of BC.	+	
Fung *et al* 2005	USA	An overall association between prudent and Western diet with a decrease in BC risk is not observed.		+
Link *et al* 2013	California	With a greater consumption of a plant-based dietary pattern, there is a reduction in BC risk.	+	
Männistö *et al*	Netherlands	The study suggests that diet may not have a role in		+

2005		the etiology of breast cancer.		
Mourouti *et al* 2015	Greece	Healthy dietary pattern seems to favorable in not having BC among women	+	
Murtaugh *et al* 2008	USA	There is no significance association between BC risk and dietary pattern		+
Nkondjock and Ghadirian 2005	Canada	The result suggest that risk of BC may not be in conjunction with food pattern		+
Sant *et al* 2007	Italy	Result indicates that salad vegetables dietary pattern protects against BC.	+	
Sieri *et al* 2004	Italy	Diet rich in olive oil and vegetables protects against BC.	+	
Terry *et al* 2001	Sweden	Result does not show any association between BC risk and dietary pattern		+
Van Ryswyk *et al* 2016	Canada	Risk of breast cancer is not modulated by diet in some Canadian women.		+
Velie *et al* 2005	USA	Traditional southern diet protects against BC risk.	+	
Wu *et al* 2009	USA	Dietary pattern with intake of meat/starches and higher legumes is associated with lower BC risk.	+	

Table 4(b) Articles from other parts of the world (others) showing Diet-Breast carcinogenesis (DBC) relationship from 2000-2017.

Authors	location	Conclusion	Yes	No
Ahmadnia *et al* 2016	Iran	Milk and diary items reduce risk of BC unlike meat products.	+	
Baglietto *et al* 2010	Australia	Dietary pattern rich in salad and fruit might protect against invasive BC.	+	
Bao *et al* 2012	China	Western dietary pattern is associated with increased BC risk.	+	
Butler *et al* 2010	Singapore	This study concludes that diet rich in vegetables and fruits have an early protective effect on BC risk.	+	
Cho *et al* 2010	Korea	Seafood and vegetables is associated with decrease in BC risk.		+
Cui *et al* 2007	China	Western dietary pattern increases risk of breast cancer in Chinese women	+	
Hirose *et al* 2007	Japan	Fatty foods and Japanese pattern have negative effect on BC risk.	+	
Jordan *et al* 2012	Tanzania	Fat intake is associated with increase in BC.	+	
Karimi *et al* 2014	Iran	A healthy dietary pattern is associated with decrease in risk of BC.	+	
Kojima *et al* 2016	Japan	There is no significant association between dairy and vegetable diet pattern with BC risk.		+
Lu *et al* 2016	China	Chinese-traditional dietary pattern might favor the effect of BC risk in Chinese women	+	
Marchioni *et al* 2008	Brazil	Western type diet promotes risk of BC	+	
Mobarakeh *et al* 2014	Iran	Prudent diet could protect against BC risk among Iranian women.	+	
Ronco *et al* 2006	Uruguay	Western diet affect the risk of BC in women	+	

Ronco *et al* 2010	Uruguay	There is no significance in BC risk with dietary pattern	+
Shin *et al* 2016	Japan	Western diet increases the risk of BC in Japanese women.	+
Tajaddini *et al* 2015	Iran	Prudent diet such as boiled potato, legumes and wheat bread reduces risk of BC	+
Tumas *et al* 2014	Argentina	Starchy foods showed a promoting effect in the risk of BC	+
Wu *et al* 2013	Taiwan	Meat and high fat intake is associated with higher BC risk.	+
Yu *et al* 2010	Korea	Dietary pattern rich in vegetable is associated with reduced risk of breast cancer.	+
Zhang *et al* 2011	China	Diet characterized with high vegetable/milk/soy and low meat is associated with lower risk of BC.	+

Table 5. Showing DBC in articles from Western world and others from 2000-2017

P=0.0452

	Western world	Others	Total
DBC			
Yes	12	18	30
No	10	3	13
Total	22	21	43

P=0.0452 Significant difference. Other countries tend to have higher freq of articles those say Yes for DBC

Table 6 Showing DBC in articles from Western world and others before 2010

P=0.2374

	Western world	Others	Total
DBC			
Yes	07	04	11
No	06	00	06
Total	13	04	17

P= 0.2374 no significant difference between western countries and others in the number of articles that say YES on effect of diets on breast carcinogenesis.

Table 7 Showing DBC in articles from Western world and others after 2010.

P=O.1881

	Western world	Others	Total
DBC			
Yes	05	14	19
No	04	03	07
Total	09	17	26

P=0.1881 no significant difference between western countries and others in the number of articles that say YES on effect of diets on breast carcinogenesis.

4.0 DISCUSSION AND CONCLUSION

4.1 DISCUSSION

Breast cancer incidence differs around the world with a vast difference between the Western and Asian population [Soerjomataram *et al.,* 2008]. Eastern-born child of immigrants has been shown to have same breast cancer risk incidence as the western compatriot despite their ancestral differences. Environmental factors such as diet; are considered as the major players in such situations considering the fact that changes in genes do not occur over just a single generation [Nasseri *et al.,* 2007]. Environmental diet and host microbiome have shown an influential role towards initiating carcinogenesis such as colorectal cancer and lungs cancer [Louis *et al.,* 2014]. Knowledge towards understanding the interrelationship between our microbiome and the type of diets we consume hold a possible influence in modifying the course of many diseases from digestive disorders to cancer malignancies within and outside the intestine. As shown in table 4(a) and 4(b) forty three studies within a time frame of 2000-2017 from Western world and other part of the world show the influence of diet pattern on breast carcinogenesis, with articles from other parts of the world showing significant figure on relevant of diet on breast cancer risk than studies from Western world (P=0.0452). The overall studies shows that Western diet [red meat, refined grains, and high-fat dairy products] have a slight significance in promoting risk of breast cancer from the results of dietary patterns of BC patients both in Western world and other parts of the world. This is in conjunction with study by Smith-Warner *et al.,* [2001]. Effect of western diet could be a factor that leads to higher incidence rate of BC in Western world and other developing countries with changing dietary pattern to Western diet. This is evident that a broad and deeper understanding about our microbial community and its interaction with diet can help in decreasing the risk of breast cancer development as well as preventing its re-occurrence, using dietary therapies in the future. Previous studies have focus on the role of viruses and some specific bacteria towards development of cancers. For example *Helicobacter pylori*, is been associated with the development of colon cancer, likewise Human Papilloma virus [HPV] with breast cancer. In this review,

mechanisms used by gut microbiome toward development of breast cancer are considered. Host microbiome used several mechanisms to increase the risk of breast cancer occurrence, this includes: secretion of genotoxins, stimulation of chronic inflammation, suppression of systemic immunity, synthesis or metabolism of toxic metabolites, and modulation of estrogenic burden.

Studies on microbiota-cancer relationship focus on local effects of organ-specific microbiota, as in the case of *Helicobacter* and colon cancer, but with recent researches emphasis were put forward, looking into the contribution of gut microbiota in the development of distal organs' cancer such as the breast. Multiple researches has indicate that a dysbiotic gut microbiome modulate systemic immunity, metabolize toxic substances such as bile acid, influences chronic inflammation and increases the amount of estrogens circulating in the body, which are all factors that aid in the development of breast malignancy [Hörmannsperger *et al.*,2012; Levkovich *et al.*, 2014]. Information that is revised in table 3(a) and 3(b) from clinical studies on direct relationship between gastrointestinal microbiome and breast cancer from BC patients suggest that, there is a compositional change in the microbiome pool of BC patients compare to healthy controls, with an increase in the number of estrogen metabolizing bacteria and pathogenic organisms such as members from the *Clostridia* genus. Other observable trait is how commensal bacteria that are augmented with prudent diet (diet rich in vegetables, milk etc) helps in reducing the effect or development of breast cancer which is most found in Asian populace. These studies show the possible effect of dysbiosis in the gut and poor diet in modulating breast neoplasm**.** Another interesting factor to consider is the mechanism or factor that disturbs the microbial composition, leading to dysbiosis. Dysbiotic state in the gut microbiome can arise through poor dieting. Studies have shown how western diet and chronic antibiotics use destabilize the gut microbiome, reducing the amount of bacterial community and elevating the level of harmful gram negative bacteria such as the *Clostridia* and *Proteobacteria* species that can perform the aforementioned task leading to systemic cancer development [Sheflin *et al.*, 2014; Schippa and Conte 2014]. Indeed, in this review, several examples on how alterations of host microbiome influence pathways that lead to the development of breast cancer have been explained. Altered microbiota components may

lead to immune modulation due to deficiency in TLR-5 which leads to tumor progression [Pfirschke *et al.*, 2015]. It is very important for oncologists to focus on the causality of the association between cancer and microbiome in promoting carcinogenesis, considering how chronic anti-biotic use disrupt the gut microbiome which in turns initiate or promotes breast tumor as shown in some studies like Rossini *et al.*, [2006], Velicer *et al*., [2004], and Tamim *et al*., [2008].

In the past, scientists only put emphasis on viral entities as the only microbial agents that can cause cancer. Recently, studies on involvement of bacteria toward development and prevention of tumor have gained the interest of scientists. Study by Kwa *et al.*, [2016] has shown how host microbiome influences the level of estrogen in the systemic circulation by deconjugation of conjugated estrogen in the guts. Estrogens are well known factors that initiate the development of breast cancer by activating estrogen receptors in the breast tissue. Gut microbiome not only helps in promoting breast carcinogenesis, but it also plays a role in alleviating the progression of breast tumor as it is discussed earlier through the metabolism of plant derived estrogen from dietary fibers known as phytoestrogen. Gut microbiome metabolize phytoestrogens into two important potent anti-cancer substances deidzein and genistein.

In summary, the host and microbiome are two components that make up the “Holobiome”, with a complex communication system between them. This symbiotic relationship between the host and the microbiome continuously affects both entity and helps maintain a healthy state and steady homeostasis. Slight alteration or cross of boundaries between host and microbiome results in detrimental effect on the host health which leads to emergence of multifactorial diseases, such as cancer. Detailed understandings about the factors that help maintain a protective balance between host and microbiome have the potential to underline a novel therapeutic approach for diseases like cancer. Extensive research will likely focus on the roles of the organ-specific microbiome and tumor formation in cancer development and progression will likely be the main focus in the future.

4.2 STUDY LIMITATIONS

This study has a limitation with regards to the quantity of articles extracted for the role of microbiome in breast cancer; very few researches were conducted in this field which has also lead to a setback in the study. Second limitation is that a meta-analysis should be run in order to get a standard result but this cannot be done due to the limited amount of articles that discuss on this field of interest.

4.3 CONCLUSION

Gut microbiome is assumed to be one of the environmental factors that could modulate the risk of breast carcinogenesis considering the fact that few percentages of breast cancer patients are genetically predisposed. There is growing evidence showing that host microbiome functions in preventing and promoting our health by limiting proliferation, inflammation and encouraging apoptosis in terms of cancer. This is only achievable in a balanced eubiotic gut microbiome. All the data discussed above indicates how disrupted microbiome pool (dysbiosis) can lead to the development and progression of breast tumor using multiple mechanisms. A dysbiotic state, caused either through poor diet or foul life style; in the gut microbiome allows the colonization of harmful microbes that can promote inflammation, release of carcinogenic microbial-derived metabolites and production of genotoxins. However, more evidence is required from clinical trials to identify a direct connection between gastrointestinal microbiome and risk of breast cancer. With better understanding of changes that can lead to dysbiosis, scientist can be able to find ways to manipulate the gut microbiome in order to avoid alterations of certain pathways that can lead to cancer formation. Interplay between diet and microbiome as well as stringent use of antibiotics in developing countries might be the reason for high breast cancer incidence.

In the future more elaborate clinical and bench-based studies are required to confirm the association between microbiome, diet and breast carcinogenesis in order to modulate new therapeutic strategies and mechanisms of improving human health.

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