



The Intersection of the Microbiome and Adiposity in Cancer Risk and Outcomes: Breast, Endometrial, and Colorectal Cancers

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Abstract

Purpose of Review We reviewed and summarized the clinical, experimental, and epidemiological evidence examining the link between the microbiome and adiposity in the pathogenesis and progression of breast, endometrial, and colorectal cancer. Investigation of this intersection offers a novel approach for both the prevention and treatment of these cancers.

Recent Findings The complexity of the gut microbiome and its association with the risk and progression of multiple cancers has gained increasing attention in recent years. Evidence suggests that gut dysbiosis may contribute to carcinogenesis through lowered microbial diversity, production of harmful metabolites, and increased inflammation. Additional risk factors for cancer, such as excess adiposity, may also affect the microbiome to alter metabolic and immune pathways, suggesting an obesity-associated gut microbiome may play a significant role in the development of cancer.

Summary We found an abundance of evidence for bidirectional communication between the microbiome and adiposity and its significance in the development of obesity-related cancers. Current therapeutic approaches for restoring microbiome homeostasis as well as targeting adiposity are also discussed herein and offer potential to reduce the cancer burden in populations with a higher risk and prevalence of obesity.

Keywords Microbiome · Adiposity · Obesity · Breast cancer · Endometrial cancer · Colorectal cancer

Introduction

Cancer is the second leading cause of death in the United States and is projected to be responsible for over 610,000 deaths in the United States in 2024 [1]. Well-established risk factors for cancer include aging, excessive alcohol consumption, chronic inflammation, dietary pattern, obesity, tobacco use, radiation and sunlight exposure, exposure to certain chemicals, and family history [1]. Over the past decade, the gut microbiome—the trillions of microbes that inhabit the

human gastrointestinal tract—has been associated with the risk and progression of multiple cancers. However, ongoing research seeks to investigate whether associations of the gut microbiome with cancer are causative or consequential.

Importantly, the gut microbiome can be modified, such as through diet and lifestyle interventions. Multiple lines of evidence demonstrate that obesity may be bidirectionally associated with the gut microbiome [2–4]. Obesity is one of many lifestyle factors associated with an increased risk for incidence and poor outcomes of multiple cancers, especially colorectal, post-menopausal breast, and endometrial cancers [5]. Mechanisms driving this association are suspected to be due to increased levels insulin and other hormones that can promote cancer growth and the pro-inflammatory environment that can occur as a result of excess adiposity [6]. Obesity can also impact patient response to cancer treatment and increase several treatment-related adverse effects, including immune dysfunction, resistance to radiation, lymphedema, and chemotherapy-induced toxicities (i.e., cardiotoxicity, peripheral neuropathy, etc.) [7, 8].

The bidirectional influence between the microbiome and adiposity offers a novel approach to investigate cancer

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prevention and treatment. Taken together, an obesity-associated gut microbiome may contribute to carcinogenesis, for example, through lowered diversity of the gut microbes and increased production of pro-inflammatory molecules like lipopolysaccharide and bile acids (Fig. 1) [9]. However, the impact of the obesity-associated microbiome on the response to and efficacy of chemotherapeutic drugs remains poorly understood. This targeted review provides a summary of the most recent epidemiologic evidence regarding interrelationships between obesity, the gut microbiome, and three potentially obesity- and gut microbiome-associated cancers (colorectal, breast, and endometrial cancers) (Table 1).

Methods

During the summer of 2023, the literature search strategy for this narrative review was developed by the Medical Librarian (MH), Biomedical Library at Moffitt Cancer Center, in collaboration with the research team. The resulting strategy is composed of 7 sections: Sentinel Articles, Gastrointestinal Microbiome, Adiposity, Breast Neoplasms, Colorectal Neoplasms, Ovarian Neoplasms, and Uterine Neoplasms. Medical Subject Headings [MeSH], synonyms, acronyms, and phrase searching were incorporated within the topical sections. Each section’s results were evaluated based upon the number of Sentinel Articles retrieved.

Utilizing Ovid MEDLINE(R) ALL < 1946 to August 23, 2023 > the search strategy was run on August 24, 2023. As specified by the team, the date limits applied were January 1, 2018, through December 31, 2023. No published search

filters were utilized within this strategy. Search details and results are listed in Appendix 1.

Microbiome and Adiposity in Colorectal Cancer Risk and Outcomes

Colorectal cancer (CRC) is the third most common cancer type and the second leading cause of cancer death among men and women in the United States [1]. Several studies have shown that specific bacterial taxa linked to obesity could play a role in the etiology of CRC [10–16]. Specifically, *Fusobacterium nucleatum*, *Helicobacter pylori*, *Streptococcus bovis*, *Clostridium septicum*, *Bacteroides fragilis*, and others that often originate in the oral cavity may be involved in the carcinogenesis of CRC [14, 17, 18]. Additionally, lower abundance of butyrate-producing bacteria *Eubacterium rectale*, *Faecali bacterium prausnitzii*, and *Enterococcus faecalis* have been found repeatedly in CRC patients [19–22]. Environmental exposures largely contribute to the composition of the gut microbiome, potentially leading to inflammation, dysplasia, and the onset of CRC [16, 23].

There are several mechanisms by which obesity may increase the risk of CRC via the gut microbiome. For example, obesity may increase the risk of CRC by reducing the abundance of short chain fatty acid (SCFA)-producing bacteria. Obesity may also contribute to systemic inflammation, which is mechanistically linked to CRC, by altering intestinal barrier function which can lead to leakage of microbial products [24]. In a study comparing the gut microbiome of CRC patients ($N=45$) with and without obesity to non-obese healthy controls ($N=20$), significantly higher levels of the microbial-related metabolites zonulin,

Fig. 1 Summary of associations and bi-directional communication between excess adiposity, the gut microbiome, and risk of cancer. Created with BioRender.com

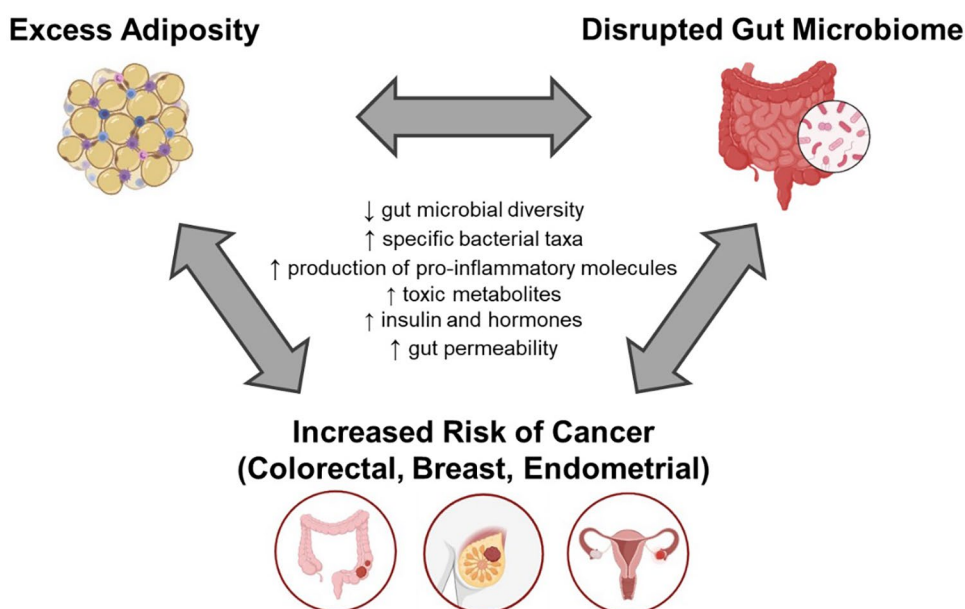


Table 1 Summary of select studies of associations of the microbiome with obesity-related cancers

Reference	Study Design (Location)	Microbiome Biospecimen	Type of Sequencing	Sample Size	Cancer Associations with Microbiome	Findings Relevant to Adiposity or Obesity
Breast Cancer (BC)						
Byrd et al. (2021) [36]	Case control (Ghana)	Fecal samples	16 S rRNA sequencing	N=379 BC cases N=414 controls	Breast cancer and non-malignant breast disease cases had: ↓ alpha diversity and beta diversity differences; ↓ abundance of <i>Bacteroides</i> , <i>Prevotella 9</i> , <i>Coprococcus 2</i> , <i>Dialster</i> , <i>Rombustia</i> , and <i>Pseudobutyrvibrio</i> ; ↓ presence of <i>Lachnospria</i> , <i>Pseudobutyrvibrio</i> , <i>Rombustia</i> , <i>Collinsella</i> ; ↑ presence of <i>Flavonifractor</i>	N/A
Zhu et al. (2018) [37]	Case control (China)	Fecal samples	Metagenomic sequencing	N=62 BC cases N=71 controls	↓ abundance of pathway for the short chain fatty acid, butyrate; ↓ alpha diversity among postmenopausal cases compared to postmenopausal controls; 45 species differed between postmenopausal cases and controls: ↑ <i>Escherichia coli</i> , <i>Klebsiella sp_1_1_55</i> , and <i>Prevotella amnii</i> ; ↓ <i>Porphyromonas uenonis</i> , <i>Eubacterium eligens</i> , and <i>Lactobacillus vaginalis</i>	N/A
Wu et al. (2019) [39]	Case-case (United States)	Fecal samples	16 S rRNA sequencing	N=25 HER2- cases N=12 HER2+ cases	Multiple differences in genera across tumor molecular subtypes (<i>Turcibacter</i> , and <i>Clostridium</i>)	↓ alpha diversity among those with higher BMI; beta diversity differences among those who are normal vs. overweight/obese
Yaghjian et al. (2021) [42]	Mammographic breast density and body mass index (United States)	Fecal samples	16 S rRNA sequencing	N=69 healthy postmenopausal women	↑ alpha diversity among women with a high breast density	↑ alpha diversity among women with lower BMI
Terrisse et al. (2021) [38]	Cohort (France)	Fecal samples	Metagenomic sequencing	N=76 early BC patients	Beta diversity differed by tumor size, Scarff Bloom & Richardson grade, axillary node involvement, and TNM staging; <i>B. uniformis</i> and <i>C. bolteae</i> <i>P. merdae</i> , <i>C. asparagiforme</i> , <i>R. intestinalis</i> , <i>B. intestinhominis</i> associated with worse prognosis	Beta diversity associated with post-chemotherapy weight gain
Zeber-Lubecka et al. (2024) [93]	Case control (Poland)	Fecal samples	Metagenomic sequencing	N=88 BC patients N=86 controls	Beta diversity differentiated pre- and post-menopausal cases and controls; ↓ alpha diversity among postmenopausal cases; multiple bacterial differences between cases and controls	N/A

Table 1 (continued)

Reference	Study Design (Location)	Microbiome Biospecimen	Type of Sequencing	Sample Size	Cancer Associations with Microbiome	Findings Relevant to Adiposity or Obesity
Aaroutse et al. (2021) [94]	Case control (Netherlands)	Fecal samples	16 S rRNA sequencing	<i>N</i> =81 post-menopausal HER+/HER2- BC patients <i>N</i> =67 post-menopausal controls	↑ abundance of and <i>Veillonellaceae</i> and <i>Dialister</i>	N/A
Früge et al. (2020) [95]	Weight Loss Trial (United States)	Fecal samples	16 S rRNA sequencing	<i>N</i> =32 overweight and obese female early-stage (0 to II) BC patients	<i>Akkermansia muciniphila</i> (AM) associated with microbiota diversity IL-6 associated with species richness, but not AM	↑ <i>Akkermansia muciniphila</i> associated with ↓ fat mass Fat mass associated with IL-6
Endometrial Cancer (EC)						
Dossus et al. (2010) [47]	Prospective Case Control (Europe)	Blood samples	Immunoassays	<i>N</i> =305 EC cases <i>N</i> =574 controls	increase in risk of endometrial cancer with elevated levels of CRP, IL6, and IL1Ra	CRP, IL6, IL1Ra association with EC risk is largely dependent on adiposity Association between adiposity and EC attenuated after adjustment for inflammatory markers
Friedenriech et al. (2013) [48]	Case control (Canada)	Blood samples	Immunoassays	<i>N</i> =519 EC cases <i>N</i> =964 controls	↑ levels of TNF- α , IL-6, and CRP with EC cases	Obesity operated through pathway increasing pro-inflammatory cytokines
Linkov et al. (2012) [55]	Randomized Control Trial (USA)	Blood samples	Immunoassays	<i>N</i> =89 Class II and Class III obesity cases <i>N</i> =43 non-obese controls	VEGF, soluble E-selectin, GH, adiponectin, IL-6, IL-7, CA-125, and IGFBP-1 significantly changed over time	Obese women 5-fold greater RR of EC BMI associated with CA 15–3, soluble E-selectin, Growth Hormone, resistin, adiponectin, IL-8, CA-125 & IGFBP-1
Walther-Antônio et al. (2016) [96]	Case Control (US Mayo Clinic)	Fecal samples	16 S rRNA sequencing qPCR	<i>N</i> =17 EC <i>N</i> =4 endometrial hyperplasia <i>N</i> =10 benign uterine conditions	↑ Firmicutes, Spirochaetes, Actinobacteria, Bacteroidetes, and Proteobacteria with EC The detection of <i>Atopobium vaginae</i> and the identified <i>Porphyromonas</i> sp. in the gynecologic tract combined with a high vaginal pH (>4.5) is associated with EC	N/A
Lu et al. (2021) [54]	Cross-sectional retrospective study. (China)	Pathology samples	16 S rRNA sequencing	<i>N</i> =25 EC <i>N</i> =25 Benign Uterine Lesions (BUL)	↑ <i>Micrococcus</i> in EC vs. BUL IL-6 and IL-17 mRNA positively correlated with the relative abundance of <i>Micrococcus</i>	N/A
Zhao et al. (2022) [52]	Case-Control (China)	Fecal samples	16 S rRNA sequencing	<i>N</i> =18 EC patients <i>N</i> =18 control	↑ <i>Ruminococcus</i> in EC	Positive association with serum TG and negative association with HDL

Table 1 (continued)

Reference	Study Design (Location)	Microbiome Biospecimen	Type of Sequencing	Sample Size	Cancer Associations with Microbiome	Findings Relevant to Adiposity or Obesity
Li et al. (2023) [53]	Case Control (China)	Fecal samples	16 S rRNA sequencing	N=33 EC N=32 controls	↓ alpha diversity in EC patients vs. controls ↓ Firmicutes, Clostridia, Clostridiales, Ruminococcaceae, Faecalibacterium, and Gemmiger_formicus ↑ Proteobacteria, Gammaproteobacteria, Enterobacteriales, Enterobacteriaceae and Shigella	N/A
Colorectal Cancer (CRC)						
Bullman et al. (2017) [9]	5 Independent Cohorts (Boston)	Patient-derived colorectal cancers	qPCR 16 S rRNA sequencing <i>Fusobacterium</i> culture	N=11 frozen primary CRCs and paired liver metastases N=77 frozen primary CRCs N=631 frozen carcinomas (<i>The Cancer Genome Atlas</i>) N=101 colorectal carcinomas and paired liver metastases N=13 primary CRCs used for patient-derived xenograft studies	<i>Fusobacterium</i> strains found in primary tumors and paired metastases	N/A
Sanchez-Alcoholado et al. (2020) [22]	Case control (Spain)	Fecal and peripheral blood samples	16 S rRNA sequencing ELISA assays NMR	N=45 obese and lean CRC patients (stages II-III) N=20 non-obese healthy controls	↑ levels of serum IL-1B and TMAO and lower IL-10 in CRC patients ↓ in community richness (Chao1 index) and microbiota diversity (Shannon index) in CRC patients	↑ serum zonulin levels in obese-CRC compared to lean-CRC and healthy More pronounced increases in pro-inflammatory markers in obese-CRC compared to non-obese CRC
Zhu et al. (2024) [23]	Comprehensive multi-center study (China, Austria, France, Germany, Italy, USA)	Fecal samples		In house samples: N=209 CRC patients with excess body weight, N=179 excess body weight controls, N=276 lean CRC patients, N=317 lean controls Total N=981 metagenome samples from multiple cohorts	↑ D-Arginine and D-ornithine metabolism, and lipopolysaccharide biosynthesis in CRC patients with excess body weight	Pathogenic microbial species, <i>Anaerobutyricum hallii</i> , <i>Clostridioides difficile</i> and <i>Fusobacterium nucleatum</i> , are specific signatures for CRC patients with excess body weight

Table 1 (continued)

Reference	Study Design (Location)	Microbiome Biospecimen	Type of Sequencing	Sample Size	Cancer Associations with Microbiome	Findings Relevant to Adiposity or Obesity
Hang et al. (2023) [27]	3 prospective cohorts (Boston)	Endoscopic and pathologic records		Nurses' Health Study (1986–2014; $N=64,425$ women), Nurses' Health Study II (1991–2015; $N=92,782$ women), and the Health Professionals Follow Up Study (1986–204; $N=46,341$ men)	Increased risk of conventional adenomas, serrated lesions, and both low-risk and high-risk polyps with higher intake of ultra-processed food	Stronger association between ultra-processed food consumption and high-risk polyps with $BMI \geq 25$ kg/m ²
Feng et al. (2015) [14]	Metagenome-wide association study (China)	Fecal samples	Metagenomic shotgun sequencing HPLC blood samples	$N=55$ healthy controls $N=42$ advanced Adenoma $N=41$ carcinoma patients	High level of <i>Bacteroides</i> in carcinoma and adenoma patients \uparrow <i>Bacteroides</i> , <i>Alistipes</i> , <i>Escherichia</i> , <i>Parvimonas</i> , <i>Bifidobacterium</i> and <i>Fusobacterium</i> in carcinoma patients \downarrow <i>Bifidobacterium animalis</i> and <i>Streptococcus thermophilus</i> in adenoma and carcinoma patients	N/A
Shoji et al. (2021) [17]	Case control (Japan)	Fecal samples	16 S rRNA sequencing	$N=36$ consecutive CRC patients $N=38$ controls	\uparrow α -diversity in CRC patients Altered abundance of the genera <i>Enterococcus</i> , <i>Capnocytophaga</i> , and <i>Polaribacter</i> in obese CRC patients \downarrow <i>Enterococcus faecalis</i> in obese versus nonobese patients \uparrow <i>Capnocytophaga</i> and <i>Polaribacter</i> in obese patients with CRC	<i>E. faecalis</i> may be associated with obesity-related colorectal cancer development
Balamurugan et al. (2018) [18]	Case control (India)	Fecal samples	RT-PCR 16 S rRNA sequencing	$N=20$ CRC patients with CRC, $N=9$ upper gastrointestinal cancer patients $N=17$ healthy volunteers	\downarrow butyrate-producing bacteria <i>Eubacterium rectale</i> , <i>Faecali bacterium prausnitzii</i> , and <i>E. faecalis</i> in CRC patients	N/A
Wu et al. (2013) [19]	Case control (China)	Fecal samples	16 S rRNA sequencing	$N=19$ CRC patients $N=20$ healthy controls	Enrichment of potential pathogens \downarrow butyrate-producing members <i>Faecali bacterium</i> and <i>Roseburia</i> \uparrow <i>Bacteroides</i>	N/A
Wang et al. (2012) [20]	Case control (China)	Fecal samples	16 S rRNA sequencing RT-PCR	$N=56$ healthy volunteers $N=46$ CRC patients	\uparrow <i>Enterococcus</i> , <i>Escherichia/Shigella</i> , <i>Klebsiella</i> , <i>Streptococcus</i> , and <i>Peptostreptococcus</i> \uparrow <i>Bacteroides fragilis</i> \downarrow Genus <i>Roseburia</i> and other butyrate-producing bacteria of the family <i>Lachnospiraceae</i> .	

Table 1 (continued)

Reference	Study Design (Location)	Microbiome Biospecimen	Type of Sequencing	Sample Size	Cancer Associations with Microbiome	Findings Relevant to Adiposity or Obesity
Coker et al. (2022) [13]	Case control (China)	Fecal samples	Metabolomic and metagenomic profiling	<i>N</i> = 118 CRC patients <i>N</i> = 140 colorectal adenomas patients <i>N</i> = 128 healthy subjects	CRC-associated metabolites were enriched in branched-chain amino acids, aromatic amino acids and aminoacyl-tRNA biosynthesis pathways. Altered microbial-related metabolites: ↑ L-alanine, glycine, L-proline, L-aspartic acid, L-valine, L-leucine, L-serine, myristic acid, phenyl lactic acid, oxoglutaric acid, L-phenylalanine, L-alpha-aminobutyric acid, phenylacetic acid, palmitoleic acid, 3-aminoisobutanoic acid and norvaline ↓ butyric acid ↑ <i>Peptostreptococcus stomatis</i> , <i>Fusobacterium nucleatum</i> , <i>Parvimonas micra</i> , <i>Peptostreptococcus anaerobius</i> and <i>Bacteroides fragilis</i> ↓ <i>Coprobacter fastidiosus</i> , <i>Eubacterium ventriosum</i> , <i>Roseburia interinalis</i> and <i>Roseburia inulivorans</i>	N/A
Thomas et al. (2019) [12]	Metagenomic Analysis on five publicly available datasets and two new cohorts, and validated the findings on two additional cohorts (Italy (5 fecal shotgun CRC datasets from 6 different countries))	Fecal samples	Shotgun metagenomic sequencing	969 fecal metagenomes: 413 samples from CRC patients, 143 from subjects with adenoma and 413 control samples	↑ species richness in gut microbiome with CRC gluconeogenesis and the putrefaction and fermentation pathways associated with CRC ↑ choline trimethylamine-lyase gene in CRC (↑ microbiome choline metabolism)	N/A

trimethylamine N-oxide (TMAO), and IL-1 β and lower levels of IL-10 were reported among CRC patients with obesity compared to patients without obesity and healthy control. These findings were hypothesized to result from an obesity-related microbial profile linked to CRC [25]. A few years later, a multi-center study also characterized the gut microbiota of obese and lean patients with CRC and found further distinct differences in microbial composition between the two groups [26]. Interestingly, patients with comorbid CRC and obesity had an increased abundance of *Clostridium difficile*, which has been previously associated with obesity [27] and could drive tumorigenesis of CRC by secreting toxin TcdB [28]. When analyzing functional alterations, increased metabolism of microbially-regulated D-Arginine and D-ornithine were found for obese CRC patients, while

pathways of inositol phosphate metabolism, synthesis, and degradation of ketone bodies were specifically enriched in lean CRC patients [26].

Dietary intake is well known to contribute to both obesity and the composition of the gut microbiome, and, in turn, to CRC risk. Red and processed meats are hypothesized to increase CRC risk by increasing production of gut bacteria-related secondary bile acids and TMAO [29]. Ultra-processed foods, which are associated with risk of weight gain and obesity and lead to unfavorable alterations of the gut microbiome, may also contribute to CRC. A study analyzing data from three large prospective US cohorts [(Nurses' Health Study (1986–2014; *n*=64,425 women), Nurses' Health Study II (1991–2015; *n*=92,782 women), and the Health Professionals Follow Up Study (1986–204;

$n=46,341$ men)] reported that, among men, high consumption of ultra-processed foods was associated with a 29% increased risk of CRC. Subgroups of ultra-processed foods (e.g., meat-based ready to eat meals, sugar sweetened beverages) were also associated with increased CRC risk for men and women [30]. In addition, a high fat diet was shown to alter gut metabolite production of, for example, lysophosphatidic acid, which impairs cell junctions and promotes CRC cell proliferation [31]. Finally, growing evidence supports a role of the gut microbiome and body composition in the prognosis of CRC patients, potentially modulating sensitivity to radiation and chemotherapy [32].

Microbiome and Adiposity in Breast Cancer Risk and Outcomes

Breast cancer is the leading cause of cancer among women in the United States, and the second leading cause of cancer death [1]. It is likely that some established breast cancer risk factors (e.g., obesity, diet) [33] and other unknown risk factors, influence the composition and function of the gut microbiome. The gut microbiome influences multiple pathways that are mechanistically linked to the initiation and growth of breast neoplasms [34–36]. Accumulating evidence supports the role of the gut microbiome in regulating endogenous estrogens [34, 37] and systemic inflammation and immunity [38, 39]. The fecal microbiome was measured via the 16 S rRNA gene among Ghanaian women with and without breast cancer in a large population-based breast cancer case-control study ($N=379$ cases and $N=414$ controls) [40]. Fecal microbiome alpha diversity was strongly inversely associated with breast cancer and the overall composition of the gut microbiome (beta diversity) differed substantially between breast cancer cases and healthy controls [40]. In another study using shotgun metagenomics to characterize the fecal microbiota of 62 breast cancer cases and 71 controls, the pathway for the short chain fatty acid, butyrate, was suggested to be inversely associated with postmenopausal breast cancer [41]. In other smaller studies, the gut microbiome was also associated with breast cancer risk factors, tumor characteristics, prognostic factors, and adverse treatment side effects [42, 43]. Further, higher cumulative days of antibiotics were associated with higher risk of incident and fatal breast cancer [44]. Taken together, emerging data support the hypothesis that the gut microbiome is an important factor mediating breast carcinogenesis.

Obesity may be inversely associated with risk of premenopausal breast cancer, and positively associated with risk of postmenopausal breast cancer, especially with postmenopausal hormone receptor-positive breast cancer risk [45]. Further, obesity is associated with a shorter time to disease recurrence and higher mortality for both premenopausal

and postmenopausal breast cancers. It is plausible that there may be strong interrelationships between the gut microbiome, obesity, and breast cancer risk and progression. For example, mammographic breast density is an established risk factor for breast cancer, with higher breast densities associated with higher breast cancer risk. In a study that investigated 16 S rRNA sequenced fecal microbiome profiles in relation to mammographic breast density and body mass index (BMI) among $N=69$ healthy postmenopausal women, alpha diversity and Firmicutes to Bacteroides ratio was found to be associated with breast density, and alpha diversity was highest among women with both a high breast density and low BMI [46]. Further, energy dense diets are risk factors for both breast cancer and obesity. The gut microbiome may play a key role in weight gain and loss, such as through harvesting energy from food [3, 47]. Finally, some forms of breast cancer are driven by estrogens that may be enhanced by adipose tissue. Some bacteria contain genes that are capable of metabolizing estrogens (hence the coined term, the ‘estrobolome’) [34]. Bile acids have bidirectional associations with the gut microbiome, and bile acid levels in circulation may also be influenced by obesity. Lithocholic acid is a secondary bile acid generated by bacteria from primary bile acids that escape enterohepatic circulation. Lithocholic acid biosynthesis was lower in patients with breast cancer compared to breast cancer free controls [48]. Taken together, there is strong plausibility that obesity is linked with both the gut microbiome and breast cancer risk.

The gut microbiome is likely influenced by breast cancer therapy [49] and may modify therapy efficacy, toxicity, and longer term outcomes [42, 50]. For example, among 24 primary HER2-positive breast cancer patients treated with neoadjuvant therapy containing trastuzumab, compared to non-responders, responders had higher alpha diversity and higher abundance of *Clostridiales*, *Bifidobacteriaceae*, *Turicibacteraceae*, and *Bacteroidales* [51]. In a prospective study among 40 early-stage breast cancer patients, the women both gained weight on average and had concomitant changes in the gut microbiome [52]. Further research should explore the significance of body composition before cancer treatment, during cancer treatment, and interactions with the gut microbiome in breast cancer outcomes.

Microbiome and Adiposity in Endometrial Cancer Risk and Outcomes

Endometrial cancer is the most common gynecological malignancy, with endocrine and metabolic pathways yet to be fully elucidated [1, 53]. Excess abdominal fat, metabolic syndrome, and higher circulating estrogen associated with obesity are well recognized risk factors for endometrial cancer [54]. Chronic inflammation may also independently, and

in interaction with other factors like insulin resistance and estrogen production, mediate obesity-related risk of endometrial cancer [55]. For example, Friedenreich et al. 2013 found that circulating levels of CRP, TNF-alpha and IL-6 were statistically significantly associated with endometrial cancer in a large case-control study [56]. Obesity is associated with the diagnosis of endometrial cancer at an earlier age, particularly the endometrioid subtype [57]. Of the two types of endometrial cancer, the most prevalent (80–90%) Type 1 endometrioid adenocarcinomas are estrogen-dependent. Most endometrial cancers have sporadic mutations and arise from endometrial hyperplasia. Type 1 endometrioid carcinomas may have gene mutations in phosphatase and tensin homolog gene (PTEN), the Kirsten ras gene (KRAS), the beta-catenin gene (CTNNB1), and DNA characterized by microsatellite instability (MSI) [58].

Much like in colorectal and breast cancer, the mechanisms by which obesity influences the gut microbiome also play a role in endometrial cancer development. Female sex hormones are bidirectionally associated with the gut microbiota [59]. Gut dysbiosis involves decreased microbial diversity, decreased gram negative and increased gram-positive bacteria, estrobolome dysfunction, and disruption of estrogen metabolism Ruminococcaceae, Proteobacteria, Gammaproteobacteria, Enterobacteriales, Enterobacteriaceae, and *Shigella* are prevalent [60, 61]. Endometrial dysbiosis is characterized by increased *Atopobium vaginae* and *Porphyromonas somerae* which set the stage for inflammation [60, 62]. *Porphyromonas somerae* combined with high pH in the vagina could be a promising risk biomarker for endometrial cancer [58, 60].

Longitudinal cohort studies and clinical trials, including Iowa Women's Health Study, European Prospective Investigation into Cancer and Nutrition (EPIC)-Oxford trial, and Re-Energize with Nutrition, Exercise and Weight Loss (RENEW) investigating the associations of diet, weight loss and associated changes in biomarkers with cancer, collectively support a role for modifiable risk factors such as metabolic syndrome and obesity in endometrial cancer risk [55, 63]. American Cancer Society estimates 70% of endometrial cancer is attributable to lifestyle factors of maintaining excess body weight through high fat, calorie dense diets and insufficient physical activity [1]. Diet has been shown to modulate estrogen and inflammation levels [64]. Physical activity improves insulin sensitivity and reduces glucose levels. Reducing adiposity reduces pro-inflammatory cytokines and increases anti-inflammatory mediators (IL-10 and adiponectin). Exercise decreases risk by reducing serum estradiol and increasing sex hormone binding globulin and reduces circulating insulin and insulin resistance [65]. Methods to manipulate hormone and immune function

through biobehavioral lifestyle changes offer hope for endometrial cancer risk reduction and treatment.

Obesity, the Gut Microbiome, and Cancer Disparities

There are extensive disparities in the cancers described above. The CRC mortality rate among non-Hispanic Black individuals is approximately 37% higher than in non-Hispanic White individuals [66]. In the United States, Black women suffer higher breast cancer mortality than other racial and ethnic groups. Indeed, Black women are 42% more likely to die from breast cancer than white women [67]. Furthermore, Black women with endometrial cancer have an 80% higher mortality rate compared to white women, due to more advanced tumor stages at diagnosis and more aggressive histologic subtypes even though occurrence is overall less common [68]. Explanations for disparities in cancer incidence and survival are likely multifactorial, including various social and structural drivers of health (SSDOH) and differences in molecular and clinical characteristics. Beyond race and ethnicity, individuals who live in highly deprived or rural areas may also fare poorer than other individuals. Further, there are differences in obesity rates by racial and ethnic group. For example, obesity disproportionately affects African American communities, with an estimated prevalence of 49.6% among non-Hispanic Black adults [69]. The gut microbiome is likely influenced by known and unknown factors related to race and ethnicity including obesity. Differences in obesity rates and the gut microbiome may reflect various SSDOH. Racial and ethnic microbiome differences may be evident as early as a few months after birth [70, 71] and can potentially result from exposures that occur as early as in utero or at birth. For example, caesarean sections are known to alter the microbiome among offspring and are performed at higher rates among racial minorities [72]. Other microbiome and adiposity influencing exposures can also accumulate over the life course such as food insecurity, access to spaces for physical activity, chronic stress due to discrimination, and other exposures [72]. Taken together, future research should aim to elucidate the interactions among obesity, the gut microbiome, and SSDOH in racial and ethnic disparities in cancer.

Interventions Targeted to the Gut Microbiome and Obesity

Microbiota dysbiosis contributes to weight gain by inducing inflammation, reducing fat and cholesterol metabolism, and decreasing insulin sensitivity [73]. Importantly, reduced biodiversity of the gut microbiome is linked to different conditions such as obesity-associated inflammatory characteristics, gastrointestinal diseases, and risk of several

cancers [47, 74, 75]. The increase of microbial biodiversity related to various interventions could have beneficial effects on the pathogenesis of these conditions.

Diet

Prebiotics stimulate the growth and activity of gut microbes, in order to improve overall health [76]. Studies have revealed that the gut microbiota can be rapidly modified by dietary changes and increasing fiber leads to better mucosal health [33, 77, 78]. Previous seminal research has demonstrated that consumption of a *very* high fiber diet can lead to improvements in the gut environment in a very rapid manner [33, 77, 78]. Experimental studies have shown that the consumption of food rich in prebiotics (i.e. dietary fiber) is strongly related to beneficial effects against obesity and alteration of the obese microbiome [79, 80]. Prebiotics are evidenced to stimulate the growth of *Lactobacillus* and *Bifidobacterium* in obese animals [81], as well as reduce the abundance of pathogenic microorganisms, such as *Firmicutes* and *Bacteroidetes* [82]. Furthermore, targeted prebiotic diets increase genes inversely associated with obesity (i.e., TYK2, CXCL1, NXP1) and suppress adipokines (FGF2) to improve metabolic function [80]. Some studies have shown that these changes in gene expression were related to improved entero-endocrine cell activity, glucose homeostasis, and leptin sensitivity in both obese and diabetic mice treated with oligofructose [83, 84]. In addition, prebiotics can also improve lipid and glucose metabolism, resulting in lower triglycerides levels, adipose tissue mass, and muscle lipid infiltration [83]. Interestingly, prebiotics can be used in combination with probiotic bacteria, termed “synbiotics”, in order to improve their beneficial effects against obesity and related metabolic disorders and diseases [85, 86].

Probiotics

Probiotics are live strains of microorganisms that, when integrated into the intestinal ecosystem, can effectively reorganize the intestinal flora and provide health benefits [87]. Their integration allows for interaction with immune cells and alteration of cytokine production to inhibit inflammatory responses, while also strengthening the gut mucosal barrier to maintain intestinal barrier stability and mucosal permeability [73]. However, probiotics are limited to specific bacterial strains for regulatory reasons (mostly within the genera *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* for yeasts), and their properties should be defined at the species and strain level [88]. A recent review of the literature summarizes that current clinical and preclinical studies have demonstrated that probiotics can potentially reduce

body weight, lower blood lipids, and improve metabolism [73]. Furthermore, many clinical studies indicate the effectiveness of probiotics in preventing, treating, and reducing the progression of several types of cancer including colorectal, liver, breast, bladder, colon, and cervical [89–94]. The results of many in vitro studies indicate anti-cancer properties of probiotics in modulating the proliferation/apoptosis of cancer cells (e.g., gastric, colonic, and myeloid leukemia cells) suggesting their beneficial use in cancer prevention and as an adjuvant treatment [95]. Despite potential benefits, probiotics have a number of limitations, including variations in formulation, differences across microbial strains included, passage through the gastrointestinal tract, and potential safety issues (e.g., especially among vulnerable cancer patients).

Exercise

Exercise counteracts obesity progression and has been demonstrated to modulate the gut microbiota. Indeed, the composition of the intestinal microflora was evidenced to be different in obese and nonobese rats and exercise improved both the composition and diversity of gut bacteria [96]. Beneficial effects of exercise on the microbiome might be mediated by decreased intestinal permeability, which prevents pathogens from crossing the intestinal barrier and reduces inflammation [88]. Furthermore, bacterial diversity is increased, including SCFA-producing species, while potential disease-causing species such as *E. coli* or *E. faecalis* are decreased [88]. The anti-inflammatory metabolite, SCFA butyrate, has been linked to exercise-related outcomes [97], which allows this to be a highly effective intervention to target both obesity and the microbiome, as obesity may increase the risk of cancers through reduced SFCA production.

Future Directions

In addition to the cancer disparities explained in this review, further gaps in knowledge regarding the link between the microbiome, adiposity, and cancer, warrant further investigation on their interrelationships. Current interventional studies include confounding factors such as diet, body composition, study design, and analytical methods, which limit the conclusions of the existing studies and add difficulty applying findings to all populations. With exercise interventions specifically, it is unclear whether other aspects of exercise prescription (such as frequency, duration, and type of exercise) may also impact the degree of changes in the microbiota. Interestingly exercise-induced changes in the microbiota were also largely reversed after cessation of activity [98]. Further experimental studies are also needed

to improve knowledge about possible combinations of diet, pre- and probiotics, the timing of intervention, and their potential anti-obesogenic effects. Interesting preclinical data on fecal microbiota transplant (FMT) may prove beneficial to the microbiota. However, most FMT research is conducted on mouse models, as fecal transplants in humans are associated with safety and ethical issues. A combination of treatments to target the microbiome and adiposity may be most beneficial for overall improved health and prevention of cancer and cancer-related outcomes.

Conclusions

Taken together, there appears to be substantial evidence for a role of the gut microbiome and adiposity, potentially interactively, in obesity-related risk and outcomes of colorectal, breast, and endometrial cancer. As accumulating evidence highlights the potential for specific microbes to be involved in carcinogenesis, interventions to change the gut microbiome and/or improve weight management offer enormous opportunity to reduce the cancer burden in all populations, and especially those disproportionately impacted by obesity and cancer.

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Declarations

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