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Review article

Obesity and Cancer

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Abstract: It is a key priority in public health to treat illnesses due to the rising frequency of obesity-related malignancies. Around 11.9% of male and 13.1% of female cancer cases worldwide have an obesity-related malignancy as their primary cause. In addition to colorectal, postmenopausal ovarian, breast, gallbladder, thyroid, and multiple myeloma cancers, endometrial, esophageal, hepatocellular carcinoma, gastric cancer, renal and pancreatic adenocarcinomas, and thyroid cancer, the relationship between obesity and cancer is clear in many anatomical sites. This article provides a thorough overview of the most recent epidemiological data on obesity and its connection to cancer in light of this urgent issue. The contradiction of weight increase and cancer risk and death. Furthermore, examining BMI differences in obesity-related malignancies offers a comprehensive grasp of the disease's complexities. These mechanisms include adipokine pathophysiology, cellular and micro environmental changes, ectopic fat accumulation, disruptions in dietary nutrients, circadian cycles, and potential factors like alteration of the intestinal flora and mechanical influences on weight. The conclusion's discussion of potential future approaches to prevention, detection, and treatment highlights the pressing need for more study and action on this important public health problem. The main objective is to increase knowledge of the complexity of obesity-related malignancies and increase awareness of it to create efficient methods for prevention and treatment. This review offers insight into how potential processes and risk factors combine on target tissues, ultimately causing them to take on a feature of cancer by addressing these important aspects. This review focuses on the Epidemiology of obesity influencing cancer, links between obesity and cancer, the influence of cancer by weight growth, somatometry, biological links, ectopic fat deposition, insulin sensitivity, adiponectin, obesity influencing widely occurring cancers, and FTO protein.

Keywords: Cancer, inflammation, the microbiome, adipokines, adiponectin, biomarkers, obesity, resisting, and visfatin

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1. INTRODUCTION

With 14.1 million registered cases and 14.1 million incident cases, and fatalities per year, cancer ranks as the second largest cause of death globally[1,2]. Despite significant advances in medical science and healthcare, cancer still substantially threatens world health. Obesity has emerged as a recognized risk factor for a variety of cancers, in addition to the well-known cancer risk factors like genetic proclivity, increasing tobacco use, illnesses, poor nutrition, excessive alcohol use, as well as other environmental exposures[3-5]. The prevalence of obesity and metabolic syndrome (Mets) has significantly increased over the past several decades, leading to predictions that cancer incidence would continue to rise due to these conditions[6]. Overweight and obesity are rising globally, which is a serious problem. Practically every developed and developing nation is affected due to being overweight. Industrialized countries have been severely affected, with pandemic levels of overweight and obesity affecting 60–70% of the adult population. Urban regions and females are more likely to experience this tendency[7,8]. Surprisingly, during the past three decades, overweight and obesity instances have been common. Worldwide has grown by 27% in adulthood and by an unsettling 47% in children[9]. This growing tendency is extremely alarming and needs to be addressed immediately. When the amount of energy consumed exceeds the amount expended through metabolism and physical exercise, obesity, a complex disorder, results. Fat is a deposition of an ectopic fat layer that accumulates, resulting in excessive or aberrant adipose tissue formation that goes beyond genetically and epigenetically forming specified adipose tissue storage. This causes various health issues and increases the likelihood of developing different disease types. Body Mass Index (BMI) values describe overweight and obesity, with BMI figures between 25 and 29.9 kg/m^2 considered overweight, whereas BMI values above 30 kg/m^2 are considered obese[10]. Beyond its link to cancer, Obesity raises the danger of several chronic diseases such as hypertension, dyslipidemia, metabolic syndrome, type 2 diabetes, non-alcoholic fatty liver, and cardiovascular disease. Additionally, new studies have revealed an intriguing connection between obesity and neurodegenerative diseases like Alzheimer's disease, underscoring the extensive effects of obesity on health[11,12]. Many potential explanations exist for the complicated and poorly understood relationship between obesity and cancer. Chronic inflammation, which is widespread in obese people, is one of the important mechanisms. Obese people have fatty tissue that produces more pro-inflammatory cytokines than normal, resulting in a chronic inflammatory condition that can accelerate the growth and spread of cancer. Furthermore, obesity isalso associated with insulin resistance and hyperinsulinemia, which can support the development of tumours. Insulin and insulin-like growth factors (IGFs) have been demonstrated to increase cell proliferation and decrease apoptosis processes that may aid in cancer development. In addition to the changes in sex hormones, obesity is connected to postmenopausal women's increased oestrogen production in adipose tissue, which has been linked to breast and endometrial malignancies. Adipokines and other hormones that are actively secreted by adipose tissue can affect the behaviour of tumours, therefore ensuring it is not only a passive energy storage depot. Adipokines, including leptin, resistin, and adiponectin, have been linked to the onset and spread of cancer. For instance, it has been demonstrated that leptin, which is overproduced in obesity, promotes angiogenesis and the proliferation of cancer cells. In contrast, adiponectin, which is decreased in obesity, has anti-inflammatory and anti-tumorigenic effects[13]. Along with influencing immune responses and enabling tumour immune evasion, obesity impacts the tumour microenvironment. Obesity can cause immune cells in the tumour microenvironment to tilt towards a pro-tumor phenotype, which aids in developing the tumour[14]. Additionally, certain cancers have a stronger correlation with fat than others. For instance, obesity, particularly the hormone receptor-positive subtype, is a well-known risk factor for postmenopausal breast cancer. Due to elevated oestrogen levels brought on by extra adipose tissue, it is also connected with a higher risk of developing endometrial cancer[15]. In addition, obesity has been linked to a higher risk of many malignancies, including esophageal, pancreatic, colorectal, kidney, and gallbladder[16]. Addressing the obesity-cancer relationship is essential for attempts to prevent and control cancer. Fighting the obesity pandemic and the related health hazards requires public health programs encouraging a balanced diet, more exercise, and weight control. Future cancer incidence rates may be significantly impacted by education on the significance of keeping a healthy weight, particularly among children and young adults. Additionally, healthcare practitioners should frequently evaluate and discuss patients' weight-related concerns with them. Regular exercise and a balanced diet high in fruits, vegetables, and whole grains can aid people in maintaining a healthy weight and lowering their chance of developing cancer. Additionally, as obesity and smoking are frequent risk factors for cancer, attempts to minimize smoking should be included in programs to fight obesity. There is still much to learn about the underlying molecular processes and potential therapeutic approaches in the obesity-cancer connection, which is the subject of continuing research. Conducting clinical studies examining how diet and lifestyle changes affect cancer risk and prognosis is crucial. The results of these trials will offer important new information on the possible advantages of weight control as a method of cancer treatment and adjuvant therapy. Thus obesity poses serious problems for world health since it is a substantial risk factor for cancer and many other chronic illnesses. A comprehensive, multifaceted strategy, including individuals, communities, healthcare systems, legislators, and researchers, are necessary to address the obesity pandemic. We can make considerable progress in this area, lowering the cost of cancer and enhancing general community health and well-being worldwide by prioritizing preventive efforts, encouraging healthy lifestyles, and deepening our knowledge of the obesity-cancer relationship.

1.1 EPIDEMIOLOGICAL PROOF

Excess body weight raises the risk of cancer in at least 13 different anatomic sites, including the endometrium, oesophagus, kidney, pancreas, colorectal, postmenopausal breast, ovarian, gallbladder, and thyroid cancers, as well as hepatocellular carcinoma, gastric cancer, meningioma, multiple myeloma, and meningioma[17]. As a result, there is enough evidence to rule out bias, confounding factors, and chance confidently and to conclude that maintaining a healthy weight lowers the danger of malignancies mentioned above. However, maintaining a healthy weight during adulthood is not the only factor contributing to the link between fat and cancer risk. Still, the chance of developing cancer at an older age (18-20) is also linked to increased, according to new

research. There is strong and well-established epidemiological data connecting obesity to cancer. Numerous extensive observational studies and meta-analyses conducted over the past few decades have repeatedly shown a direct link between excess body weight and a higher risk of developing cancer[18]. This research included a variety of populations from other nations, thus enhancing the validity of the results. The link between fat and cancer may have several possible causes. Chronic low-grade inflammation with extra adipose tissue is one important contributing factor. A favorable environment for the formation and development of tumours is produced by the secretion of a variety of pro-inflammatory cytokines and hormones by adipose tissue. In addition, obesity is linked to insulin resistance and hyperinsulinemia, which can encourage cancer cell growth. Numerous renowned organizations, including the International Agency for Research on Cancer (IARC), have classified obesity as a known carcinogen due to the strength of the evidence from epidemiological research.[19] Therefore, public health measures targeted at lowering obesity are crucial for avoiding not just cardiovascular illnesses and diabetes but also for reducing the incidence of cancer. Recent epidemiology findings have introduced a thought-provoking hypothesis that obesity might paradoxically act as a protective factor for certain cancer types in terms of mortality and relevant incidence. Surprisingly, obesity has been connected with a lower risk of developing breast cancer in premenopausal women, non-small cell lung cancer (NSCLC), and head and neck cancers[20]. This intriguing phenomenon, often called the "obesity paradox," has primarily been cardiovascular, renal, pulmonary, sepsis, and metabolic research. Still, its implications in the context of cancer have received relatively less attention and exploration[21-26]. The observed protective effect of obesity on certain cancer types has puzzled researchers and raised questions about the underlying mechanisms driving this phenomenon. It is essential to highlight that the concept of the obesity paradox is not universally applicable across all cancer types; indeed, for many cancers, obesity remains a well-established risk factor. However, the emerging evidence in support of this paradoxical association warrants further investigation to unravel its potential implications for cancer prevention and treatment strategies

1.2 THE EFFECTS OF WEIGHT GROWTH AND DECREASE ON CANCER RISK

Weight gain and weight loss both play significant roles in modulating cancer risk. While Body Mass Index (BMI) is commonly used to assess obesity, weight growth in adults has emerged as a more accurate metric indication for understanding the changing characteristics of obesity during adulthood and its association with a risk of cancer. Numerous studies have demonstrated that adult weight gain is linked to an elevated risk of various cancers. Specifically, esophageal adenocarcinoma, colorectal cancer (particularly in males), pancreatic cancer, liver cancer, gallbladder cancer (in women), renal cancer, postmenopausal breast cancer, endometrial cancer, ovarian cancer, advanced-stage prostate cancer are all examples of cancers that can occur after menopause are among the cancers associated with adult weight gain based on data from the World Cancer Research Fund (WCRF) project [27,28]. On the other hand, intentional weight loss has been linked to a decreased risk of cancer, particularly obesity-related malignancies in women. This underscores the clear relationship between excess body weight and cancer risk, highlighting the importance of weight management and lifestyle interventions in cancer prevention. Furthermore, evidence suggests that significant weight loss can lead to a substantial decline in cancer mortality. However, it is essential to acknowledge that clinical trials examining the relationship between weight loss and cancer outcomes have demonstrated endpoint and design heterogeneity, making it challenging to draw universal conclusions[29].

1.3 INDICATORS OF SOMATOMETRY

While BMI is routinely used to assess body weight and obesity, it has various limitations that make it incorrect for particular populations and body shapes. For starters, it is not appropriate to analyze the senior population, as they may undergo height loss and/or acquire sarcopenia (loss of muscle mass) due to the normal aging process. This can lead to underestimating the risk of obesity in elderly people. Second, BMI may be inappropriate for people of Asian heritage. According to research, persons of Asian race had greater body fat percentages at lower BMI values than other ethnic groups. As a result, Obesity prevalence may be underestimated by BMI in Asian communities, thus misclassifying health concerns. Third, BMI may not accurately assess individuals of extreme height or very muscular. In the case of extremely tall individuals, BMI may overestimate obesity risk due to their increased height. In contrast, BMI may underestimate obesity in very muscular individuals, as muscle mass can influence body weight without necessarily indicating higher fat levels. Furthermore, the prevalence of visceral obesity may be underestimated by BMI, defined as fat buildup around internal organs and associated with higher health risks. Visceral obesity is linked to metabolic abnormalities and an increased risk of chronic illnesses such as cancer[30]. Because of the limits of BMI in correctly diagnosing visceral obesity, there may be misclassifications of obesity status and, as a result, biases in the relationship between obesity/overweight and cancer, potentially leading to null effects or underestimating the real risk. Given these limitations, it is critical to recognize that while BMI is a simple and frequently used metric, it should not be utilized as the sole predictor of health or cancer risk. Instead, while analyzing an individual's health and cancer risk, healthcare practitioners should evaluate several indicators such as body composition study, waist circumference, waist-to-hip ratio, and general lifestyle behaviours. Advances in science and technology may lead to more precise and personalized methods of determining body composition and obesity-related health concerns in the future. Individualizing evaluations and integrating additional indicators beyond BMI will be critical in gaining a more thorough knowledge of obesity's influence on cancer risk and devising focused preventative treatments. Regardless of BMI constraints, supporting healthy lifestyle behaviors such as a balanced diet, regular physical exercise, and weight control remains critical in minimizing the burden of obesity-related illnesses such as cancer.

1.4 THE BIOLOGICAL LINK BETWEEN OBESITY AND CANCER

The trio's function obesity/ Cancer-related obesity, insulin resistance (IR), and adipocytokines is a complicated and varied topic of study. While the precise processes connecting

obesity and adiposopathy to cancer etiopathogenesis remain unknown, many significant routes have been identified:

1. Hyperinsulinemia/IR and anomalies in the IGF-I (insulin-like growth Factor-I) system and signaling are important. Obesity can cause insulin and IGF-I levels to be dysregulated, resulting in increased cell proliferation and decreased apoptosis, which can promote cancer growth and progression.[31]
2. Obesity affects the production and route of sperm hormones. In women, excess adiposity can lead to greater oestrogen levels related to hormone-dependent malignancies such as breast and endometrial cancer.[32]
3. Obesity is associated with subclinical persistent low-grade inflammation and oxidative stress. Obese people's adipose tissue generates pro-inflammatory cytokines, contributing to a chronic inflammatory state that can encourage cancer development.[33]
4. Obesity-related cancer risk is connected with changes in adipocytokine pathogenesis[34]. Adipocytokines are signalling molecules adipose tissue generates that can alter cancer cell behaviour, angiogenesis, and metastasis.
5. Ectopic fat deposition factors are significant contributors. Ectopic fat accumulates in organs other than adipose tissue and can impair cellular function and induce cancer in the afflicted organs[35].
6. Obesity and adiposopathy alter the tumour microenvironment, influencing cellular perturbations and tumour growth.
7. Obesity may affect the immune response, creating a more favourable environment for tumour development and immune evasion.[36]

Understanding these complicated networks is critical for creating tailored therapies to reduce obesity-related cancer risks. Weight control, frequent physical exercise, and a balanced diet are lifestyle changes that can help lessen the influence of these pathways on cancer development. Furthermore, targeting chronic inflammation and oxidative stress by behavioural or pharmacological therapies may offer promise for cancer prevention. As research advances, efforts should be focused on discovering particular biomarkers and treatment targets related to the obesity-cancer link. Precision medicine techniques considering individual variations in genetic and metabolic profiles may give personalized solutions to reduce cancer risks linked with obesity and adiposity.

1.5 FACTORS RELATED TO ECTOPIC FAT DEPOSITION

Ectopic local adipose tissue may be a greater risk factor for site-specific malignancies. According to the Framingham Heart Study, the risk of malignancy may be higher in metabolically unhealthy obesity (MUO) people than in metabolically healthy obesity (MHO) adults.[37]Local ectopic fat tissue, such as breast, bone marrow, intrahepatic, and intrapancreatic adipose tissues, is toxic and carcinogenic in the development of breast, haematological, liver, and pancreatic cancers, according to emerging findings from epidemiologic and translational research investigations [38-40]The most abundant adipokine in blood, adiponectin, is the first hormone to become dysregulated (hypoadiponectinemia) as a result of intrabdominal and ectopic fat distribution, leading to IGF dysregulation, inflammation, estrogen/progesterone imbalance, and, finally, neoplastic transformation [41.] Adiponectin also has an indirect anti-tumor impact via insulin sensitization and anti-inflammatory effects. Several epidemiological studies have linked hypoadiponectinemia to an increased risk of obesity-related breast, endometrial, prostate, colon, pancreatic, and hematologic cancers.

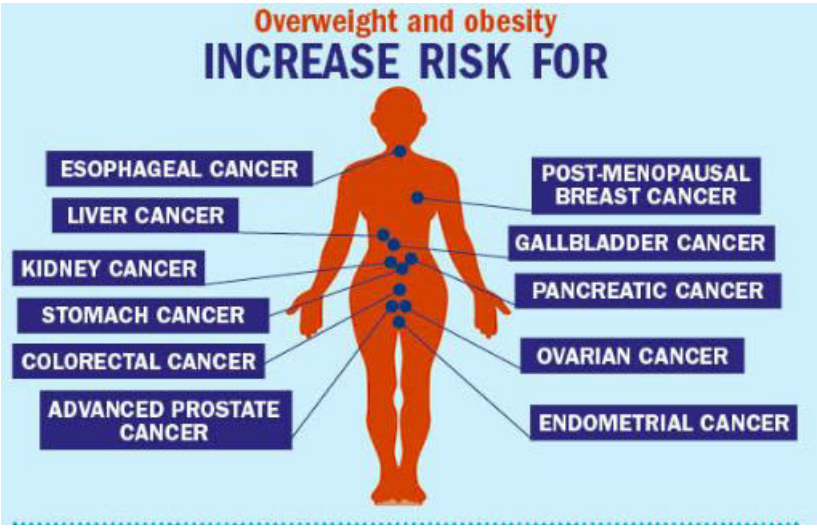

Fig 1: Overweight and Obesity

1.6 CANCER AND OBESITY

Tumour formation is a complicated process involving complex interactions within the local microenvironment. Various signals are delivered inside this microenvironment, boosting cell growth and survival strategies. Furthermore, tumour cells might avoid detection by the immune system by inducing tolerance in cytotoxic host T cells.)[42-43]. As our understanding of cancer biology advances, so does our understanding of the significance of lifestyle variables in the association between fat and cancer. Notably, some food patterns have been found as risk factors for different cancers. High consumption of red and processed meats, for example, has been connected to an increased risk of colon cancer, and this dietary pattern is also linked to obesity, perhaps contributing to the obesity-cancer relationship[44]. As a result, lifestyle changes such as dietary changes, exercise, and weight

control have enormous potential in lowering cancer risk and improving overall health outcomes.

1.7 INSULIN SENSITIVITY

Insulin resistance, widespread in obese people, is characterized by high insulin levels and is a well-known cancer-influencing element (2001)[45-47] Significant changes in inflammatory marker levels are associated with this syndrome (Lee & Lee, 2014)[48]. Obesity-related insulin resistance and cancer risk may indicate an underlying abnormality discovered in the insulin/insulin-like growth factor-1 (IGF-1) axis. Men had a higher risk of colorectal cancer (Ma et al., 1999)[49]; however, Wolpin et al. (2009[50] found no relationship. Furthermore, a case-control experiment found no link between IGF-1 and premenopausal or postmenopausal breast cancer[51]. Understanding the complexity of insulin resistance and IGF-1 signalling within the framework of obesity-related cancer risk is critical in human medical sciences for creating tailored preventive and treatment techniques.

1.8 *ADIPONECTIN*

Adiponectin, a peptide hormone, is important for glucose metabolism because it improves insulin sensitivity and glucose absorption while promoting fatty acid oxidation[52]. Adiponectin levels are considerably lower in fat peoplethan those with a BMI normal[53]. Adiponectin deficiency is linked to an increased risk of cancer and illness severity. Several studies have found a negative relationship between the amounts of circulating adiponectin and cancer danger, indicating that it may play a role in cancer prevention or progression[54]. Furthermore, evidence shows that adipose tissue secretes a significant part of circulating adiponectin, adding to total body levels. Ceruloplasmin, a protein involved in angiogenesis, is found in increased concentrations in obese people, potentially increasing the development of numerous malignancies[55]. Understanding the complicated relationships between adiponectin, obesity, and cancer is critical for understanding the processes that may relate metabolic states to disease consequences. Further research into the complicated roles of adiponectin and its potential therapeutic uses may offer new pathways for controlling insulin resistance, obesity-related health issues, and cancer prevention. Furthermore, research into the complex interaction between adiponectin and ceruloplasmin might lead to new targets for cancer treatment, emphasizing angiogenesis suppression to slow tumour development. Overall, understanding the role of adiponectin in glucose metabolism and cancer formation has important implications for human medical science and developing tailored therapies for improved health outcomes.

1.9. Metabolism of Fatty Acids

Fatty Acid Synthase (FAS) catalyses the de novo synthesis of long-chain fatty acids required for cellular energy metabolism and membrane function (Wakil, 1989)[56.] Several studies have found a relationship between high FAS expression and poor patient outcomes in malignancies ranging from the prostate to colon to breast to gastrointestinal to ovarian (Rossi et al., 2006)[57-59]. In contrast, blocking FAS has shown potential in cancer treatment ((2010)[60-62]revealed a frequent FAS polymorphism in men with higher BMI ranges (BMI 25 kg/m^2), which corresponded with an elevated risk of prostate cancer and death in the setting of human illnesses, especially prostate cancer. The researchers hypothesised that energy balance, as expressed by adiposity levels, may change the oncogenic impact of FAS overexpression in colon cancer cells, implying that a high energy level could promote tumour growth. Understanding the intricate relationship between FAS and cancer is critical for progressing cancer therapy options. Targeting FAS may provide a possible therapeutic pathway to battle cancer growth, allowing for better patient outcomes. Furthermore, investigating the link between FAS polymorphisms and obesity-related malignancies might lead to personalized therapies that address cancer risk and general health in those with higher BMI ranges.

1.10. Inflammation that lasts a long time

Chronic inflammation has been linked to various non-infectious physiological problems,as reported by Calle and Kaaks (2004); Musso et al., 2010; Cottam et al., 2010; George et al., 2017[63-66]. Furthermore, because pro-inflammatory cytokines such as TNF- and IL-6 are secreted, chronic inflammation is increasingly recognized in tumour development and progression, both locally and systemically (Grivennikov et al., 2009)[67]. Obesity, defined by excessive fat buildup, is a complicated medical disorder characterized by persistent inflammation. Obese people have an oversupply of pro-inflammatory cytokines in their adipose tissue, contributing to systemic low-grade inflammation. This persistent inflammatory state fosters tumour formation and proliferation, raising the risk of many chronic illnesses. Chronic inflammation has been linked to the development of numerous malignancies, including colon, breast, and prostate cancer, according to research. Pro-inflammatory cytokines promote cell proliferation, suppress apoptosis, and promote angiogenesis, contributing to tumour development and metastasis. Furthermore, prolonged inflammation can cause DNA damage and genomic instability, further fuelling carcinogenesis. Understanding the factors contributing to cancer and other illnesses is essential for creating targeted therapeutics. Medical researchers want to decrease inflammation and its negative consequences on human health by targeting certain pro-inflammatory molecules or pathways. These approaches can improve patient outcomes and public health by preventing and treating chronic inflammation-related disorders.

1.11. Obesity and the risk of cancer

Obesity is recognized as a substantial independent risk factor for various malignancies, with some studies attributing over 40% of all cancer diagnoses to being overweight or obese[68]. Endometrial, postmenopausal breast and colorectal cancers account for more than 60% of all obesity-related cancer cases[69-70]. Socio-demographic characteristics may influence the impact of overweight and obesity on cancer risks. Weight growth over time has also been related to an increased chance of acquiring specific malignancies, demonstrating a clear correlation between weight and cancer risk. Adult weight growth, however, was not linked to an increased risk of pre-menopausal breast, colorectal (women), pancreatic, or thyroid cancer. The link between obesity and breast cancer changes depending on the menopausal state, with a continuous positive linear relationship between high BMI and postmenopausal breast cancer incidence[71-72], earlier start, and lower cancer-free survival[73]. Disturbingly, a worrying trend of malignancies, particularly obesity-related cancers, are

becoming diagnosed at younger ages[74]. This trend may be due in part to rising rates of childhood obesity. For example, colon cancer, which used to be more common in those over 67, is now more common in people under 50 and [75]. These findings emphasise the vital need of tackling obesity as a preventable cancer risk factor. Early treatments supporting good weight management and lifestyle choices are critical to lowering the burden of obesity-related malignancies and improving cancer outcomes, especially for breast, endometrial, and colorectal cancers. To reduce the growing prevalence of obesity-related malignancies and protect public health, public health measures must prioritise obesity prevention and awareness activities, addressing younger and older populations.

1.11.1. Cancer of The Breast

Numerous studies have found strong and consistent evidence that excess weight and weight gain are associated with an increased risk of postmenopausal breast cancer. While the evidence for male breast cancer is sparse, the link between obesity and postmenopausal breast cancer is well-established[76]. In postmenopausal women who do not utilise hormone treatment (HT), adipose tissue, often known as body fat, becomes the primary source of oestrogen production. As a result, it is not unexpected that the risk of breast cancer increases dramatically in women with larger body weights, especially those who do not use HT[77]. Obesity and postmenopausal breast cancer have a complicated relationship. Adipose tissue produces hormones such as oestrogen, which can promote the development of hormone receptor-positive breast cancer cells. Higher amounts of oestrogen in the bloodstream can fuel tumour formation and progression, increasing the risk of breast cancer[78]. Obesity is also linked to persistent low-grade inflammation, insulin resistance, and changes in other hormonal pathways, all of which can contribute to cancer development and complicate treatment results. Understanding these associations is crucial for public health measures focusing on lowering breast cancer incidence. Targeted programs encouraging healthy weight maintenance, regular physical exercise, and lifestyle changes may assist postmenopausal women reduces their risk of breast cancer. Lifestyle modifications are especially important for persons unable to utilise hormone therapy for various reasons. By addressing the influence of obesity on breast cancer risk, healthcare practitioners may empower women to make educated decisions and proactively reduce their susceptibility to this common disease.

1.11.2. Colorectal Cancer

Consistent evidence suggests a dose-response association between BMI and waist circumference and increased risk of the illness, with males being at a larger risk than women[79]. This link between fat and cancer is especially disturbing considering the increasing growth in overweight and obese people worldwide. Obesity has been identified as a serious public health hazard by the World Health Organisation (WHO), and its influence on cancer incidence adds to the urgency of addressing this issue. Notably, the association between obesity and cancer is not restricted to a few kinds; it extends across various cancer sites, making it a widespread and significant contributor to the worldwide cancer burden. Chronic inflammation, insulin resistance, and altered sex hormone levels, as previously established, are among the major processes behind the obesity-cancer relationship. Chronic inflammation, in particular, is important in cancer genesis and development, providing a milieu favourable to tumour growth and metastasis. Furthermore, changes in adipokine production caused by obesity impact tumour behaviour and either boost or inhibits cancer cell proliferation, angiogenesis, and immunological responses. Understanding these underlying processes is critical for developing effective measures to reduce obesity's influence on cancer risk. Promoting access to inexpensive, nutritious food alternatives and generating opportunities for physical exercise at the community level can contribute to population-wide initiatives to avoid obesity leading to cancer risk. Public health campaigns and educational programs can raise awareness about the connection between obesity and cancer, urging people to act proactively towards a healthy lifestyle. The relationship between fat and cancer is obvious and requires immediate action. With the worldwide obesity pandemic showing no signs of abating, efforts to prevent and manage obesity must be stepped up to reduce the influence on cancer incidence. Recognizing the link between obesity and cancer risk, the public health community, healthcare providers, governments, and individuals must work together to promote healthy lifestyles, enhance access to nutritious food, and establish physical activity-friendly environments. By tackling obesity as a modifiable risk factor for cancer, we may make great progress in lowering the global cancer burden and improving population health and well-being.

1.11.3. Endometrial Cancer

Weight was a particularly substantial risk factor for type I endometrial cancer, the most frequent kind comprising endometrial adenocarcinomas. Type I endometrial cancer often develops due to excessive oestrogen exposure caused by obesity, resulting in unopposed oestrogen stimulation of the endometrium[80]. Obese people's increased oestrogen production from adipose tissue leads to the proliferation of endometrial cells and the development of hyperplasia, a precursor to cancer. As a result, obese women are at a larger risk of getting type I endometrial cancer than non-obese women. This link between obesity and endometrial cancer emphasizes the necessity of combating the obesity pandemic as a preventative intervention for this common gynecologic disease. Healthcare practitioners should be proactive in teaching women about the relationship between obesity and endometrial cancer risk and supporting lifestyle changes that improve weight management and general health. Public health programs that promote awareness about the need to keep a healthy weight and engage in regular physical exercise can also play an important role in lowering the worldwide burden of endometrial cancer and enhancing women's quality of life. We can stop the growth in obesity-related endometrial cancer cases and make substantial achievements in the battle against cancer by using a holistic approach that combines individual behavioural adjustments with societal and policy-level initiatives.Continued research into the molecular and cellular mechanisms underlying the obesity-cancer link and clinical studies examining the impact of weight loss and lifestyle interventions on cancer outcomes will be required to inform evidence-based cancer prevention and management strategies. Finally, by recognising and addressing obesity as a substantial modifiable risk factor for cancer, we can empower individuals to take control of their health and lessen the personal and social burden of this deadly illness.

1.11.4. Esophageal Cancer

Numerous research, including both genders and varied geographic locations, have consistently found a statistically significant positive dose-response connection between BMI and esophageal cancer risk[781]. In numerous well-conducted prospective investigations[82,83], abdominal obesity, measured by several metrics, including waist circumference, was associated with esophageal cancer. These findings highlight the significant role of obesity in developing esophageal cancer and emphasise the need to address weight management as an important part of cancer prevention and control efforts. Further investigation is required into the underlying processes and potential strategies to minimize this risk. Several epidemiological studies have examined the link between obesity and the risk of oesophageal adenocarcinoma. There have been several studies on general obesity, as measured by body mass index (BMI), but few on abdominal obesity, as measured by waist circumference or waist-to-hip ratio[84]. Some studies provide results on oesophageal cancer alone, while others report outcomes on oesophageal adenocarcinoma and the anatomically related stomach cardia adenocarcinoma together[85]. Abdominal obesity, which reflects the quantity of metabolically active visceral fat, may be more relevant than general obesity regarding the risk of Barrett's oesophagus and oesophageal cancer. It has been hypothesized that abdominal obesity, irrespective of BMI and GERD, is related to Barrett's oesophagus and oesophageal cancer[86]. The EPIC research examined the relationship between general and abdominal obesity and oesophageal and gastric cancer incidence. In this prospective analysis using baseline anthropometry, both general obesity as evaluated by BMI and abdominal obesity as defined by waist circumference or waist-to-hip ratio were highly related to the risk of oesophageal adenocarcinoma. Because carcinogenesis is a protracted process that might take decades, it is plausible that obesity, not just throughout maturity but also earlier in life, may influence cancer risk. Epidemiological studies show that being overweight or obese throughout infancy or adolescence is associated with a higher risk of cancer later in life, such as colorectal neoplasia[87]. The association between pre-diagnostic obesity and better survival among oesophageal cancer patients may be consistent with the "obesity paradox," which has also been observed in cardiovascular and metabolic diseases and may be related to reverse causation or a special selection bias. Still, it could also indicate a true association[87].

1.11.5. Oral Cancer

Esophageal cancer and Oral cancer are both types of malignancies that affect the digestive system. While they primarily manifest in different anatomical regions—oral cancer affecting the mouth and esophageal cancer affecting the esophagus—they share certain risk factors and challenges. Biosensors have emerged as promising tools for early detection and monitoring of both oral and esophageal cancers. These biosensors are designed to detect specific biomarkers associated with cancer development, such as genetic mutations or protein overexpression. In the case of oral cancer, biosensors can detect changes in saliva composition, allowing for non-invasive and rapid screening. Similarly, biosensors for esophageal cancer can be developed to analyze biomarkers in saliva or even in the lining of the esophagus.[113] Oral cancers, a malignancy affecting the mouth and oral cavity, poses a significant global health challenge. In the search for effective therapeutic strategies, the potential of natural compounds has gained attention. Piperine, a bioactive compound found in black pepper, has been investigated for its anticancer properties, particularly in the context of oral cancer. Research suggests that piperine exhibits various beneficial effects, including anti-inflammatory, antioxidant, and anti-tumor activities. Its ability to modulate key cellular pathways involved in cancer progression makes it a promising candidate for complementary treatment approaches. Studies have indicated that piperine could inhibit the growth of oral cancer cells, induce apoptosis (programmed cell death), and mitigate metastasis. While more extensive research is needed to fully understand the mechanisms underlying piperine's effects on oral cancer, these findings highlight its potential as a natural compound that could contribute to future therapeutic interventions against this challenging disease.[114]

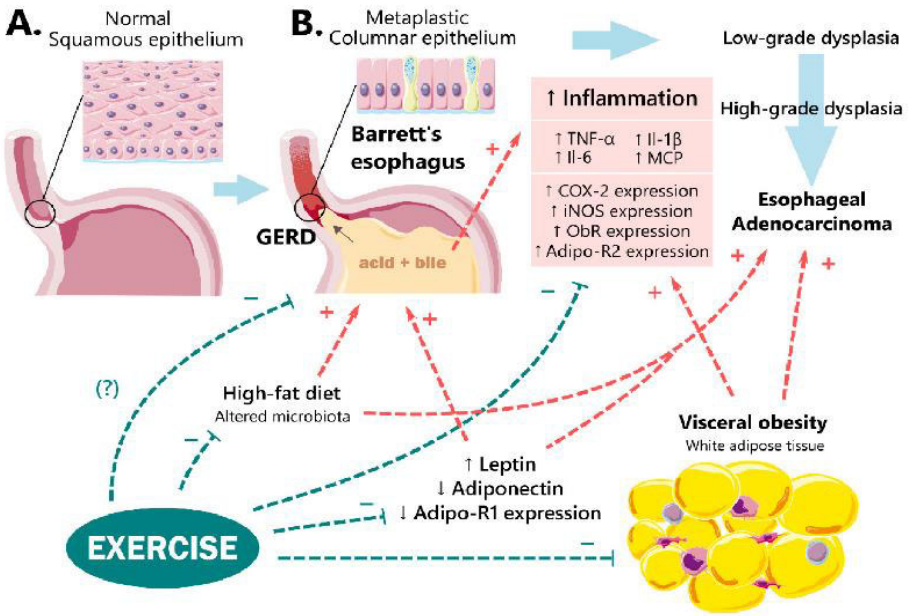

Fig 2: Normal esophageal squamous epithelium reflecting healthy esophagus[89]

1.11.6. Kidney Cancer

This relationship was found in almost all investigations, and it was stable across gender and areas of the world. Several large-scale epidemiological studies worldwide have consistently substantiated the relationship between obesity and an increased risk of kidney cancer. Obesity is a substantial risk factor for various cancers, regardless of geographic region or demographic category, according to the early findings. The evidence gained from multiple groups spanning various nationalities and socioeconomic backgrounds strengthens the robustness of the obesity-cancer relationship. As a result, treating obesity remains a top public health priority in the global battle against cancer. The waist circumference and waist-to-hip ratio measure abdominal or central obesity, a major contributor to metabolic disorders such as insulin resistance and hyperinsulinemia. Several studies that looked at Waist Circumference, Weight Change, and the Risk of Renal cell carcinoma discovered favourable relationships[90]. Obesity impacts kidney carcinogenesis through unknown mechanisms; however, various probable theories exist. RCC (Renal Cell Carcinma) is referred to be a "metabolic disorder." The genes linked to kidney cancer are all linked to the ability of cells to recognize oxygen, nutrients, and energy[91]. Furthermore, type 2 diabetes and hypertension, linked to metabolic syndrome, are linked to an increased risk of RCC.[92] This shows that insulin, as well as the interconnected hormonal systems of the insulin-like growth factor (IGF) axis, sex hormones, and adipokines, play a role.

1.11.7. Pancreatic Cancer

Most research involving both genders has repeatedly reported a substantial positive dose-response connection between BMI and pancreatic cancer risk. This strong link emphasizes the vital need to combat the worldwide obesity pandemic as a primary preventative step against cancer and other chronic illnesses. Ongoing research studies into the underlying processes and possible therapies offer great promise for guiding successful measures to reduce the impact of obesity on pancreatic cancer incidence and enhance public health outcomes worldwide. The molecular processes and signalling pathways contributing to clinical events leading to pancreatic cancer remain unknown. According to one interpretation, adipose tissue enlargement generates the formation of connective tissue, or desmoplasia, which supports the survival and migration of malignant cells[93]. Desmoplasia comprises extracellular matrix proteins, pancreatic stellate cells, and immune cells, and it is a metabolically active tissue that secretes many cytokines and growth factors, promoting cancer growth. Desmoplasia induces changes in general tissue structure and interstitial fluid pressure, contributing to chemoresistance. The role of desmoplasia in pancreatic cancer is currently being studied. However, research suggests that obesity has a significant role.

1.11.8. Ovarian Cancer

Control studies examining the connection between BMI and epithelial ovarian cancer have consistently found a favourable dose-response relationship. Compared to women of normal weight, the risk of ovarian cancer is enhanced in overweight women[94], with a relative risk of roughly 1.1, and obese women face an even greater relative risk of approximately 1.2. These findings highlight the significance of addressing obesity as a modifiable risk factor in the context of ovarian cancer prevention and public health strategies. Obesity has been demonstrated to raise circulating oestrogen and androgen levels, especially in postmenopausal women, and these endogenous sex hormones have been linked to the development of ovarian cancer. Although epidemiologic data on pre-diagnostic oestrogen concentrations and ovarian cancer risk is weak and not supporting, oestrogens may be favourably related to ovarian cancer risk by increasing ovarian epithelial cell proliferation. Some observational studies support the concept that increased circulating testosterone levels may increase the risk of ovarian cancer. [95]PCOS, a prevalent benign gynecologic condition characterized by hyperandrogenism, has been linked to an increased risk of ovarian cancer. Overall, sex hormones may have a role in distinct subtypes of ovarian cancer, lending support to the investigation of obesity and ovarian cancer by histologic subtype. Fatty acids are released into the blood by adipose tissues, which are essential for lipid production and metabolism. Significant evidence suggests that lipid production and metabolism are dysregulated in ovarian tumours[96].

1.11.9. Lymphoma

Numerous prospective, case-control, and meta-analysis studies consistently show a significant relationship between high body weight and the risk of diffuse large B-cell lymphoma (DLBCL), the most common kind of non-Hodgkin lymphoma (NHL). These studies' findings emphasise the importance of keeping a healthy weight and its possible influence on lowering the risk of developing DLBCL and other lymphoma subtypes. As the worldwide incidence of obesity rises, it becomes increasingly important to address this modifiable risk factor to reduce the burden of lymphomas and enhance public health outcomes.

Lymphomas are lymphoid tumours that appear as solid tumour masses. This illness is classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). HL accounts for approximately 8% of all malignant lymphoid neoplasms and is characterised by mature B lymphocytes, which correspond to the so-called Reed-Sternberg (RS) cell, which accounts for less than 1% of the overall tumour[97]. NHL, on the other hand, accounts for most malignant lymphoid neoplasms and involves mature B cells and T and NK lymphocytes. DLBCL (diffuse large B-cell lymphoma) is the most common subtype of NHL.The link between fat and lymphoma has been widely debated throughout the years. A higher BMI appears to increase the risk of lymphoma, although other studies have identified non-significant positive connections or no correlations between the two illnesses. This is likely related not only to the fact that HL and NHL are heterogeneous illnesses with various histological subtypes but also to other characteristics like location, gender, or age, as previously described. In keeping with this view, it [98]concluded that there was no evidence to support obesity as a determining parameter for all forms of NHL combined; however, it discovered[99] that obesity was connected with the risk of HL and the majority of types of NHL.Obesity has also been proposed as a risk factor for developing NHL, and the link between obesity and the risk of small lymphocytic lymphoma (SLL) is debatable. In this context, the phrase "obesity paradox" was developed to describe why fat people may have a better prognosis than their healthy or underweight counterparts. The obesity paradox has been

linked to cardiovascular disease and cancer. Excess adiposity has been shown to influence the aggressiveness of Hodgkin Reed-Sternberg lymphoma cells by several pathways, including hypertrophied adipocytes, adipose stem cells, angiogenesis, and the generation of pro-tumoral adipokines. Circulating IL-8 is another cytokine generated by adipocytes that have been reported to be considerably greater in obese people compared to non-obese controls, enhancing inflammation and being linked to many forms of lymphomas[100]. Elevated levels of IL-8 have been found in gastrointestinal FL and MALT lymphomas, as well as DLBCL cells, which eventually recruit neutrophils producing APRIL: a factor that promotes the development of various types of tumours and has been linked to poor survival in DLCBL due to DNA methylation and acetylation[101].

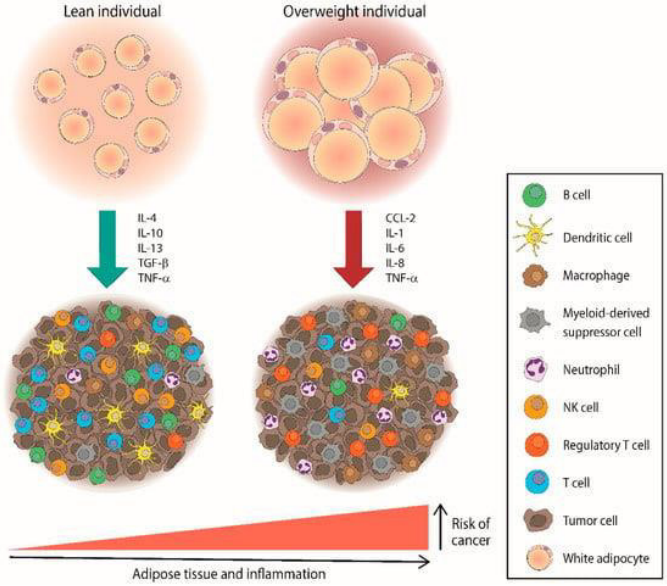

Fig 2: Due to the buildup of pro-inflammatory mediators and immune-suppressive cells in the tumour microenvironment, overweight people may be at an increased risk of developing cancer, including lymphomas.[102]

1.11.10. Gallbladder Cancer

Several studies have found a statistically significant positive dose-response connection between BMI and cancer risk. In a meta-analysis, the relative risk was around 1.2 for overweight people and around 1.6 for obese people [103]. These findings emphasise the need to tackle the obesity pandemic as a vital tool for cancer prevention and the need for more studies to understand the processes behind the obesity-cancer association. A significant and favorable dose-response association between Body Mass Index (BMI) and the risk of acquiring gall bladder cancer has been consistently shown by numerous studies[104]. A meta-analysis assessed the relative risk for people who are overweight to be about 1.2 and for people who are obese to be about 1.6 .[105]These startling results highlight the crucial significance of combating the obesity pandemic as a key strategy for cancer prevention. It emphasizes the critical need for all-encompassing efforts to fight obesity, not only because of its effects on general health but also because it is a key factor in lowering cancer risk. However, the precise underlying mechanisms are still unknown, despite the established link between obesity and cancer risk. Therefore, more investigation into the complex mechanisms that connect fat with the onset of cancer is necessary. We can create more focused and efficient strategies for both the management of obesity and the prevention of cancer by dissecting the complexity of this link, ultimately leading to better public health results.

1.11.11. Liver Cancer (Hepatocellular Carcinoma)

Several case-control studies have consistently shown a favourable relationship between BMI and the risk of hepatocellular carcinoma (HCC) or liver cancer [106]. Notably, nonalcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide and is strongly connected to obesity [107](46). NAFLD advancement can result in cirrhosis, a substantial risk factor for developing hepatocellular carcinoma[108]. This complex link between obesity, NAFLD, and liver cancer emphasizes the critical need for focused therapies and public health programs aiming at reducing obesity and its related health effects to reduce the growing burden of liver cancer. Body Mass Index (BMI) and the risk of hepatocellular carcinoma (HCC), also called liver cancer, have repeatedly been positively correlated in numerous case-control studies [109]. The fact that nonalcoholic fatty liver disease (NAFLD) has overtaken all other liver disorders as the most common in the world is notable. Cirrhosis, a substantial risk factor for hepatocellular carcinoma, can develop as NAFLD worsens[110]. This complex interplay between obesity, NAFLD, and liver cancer highlights the urgent need for therapeutic interventions specifically targeted at reducing obesity and its associated health consequences, as well as for public health initiatives that aim to reduce the rising burden of liver cancer. Controlling and preventing obesity is essential for reducing the incidence of liver cancer, which is on the rise. The relationship between high BMI, NAFLD, and hepatocellular carcinoma can be better understood by healthcare experts, who can then use this information to create earlier detection and intervention techniques. Encouragement of lifestyle changes like eating a balanced diet and getting regular exercise can aid in weight control and significantly lower the risk of developing liver cancer. Public health campaigns should include raising awareness of the effects of obesity and the value of early identification of liver problems in addition

to individual-level measures. People can make wise lifestyle decisions and take precautions to protect their liver health by increasing their health literacy. In addition, early detection and treatment of NAFLD should be a top priority for medical professionals to stop the development of cirrhosis and liver cancer. The early detection and treatment of liver illnesses can benefit from increasing awareness among medical professionals and instituting regular screening procedures. The research connecting obesity, NAFLD, and hepatocellular carcinoma emphasizes the need for comprehensive solutions to this public health issue.

1.11.12. FTO (Fat Mass And Obesity-Associated Protein)

FTO (Fat Mass and Obesity-Associated) protein is important in developing overweight/obesity and cancer. FTO, the first m6A demethylase discovered, modulates the expression of critical target genes by post-transcriptionally lowering their m6A levels, influencing mRNA stability and splicing[111]. This pathway promotes adipogenesis, carcinogenesis, and treatment resistance in cancer cells. Notably, FTO SNPs and being overweight/obese are closely linked to elevated cancer risk, indicating that FTO's metabolic function may contribute to its carcinogenic effects (Figure 3). The association between FTO gene variations and cancer risk shows that obesity is likely linked to cancer development. As a result, targeting FTO is a possible therapeutic option for malignancies that overexpress this gene. The discovery of more effective and selective FTO inhibitors, in particular, might offer up new pathways for cancer therapy. When coupled with other therapeutic medicines, these inhibitors may be more effective in treating specific forms of cancer. Finally, knowing the varied functions of FTO in both overweight/obesity and cancer development gives vital insights into the intricate interplay between metabolism and cancer formation. Researchers can uncover novel therapy options by studying the molecular pathways through which FTO regulates gene expression and cellular activities. FTO inhibition shows enormous potential for future cancer therapies, providing a realistic druggable target that might greatly alter cancer care and patient outcomes. Harnessing the potential of FTO inhibition might lead to more personalised and effective cancer medicines in the clinical situation as precision medicine advances.

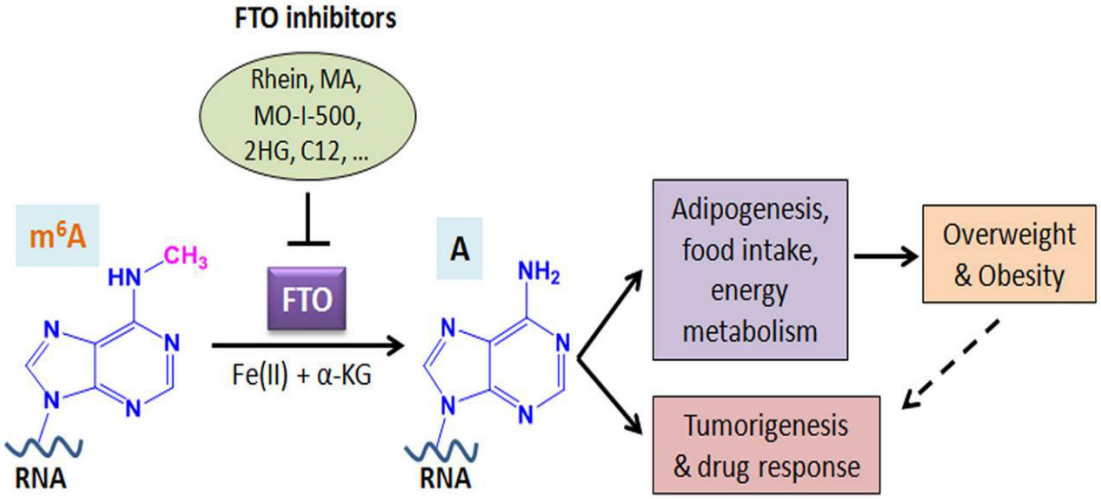

Fig 3 FTO's involvement in RNA m6A alteration, overweight/obesity, and tumorigenesis/drug response are depicted schematically[112].

2. CONCLUSION

The complex interaction between the host and the microbial population extends beyond passive involvement in cancer formation; dysbiosis plays an important role in carcinogenesis, influencing the response to anticancer medicines, particularly immunotherapy. Targeting the microbiota might transform cancer management by addressing intestinal dysbiosis, toxic metabolites, antitumoral immune responses, and anticancer therapy effectiveness. Exogenous techniques to modulate gut microbiota may offer promise in impacting cancer outcomes at several locations. Preclinical research has shown that faecal microbiota transplantation and probiotics have the potential to improve immunotherapy responses and reduce treatment-related adverse effects. Furthermore, new evidence suggests that changes in food and lifestyle might affect the makeup and function of the gut microbiome, thereby impacting cancer development and treatment results. However, substantial randomised controlled studies must confirm and corroborate these findings to bridge the gap between experimental research and clinical application. To optimize treatment methods, the intricacy of the microbiota-host interplay must be carefully considered and investigated. This technique may serve as a prediction tool for modifying the microbiome in the adjuvant therapeutic management of neoplastic illnesses, complementing cancer treatment regimens, and improving patient outcomes by combining current knowledge. Personalized medicine, which incorporates a person's unique microbiome profile, might lead to more effective and well-tolerated medicines. Understanding the complexities of the microbiota-host interplay opens up a viable route for developing cancer therapies and personalized medicine in the battle against this ferocious illness. Collaboration among researchers, physicians, and industry stakeholders is critical for translating these exciting findings into clinically relevant therapies, eventually leading to better cancer outcomes and quality of life for patients worldwide.

3. AUTHORS CONTRIBUTION STATEMENT

Dr. Somenath Ghosh, Kiruthika Balasubramanian, J Andrews Milton conceived the study and was responsible for the overall direction, analysis, and planning. Dr. Vinayak B Angadi, Hadi Kuriri carried out the implementation. Dr. Radhika took the lead in writing the manuscript. Dr. Somenath Ghosh, Dr.

Umesh Ghate provided critical feedback, reviewed, and helped in the final corrections of the manuscript.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

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