Gut microbiome versus thyroid cancer: Association and clinical implications (Review)

MALI WANG and YUCHUN ZHU

Department of Nuclear Medicine, The First People's Hospital of Kunshan, Kunshan, Jiangsu 215300, P.R. China

Received January 26, 2025; Accepted April 14, 2025

DOI: 10.3892/ol.2025.15114

Abstract. Thyroid cancer (TC) is one of the most prevalent endocrine tumors, and its incidence rates are increasing. Recent studies have shown that TC disrupts the gut microbiomes (GM) by influencing the levels of thyroid hormones, estrogen levels, weight and insulin resistance. Traditional treatments, including thyroid surgery, radioactive iodine (RAI) therapy and checkpoint inhibitors, also alter the GM. Additionally, GM affects the proliferation of TC by influencing chronic inflammation and metabolism (e.g., effects on short-chain fatty acids and amino acid metabolism). Notable changes in the GM of patients with TC include increased numbers of *Clostridium*, *Streptococcus*, *Proteus* and *Lachnospiraceae*, and decreased numbers of *Lactobacillus*, *Prevotella* and *Ruminococcaceae* bacteria. In addition, the GM may serve as a biomarker for diagnosis, prognosis and predicting metastasis in patients with TC, potentially enhancing diagnostic efficiency. Furthermore, the GM presents an opportunity to improve the efficacy of RAI therapy and immunotherapy in patients with TC. Probiotic combination approaches may also enhance clinical outcomes and the quality of life for individuals with TC. In conclusion, the present review discussed how there are bidirectional causal relationships between the GM and TC, emphasizing the role of the 'gut-thyroid' axis. *Clostridium*, *Streptococcus*, *Proteus* and *Lachnospiraceae* may be potential risk factors, whereas *Lactobacillus*, *Prevotella* and *Ruminococcaceae* may have protective roles for TC. Further investigations into macrobiotics-associated mechanisms should prove to be helpful in terms of optimizing strategies for the early prevention and treatment of TC.

Correspondence to: Dr Yuchun Zhu, Department of Nuclear Medicine, The First People's Hospital of Kunshan, 566 Qianjin East Road, Kunshan, Jiangsu 215300, P.R. China
E-mail: 13621950757@163.com

Abbreviations: BMI, body mass index; FMT, fecal microbiota transplantation; FT3, free triiodothyronine; GM, gut microbiomes; IGF-1, insulin-like growth factor-1; LPS, lipopolysaccharides; NIS, sodium/iodine symporter; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; SCFAs, short-chain fatty acids; TC, thyroid cancer; THW, thyroid hormone withdrawal; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone

Key words: thyroid cancer, gut microbiota, metabolism, radio-iodine therapy, probiotics

Contents

1. Introduction

It has become established that the intricate association between humans and their microbiota is vital for human health (1). Various factors, including diet, antibiotic use, genetics and the environment, significantly shape the composition of the microbiota, which matures in humans at an age of ~3 years, but continues to evolve throughout life (1). The GM comprises ~10^{13}-10^{14} microorganisms, which fulfill essential roles beyond digestive balance, including nutrient assimilation, metabolic homeostasis, hormonal modulation and immune regulation (2,3). The lymphocytes within the intestinal mucosa orchestrate responses to microorganisms, making the microbiota a key factor in determining an individual's health status (4,5). Microbiota disturbances have also been shown to contribute to numerous diseases (6), including thyroid cancer (TC). Previous studies (7-11) investigating the relationship between the microbiota and tumors (e.g., colorectal tumors) have reported that the microbiota found in different parts of the body, including the gut, mouth and within tumors (12-20), can influence cancer growth and metastasis due to the common embryonic lineage that thyroid follicular cells share with gastric mucosal cells (21). Thyroid disorders have been shown to be closely tied to thyroid hormone levels and function, as well as the composition of the intestinal flora (22). Furthermore, the gut-brain axis allows intestinal microorganisms to modulate immune, metabolic and endocrine interactions (23). Several studies have linked intestinal microbiota with thyroid-associated conditions, including Graves' disease, Hashimoto's thyroiditis and TC, highlighting

the importance of maintaining a healthy intestinal flora for thyroid disease prevention (24-26).

TC, a common endocrine malignancy, has seen an increased global incidence in recent years, particularly among women, suggesting sex-associated factors (27-32). Although various risk factors, such as smoking, obesity, hormone exposure, family history and environmental factors, have been implicated in the development of TC, the precise causes underlying the disease remain largely unknown (33). Several studies have demonstrated a significant association between the gut microbiome and risk factors for TC, indicating its potential role in TC pathogenesis. There is evidence to suggest a possible association between microbiome diversity and composition with risk factors for thyroid diseases, including hormonal imbalances and obesity (34-36). TC is typically treated with thyroid surgery, radioactive iodine (RAI) therapy and thyroid-stimulating hormone (TSH) suppression (37). However, these treatments have been shown to lead to various side effects (38-41), potentially compromising patients' quality of life (41,42). Recently, one randomized clinical trial demonstrated that probiotics may help reduce postoperative reaction and complications, possibly through modifying the gut and oral microbiota (43). This suggests that the GM may fulfill a crucial role in the development, prevention, diagnosis, treatment and management of TC. Therefore, a comprehensive understanding of the interaction between GM and TC is crucial for improving clinical outcomes and patient care.

The present review aims to integrate and explore this crucial interplay between GM and TC, offering novel avenues or strategies for enhancing the understanding and management of TC.

2. Association between GM and TC

Previous studies have indicated a strong link between the composition of the GM and the risk of TC, although the exact causal association remains controversial (Table I). One study (44) employed 16S rRNA sequencing, which showed that patients with TC had a higher richness and alpha diversity of intestinal flora compared with healthy individuals. Of note, the *Firmicutes*/*Bacteroidetes* ratio was found to be markedly elevated, similarly to patterns observed in other cancers, including breast cancer and colon cancer (45-47). In another study (48), it was shown that patients with TC had lower numbers of *Butyricum* and *Lactobacillus*, which was found to be connected with trace elements such as selenium, which protect the thyroid and fight against oxidative stress, whereas the numbers of *Clostridium*, *Neisseria* and *Streptococcus* were enhanced. Furthermore, TSH was positively correlated with *Porphyromonas* ($r=0.57$; $P<0.01$), triiodothyronine was correlated with *Streptococcus* ($r=0.43$; $P<0.001$) and thyroglobulin was negatively correlated with *Bacteroides* and *Lactobacillaceae* ($r=-0.43$; $P<0.001$), suggesting that these genera could serve as biomarkers for TC (48). A subsequent study (49) reported changes in the GM of patients with TC, marked by increased numbers of *Bacteroidetes*, *Clostridium* and *Lachnospiraceae*, whereas the numbers of *Prevotella* and *Faecalibacterium* were decreased. This research group also identified a four-genus signature ('g_Hungatella', 'g_Alistipes', 'g_Bacterium', and 'g_Phascolarctobacterium'), which suggested that patients with TC also had metastatic lymphadenopathy. However, their findings contradicted those of other studies (48-50), as they observed reduced richness and diversity of intestinal microbiota in patients with TC. Additionally, a study by Lu *et al* (50) noted a decrease in lipid metabolism-associated genera and elevated levels of 27-hydroxycholesterol, whereas other research groups (44,51) described shifts in microbiota composition, with increased numbers of *Escherichia coli* and decreased numbers of *Bacteroides vulgatus* in patients with TC. Furthermore, several Mendelian randomization analyses have been published (51-58), which suggested a potential bidirectional causal association between GM composition and TC. For instance, *Streptococcus* and bacteria of the class *Betaproteobacteria* were identified as risk factors and protective factors for TC, respectively. Taken together, these findings have highlighted the importance of understanding the role of GM in the development and progression of TC.

Overall, alterations of the GM in patients with TC have been shown to include increases in the numbers of *Clostridium*, *Streptococcus*, *Proteus* and *Lachnospiraceae* bacteria, alongside decreases in the numbers of *Lactobacillus*, *Prevotella* and *Ruminococcaceae*. The populations of clinical trials mentioned in Table I (details of gut microbiota composition in TC) are Asian (44,48-51), whereas the populations of Mendelian randomization studies (52-57) are from various ethnicities. The conflicting findings of the above studies on microbiota diversity may be attributed to small sample sizes, differences in the demographics, tumor stage and treatment, or dietary considerations. Furthermore, it should be noted that these studies only used 16S rRNA sequencing, thereby necessitating the use of further, more advanced methods.

Fig. 1 illustrates the different types of interaction of gut microbiomes with TC. Recent studies have illuminated the critical role of GM in cancer development, particularly regarding how they impact the replication and integrity of the host DNA (6-21). Pathogenic bacteria may manipulate host cancer cells, thereby resulting in abnormal hormone production and immune system dysfunction, ultimately leading to tumor formation (58,59). Changes in the gut flora have also been shown to trigger the release of toxins that harm DNA and impede DNA repair mechanisms (60). For instance, the promotion of p53 degradation by *Shigella flexneri* in host cells can increase the risk of DNA damage and mutations, ultimately leading to tumor formation. Furthermore, certain bacteria, such as *Clostridiaceae* (61), have been linked to carcinogenic effects, whereas *Streptococcus* has been associated with heightened risks of adenoma and cancer (62).

Another significant mechanism involves inflammation. Cancer-associated microbiota and pattern recognition receptors, such as Toll-like receptors, have been linked to the activation of nuclear factor κB (NF-κB) signaling in the tumor microenvironment (63). This process sets off a chain reaction of chronic inflammation, causing both the continuous damage and repair of epithelial cells and the release of cytokines, promoting malignancy (64). The inflammatory response also stimulates immune cells to release cytokines, thereby enhancing cell proliferation, inhibiting apoptosis and deactivating tumor suppressor genes via the NF-κB and STAT3 signaling pathways (65).

Table I. Details of gut microbiota composition in TC.

First author, year	Patients (n)	Microbiota main findings	Methodology	(Refs.
Feng *et al*, 2019	TC (n=30), HCs (n=35)	TC: e.g., *Escherichia-Shigella*, *Clostridium sensu stricto 1*, *Klebsiella*↑ *Bacteroides*, *Prevotella 9*, *Roseburia*, *Megamonas* ↓	Single-center, cross-sectional study involving preoperative patients with PTC using 16S rRNA sequencing	(44)
Zhang *et al*, 2019	TC (n=20), Thyroid nodules (n=18), HCs (n=36)	TC: e.g., *Neisseria and Streptococcus* ↑ *Butyricimonas and Lactobacillus* ↓	Cohort study including preoperative patients with PTC and healthy individuals using 16S rRNA sequencing	(48)
Yu *et al*, 2022	TC (n=90), HCs (n=90)	TC: e.g., *G Bacteroides*, *g Lachnoclostridium*, *g no-rank f Lachnospiraceae* ↑ *g Prevotella 9*, *g Collinsella*, *g Faecalibacterium*, *g Dorea*↓ *g Ruminococcaceae UCG-014*, *g Ruminococcaceae UCG-002*↓ *g Subdoligranulum* ↓	88 PTC and 2 FTC; 60 each exploratory, 30 each validation cohorts utilizing 16S rRNA sequencing	(49)
Lu *et al*, 2022	TC (n=50), HCs (n=58)	TC: e.g., *G Fusobacterium and g Alistipes* ↑ *g Hungatella and g Phascolarctobacterium* ↓	Cohort study including postoperative patients and healthy controls by 16S rRNA sequencing	(50)
Ishaq *et al*, 2022	TC (n=16), HCs (n=10)	TC: e.g., *Escherichia coli* ↑, *Bacteroides vulgates* ↓	Cohort study recruiting patients with TC with normal thyroid function using metagenomic high-throughput sequencing	(51)
Quan *et al*, 2023	TC (n=701)	Risk factors: e.g., *Genus Ruminiclostridium9*, *class Mollicutes*, *genus RuminococcaceaeUCG004*, *genus Paraprevotella and phylum Tenericutes* Protective factors: e.g., *Phylum Actinobacteria*	Mendelian randomization study	(52)
Sun *et al*, 2024	TC (n=1,525), HCs (n=259,583)	Risk factors: e.g., *Family Christensenellaceae*, *family Victivallaceae*, *genus Methanobrevibacter*, *genus Ruminococcus2*, *genus Subdoligranulum and Phylum Verrucomicrobia* Protective factors: e.g., *Betaproteobacteria*, *family XI*, *genus Sutterella* Reverse analysis: e.g., *Genus Ruminococcus2* ↓	Mendelian randomization study	(53)
Hou *et al*, 2023	TC (n=6,699), HCs (n=1,620,354)	Risk factors: e.g., *Ruminococcaceae UCG004 genus*, *Olsenella genus*, *Streptococcaceae family*, *ketogluconate metabolism*, *pentose phosphate pathway and L-arginine degradation II in AST pathway*	Mendelian randomization study	(54)
Zhu *et al*, 2023	TC (n=6,699), HCs (n=1,613,655)	Risk factors: e.g., *Butyrivibrio*, *Fusicatenibacter*, *Oscillospira*,	Mendelian randomization study	(55)

Table I. Continued.

First author, year	Patients (n)	Microbiota main findings	Methodology	(Refs.)
		Ruminococcus2, *and Terrisporobacter* Protective factors: e.g., *Olsenella and Ruminococcaceae UCG004* *Reverse analysis:* e.g., *Bacillales* ↑ *Holdemanella* ↓		
Zhou *et al*, 2024	TC (n=989), HCs (n=217,803)	Risk factors: e.g., Phylum *Euryarchaeota*, *families Christensenellaceae*, *Victivallaceae*, *genera Methanobrevibacter*, *Ruminococcus2*, *Subdoligranulum* Protective factors: e.g., *Betaproteobacteria*, *family XI*, *genera Anaerofilum*, *Odoribacter*, *Sutterella*, *alongside order Burkholderiales* Reverse analysis: e.g., *Defluviitaleaceae*, *genus Ruminococcus gauvreauii group*, *genus Coprobacter*, *genus Defluviitaleaceae UCG011*, *genus family XIII UCG001 and genus Prevotella9* ↓	Mendelian randomization study	(56)
Hu *et al*, 2024	TC (n=649), HCs (n=431)	Risk factors: e.g., *Class Mollicutes*, *Phylum Tenericutes*, *genus Eggerthella*, *and Order Rhodospirillales* Protective factors: e.g., *Genus Eubacteriumfissicatena group*, *genus Lachnospiraceae UCG008*, *genus Christensenellaceae R-7 group and genus Escherichia Shigella*	Mendelian randomization study	(57)

TC, thyroid cancer; HCs, healthy controls; PTC, papillary thyroid cancer; FTC, follicular thyroid carcinoma; F/B, Firmicutes to Bacteroidetes ratio; FT3, free triiodothyronine; rRNA, ribosomal RNA; TSH, thyroid-stimulating hormone; ↑, increase; ↓, decrease; +, enrichment.

The production of short-chain fatty acids (SCFAs) (34) by certain gut bacteria may also compromise intestinal barrier function, resulting in increased permeability and immune dysfunction. In patients with papillary thyroid carcinoma (PTC), disruptions in tryptophan metabolism were shown to lead to reduced levels of aryl hydrocarbon receptor agonists, which adversely affect intestinal defenses (66). A higher abundance of *Lachnospiraceae* may also disturb the balance of regulatory T cells (Treg) and helper T Treg/Th17 (Th17) cells, which facilitates immune escape TC (67,68). Furthermore, diets rich in protein and plant-based foods cause a reduction in the levels of anti-inflammatory SCFAs generated from *Prevotellaceae* and *Ruminococcaceae*, thereby potentially accelerating TC development. Specific bacteria, such as *Bacteroidetes* and *Ruminococcus*, have also been shown to be crucial in maintaining intestinal homeostasis and regulating disease progression (9,69). Furthermore, patients with TC often exhibit elevated levels of TSH and free triiodothyronine (FT3), which are associated with changes in gut microbiomes.

3. Intestinal bacteria serve important roles in TC through metabolism

Thyroid-associated micronutrients and GM. The adult body stores 15-20 mg iodine in the thyroid gland, absorbed through the sodium/iodine symporter (NIS) present in the stomach,

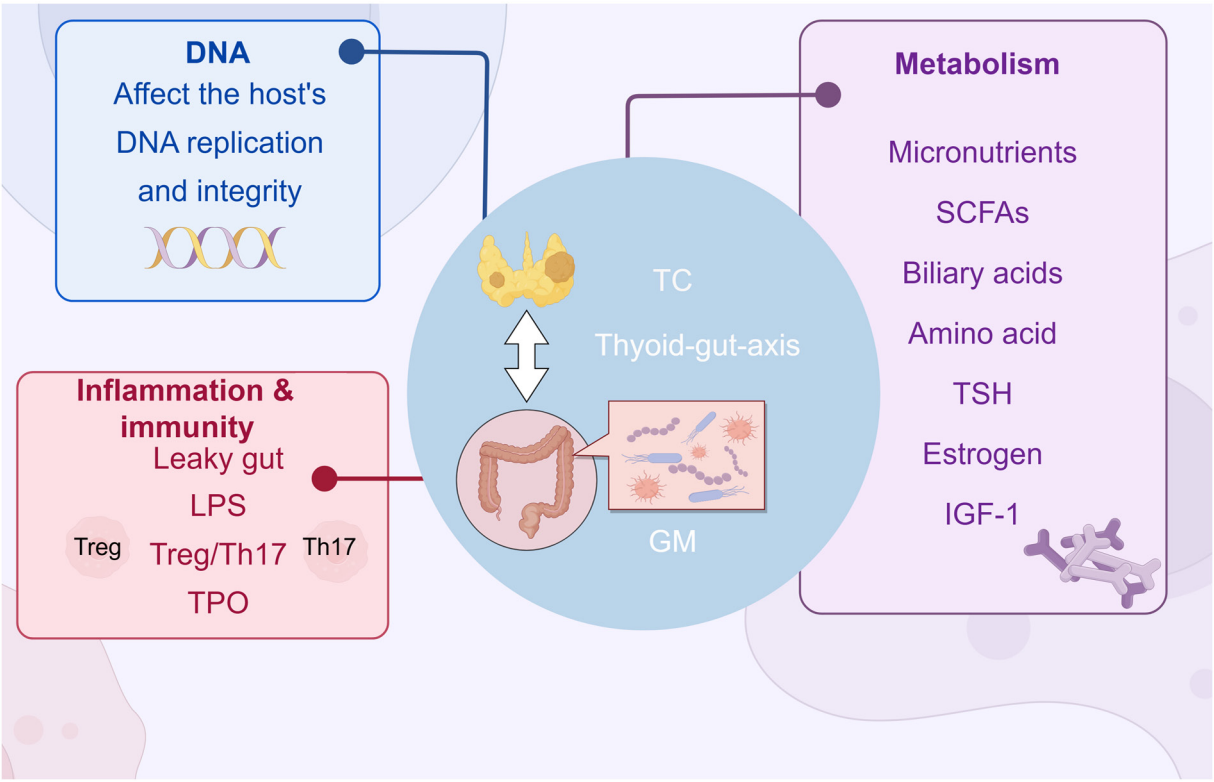

Figure 1. Interaction between GM and TC. The figure was generated using FigDraw. GM, gut microbiota; IGF-1, insulin-like growth factor-1; LPS, lipopolysaccharides; SCFAs, short-chain fatty acids; TC, thyroid cancer; TPO, thyroid peroxidase; Treg, regulatory T cells; Th17, helper T cell 17; TSH, thyroid-stimulating hormone.

duodenum and jejunum. Both the thyroid gland and extra-glandular tissues express NIS, with iodine also being absorbed via the cystic fibrosis and salt multivitamin transporters (70-72). Previous studies have identified that individuals with inflammatory bowel disease may have lower levels of *Firmicutes* and *Bacteroidetes*, leading to iodine malabsorption and decreased rates of thyroid hormone synthesis, suggesting a potential association between iodine absorption and GM (73,74). Furthermore, thyroid hormones influence the motility of the small intestine, which, in turn, affects the composition of the intestinal flora. Therefore, it may be proposed that changes in GM due to the prevailing thyroid conditions may affect iodine uptake, the synthesis of thyroid hormones and RAI treatment efficacy, and these aspects warrant further research.

A previous study by Lamberti *et al* (75) highlighted the significance of selenium bioavailability in relation to *Lactobacillus*. In addition, Zhang *et al* (48) identified both a depletion in the level of *Lactobacillus* and a reduction in selenium bioavailability in patients with TC. Selenium in the thyroid is crucial both for the proper function of deiodinase and for thyroid hormone metabolism, also presenting a risk factor for TC (76). Selenoproteins also provide antioxidant protection for thyroid cells, showing that a reduction in *Lactobacillus* levels may contribute to TC progression via lowering selenium levels and promoting oxidative damage to thyroid cells through increased rates of TSH secretion. Iron is also crucial for thyroid function due to the important roles it has in the proper functioning of the enzyme thyroid peroxidase (TPO) and in hormone storage. GM also compete with their host for iron absorption. An iron-poor diet hinders bacterial growth, whereas a diet rich in iron reduces microbiota diversity (77). Finally, zinc supplements have been demonstrated to help beneficial bacteria to grow, and this growth correlates with *Lactobacillus* and *Bifidobacterium* in autoimmune thyroid diseases (77).

Value of GM in the metabolism of SCFAs, amino acids, lactose and other compounds. SCFAs, such as butyric, acetic and propionic acids, are essential compounds produced by GM, particularly *Flachnospiraceae* and *Butyricimonas*, which are potentially able to prevent cancer (78-80). A study by Wang *et al* (81) highlighted that *Lactobacillus* species produce pyruvate through glycolysis, thereby promoting butyrate production, which serves to support normal cell growth and inhibit tumor cell proliferation. A different study (82) demonstrated how butyrate leads to a decrease in the expression level of c-Myc and the resultant inhibition of microRNA (miR)-92a transcription, thereby promoting apoptosis in colon cancer cells. Furthermore, SCFAs fulfill a crucial role in reducing chronic vascular inflammation by regulating the levels of inflammatory cytokines, such as interleukin (IL)-6 and IL-8, and modulating endothelial activation (83). Butyrate was shown to strengthen intestinal immune barriers, thereby decreasing pro-inflammatory factors, and inhibiting inflammation-associated pathways (84). Furthermore, SCFAs, derived from the fermentation of dietary fibers, were shown to induce apoptosis of TC cells and to promote cell cycle arrest (G1 and G_2/M). They also inhibit histone deacetylases, increasing the expression of the p21, p27 and Bax genes, as well as that of Notch1 protein, while causing a decrease in the

expression of pro-survival genes, such as Bcl-2, Bcl-xL and cyclins A and B, and reducing the activities of cyclin-dependent kinase 1 and 2. Additionally, the NIS was found to be significantly upregulated, and the level of thyroglobulin mRNA was increased, thereby enhancing iodine uptake (85-90). However, previous studies (44,48) have also demonstrated a decrease in the numbers of SCFA-producing bacteria in patients with TC, potentially increasing the TC cancer risk due to lower butyrate levels. This reduction in the numbers of SCFA-producing bacteria may affect *Lactobacillus* species, thereby compromising butyrate production and leading to the dysregulation of thyroid malignancies and inflammatory responses. Therefore, modulating the levels of SCFAs may be a means of improving tumor cell sensitivity to RAI by increasing the expression of NIS, thereby providing valuable insights into future therapeutic strategies.

The GM are also able to influence the metabolism of amines and secondary bile acids. For instance, histamine, an amine metabolism byproduct, has been shown to stimulate tumor cell growth (44,91). In addition, cholesterol and 27-hydroxycholesterol have both been linked with increased aggressiveness in TC, with 27-hydroxycholesterol being associated with the Christensenellaceae R7 group, potentially promoting estrogen receptor-driven TC growth (50,92). Furthermore, a study by Wang (65) using the Kyoto Encyclopedia of Genes and Genomes database data revealed important roles for amino acid metabolites and specific bacteria in PTC development, particularly regarding tryptophan metabolism, as this affects intestinal permeability and immune responses. Disruptions in bacterial amino acid metabolism may therefore contribute to PTC by fostering inflammatory and immunosuppressive conditions.

Changes in intestinal flora are a potential factor in TC development. Changes in the numbers/levels of gut bacteria may activate galactose and ketone body metabolic pathways, which result in the fueling of TC progression (93,94). Feng *et al* (44) found a notable decrease in the number of *Megamonas* bacteria, accompanied by elevated flavonoid levels in patients with TC; therefore, these flavonoids were negatively correlated with the abundance of *Megamonas*. Flavonoids affect the TPO enzyme, disrupting thyroid hormone synthesis either by altering the structure of TPO or by competitively inhibiting its activity (95). This disruption may lead to reduced hormone production and increased serum TSH levels, which are recognized as a risk factor for TC development (69,96). Taken together, these findings emphasize the interplay between gut flora and TC progression, highlighting the necessity of exploring further the association between GM metabolism and thyroid tumorigenesis.

Impact of intestinal flora and thyroid-related hormones on TC

TSH. Previous studies (76,96) have highlighted a troubling link between elevated levels of TSH and increases in the risk and progression of thyroid malignancies, even in cases where the TSH levels fell within the normal range, or where those affected were young men. Elevated TSH and FT3 levels are potential risk factors for PTC (69). Furthermore, a study by Zhang *et al* (48) suggested a potential connection between intestinal dysbiosis and TC, with certain bacterial species such as *Porphyromonas* and *Streptococcus* being associated with higher TSH and FT3 levels. Patients with TC typically exhibit increased TSH and FT3 levels, with FT3 being inversely correlated with beneficial bacteria such as *Lactobacillus*, which produce SCFAs and exert anti-inflammatory effects. Collectively, these findings emphasize the complex associations among thyroid hormones, GM and the risk of TC (69-71).

Estrogen. Having a history of breast cancer significantly increases the likelihood of developing TC, particularly when there is a positive family history (97). The level of estrogen, a known risk factor for breast cancer, may be increased due to its conversion from bound to free estrogen in the gut (98,99). This rise in circulating estrogen has been connected to TC development, particularly through estrogen receptor (ER) activation, including activation of the ER subtype ERα, which is highly expressed in PTC tissues (100-102). ERα activation may impede the tumor-suppressive effects of miR-299-5p, thereby promoting TC progression (103). Furthermore, estrogen has been shown to induce proangiogenic changes in endothelial cells, fostering tumor growth and metastasis. Intestinal dysbiosis, coupled with elevated estrogen levels, may significantly contribute to the development of TC in women. This underscores the need to improve the understanding of the association between hormones, gut health and cancer in order to develop potential targeted prevention and treatment strategies for TC.

Obesity and insulin resistance. Obesity and insulin resistance exert a crucial impact on TC development. A previous study by He *et al* (104) demonstrated a close correlation between body mass index (BMI) and the incidence of TC, where higher BMI values were associated with an increased risk of TC. Previous studies (44,105) have also indicated that changes in gut bacteria composition, specifically decreased numbers of *Bacteroidetes* and increased numbers of *Firmicutes* bacteria, are associated with TC in obese individuals. Individuals with obesity consuming high-fat diets often have increased Gram-negative bacteria levels, leading to the production of lipopolysaccharides that trigger chronic intestinal inflammation (106). This increase in inflammation may disrupt the integrity of the intestinal barrier, allowing bacteria to enter into the bloodstream, resulting in chronic inflammation in adipose tissue. Chronic inflammation often leads to insulin resistance (107), which is associated with an increased risk of various malignancies, including TC. Insulin resistance, in turn, elicits increases in the level of insulin-like growth factor-1 (IGF-1), which is overexpressed in TC. High levels of IGF-1 can fuel cancer growth by promoting cell malignancy and inhibiting apoptosis. Insulin, acting as a growth factor, activates pathways that further enhance the risk of developing TC (108,109). Additionally, the disruption of the IGF axis by high insulin levels may contribute to the progression of TC (110). Previous studies (111,112) identified high expression levels of IGF-1 and IGF-1 receptor in patients with TC, suggesting that IGF-1 enhances tumor growth through TSH stimulation, thereby activating the AKT and Raf-1/MEK/ERK signaling pathways and promoting tumor proliferation. Considered altogether, the future treatment of TC should focus on weight control as an important factor acting against this malignancy, where obesity and insulin resistance need to be strategically avoided or overcome.

4. The role of GM in the treatment of TC

Surgery, probiotics and fecal microbiota transplantation. Studies have revealed the changes that occur in the GM of patients with TC when compared with healthy individuals (44,48,49). Despite the small sample sizes used in sequencing studies, these findings have raised important questions regarding post-operative alterations in the GM of patients with TC. One study (113), which utilized 16S RNA sequencing, demonstrated that patients with TC had a lower fecal microbial community richness compared with healthy individuals, with six bacterial species, including *Bacteroidetes*, *Blautia*, *Eubacterium rectum*, *Bifidobacterium*, *Eubacterium hallii* and *Fusobacterium*, exhibiting notable differences. Interestingly, no significant disparities were observed between the thyroid peroxidase antibody positive and thyroid peroxidase antibody negative groups. The impact of GM on the prognosis and complications of patients with TC following thyroidectomy cannot be overstated. For instance, one study noted a negative correlation between the abundance of Bifidobacteriales and the occurrence and severity of post-operative nausea and vomiting in female patients, thereby suggesting that regulating GM may alleviate these symptoms (114). In addition, patients with PTC often need to have the dosage level of levothyroxine hormone adjusted post-surgery. Probiotics have also been shown to affect the absorption of levothyroxine, necessitating lower dosage adjustments (115). A randomized controlled trial involving thyroid hormone withdrawal (THW) combined with probiotics demonstrated that patients who received probiotics experienced improvements in microbial dysbiosis and reduced withdrawal side effects compared with those who received a placebo. These findings emphasized the importance of GM management in post-operative care (43,116).

A growing number of studies have supported the potential of fecal microbiota transplantation (FMT) as a promising treatment for different types of TC and associated complications (117). A previous study by Routy *et al* (118) showed that modulating the microbiome via the application of FMT may lead to enhancements in the effectiveness of cancer immunotherapy, particularly when combined with immune checkpoint inhibitors (ICIs) that target the cytotoxic T-lymphocyte associated protein 4 and programmed cell death protein 1 (PD-1) pathways. Personalized GM modulation, including FMT during PTC treatment, may also promote positive responses to ^{131}I therapy (119). FMT is also being studied for its applicability in various other thyroid-associated conditions, including primary hypothyroidism (120-122). Probiotics have also demonstrated promising results. A previous study revealed that administering one specific probiotic led to notable decreases in the levels of *Firmicutes* and circulating autoantibodies in patients with Graves' disease, leading to lower recurrence rates 6 months after antithyroid treatment (123). Probiotics such as *Bacillus subtilis*, *Bifidobacterium* and *Lactobacillus*, derived from *Firmicutes* and *Actinobacteria*, positively impact gut flora composition and metabolic pathways in patients with PTC. Furthermore, this study revealed reduced levels of specific amino acids that are closely associated with gut flora and metabolic processes. Therefore, patients with PTC may benefit from amino acid supplementation to restore microbial balance and metabolic functions. However, further studies are required to fully understand the association between changes in GM and prognosis, in order to address current gaps in knowledge within this field.

RAI therapy. The microbiota is able to significantly influence the effectiveness and toxicity of various anticancer therapies, including chemotherapy and immunotherapy (85). RAI therapy, a key adjuvant treatment for TC, is often used following thyroidectomy (124). ^{131}I treatment, particularly multiple high doses of RAI therapy, in patients with TC may disrupt the balance of GM and the radiation-sensitive pathways of linoleic acid, arachidonic acid and tryptophan metabolites (125). However, RAI may cause complications such as salivary gland inflammation, leading to xerostomia (also known as dry mouth), with dysfunction rates reported as high as 72.73% (126). Dry mouth negatively diminishes patients' long-term quality of life through disrupting normal salivary secretion. Furthermore, THW following RAI treatment may cause fatigue, constipation, weight gain, edema and hypercholesterolemia, thereby reducing the patients' quality of life (38-42). Probiotics have emerged as a strategy to manipulate the microbiota in order to improve outcomes during anticancer treatment. Several randomized clinical trials have demonstrated that probiotics may reduce the incidence of complications in patients with THW postoperatively by restoring microbiota diversity (43,127,128). One study found that patients with dry mouth had a higher *Firmicutes*-to-*Bacteroidetes* ratio, and an increased abundance of *Streptococcus* (128). In addition, the abundance of inflammation-associated bacteria, such as *Neisseria*, *Veillonella*, *Porphyromonas*, *Corynebacterium* and *Capnocytophaga*, was found to be higher in patients with dry mouth (129,130). For instance, *Prevotella* may promote inflammation via Toll-like receptor 2 activation and Th17 cell-mediated immune responses (131); however, probiotics were able to decrease the abundance of bacteria associated with dry mouth, such as *Prevotella_9*, *Haemophilus*, *Fusobacterium* and *Lautropia*, and their use is anticipated to lead to improvements regarding a series of side effects caused by RAI treatment and THW.

GM may also serve as a predictor of the responses of patients with PTC to RAI therapy or ^{131}I treatment. Researchers have found that butyric acid-producing *Dorea* serve as an independent predictor of the response to ^{131}I treatment, suggesting that increasing the abundance of *Dorea* and *Bifidobacterium* in the GM may lead to improvements in the response rates of postoperative patients with PTC (119). In addition, macrogenomic sequencing revealed markedly lower *Faecalibacterium prausnitzii* levels in patients post-RAI treatment compared with healthy controls (132). This species produces anti-inflammatory butyrate, potentially mitigating radiation-induced damage (132). Another study (133) also reported that the gut microecology was disrupted by post-high-dose ^{131}I therapy, with arachidonic acid acting as a key metabolite in radioprotection. In addition, GM and RAI-refractory papillary TC may be associated via different mechanisms that are connected with NIS regulation, although the exact role of GM in this context has yet to be fully elucidated (134). Additional studies in this regard may have important clinical implications and lead to the discovery of probiotics that facilitate the treatment of RAI-refractory TC.

In 2005, the European Medicines Agency approved the use of recombinant human TSH (rhTSH) for TSH stimulation prior to RAI in patients with TC subjected to thyroidectomy. This involves two intramuscular injections of 0.9 mg rhTSH, followed by RAI administration on the third day, allowing patients to continue thyroid hormone supplementation and avoid profound hypothyroidism. Although treatment with rhTSH may cause side effects such as nausea and fatigue, it has been shown to reduce the long-term salivary gland dysfunction that is associated with RAI (135). Another study, by Horvath *et al* (136), revealed that administering lower RAI doses in low-to-intermediate-risk patients resulted in comparable 5-year survival rates, yet with fewer adverse effects, when rhTSH was included as a part of the regimen compared with THW. However, further research is needed to confirm these findings, and to investigate the potential of probiotics or fecal microbiota transplantation to alleviate rhTSH side effects and to reduce salivary gland dysfunction following RAI (137). In conclusion, numerous additional studies are required to properly investigate the best use of RAI therapy (whether using THW or rTSH) combined with intestinal flora stabilization therapy.

Immunotherapy. The intestinal flora exerts a critical role in modulating the PD-1/programmed death ligand 1 (PD-L1) pathway and regulating the efficacy of ICIs. Given that >70% of immune cells reside in the intestine, the GM enhances the host's mucosal immune response, thereby strengthening epithelial tight junctions and mitigating pathogen invasion. A study by Sivan *et al* (138) reported that bifidobacteria enhance anti-tumor activity when combined with ICIs, thereby preventing tumor progression and significantly boosting the efficacy of ICIs by activating dendritic cells and enhancing $CD8^+$ T-cell activation through resistance to the negative regulation mediated by PD-1/PD-L1. PD-L1 expression is significantly higher in thyroid tumors, with positive rates ranging from 6.1-82.5% in patients with PTC, and from 22.2-81.2% in patients with anaplastic TC. In spite of the fact that ICIs show promise in terms of treating invasive and iodine-refractory TC (139), the 2020 ASCO Phase II trial of spartalizumab (PDR001) revealed a 35% response rate, although some of the patients exhibited drug resistance (140). Controlling the gut flora may mitigate primary resistance, with *E. muciniphila* having been shown to be associated with improved ICI responses via IL-12 (118). The intestinal flora has also been shown to enhance the responses of patients with melanoma to ICIs, particularly through *Faecalibacterium*, which boosts effector T-cell functions (141). Additionally, the intestinal flora impacts Th17 and Treg cell differentiation, with *Firmicutes* and *Lachnospiraceae* being found to be enriched in patients with TC, further implicating the GM in regulating immune functions and tumor immunotherapy outcomes via mechanisms such as SCFA-mediated production (141). Taken together, these findings have demonstrated that controlling the intestinal flora may represent a significant breakthrough in improving tumor immunotherapy.

5. Conclusion

The GM has been shown to perform a range of crucial roles in immune regulation, hormone control, metabolic equilibrium and nutritional absorption (2,3). As a result, the microbiota has been associated with the proliferation of cancer cells (4,5), which may be useful in the diagnosis and prognosis of cancer. In particular, the GM has been shown to influence TC proliferation directly and indirectly via various mechanisms, including chronic inflammation, regulation of trace elements, metabolism of a range of compounds (e.g., SCFAs and amino acids), hormones (e.g., TSH, FT3 and estrogen) and insulin resistance. However, the precise details of these mechanisms remain unclear and further studies are required. TC causes GM dysbiosis and changes in the gut microbiome may correlate with the prognosis of patients with TC. For the majority of patients with TC, the cancer typically grows slowly and these patients have a better prognosis. However, ~1% of TC cases are anaplastic TC, which has a poor prognosis and is associated with rapid progression and high mortality rates, with a one-year survival rate of only 20%. Although checkpoint immunotherapy is commonly used for anaplastic TC, few patients survive beyond 2 years following diagnosis (142). Currently, surgical removal and adjuvant therapies are effective for TC, although patients must be treated with dosages of levothyroxine (via THW or rTSH) post-surgery, and this is associated with a number of complications that lower patients' quality of life (38-42,124-126). Changes in GM have been associated with thyroid surgery, RAI and checkpoint inhibitors, suggesting that GM may serve as biomarkers for TC diagnosis and prognosis. In addition, the combined use of probiotics and FMT may enhance the quality of life for patients with TC, and improve the prognosis for patients with anaplastic TC. However, further studies, particularly randomized controlled trials and high-quality observational studies, are required to confirm these hypotheses. Ultimately, exploring the specific mechanisms that link GM with TC may provide novel insights into new therapies for TC.

Acknowledgements

Not applicable.

Funding

This study was funded by the Kunshan First People's Hospital Innovation Team Development Program (grant no. Y24-071-101366), a horizontal project supported by Shanghai United Imaging Healthcare Co., Ltd. and Kunshan First People's Hospital (grant no. H23-126-101180), and the 2022 National Key Laboratory of Radiation Medicine and Radiation Protection Open Topics (grant no. GZK1202219).

Availability of data and materials

Not applicable

Authors' contributions

MW designed the study, wrote the manuscript and performed a literature search. YZ critically reviewed, edited and approved the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Virili C, Fallahi P, Antonelli A, Benvenga S and Centanni M: Gut microbiota and Hashimoto's thyroiditis. Rev Endocr Metab Disord 19: 293-300, 2018.
2. Shanahan F: The gut microbiota in 2011: Translating the microbiota to medicine. Nat Rev Gastroenterol Hepatol 9: 72-74, 2011.
3. Walsh CJ, Guinane CM, OToole PW and Cotter PD: Beneficial modulation of the gut microbiota. FEBS Letters 588: 4120-4130, 2014.
4. Power SE, OToole PW, Stanton C, Ross RP and Fitzgerald GF: Intestinal microbiota, diet and health. Br J Nutr 111: 387-402, 2014.
5. Gao L, Wang JY, Ma SF and Li SJ: Research progress on the relationship between intestinal flora and thyroid-related diseases. J Shanxi Med Univ 5: 707-710, 2023.
6. Kamada N, Chen GY, Inohara N and Núñez G: Control of pathogens and pathobionts by the gut microbiota. Nat Immunol 14: 685-690, 2013.
7. Sears CL and Garrett WS: Microbes, microbiota, and colon cancer. Cell Host Microbe 15: 317-328, 2014.
8. Schwabe RF and Jobin C. The microbiome and cancer. Nat Rev Cancer 13: 800-812, 2013.
9. Louis P, Hold GL and Flint HJ: The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol 12: 661-672, 2014.
10. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C and Flavell RA: Inflammation-induced cancer: Crosstalk between tumours, Immune cells and microorganisms. Nat Rev Cancer 13: 759-771, 2013.
11. Irrazábal T, Belcheva A, Girardin SE, Martin A and Philpott DJ: The multifaceted role of the intestinal microbiota in colon cancer. Mol Cell 54: 309-320, 2014.
12. De Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D and Plummer M: Global burden of cancers attributable to infections in 2008: A review and synthetic analysis. Lancet Oncol 13: 607-615, 2012.
13. Liu J, Luo M, Zhang Y, Cao G and Wang S: Association of high-risk human papillomavirus infection duration and cervical lesions with vaginal microbiota composition. Ann Transl Med 8: 1161, 2020.
14. Mitra A, MacIntyre DA, Ntritsos G, Smith A, Tsilidis KK, Marchesi JR, Bennett PR, Moscicki AB and Kyrgiou M: The vaginal microbiota associates with the regression of untreated cervical intraepithelial neoplasia 2 lesions. Nat Commun 11: 1999, 2020.
15. Tango CN, Seo SS, Kwon M, Lee DO, Chang HK and Kim MK: Taxonomic and functional differences in cervical microbiome associated with cervical cancer development. Sci Rep 10: 9720, 2020.
16. Wu S, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, Huso DL, Brancati FL, Wick E, McAllister F, *et al*: A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med 15: 1016-1022, 2009.
17. Housseau F and Sears CL: Enterotoxigenic Bacteroides fragilis (ETBF)-mediated colitis in Min (Apc+/-) mice: A human commensal-based murine model of colon carcinogenesis. Cell Cycle 9: 3-5, 2010.
18. Liu Q, Sun W and Zhang H: Interaction of gut microbiota with endocrine homeostasis and thyroid cancer. Cancers 14: 2656, 2022.
19. Li JZ, Ma DS and Ma ZJ: Research progress on the correlation between intestinal flora and thyroid cancer. Chin J General Surg 6: 482-484, 2021.
20. Xie Z, Zhou J, Zhang X and Li Z: Clinical potential of microbiota in thyroid cancer therapy. Biochimica Et Biochim Biophys Acta Mol Basis Dis 1870: 166971, 2024.
21. Cellini M, Santaguida MG, Virili C, Capriello S, Brusca N, Gargano L and Centanni M: Hashimotos thyroiditis and autoimmune gastritis. Front Endocrinol (Lausanne) 8: 92, 2017.
22. Virili C and Centanni M: 'With a little help from my friends'-The role of microbiota in thyroid hormone metabolism and enterohepatic recycling. Mol Cell Endocrinol 458: 39-43, 2017.
23. Jašarević E, Morrison KE and Bale TL: Sex differences in the gut microbiome-brain axis across the lifespan. Philos Trans R Soc Lond B Biol Sci 371: 20150122, 2016.
24. Covelli D and Ludgate M: The thyroid, the eyes and the gut: A possible connection. J Endocrinol Invest 40: 567-576, 2017.
25. Ishaq HM, Mohammad IS, Guo H, Shahzad M, Hou YJ, Ma C, Naseem Z, Wu X, Shi P and Xu J: Molecular estimation of alteration in intestinal microbial composition in Hashimotos thyroiditis patients. Biomed Pharmacother 95: 865-874, 2017.
26. Zhao F, Feng J, Li J, Zhao L, Liu Y, Chen H, Jin Y, Zhu B and Wei Y: Alterations of the gut microbiota in hashimotos thyroiditis patients. Thyroid 28: 175-186, 2018.
27. Du L, Li R, Ge M, Wang Y, Li H, Chen W and He J: Incidence and mortality of thyroid cancer in China, 2008-2012. Chin J Cancer Res 31: 144-151, 2019.
28. Cabanillas ME, McFadden DG and Durante C: Thyroid cancer. Lancet 388: 2783-2795, 2016.
29. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136: E359-E386, 2015.
30. Kitahara CM and Sosa JA: The changing incidence of thyroid cancer. Nat Rev Endocrinol 12: 646-653, 2016.
31. Lortet-Tieulent J, Franceschi S, Dal Maso L and Vaccarella S: Thyroid cancer 'epidemic' also occurs in low- and middle-income countries. Int J Cancer 144: 2082-2087, 2019.
32. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
33. Kim J, Gosnell JE and Roman SA: Geographic influences in the global rise of thyroid cancer. Nat Rev Endocrinol 16: 17-29, 2020.
34. Maruvada P, Leone V, Kaplan LM and Chang EB: The human microbiome and obesity: Moving beyond associations. Cell Host Microbe 22: 589-599, 2017.
35. Stefura T, Zapała B, Gosiewski T, Skomarovska O, Dudek A, Pędziwiatr M and Major P: Differences in compositions of oral and fecal microbiota between patients with obesity and controls. Medicina (Kaunas) 57: 678, 2021.
36. Dong T, Zhao F, Yuan K, Zhu X, Wang N, Xia F, Lu Y and Huang Z: Association between serum Thyroid-stimulating hormone levels and salivary microbiome shifts. Front Cell Infect Microbiol 11: 603291, 2021.
37. Nabhan F, Dedhia PH and Ringel MD: Thyroid cancer, recent advances in diagnosis and therapy. Int J Cancer 149: 984-992, 2021.
38. Lee J, Yun MJ, Nam KH, Chung WY, Soh EY and Park CS: Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. Thyroid 20: 173-179, 2010.
39. Schroeder PR, Haugen BR, Pacini F, Reiners C, Schlumberger M, Sherman SI, Cooper DS, Schuff, KG, Braverman LE, Skarulis MC, *et al*: A comparison of short-term changes in health-related quality of life in thyroid carcinoma patients undergoing diagnostic evaluation with recombinant human thyrotropin compared with thyroid hormone withdrawal. J Clin Endocrinol Metab 91: 878-884, 2006.
40. Rubic M, Kuna SK, Tesic V, Samardzic T, Despot M and Huic D: The most common factors influencing on quality of life of thyroid cancer patients after thyroid hormone withdrawal. Psychiatr Danub 26: 520-527, 2014.
41. Sigal GA, Tavoni TM, Silva BMO, Kalil Filho R, Brandão LG and Maranhão RC: Effects of Short-term hypothyroidism on the lipid transfer to High-density lipoprotein and other parameters related to lipoprotein metabolism in patients submitted to thyroidectomy for thyroid cancer. Thyroid 29: 53-58, 2019.
42. Singh R, Tandon A, Gupta SK and Saroja K: Optimal levothyroxine replacement adequately improves symptoms of hypothyroidism; residual symptoms need further evaluation for other than hypothyroidism causation. Indian J Endocrinol Metab 21: 830-835, 2017.

43. Lin B, Zhao F, Liu Y, Wu X, Feng J, Jin X, Yan W, Guo X, Shi S, Li Z, *et al*: Randomized clinical trial: Probiotics alleviated Oral-Gut microbiota dysbiosis and thyroid hormone Withdrawal-related complications in thyroid cancer patients before radioiodine therapy following thyroidectomy. Front Endocrinol (Lausanne) 13: 834674, 2022.
44. Feng J, Zhao F, Sun J, Lin B, Zhao L, Liu Y, Jin Y, Li S, Li A and Wei Y: Alterations in the gut microbiota and metabolite profiles of thyroid carcinoma patients. Int J Cancer 144: 2728-2745, 2019.
45. Feng Q, Liang S, Jia H, Stadlmayr A, Tang L, Lan Z, Zhang D, Xia H, Xu X, Jie Z, *et al*: Gut microbiome development along the colorectal adenoma-carcinoma sequence. Nat Commun 6: 6528, 2015.
46. Fuhrman BJ, Feigelson HS, Flores R, Gail MH, Xu X, Ravel J and Goedert JJ: Associations of the fecal microbiome with urinary estrogens and estrogen metabolites in postmenopausal women. J Clin Endocrinol Metab 99: 4632-4640, 2014.
47. Jeffery IB, OToole PW, Öhman L, Claesson MJ, Deane J, Quigley EM and Simrén M: An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. Gut 61: 997-1006, 2012.
48. Zhang J, Zhang F, Zhao C, Xu Q, Liang C, Yang Y, Wang H, Shang Y, Wang Y, Mu X, *et al*: Dysbiosis of the gut microbiome is associated with thyroid cancer and thyroid nodules and correlated with clinical index of thyroid function. Endocrine 64: 564-574, 2019.
49. Yu X, Jiang W, Kosik RO, Song Y, Luo Q, Qiao T, Tong J, Liu S, Deng C, Qin S, *et al*: Gut microbiota changes and its potential relations with thyroid carcinoma. J Adv Res 35: 61-70, 2022.
50. Lu G, Yu X, Jiang W, Luo Q, Tong J, Fan S, Chai L, Gao D, Qiao T, Wang R, *et al*: Alterations of gut microbiome and metabolite profiles associated with anabatic lipid dysmetabolism in thyroid cancer. Front Endocrinol (Lausanne) 13: 893164, 2022.
51. Ishaq HM, Mohammad IS, Hussain R, Parveen R, Shirazi JH, Fan Y, Shahzad M, Hayat K, Li H, Ihsan A, *et al*: Gut-Thyroid axis: How gut microbial dysbiosis associated with euthyroid thyroid cancer. J Cancer 13: 2014-2028, 2022.
52. Quan Z, Zhang X, Wang S and Meng Y: Causal analysis of the gut microbiota in differentiated thyroid carcinoma: A two-sample Mendelian randomization study. Front Genetics 14: 1299930, 2023.
53. Sun X, Chen S, Zhao S, Wang J and Cheng H: Causal relationship of genetically predicted gut microbiota with thyroid cancer: A bidirectional two-sample mendelian randomization study. Front Endocrinol (Lausanne) 15: 1284472, 2024.
54. Hou T, Wang Q, Dai H, Hou Y, Zheng J, Wang T, Lin H, Wang S, Li M, Zhao Z, *et al*: Interactive association between gut microbiota and thyroid cancer. Endocrinology 165: bqad184, 2023.
55. Zhu F, Zhang P, Liu Y, Bao C, Qian D, Ma C, Li H and Yu T: Mendelian randomization suggests a causal relationship between gut dysbiosis and thyroid cancer. Front Cell Infect Microbiol 13: 1298443, 2023.
56. Zhou J, Zhang X, Xie Z and Li Z: Exploring reciprocal causation: Bidirectional mendelian randomization study of gut microbiota composition and thyroid cancer. J Cancer Res Clin Oncol 150: 75, 2024.
57. Hu S, Tang C, Wang L, Feng F, Li X, Sun M and Yao L: Causal relationship between gut microbiota and differentiated thyroid cancer: A two-sample Mendelian randomization study. Front Oncol 14: 1375525, 2024.
58. Yan S, He J, Yu X, Shang J, Zhang Y, Bai H, Zhu X, Xie X and Lee L: Causal relationship between gut microbiota and thyroid nodules: A bidirectional two-sample Mendelian randomization study. Front Endocrinol (Lausanne) 15: 1417009, 2024.
59. Knezevic J, Starchl C, Tmava Berisha A and Amrein K: Thyroid-gut-axis: How does the microbiota influence thyroid function? Nutrients 12: 1769, 2020.
60. Cao Y, Oh J, Xue M, Huh WJ, Wang J, Gonzalez-Hernandez JA, Rice TA, Martin AL, Song D, Crawford JM, *et al*: Commensal microbiota from patients with inflammatory bowel disease produce genotoxic metabolites. Science 378: eabm3233, 2022.
61. Trapani KM, Boghossian LJ and Caskey E: Clostridium subterminale septicemia in a patient with metastatic gastrointestinal adenocarcinoma. Case Rep Infect Dis 2018: 6031510, 2018.
62. Dahmus JD, Kotler DL, Kastenberg DM and Kistler CA: The gut microbiome and colorectal cancer: A review of bacterial pathogenesis. J Gastrointest Oncol 9: 769-777, 2018.
63. Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, Clancy TE, Chung DC, Lochhead P, Hold GL, *et al*: Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe 14: 207-215, 2013.
64. Fan Y, Mao R and Yang J: NF-κB and STAT3 signaling pathways collaboratively link inflammation to cancer. Protein Cell 4: 176-185, 2013.
65. Wang HP: Multiomics study on screening biomarkers for papillary thyroid cancer (Doctors thesis). China Medical University, Liaoning, 2024.
66. Zhang L, Chen J, Xu C, Qi L and Ren Y: Effects of iodine-131 radiotherapy on Th17/Tc17 and Treg/Th17 cells of patients with differentiated thyroid carcinoma. Exp Ther Med 15: 2661-2666, 2018.
67. Wang AY, Li CY, Xue G and Wang JF: The relationship between intestinal flora and thyroid disease. J Otorhinolaryngol Ophthalmol Shandong Univ 1: 132-139, 2023.
68. McBrearty N, Arzumanyan A, Bichenkov E, Merali S, Merali C and Feitelson M: Short chain fatty acids delay the development of hepatocellular carcinoma in HBx transgenic mice. Neoplasia 23: 529-538, 2021.
69. Zhao H, Li H and Huang T: High urinary iodine, thyroid autoantibodies, and Thyroid-stimulating hormone for papillary thyroid cancer risk. Biol Trace Elem Res 184: 317-324, 2018.
70. Guerrero-Preston R, Godoy-Vitorino F, Jedlicka A, Rodríguez-Hilario A, González H, Bondy J, Lawson F, Folawiyo O, Michailidi C, Dziedzic A, *et al*: 16S rRNA amplicon sequencing identifies microbiota associated with oral cancer, human papilloma virus infection and surgical treatment. Oncotarget 7: 51320-51334, 2016.
71. Zhao J, Nian L, Kwok LY, Sun T and Zhao J: Reduction in fecal microbiota diversity and short-chain fatty acid producers in Methicillin-resistant Staphylococcus aureus infected individuals as revealed by PacBio single molecule, real-time sequencing technology. Eur J Clin Microbiol Infect Dis 36: 1463-1472, 2017.
72. Wang YY, Zhang JY, Jin XR and Wang NP: Research progress on the relationship between intestinal flora and thyroid diseases. Prog Modern Gen Surg China 26: 793-796, 2023.
73. Fröhlich E and Wahl R: Microbiota and thyroid interaction in health and disease. Trends Endocrinol Metab 30: 479-490, 2019.
74. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N and Pace NR: Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci USA 104: 13780-13785, 2007.
75. Lamberti C, Mangiapane E, Pessione A, Mazzoli R, Giunta C and Pessione E: Proteomic characterization of a selenium-metabolizing probiotic Lactobacillus reuteri Lb26 BM for nutraceutical applications. Proteomics 11: 2212-2221, 2011.
76. Tam AA, Ozdemir D, Aydın C, Bestepe N, Ulusoy S, Sungu N, Ersoy R and Cakir B: Association between preoperative thyrotrophin and clinicopathological and aggressive features of papillary thyroid cancer. Endocrine 59: 565-572, 2018.
77. Pushalkar S, Hundeyin M, Daley D, Zambirinis CP, Kurz E, Mishra A, Mohan N, Aykut B, Usyk M, Torres LE, *et al*: The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. Cancer Discov 8: 403-416, 2018.
78. Virili C, Stramazzo I, Bagaglini MF, Carretti AL, Capriello S, Romanelli F, Trimboli P and Centanni M: The relationship between thyroid and human-associated microbiota: A systematic review of reviews. Rev Endocr Metab Disord 25: 215-237, 2024.
79. Kiss B, Mikó E, Sebő É, Toth J, Ujlaki G, Szabó J, Uray K, Bai P and Árkosy P: Oncobiosis and microbial metabolite signaling in pancreatic adenocarcinoma. Cancers (Basel) 12: 1068, 2020.
80. Pitt JM, Vétizou M, Gomperts Boneca I, Lepage P, Chamaillard M and Zitvogel L: Enhancing the clinical coverage and anticancer efficacy of immune checkpoint blockade through manipulation of the gut microbiota. Oncoimmunology 6: e1132137, 2017.
81. Wang SP, Rubio LA, Duncan SH, Donachie GE, Holtrop G, Lo G, Farquharson FM, Wagner J, Parkhill J, Louis P, *et al*: Pivotal roles for pH, Lactate, and Lactate-utilizing bacteria in the stability of a human colonic microbial ecosystem. mSystems 5: e00645-e00620, 2020.
82. Hu S, Liu L, Chang EB, Wang JY and Raufman JP: Butyrate inhibits pro-proliferative miR-92a by diminishing c-Myc-induced miR-17-92a cluster transcription in human colon cancer cells. Mol Cancer 14: 180, 2015.
83. Li M, van Esch BCAM, Henricks PAJ, Garssen J and Folkerts G: Time and concentration dependent effects of short chain fatty acids on lipopolysaccharide- or tumor necrosis factor α-Induced endothelial activation. Front Pharmacol 9: 233, 2018.

84. Zhang JT, Yi M, Li ZJ and Sun SX: Research progress on the mechanism of butyrate in inflammatory response. J Immunology 12: 1101-1104, 2015.
85. Zhou L, Zhang M, Wang Y, Dorfman RG, Liu H, Yu T, Chen X, Tang D, Xu L Yin Y, *et al*: Faecalibacterium prausnitzii produces butyrate to maintain Th17/Treg balance and to ameliorate colorectal colitis by inhibiting histone deacetylase 1. Inflamm Bowel Dis 24: 1926-1940. 2018.
86. Rathod M, Kelkar M, Valvi S, Salve G and De A: FOXA1 Regulation turns Benzamide HDACi treatment effect-specific in BC, Promoting NIS gene-mediated targeted radioiodine therapy. Mol Ther Oncolytics 19: 93-104, 2020.
87. Greenberg VL, Williams JM, Cogswell JP, Mendenhall M and Zimmer SG: Histone deacetylase inhibitors promote apoptosis and differential cell cycle arrest in anaplastic thyroid cancer cells. Thyroid 11: 315-325, 2001.
88. Xiao X, Ning L and Chen H: Notch1 mediates growth suppression of papillary and follicular thyroid cancer cells by histone deacetylase inhibitors. Mol Cancer Ther 8: 350-356, 2009.
89. Duan H, Wang L, Huangfu M and Li H: The impact of microbiota-derived short-chain fatty acids on macrophage activities in disease: Mechanisms and therapeutic potentials. Biomed Pharmacother 165: 115276, 2023.
90. Shen WT, Wong TS, Chung WY, Wong MG, Kebebew E, Duh QY and Clark OH: Valproic acid inhibits growth, induces apoptosis, and modulates apoptosis-regulatory and differentiation gene expression in human thyroid cancer cells. Surgery 138: 979-985, 2005.
91. Aponte-López A, Fuentes-Pananá EM, Cortes-Muñoz D and Muñoz-Cruz S: Mast cell, the neglected member of the tumor microenvironment: Role in breast cancer. J Immunol Res 2018: 2584243, 2018.
92. Revilla G, Pons MP, Baila-Rueda L, García-León A, Santos D, Cenarro A, Magalhaes M, Blanco RM, Moral A, Ignacio Pérez J, *et al*: Cholesterol and 27-hydroxycholesterol promote thyroid carcinoma aggressiveness. Sci Rep 9: 10260, 2019.
93. Shang X, Zhong X and Tian X: Metabolomics of papillary thyroid carcinoma tissues: Potential biomarkers for diagnosis and promising targets for therapy. Tumour Biol 37: 11163-11175, 2016.
94. Li JZ: Research on the correlation between papillary thyroid carcinoma and intestinal flora (Masters thesis). QingHai University, Xining, 2023.
95. Mahfoudi R, Djeridane A, Benarous K, Gaydou EM and Yousfi M: Structure-activity relationships and molecular docking of thirteen synthesized flavonoids as horseradish peroxidase inhibitors. Bioorg Chem 74: 201-211, 2017.
96. Danilovic DLS, Ferraz-de-Souza B, Fabri AW, Santana NO, Kulcsar MA, Cernea CR, Marui S and Hoff AO: 25-Hydroxyvitamin D and TSH as risk factors or prognostic markers in thyroid carcinoma. PLoS One 11: e0164550, 2016.
97. Huang NS, Chen XX, Wei WJ, Mo M, Chen JY, Ma B, Yang SW, Xu WB, Wu J, Ji QH, *et al*: Association between breast cancer and TC: A study based on 13 978 patients with breast cancer. Cancer Med 7: 6393-6400, 2018.
98. Ervin SM, Li H, Lim L, Roberts LR, Liang X, Mani S and Redinbo MR: Gut microbial β-glucuronidases reactivate estrogens as components of the estrobolome that reactivate estrogens. J Biol Chem 294: 18586-18599, 2019.
99. Pollet RM, DAgostino EH, Walton WG, Xu Y, Little MS, Biernat KA, Pellock SJ, Patterson LM, Creekmore BC, Isenberg HN, *et al*: An atlas of β-Glucuronidases in the human intestinal microbiome. Structure 25: 967-977.e5, 2017.
100. Rubio GA, Catanuto P, Glassberg MK, Lew JI and Elliot SJ: Estrogen receptor subtype expression and regulation is altered in papillary thyroid cancer after menopause. Surgery 163: 143-149, 2018.
101. Qiu YB, Liao LY, Jiang R, Xu M, Xu LW, Chen GG and Liu ZM: PES1 promotes the occurrence and development of papillary thyroid cancer by upregulating the ERα/ERβ protein ratio. Sci Rep 9: 1032, 2019.
102. Wang Z, He L, Sun W, Qin Y, Dong W, Zhang T, Zhang P and Zhang H: miRNA-299-5p regulates estrogen receptor alpha and inhibits migration and invasion of papillary thyroid cancer cell. Cancer Manag Res 10: 6181-6193, 2018.
103. Vannucchi G, De Leo S, Perrino M, Rossi S, Tosi D, Cirello V, Colombo C, Bulfamante G, Vicentini L and Fugazzola L: Impact of estrogen and progesterone receptor expression on the clinical and molecular features of papillary thyroid cancer. Eur J Endocrinol 173: 29-36, 2015.
104. He Q, Sun H, Li F and Liang N: Obesity and risk of differentiated thyroid cancer: A large-scale case-control study. Clin Endocrinol (Oxf) 91: 869-878, 2019.
105. Riva A, Borgo F, Lassandro C, Verduci E, Morace G, Borghi E and Berry D: Pediatric obesity is associated with an altered gut microbiota and discordant shifts in Firmicutes populations. Environ Microbiol 19: 95-105, 2017.
106. Watanabe H, Katsura T, Takahara M, Miyashita K, Katakami N, Matsuoka TA, Kawamori D and Shimomura I: Plasma lipopolysaccharide binding protein level statistically mediates between body mass index and chronic microinflammation in Japanese patients with type 1 diabetes. Diabetol Int 11: 293-297, 2020.
107. De Melo TG, Souza AL, Ficher E, Fernandes AM, Montali Da Assumpção LV, Monte Alegre S and Zantut-Wittmann DE: Reduced insulin sensitivity in differentiated thyroid cancer patients with suppressed TSH. Endo Res 43: 73-79, 2018.
108. Heidari Z, Abdani M and Mansournia MA: Insulin resistance associated with differentiated thyroid carcinoma: Penalized conditional logistic regression analysis of a matched case-control study data. Int J Endocrinol Metab 16: e14545, 2018.
109. Knuppel A, Fensom GK, Watts EL, Gunter MJ, Murphy N, Papier K, Perez-Cornago A, Schmidt JA, Smith Byrne K, Travis RC and Key TJ: Circulating Insulin-like Growth Factor-I concentrations and risk of 30 cancers: Prospective analyses in UK Biobank. Cancer Res 80: 4014-4021, 2020.
110. Vella V and Malaguarnera R: The emerging role of insulin receptor isoforms in TC: Clinical implications and new perspectives. Int J Mol Sci 19: 3814, 2018.
111. Manzella L, Massimino M, Stella S, Tirrò E, Pennisi MS, Martorana F, Motta G, Vitale SR, Puma A, Romano C, *et al*: Activation of the IGF axis in thyroid cancer: Implications for tumorigenesis and treatment. Int J Mol Sci 20: 3258, 2019.
112. Li YH, Gao XF, Guo TT, Zhang J, Zhang CZ and Li J: Research progress on the mechanism of obesity combined with thyroid cancer. Chin J Gen Surg 4: 311-315, 2023.
113. Song YC, Yu XQ and Li D: Structural changes of gut microbiota in papillary thyroid carcinoma patients with postoperative hypothyroidism. J Tongji Univ 2: 144-151, 2019.
114. Tang YJ: Relationships of Preoperative Gut Microbiota and Postoperative Nausea and Vomiting in Female Patients Undergoing Thyroid Cancer Surgery: A Prospective Observational Study (Masters thesis). Fujian Medicine University, Fuzhou, China, 2023.
115. Spaggiari G, Brigante G, De Vincentis S, Cattini U, Roli L, De Santis MC, Baraldi E, Tagliavini S, Varani M, Trenti T, *et al*: Probiotics ingestion does not directly affect thyroid hormonal parameters in hypothyroid patients on levothyroxine treatment. Front Endocrinol (Lausanne) 8: 316, 2017.
116. Ludgate ME, Masetti G and Soares P: The relationship between the gut microbiota and thyroid disorders. Nat Rev Endocrinol 20: 511-525, 2024.
117. Chen D, Wu J, Jin D, Wang B and Cao H: Fecal microbiota transplantation in cancer management: Current status and perspectives. Int J Cancer 145: 2021-2031, 2019.
118. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, *et al*: Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 359: 91-97, 2018.
119. Zheng L, Zhang L, Tang L, Huang D, Pan D, Guo W, He S, Huang Y, Chen Y, Xiao X, *et al*: Gut microbiota is associated with response to ^{131}I therapy in patients with papillary thyroid carcinoma. Eur J Nucl Med Mol Imaging 50: 1453-1465, 2023.
120. Moshkelgosha S, Verhasselt HL, Masetti G, Covelli D, Biscarini F, Horstmann M, Daser A, Westendorf AM, Jesenek C, Philipp S, *et al*: Modulating gut microbiota in a mouse model of Graves orbitopathy and its impact on induced disease. Microbiome 9: 45, 2021.
121. Su X, Yin X, Liu Y, Yan X, Zhang S, Wang X, Lin Z, Zhou X, Gao J, Wang Z and Zhang Q: Gut dysbiosis contributes to the imbalance of Treg and Th17 cells in graves disease patients by propionic acid. J Clin Endocrinol Metab 105: dgaa511, 2020.
122. Su X, Zhao Y, Li Y, Ma S and Wang Z: Gut dysbiosis is associated with primary hypothyroidism with interaction on gut-thyroid axis. Clin Sci (Lond) 134: 1521-1535, 2020.
123. Docimo G, Cangiano A, Romano RM, Pignatelli MF, Offi C, Paglionico VA, Galdiero M, Donnarumma G, Nigro V, Esposito D, *et al*. The Human Microbiota in endocrinology: Implications for pathophysiology, treatment, and prognosis in thyroid diseases. Front Endocrinol (Lausanne) 11: 586529, 2020.

124. Lin JD, Chao TC, Huang MJ, Weng HF and Tzen KY: Use of RAI for thyroid remnant ablation in well-differentiated thyroid carcinoma to replace thyroid reoperation. Am J Clin Oncol 21: 77-81, 1998.
125. Lu G, Gao D, Liu Y, Yu X, Jiang W and Lv Z: Early and long-term responses of intestinal microbiota and metabolites to 131I treatment in differentiated thyroid cancer patients. BMC Medicine 22: 300, 2024.
126. Luster M, Clarke SE, Dietlein M, Lassmann M, Lind P, Oyen WJG, Tennvall J and Bombardieri E; European Association of Nuclear Medicine (EANM): Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 35: 1941-1959, 2008.
127. Panebianco C, Andriulli A and Pazienza V: Pharmacomicrobiomics: Exploiting the drug-microbiota interactions in anticancer therapies. Microbiome 6: 92, 2018.
128. Lin B, Zhao F, Liu Y, Sun J, Feng J, Zhao L, Wang H, Chen H, Yan W, Guo X, *et al*: Alterations in oral microbiota of differentiated thyroid carcinoma patients with xerostomia after radioiodine therapy. Front Endocrinol (Lausanne) 13: 895970, 2022.
129. Feller L, Altini M and Lemmer J: Inflammation in the context of oral cancer. Oral Oncol 49: 887-892, 2013.
130. Atarashi K, Suda W, Luo C, Kawaguchi T, Motoo I, Narushima S, Kiguchi Y, Yasuma K, Watanabe E, Tanoue T, *et al*: Ectopic colonization of oral bacteria in the intestine drives TH1 cell induction and inflammation. Science 358: 359-365, 2017.
131. Larsen JM: The immune response to Prevotella bacteria in chronic inflammatory disease. Immunology 151: 363-374, 2017.
132. Mahowald MA, Rey FE, Seedorf H, Turnbaugh PJ, Fulton RS, Wollam A, Shah N, Wang C, Magrini V, Wilson RK, *et al*: Characterizing a model human gut microbiota composed of members of its two dominant bacterial phyla. Proc Natl Acad Sci USA 106: 5859-5864, 2009.
133. Lu G, Gao D, Jiang W, Yu X, Tong J, Liu X, Qiao T, Wang R, Zhang M, Wang S, *et al*: Disrupted gut microecology after high-dose ^{131}I therapy and radioprotective effects of arachidonic acid supplementation. Eur J Nucl Med Mol Imaging 51: 2395-2408, 2024.
134. Samimi H and Haghpanah V: Gut microbiome and radioiodine-refractory papillary thyroid carcinoma pathophysiology. Trends Endocrinol Metab 31: 627-630, 2020.
135. Coerts HI, de Keizer B, Marlowe RJ and Verburg FA: Recombinant or endogenous TSH for RAI therapy in thyroid cancer: State of knowledge and current controversies. Eur J Endocrinol 188: lvad006, 2023.
136. Horvath E, Skoknic V, Majlis S, Tala H, Silva C, Castillo E, Whittle C, Niedmann JP and González P: Radioiodine-induced salivary gland damage detected by ultrasonography in patients treated for papillary TC: Radioactive iodine activity and risk. Thyroid 30: 1646-1655, 2020.
137. Sunavala-Dossabhoy G and Petti S: Effect of recombinant human thyroid stimulating hormone on long-term salivary gland dysfunction in thyroid cancer patients treated with RAI. A systematic review. Oral Oncol 136: 106280, 2023.
138. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, Benyamin FW, Lei YM, Jabri B, Alegre ML, *et al*: Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 350: 1084-1089, 2015.
139. Shi X, Yu PC, Lei BW, Li CW, Zhang Y, Tan LC, Shi RL, Wang J, Ma B, Xu WB, *et al*: Association between programmed death-ligand 1 expression and clinicopathological characteristics, structural recurrence, and biochemical recurrence/persistent disease in medullary thyroid carcinoma. Thyroid 29: 1269-1278, 2019.
140. Capdevila J, Wirth LJ, Ernst T, Ponce Aix S, Lin CC, Ramlau R, Butler MO, Delord JP, Gelderblom H, Ascierto PA, *et al*: PD-1 blockade in anaplastic thyroid carcinoma. J Clin Oncol 38: 2620-2627, 2020.
141. Xu JW and Gu J: Research progress on the relationship between intestinal flora and thyroid cancer. J Clin Oncol 2: 176-180, 2021.
142. Schlumberger M and Leboulleux S: Current practice in patients with differentiated TC. Nat Rev Endocrinol 17: 176-188, 2021.