

# Oncometabolites as biomarkers in thyroid cancer: a systematic review

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**Introduction:** Thyroid cancer (TC) is an important common endocrine malignancy, and its incidence has increased in the past decades. The current TC diagnosis and classification tools are fine-needle aspiration (FNA) and histological examination following thyroidectomy. The metabolite profile alterations of thyroid cells (oncometabolites) can be considered for current TC diagnosis and management protocols.

**Methods:** This systematic review focuses on metabolite alterations within the plasma, FNA specimens, and tissue of malignant TC contrary to benign, goiter, or healthy TC samples. A systematic search of MEDLINE (PubMed), Scopus, Embase, and Web of Science databases was conducted, and the final 31 studies investigating metabolite biomarkers of TC were included.

**Results:** A total of 15 targeted studies and 16 untargeted studies revealed several potential metabolite signatures of TC such as glucose, fructose, galactose, mannose, 2-keto-D-gluconic acid and rhamnose, malonic acid and inosine, cholesterol and arachidonic acid, glycosylation (immunoglobulin G [IgG] Fc-glycosylation), outer mitochondrial membrane 20 (TOMM20), monocarboxylate transporter 4 (MCT4), choline, choline derivatives, myo-/scyllo-inositol, lactate, fatty acids, several amino acids, cell membrane phospholipids, estrogen metabolites such as 16 alpha-OH E1/2-OH E1 and catechol estrogens (2-OH E1), and purine and pyrimidine metabolites, which were suggested as the TC oncometabolite.

**Conclusion:** Citrate was suggested as the first most significant biomarker and lactate as the second one. Further research is needed to confirm these biomarkers as the TC diagnostic oncometabolite.

**Keywords:** biomarkers, oncometabolites, thyroid cancer, TC, systematic review

## Introduction

Thyroid cancer (TC) is the most common endocrine-related tumor in the past decades, and its incidence has been increasing all over the world.<sup>1-4</sup> The starting point of TC is the thyroid nodule formation detectable by ultrasonography (US) evaluations.<sup>5,6</sup> Thyroid nodules are mostly benign, and the current gold standard discriminative tool between TC and benign thyroid nodules (BTNs) is a cytopathologic analysis of percutaneous fine-needle aspiration (FNA) specimens.<sup>7</sup> FNA is a simple test that samples a small amount of tissue from the thyroid with a very thin (or “fine”) needle.<sup>8-11</sup> Histopathological report of FNA has a weak point of indeterminate results, negative predictive value, and high cost.<sup>12,13</sup> Hence, there is an extreme need to find molecular markers either to support FNA or to take the place of FNA.<sup>14-17</sup>

Increasing evidence indicates that tumor-associated mutations represent key factors resulting in different profiles of the cancerous cells’ genomics, epigenomics, transcriptomics, proteomics, and metabolomics.<sup>18-20,117,118</sup> Metabolomics is an extensive-scale study of small molecules (>1,000 Da), generally popular as metabolites, within cells,

biofluids, tissues, or organisms.<sup>21–23</sup> The major dissimilarities between cancerous cells and their counterpart noncancerous cells are their metabolites, which are called “oncometabolites”.<sup>24</sup> For the first time, it was revealed in 1927 that tumors display a unique metabolic phenotype, and their glucose level is up to 200 times more than that of normal cells.<sup>25</sup> Despite ignorance of oncometabolite impact on cancer diagnosis and management by 1970s, oncometabolites were rediscovered in the past decades.<sup>26</sup> Oncometabolites are intrinsic metabolites that either start or continue tumor growth and metastasis. The primary oncometabolite was 2-hydroxyglutarate (2HG), which was recognized as a main metabolite with much higher concentrations in gliomas than normal cells.<sup>27</sup> Main oncometabolites can be classified into six hallmarks: 1) those involved in glucose and amino acid uptake, 2) use of adaptable modes of nutrient gaining, 3) use of glycolysis/tricarboxylic acid (TCA) cycle and NADPH production, 4) augmented demand for nitrogen, 5) modifications in metabolite-driven gene regulation, and 6) metabolic contacts with the microenvironment. In fact, limited tumors show all six hallmarks together, and each one can be an indicator of tumor and can guide scientists to the exact tumor classification and higher efficient tumor management policies.<sup>28</sup> There are nine oncometabolites in different types of TCs: 2HG, glucose, fumarate, succinate, sarcosine, glutamine, asparagine, choline, and lactate.<sup>29</sup> Recently, some studies on

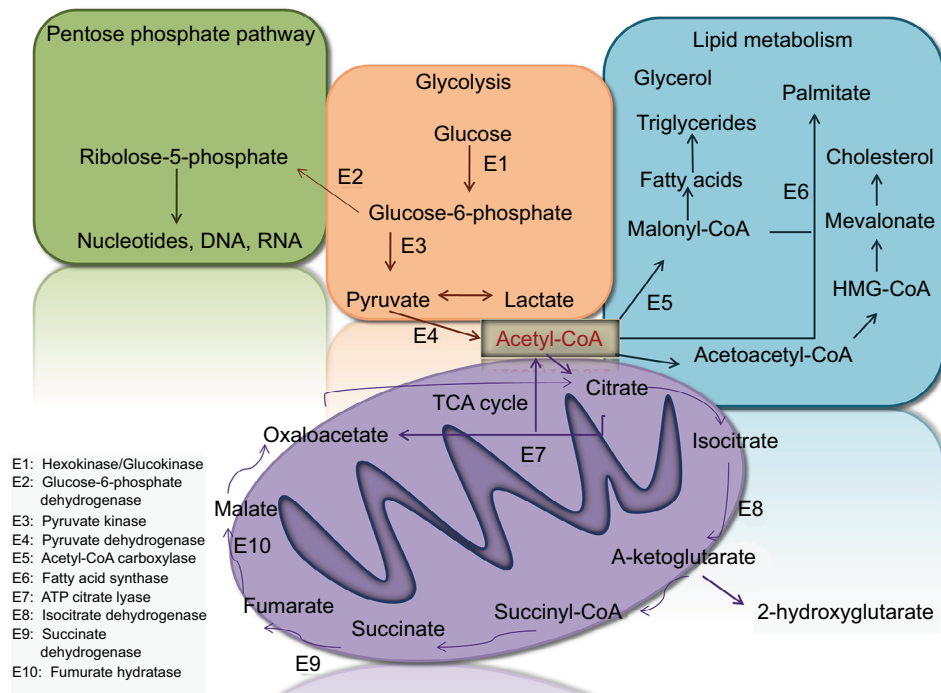
the metabolomics analysis of FNA specimens of thyroid nodules have suggested the benefit of oncometabolites approach as the potential application for the cooperative diagnosis tool of TC.<sup>30–33</sup> Several metabolic pathways linking it to the TCA, pentose phosphate pathway, and lipid metabolism are candidate biomarkers to discriminate between normal and cancer cells (Figure 1).

Here, we present the first meticulous summary of the entire available primary research to evaluate the potential of oncometabolites as the discriminative molecular marker between TC and BTNs.

## Research design and methods

### Search strategy

The study was conducted according to International prospective register of systematic reviews PROSPERO code: CRD42018088928 ([http://www.Crd.york.ac.uk/PROSPERO/display\\_record.php?ID=CRD42018088928](http://www.Crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018088928)). All related literature searches from four main databases including MEDLINE (PubMed), Scopus, Embase, and Web of Science for relevant articles were retrieved from January 1, 1998, to end of March 2018 with the key words grouping of “metabolomics”, “metabonomics”, “oncometabolites”, “metabolic profiling”, combined with “Thyroid Neoplasm”, “Thyroid Carcinoma”, “Thyroid Adenoma”, “Thyroid Nodules”, and “Thyroid Cancer” ([Supplementary materials](#)). To minimize



**Figure 1** Several metabolic pathways in normal and cancer cells.  
**Abbreviation:** TCA, tricarboxylic acid.

selection bias, two independent investigators (BA and MS) autonomously checked titles, abstracts, and available full-text articles for application. Further articles were recognized by checking the reference lists from the selected studies. Disagreements were fixed by agreement and discussion with a third researcher (KG).

## Eligibility criteria

All nominated studies were reviewed by two authors independently and according to their title and abstract were categorized as the included one or excluded one. The inclusion criteria were as follows: 1) participants included thyroid patients with TC; 2) the control population was specified (eg, patients with BTN, goiter patients, or healthy subjects); 3) all metabolomics detection techniques such as HPLC, ultra performance liquid chromatography (ULC), mass spectrometry (MS), tandem mass spectrometry (TMS), and nuclear magnetic resonance (NMR) spectroscopy were selected; and 4) metabolites were examined in plasma, serum, urine, or FNA specimens. Research studies were excluded if they 1) analyzed metabolite profiles in animals (in vivo studies), 2) analyzed metabolite profiles in cell culture (in vitro studies), or 3) did not contain a suitable control group.

## Data extraction and analysis

All data on population distinctiveness and indicative oncometabolites were entered in Excel. FK had performed the data completion steps, which was confirmed by another researcher (MP). Due to the inadequate quantity of studies related to TC and metabolomics, and the extensive method-

ological heterogeneity and the significant dissimilarities in study population characteristics, an assessable meta-analysis of the data was not applicable.

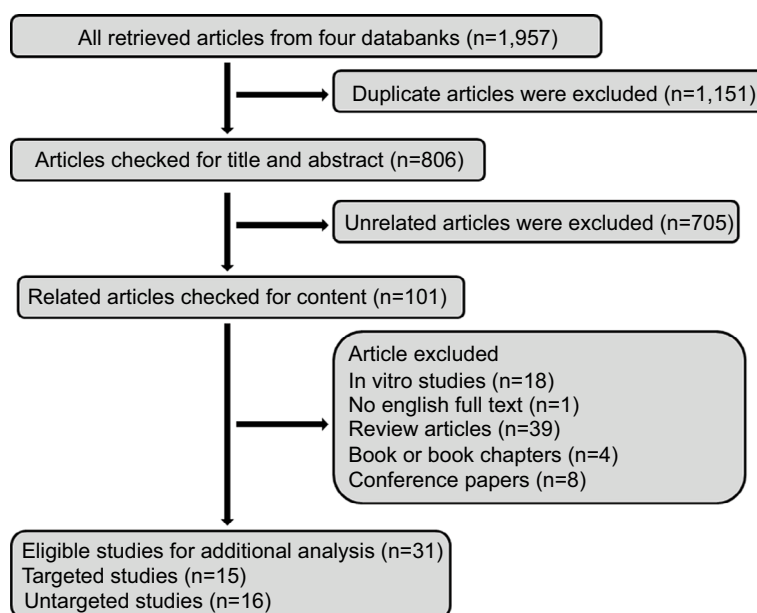
## The quality assessment tools

Here, we used Quality Assessment of Diagnostic Accuracy Assessment (QUADAS) and The Newcastle–Ottawa Scale (NOS) assessment tools to assess the methodological quality of the selected research articles. QUADAS and NOS were used to evaluate quality issues particular for “-omics” (QUADOMICS) more than the quality assessment of studies involving in systematic reviews.<sup>34,35</sup> Each research article that scored 12/16 or more on the QUADOMICS tool together with 6/8 or more on NOS were considered as “high quality”, while each research article that scored 11/16, 5/8, or less were considered as “low quality”.

## Results

### Study selection and characteristics

The selection algorithm and results of study selection are presented in Figure 2. A total of 806 articles were retrieved after duplication deletion, including 374 articles from PubMed, 293 from Scopus, 83 from Web of Science, and 56 from Embase. After deleting the review, in vivo/in vitro studies, and book or conference paper with no available full-text articles, the final 31 articles were chosen for further considerations. A total of 15 studies with targeted metabolites (Table 1) and 16 studies with untargeted metabolites methods (Table 2) were selected. Two studies with targeted metabolites were removed because of low quality after quality assessment.



**Figure 2** Flow diagram of study selection for the current systematic review.

Table 1 Thirteen targeted studies related to the cometabolites in TC

Title of article	First author	Year	Country	Sample size	Type of study	Metabolite measurement techniques	List of targeted metabolites	Significant different metabolites
1. Unbalanced estrogen metabolism in TC <sup>36</sup>	Muhammad Zahid	2013	USA (Omaha)	n: 40 TC n: 40 HI	Case/control	ULC TMS	Catechol estrogen quinones, estrogen-3,4-quinines, 38 estrogen metabolites (conjugates and DNA adducts) Estrogens (E1 and E2)	Estrogen metabolites
2. A SSEAT for "Functional" BiomarkerDiscovery <sup>37</sup>	Josep Villanueva	2008	USA (New York)	n: 48 metastatic TC n: 48 HI	Case/control	MALDI-TOF MS	Fibrinogen $\alpha_2$ C3f (complement C3), complement C4 precursor ITIH4, apolipoprotein A-IV Clusterin precursor, C-terminus of $\beta$ -chain minus Arg-transthyretin precursor Seven glycosylation features for IgG	N/A
3. Human IgG Fc-glycosylation profiling reveals associations with age, sex, female sex hormones, and TC <sup>38</sup>	Guoqiang Chen	2012	China	n: 138 TC	Case/control	MALDI-FTICR		Fc-glycosylation
4. Multicompartment metabolism in papillary thyroid cancer <sup>39</sup>	Joseph M. Curry	2016	USA	n: 27 NTC n: 6 FA n: 5 MNG	Case/control	IHC	TOMM20 MCT4	Multiple tumor compartments with glycolysis in fibroblasts and OXPHOS
5. Biochemical markers in the follow-up of medullary thyroid cancer <sup>40</sup>	Jan Willem B. de Groot	2006	The Netherlands	n: 46 MTC	Prospective study	GC	Calcitonin and CEA, plasma tryptophan Plasma platelet serotonin, urine 5-hydroxyindole acetic acid, MIMAA, 3-MT, HVA, VMA, VA, MOPEG, DOPAC Sphingosine kinase 1 metabolites	Plasma calcitonin Carcinoembryonic antigen, chromogranin A Sphingosine kinase 1
6. Predictive value of sphingosine kinase 1 expression in papillary thyroid carcinoma <sup>41</sup>	SUNG-IM DO	2017	Korea	n: 110 PTC n: 16 MNG n: 81 NTC	Case/control	IHC		
7. Metabolic changes enhance the cardiovascular risk with differentiated thyroid carcinoma – a case-control study from Manipal Teaching Hospital of Nepal <sup>42</sup>	Ankush Mittal	2012	Nepal	n: 50 DTC n: 50 HI	Case/control	ELISA CHOD-PAP and GPO-PAP method	FT3, fT4, TSH, total cholesterol Triglycerides, HDL, LDL, VLDL glucose, insulin, fibrinogen CRP	Hypercoagulable state Atherogenic lipid profile
8. 3, 30-Diindolylmethane modulates estrogen metabolism in patients with TPD: a pilot study <sup>43</sup>	Shilpi Rajoria	2011	New York, New Jersey	n: 7 TPD	Clinical trial study (a pilot study)	GC-MS	Estrogen metabolites 2-hydroxyestrones (C-2) 16 $\alpha$ -hydroxyestrone (C-16)	Antiestrogenic activity that results in more of C-2 product compared with C-16

(continued)

Table 1 (continued)

Title of article	First author	Year	Country	Sample size	Type of study	Metabolite measurement techniques	List of targeted metabolites	Significant different metabolites
10. Perioperative dynamics and significance of amino acid profiles in patients with cancer <sup>45</sup>	Yu Gu	2015	China	n: 56 GC n: 28 BC n: 33 TC	Case/control	Amino acid analyzer with spectrophotometrical detection	PFAAs (Asp, Thr, Ser, Glu, Gly, Ala, Cys, Val, Met, Ile, Leu, Tyr, Phe, Lys, His, Arg, Pro, NH <sub>3</sub> , NEAAs, EAAs, BCAAs, GAAs, TAAs)	PFAA
11. Estrogens in female TC: alteration of urinary profiles in preoperative cases and postoperative cases <sup>46</sup>	Seon Hwa Lee	2003	South Korea	n: 18 premenopausal PTC women (preoperative and postoperative patients in luteal phase)	Case/control	Highly sensitive GC-MS	Estrogen metabolites 16alpha-OH E1/2-OH E1 Catechol estrogens (2-OH E1)	2-hydroxylation in estrogen metabolism
12. Increased expression of phosphatidylcholine (16:0/18:1) and (16:0/18:2) in thyroid papillary cancer <sup>47</sup>	Seiji Ishikawa	2012	Japan	n: 7 TC cases	Case series	HE-stained, tandem mass (MS/MS) analysis, imaging mass spectrometry analysis	Phosphatidylcholine (16:0/18:1), phosphatidylcholine (16:0/18:2), sphingomyelin (d18:0/16:1)	Phosphatidylcholine Sphingomyelin
13. Application of metabolomics in prediction of lymph node metastasis in papillary thyroid carcinoma <sup>48</sup>	Ji Won Seo	2018	Korea	n: 52 metastatic PTC	Case series	H-NMR spectroscopy	Isoleucine, leucine, valine, lactate, threonine, alanine, uracil, lysine, glutamate, methionine, aspartate, choline, phosphocholine, glycerophosphocholine, taurine, myo-inositol, glycine, phosphoethanolamine, inosine, thyrosine, hypoxanthine, formate, succinate, uridine	Lactate

**Abbreviations:** 3-MT, 3-methoxytyramine; aMT6, melibiose 6-sulfatoxymelatonin; BC, breast cancer; CEA, carcinoembryonic antigen; C3f, complement C3f; DOPAC, 3,4-Dihydroxyphenylacetic acid; DTC, differentiated thyroid carcinoma; FPA, fibrinogen  $\alpha$ ; FT3, free triiodothyronine; FT4, free thyroxine; GC, gastric cancer; GC-MS, gas chromatography–mass spectrometry; GC-TOF-MS, gas chromatography–time-of-flight mass spectrometry; GLA, alpha-galactosidase; HDL, high-density lipoprotein; HI, healthy individual; HVA, homovanillic acid; IHC, immunohistochemistry; ITH4, inter- $\alpha$ -trypsin inhibitor heavy chain H4; LDL, low-density lipoprotein; MALDI-FTICR, matrix-assisted laser desorption ionization–Fourier transform ion cyclotron resonance; MALDI-TOF MS, matrix assisted laser desorption ionization–time of flight mass spectrometry; MCT4, monocarboxylate transporter 4; MIMAA, N'-methylimidazole acetic acid; MNG, multinodular goiter; MOPEG, 3-methoxy-4-hydroxyphenylglycol; MTC, medullary thyroid cancer; N/A, not applicable; NAT, normal adjacent tissue; OA, oxaloacetate; OXPHOS, Mitochondrial oxidative phosphorylation; PFAA, plasma-free amino acid; PHE, phenylalanine; PTC, papillary thyroid carcinoma; PUFA, polyunsaturated fatty acid; SEAT, Sequence-specific Exopeptidase Activity Test; TC, thyroid cancer; TMS, tandem mass spectrometry; TOMM20, translocase of outer mitochondrial membrane 20; TSH, thyroid-stimulating hormone; TPD, thyroid proliferative disease; ULC, ultra performance liquid chromatography; VA, valine; VLDL, very-low-density lipoprotein.

Table 2 The list of 16 untargeted studies related to the cometabolites in TC

Title of article	First author	Year	Country	Sample size	Type of study	Metabolite measurement techniques	Significant different metabolites
1. Development of data independent acquisition workflows for metabolomic analysis on a quadrupole-orbitrap platform <sup>49</sup>	Juntuo Zhou	2017	China	n: 30 TC n: 27 HI	Case/ control	LC-DIA-MS	Carnitine Trimethylamine N-oxide Some amino acids
2. Analysis on the metabolite composition of serum samples from patients with papillary thyroid carcinoma using NMR <sup>50</sup>	Wen-Xin Zhao	2015	China	n: 20 PTC n: 20 BTN n: 20 HI	Case/ control	NOEPR-CPMG NMR	A list of metabolites involves glucose metabolism, lipids, amino acids, and nucleic acid
3. Detection of metastatic breast and TC in lymph nodes by desorption electrospray ionization mass spectrometry imaging <sup>51</sup>	Jialing Zhang	2017	USA	n: 18 NLN n: 8 LNMP n: 16 LNMBC	Case/ control	DESI-MS	Ceramides Glycerophosphoinositol
4. Serum metabolic profiling and features of papillary thyroid carcinoma and nodular goiter <sup>52</sup>	Zhenzhen Yao	2011	China	n: 30 PTC n: 80 MNG n: 30 HI	Case/ control	Liquid chromatography-LTQ Orbitrap MS	3-Hydroxybutyric acid
5. Distinct metabolomic profiles of papillary thyroid carcinoma and benign thyroid adenoma <sup>53</sup>	Yanan Xu	2015	China	n: 57 PTC n: 48 BTA	Case/ control	GC-TOFMS UPLC-Q-TOF-MS	Purine and pyrimidine metabolites Taurine Hypotaurine
6. Serum and urine <sup>1</sup> H NMR-based metabolomics in the diagnosis of selected thyroid diseases <sup>54</sup>	Wojciech Wojtowicz	2017	Poland	n: 20 NN n: 13 FA n: 17 TC n: 17 HI	Case/ control	NMR	Amino acids: alanine, creatine, glutamine, tyrosine, valine Carboxylic acids: acetate, citrate, formate, lactate Monosaccharides: glucose Alcohols: glycerol Imidazolinones: creatinine
7. Metabolic alteration of urinary steroids in premenopausal and postmenopausal women and men with papillary thyroid carcinoma <sup>55</sup>	Man Ho Choi	2011	Korea	n: 21 premenopausal female n: 19 postmenopausal female n: 16 male PTC	Case/ control	GC-MS	Androgens Androstenedione Androstenediol 16 $\alpha$ -hydroxy DHEA Corticoid

(continued)

Table 2 (continued)

	Title of article	First author	Year	Country	Sample size	Type of study	Metabolite measurement techniques	Significant different metabolites
9.	Metabolomics approach to thyroid nodules: a high-resolution magic-angle spinning NMR-based study <sup>31</sup>	Paolo Miccoli	2012	Italy, France, Brazil	n: 28 PTC n: 40 FA n: 4 BN	Case/control	HRMAS HRMAS-NMR	Lactate Taurine Phosphocholine Myo-inositol Scyllo-inositol
10.	Metabolomic analysis of percutaneous fine-needle aspiration specimens of thyroid nodules: potential application for the preoperative diagnosis of TC <sup>57</sup>	Inseon Ryoo	2016	Korea	n: 35 PTC n: 69 BN	Case/control	NMR	Lactate Glycine Citrate Glutamine Glutamate Choline O-phosphocholine
11.	A distinct serum metabolic signature of distant metastatic papillary thyroid carcinoma <sup>58</sup>	Chen-Tian Shen	2017	China	n: 37 distant metastatic PTC n: 40 ablation group	Case/control	GC-TOF-MS	Phthalimide, cyclohexanamine, aminoxyacetic acid, 3-hydroxypropionate, carbamate, canavanine, creatine, asparagine, uridine, 4-deoxyuridine, 2-hydroxypyridine, $\gamma$ -aminobutyric acid, myo-inositol, pyroglutamic acid, stearic acid, palmitic acid, fructose, heptadecanoic acid, phenyl acetate, glycerol-3-phosphate, lactose, arachidic acid, uric acid, valine, palmitoleic acid, $\gamma$ -linoleic acid, parabanic acid, picolinic acid, oxalic acid, uracil, d-altrose
12.	Toward the reliable diagnosis of indeterminate thyroid lesions: a HRMAS NMR-based metabolomics case of study <sup>59</sup>	Liborio Torregrossa	2012	Italy, France, Brazil	n: 72 PTC	Case series	HRMAS	$\uparrow$ PHE, taurine, and lactate $\downarrow$ Choline and choline derivatives $\downarrow$ myo- and scyllo-inositol
13.	Exhaled breath volatile biomarker analysis for TC <sup>60</sup>	Lei Guo	2015	China	n: 39 PTC n: 25 MNG	Case/control	GC/MS	Sulfurous acid, cyclohexylmethyl hexyl ester, isolongolene-5-ol, 3,5-Decadien-7-yne, 6-t-butyl-2,2,9-tetramethyl, cyclohexanone, 4-hydroxybutyric acid, phenol, 2,2-dimethyldecane, ethylhexanol, ethylene glycol mono vinyl ester, cyclopropane, 1-bromo-1-(3-methyl-1-pentenylidene)-2,2,3,3-tetramethyl, (3-Methyl-oxiran-2-yl)-methanol, cyclopentane, 1,1,3-trimethyl-3-(2-methyl-2-propenyl), trans-2-dodecen-1-ol
14.	Association of PBDEs and hydroxylated metabolites (OH-PBDEs) serum levels with thyroid function in TC patients <sup>61</sup>	Sisi Lui	2017	China	n: 33 PTC	Case series	Chemiluminescence enzyme immunoassay	Diphenylethers (PBDEs) Hydroxylated metabolites (OH-PBDEs)
15.	Noninvasive diagnosis of papillary thyroid microcarcinoma: a NMR-based metabolomics approach <sup>62</sup>	Jinghui Lu	2016	China, Italy	n: 35 PTC	Case series	HRMAS H-NMR	Lysine Glutamate Tyrosine Catecholamines (dopamine, norepinephrine, and epinephrine)

(continued)

Table 2 (continued)

Title of article	First author	Year	Country	Sample size	Type of study	Metabolite measurement techniques	Significant different metabolites
16. Follicular adenomas exhibit a unique metabolic profile. <sup>1</sup> H NMR studies of thyroid lesions <sup>63</sup>	Stanisław Deja	2013	Poland	n: 45 TC n: 19 HI	Cohort	<sup>1</sup> H-NMR	Isoleucine, valine, alanine, NACs, methionine, citrate, creatine, choline, GPC, scyllo-inositol, taurine, glycine, myo-inositol, lactate, histidine, tyrosine, phenylalanine

**Abbreviations:** BN, benign nodule; BTA, benign thyroid adenoma; BTN, benign thyroid nodule; DESI-MS, desorption electrospray ionization mass spectrometry; DHEA, dehydroepiandrosterone; FA, follicular adenoma; GC-TOF-MS, gas chromatography-time-of-flight mass spectrometry; GC-MS, gas chromatography-mass spectrometry; HI, healthy individual; HRMAS, high-resolution magic angle spinning; LC-DIA-MS, liquid chromatography-data independent-mass spectrometry; LNMBC, lymph node with metastatic breast cancer; LNMP, lymph node with metastatic NAC; N-acetyl-cysteine; PHE, phenylalanine; PTC, MNG, multinodular goiter; NAT, normal adjacent tissue; NOEPR, nuclear over Hauser effect spectroscopy with P re-saturation; CPMG, Carr-Purcell-Me boom-Gill sequence; NLN, normal lymph node; NMR, nuclear magnetic resonance; NN, non-neoplastic nodule; OH-PBDE, hydroxylated polybrominated diphenylether; PBDE, polybrominated diphenylether; PTC, papillary thyroid carcinoma; TC, thyroid cancer; UPCL-Q-TOF-MS, The ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry.

The sample size of the study population was different from one case report that discussed 138 TC cases. Five studies were conducted in USA, 12 in China, five in Korea, two in Poland, two in Italy, one in Japan, one in Nepal, and one in the Netherlands. Both case/control and case report/series were included in the studies. In most case/control studies, the metabolites were compared between TC as the case group with healthy individuals and BTN or goiter patients as the controls. Exceptionally in two studies, the case/control was based on menopause TC and non-menopause TC. One study in Nepal evaluated the oncometabolites in differentiated thyroid carcinoma (DTC) with an increasing risk of cardiovascular disease. The oncometabolites included amino acids such as isoleucine, leucine, valine, lactate, threonine, alanine, uracil, lysine, glutamate, methionine, aspartate, choline, phosphocholine, glycerophosphocholine, taurine, myo-inositol, glycine, phosphoethanolamine, inosine, tyrosine, hypoxanthine, formate, succinate, and uridine; carboxylic acids such as acetate, citrate, fumarate, and lactate; monosaccharides such as glucose and glycosylation; estrogen metabolites such as 16 alpha-OH E1/2-OH E1 and catechol estrogens (2-OH E1); lipids such as total cholesterol, triglycerides, HDL, LDL, and VLDL; fibrinogen; calcitonin; and carcinoembryonic antigen (CEA). The unique phospholipids of bilayer membrane (phosphatidylcholine, phosphatidylcholine, and sphingomyelin) in addition to thyroid hormones, free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) were also included in the list of metabolites. Some studies used the oncometabolites for TC diagnosis and some for follow-up and management of TC patients.

Amongst all selected studies in this systematic review, two studies were considered metabolite profile of premenopausal women. A targeted study conducted in Manipal Teaching Hospital of Nepal suggested that the hypercoagulable state atherogenic lipid profile is the different metabolite correlated with an increasing risk of cardiovascular disease in DTC patients. Other studies considered the different metabolite profiles as the discriminative tool of thyroid malignancy.

## Discussion

Cancer studies highlighted the fact that cancer cells are common in biological capabilities such as constant proliferative signaling, growth suppressor's avoidance, resistance to cell death, replicative immortality, high angiogenesis, reprogrammed energy metabolism, immune-mediated destruction, invasion, and metastasis.<sup>11,64,65,119</sup> Metabolic reprogramming orchestrates cancer cell properties, so "cancer metabolism" became an important research topic for cancer management. The first study on cancer metabolism in 1924 suggested that the cancer phenotype for glucose metabolism is unique one



and with higher ability of glucose uptake and lactate production is typical in several tumors.<sup>66</sup> These pathways are named as “aerobic glycolysis” or the “Warburg effect”, which has the effect on the extracellular fluid around tumor tissue and change it to acidic pH.<sup>67–69</sup> Glucose is the critical source of carbon that helps in the maintenance of cancer cell anabolism, TCA anaplerosis, aerobic glycolysis, hexokinase II activation, and modified signal transduction.<sup>70,71</sup> Glucose was the most frequent metabolite elevated in most cancers<sup>26,72,73</sup> and has been used as the oncometabolite of TCs in both targeted<sup>42,44</sup> and untargeted studies.<sup>50,54,56</sup> Analysis of the serum metabolic alterations among PTC, benign thyroid tumor, and healthy controls suggested that glucose metabolism cannot be the only important metabolite because metabolism of lipids, amino acids, and nucleic acids is important as well.<sup>50</sup> Moreover, it was shown that the *mRNA* quantity of metabolic enzyme-coding genes resulting in different glucose, fructose, galactose, mannose, 2-keto-D-gluconic acid and rhamnose, malonic acid and inosine, cholesterol and arachidonic acid significantly increased in PTC.<sup>56</sup> These studies were confirmed by detecting 31 different metabolites related to amino acid, lipid, glucose, vitamin metabolism, and diet/gut microbiota interaction.<sup>74</sup>

Metabolome analysis of amino acid profile is under consideration for biomarkers of thyroid malignancy. The plasma-free amino acid (PFAA) profiles of breast cancer, gastric cancer, and TC patients and investigation of their diagnostic potential were shown in the study by Gu et al.<sup>75</sup> Carnitine, trimethylamine N-oxide (TMAO), proline, glutamine, and asparagine were known as the most significant metabolites of 392 metabolites in TC.<sup>49</sup> In serum specimens of papillary TC patients, the amount of metabolites like valine, leucine, isoleucine, lactic acid, alanine, glutamic acid, lysine, glycine, whereas the lipids, choline, tyrosine decreased.<sup>76</sup> Similarly alanine, creatine, glutamine, tyrosine, and valine in both serum and urine of TC patients were diagnosed by H NMR-based method.<sup>77</sup>

Glycosylation is one of the most frequent posttranslational modification reactions, and almost half of all proteins in eukaryotes are glycosylated.<sup>11,78</sup> Some findings revealed the potential of IgG glycosylation as a biomarker for inflammation, metabolic health, and cancers.<sup>79,80</sup> In TC, it was suggested that human IgG Fc-glycosylation profiling could be linked with age, sex, female sex hormones, and TC risk.<sup>38</sup> IgG glycosylation in addition to glycans, glycome and glycoproteome are important in controlling thyroid cancer development and progression.<sup>81,82</sup> The translocase of outer

mitochondrial membrane 20 (TOMM20), a marker of oxidative phosphorylation, and monocarboxylate transporter 4 (MCT4), a marker of glycolysis, are candidate metabolites for aggressive behavior of TC.<sup>39</sup>

High levels of lactate and choline and low levels of citrate, glutamine, and glutamate in malignant thyroid nodules were reported by Ryoo et al<sup>33</sup> and suggested them as the discriminative biomarker for determining the preoperative metabolomic profiles of thyroid nodules. Lactate is often augmented in several malignancies including head and neck cancers.<sup>30,31,83,84</sup> High lactate level is the sign of glycolytic pathway increasing in response to hypoxia or ischemia in tumor tissues.<sup>85–87</sup> Lactogenesis, an important step for the production of lactate, is started and triggered by gene mutations (the Warburg effect), so deregulated lactate metabolism and signaling are the critical elements in carcinogenesis.<sup>88</sup> Lactate was established as an important factor in terms of cancer cell mobility and immune suppressor molecule that promote the tumor evasion as well.<sup>89,90</sup> Lactate was found to be the most promising metabolite for discrimination of lymph node metastasis from nonmetastatic TC.<sup>48</sup> Two studies confirmed that reduced levels of fatty acids and elevated levels of several amino acids (phenylalanine, tyrosine, lactate, serine, cystine, lysine, glutamine/glutamate, taurine, leucine, alanine, isoleucine, and valine) in papillary thyroid microcarcinoma (PTMC) and rise of phenylalanine, taurine, and lactate and a reduction of choline and choline derivatives, myo- and scyllo-inositol in the malignant tumors vs to the benign ones.<sup>59,62</sup>

Phospholipids are esters of glycerol, fatty acids, phosphoric acid, and other alcohols. Nearly, all frequent phospholipids are phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, and phosphatidylserine. Evidence showed that phosphatidylcholine, the major phospholipid element of eukaryotic membranes, like choline metabolites resulting from its metabolism, has an important role in cancer proliferation and survival.<sup>91</sup> In thyroid malignancies, the increased multiplication and proliferation of cancer cells are linked to the increased choline contents even in FNA specimen.<sup>47,57,92</sup> Choline was in the list of discriminative oncometabolites of TC with lymph node metastasis from non-metastatic one.<sup>48</sup> These findings are contradictory with a study in which the content of lipids, choline, and tyrosine decreased in malignant TC compared to that in the benign one.<sup>31,50</sup>

Another metabolite that increased as the result of glycolysis in TC is glycine. It could be one of the essential metabolites in tumorigenesis and mitochondrial synthesis,

and consumption of glycine was suggested as a discriminative metabolites triggering the cancer cell growth and development.<sup>33</sup> Glycine dehydrogenase enzyme (GLDC), which cleavages glycine and mediates folate cycle charging, is highly expressed in tumor-promoting cells.<sup>93–95</sup>

Oncometabolomic analysis revealed that citrate uptake largely affected cancer cell metabolism through citrate-dependent metabolic pathways, and the extracellular citrate is provided to cancer cells through a plasma membrane-specific variant of the mitochondrial citrate transporter (pmCiC).<sup>96</sup> In the study by Ryoo et al,<sup>57</sup> it was suggested that citrate was the most powerful discriminator oncometabolite for diagnosis of TC. Previous studies also indicated that ATP citrate lyase, essential for cell proliferation, is upregulated in some human malignancies such as lung, colorectal, and ovarian cancers.<sup>97,98</sup> The inhibition of ATP citrate lyase can block the proliferation of multiple tumor cell lines.<sup>99</sup>

The role of isocitrate dehydrogenase (IDH) mutations and D-2-HG accumulation in malignancy has increased recently.<sup>100</sup> 2-HG has been considered as oncometabolites and epigenetic modifiers in different malignancies such as gliomas,<sup>101–103</sup> myelogenous leukemia,<sup>104</sup> and renal cancer.<sup>105</sup> Non-synonymous variants of *IDH1* gene have been detected in thyroid carcinomas, and in PTC, the increased levels of 2-HG were reported.<sup>106–109</sup> However, it has not been considered as an oncometabolite in TCs.

There are three main forms of estrogen in the human body: estradiol, estrone, and estriol. These forms of estrogen together with estrogen receptor and other estrogen metabolites (16 alpha-OH E1/2-OH E1 and catechol estrogens [2-OH E1]) are more commonly associated with cancer risk.<sup>110,111</sup> For checking the possible outcome of estrogens in premenopausal female TC, the concentrations of 14 estrogens were assessed in the urine of patients with PTC preoperatively and postoperatively, and it was confirmed that low mean value of 16 $\alpha$ -OH E1/2-OH E1 was observed in preoperative patients, and it was considerably dissimilar to the ratio of postoperative TC cases. The increase of 2-hydroxylation in estrogen metabolism may have a noteworthy relationship with the risk of TC formation in females.<sup>46</sup> Moreover, it was shown that higher exposure to estrogens can increase the risk for TC, and 38 urinary estrogen metabolites were checked by Zahid et al, they suggested the unbalanced estrogen metabolism and formation of estrogen-DNA adducts as the role player in the initiation of TC.<sup>36</sup> Supporting information indicated to anti-estrogenic dietary supplement function of 3,3'-diindolylmethane (DIM) to help reduce the risk of developing thyroid proliferative disease (TPD).<sup>43</sup>

In addition, the synthesis of purines and pyrimidine is upregulated in cancer cells, and the catalyzing enzymes of

this pathway including thymidylate synthase and inosine synthetase 2 are subjected to Myc-induced upregulation.<sup>112,113</sup> Glutamine is a nitrogen source for multiple steps of both purine and pyrimidine synthesis.<sup>114</sup> Glutamine is a critical nutrient indispensable for cancer cell growth and is the new therapeutic target in cancers.<sup>115,116</sup> In preoperative percutaneous FNA specimens of TC, it was shown that glutamine and glutamate are presented with lower relative concentrations.<sup>50,57</sup> These results were generally in agreement with a previous finding obtained using surgical specimens.<sup>59</sup> Pathway analysis indicated the “alanine, aspartate and glutamate metabolism” and “inositol phosphate metabolism” as the most relevant pathways in thyroid carcinogenesis.<sup>74</sup> However, gastric cancer cells was promoted by cysteine, but inhibited by alanine and glutamic acid because alanine and glutamic acid induced apoptosis of gastric cancer cells.<sup>45</sup> Follicular adenomas exhibit a unique metabolic profile with several oncometabolite profiles including glutamine.<sup>63</sup>

## Conclusion

Because of the complexity of thyroid carcinogenesis, a wide range of oncometabolites is suggested as TC diagnostic markers. Potential biomarkers common to all thyroid lesions were mainly fatty acids, amino acids, cell membrane phospholipids, estrogen metabolites (16 alpha-OH E1/2-OH E1 and catechol estrogens[2-OH E1]), purine and pyrimidine metabolites, citrate, glucose, mannose, pyruvate, and 3-hydroxybutyrate glycosylation (IgG Fc-glycosylation), TOMM20, MCT4, choline, choline derivatives, myo-/scyllo-inositol, and lactate. Among all metabolites, citrate was suggested as the first most significant oncometabolite and lactate as the second one in thyroid malignancies.

## Abbreviations

BC, breast cancer; BN, benign nodule; BTA, benign thyroid adenoma; BTN, benign thyroid nodules; CEA, carcinoembryogenic antigen; CPMG, Carr-Pure-Me boom-Gill sequence; DESI-MS, desorption electrospray ionization mass spectrometry; DTC, differentiated thyroid carcinoma; FA, follicular adenoma; FTC, follicular thyroid cancer; GC, gastric cancer; GC-TOF-MS, gas chromatography time-of-flight mass spectrometry; HI, healthy individual; HRMAS, high-resolution magic angle spinning; LC-DIA-MS, liquid chromatography–data independent-mass spectrometry; LNMBC, lymph node with metastatic breast cancer; LNMP, lymph node with metastatic PTC; MNG, multinodular goiters; MTC, medullary thyroid cancer; NAT, normal adjacent tissue; NLN, normal lymph node; NMR, nuclear magnetic resonance; NN, non-neoplastic nodule; NOEPR, nuclear over Hauser

effect spectroscopy with P resaturation; NTC, noncancerous thyroid tissue; PTC, papillary thyroid carcinoma; TCP, thyroid cancer patients; TMS, tandem mass spectrometry; TPD, thyroid proliferative disease; ULC, ultra performance liquid chromatography; UPLC–QTOFMS, ultra-performance liquid chromatography–quadruple time-of-flight mass spectrometry; UTC, undifferentiated thyroid carcinoma.

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## Disclosure

The authors report no conflicts of interest in this work.

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