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Review Article

Review Article

Current status of serum metabolites biomarkers for polyps and colorectal cancer: a systematic review

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Abstract

Background: Early detection of colorectal cancer (CRC) is crucial to enhance the disease treatment and prognosis of patients. Colonoscopy remains the gold standard for CRC detection; however, it requires trained personnel with expensive tools. Currently, serum metabolites have been discovered to be used to discriminate patients with polyps and CRC. This study aimed to identify the most commonly detected predictive serum metabolites for polyps and CRC.

Methods: A systematic search of the Web of Science, PubMed, and Cochrane Library databases was conducted using PRISMA guidelines. Ten studies investigating serum metabolite biomarkers of CRC and polyps using different analytical platforms and study populations were included. QUADOMICS tool was used to analyse the quality of the included studies. All reported metabolites were then enriched into the pathways using MetaboAnalyst 5.0.

Results: We found that several potential signature metabolites overlapped between studies, including tyrosine, lysine, cystine, arabinose, and lactate for CRC and lactate and glutamate for polyps. The most affected pathways related to CRC were the urea cycle, glutathione metabolism, purine metabolism, glutamate metabolism, and ammonia recycling. In contrast, those affected in the polyps were the urea cycle, glutamate metabolism, glutathione metabolism, arginine and proline metabolism, and carnitine synthesis.

Conclusions: This review has found commonly detected serum metabolites for polyps and CRC with huge potential to be used in clinical settings. However, the differences between altered pathways in polyps and CRC, other external factors, and their effects on the regulation level, sensitivity, and specificity of each identified metabolite remained unclear, which could benefit from a further extensive cohort study and well-defined analysis equipment.

Keywords: serum biomarker; metabolomics; colorectal carcinoma; colorectal adenoma; screening tool

Introduction

Colorectal cancer (CRC) is one of the most frequent causes of cancer-related deaths worldwide, with an incidence of 14% and a mortality of 12.9% [1]. CRC has been reported to commonly occur among the elderly aged 50 and above [2]. However, current trends show that it was also detected among adults aged 40 and below [2], mainly caused by the patient's family history of CRC, their daily lifestyles, and exercise patterns [3]. These have contributed to the emergence of CRC cases worldwide over the years. Since patients with early-stage CRC can be cured with minimally invasive therapy, including endoscopic resection, it is essential to identify patients with early-stage CRC by mass screening [4].

Colonoscopy remains the gold standard procedure for polyps and CRC detection. However, it is an invasive method that involves high costs and is time-consuming [4]. The American Cancer Society recommends either stool-based tests (faecal occult blood test or DNA) or structural tests (colonoscopy) for adults aged 50 years and older [5]. Although faecal occult blood test is a popular non-invasive method available for CRC detection, it is well known to exert many false positives and is easily affected by non-specific bleeding, thus initiating unnecessary invasive examinations [4, 6]. Serum carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9) are also commonly used as less-invasive biomarkers in clinical practice; however, their sensitivities are very low, and they cannot accomplish early-stage detection of CRC and colorectal polyps [7].

Research on non-invasive biomarkers for CRC and/or colorectal polyp detection has been conducted by using various materials, including faeces, serum, plasma, and urine [4]. Metabolomics profiling is a popular method for disease biomarker identification. It is one of the omics sciences besides proteomic, genomic, and transcriptomic; it investigates the changes of small molecules called metabolites presented in a biological system that can be used as disease biomarkers to reveal disease etiology [8]. Serum metabolomics profiling has become increasingly popular for CRC biomarker identification due to its less invasiveness. Compared with other diagnostic tools, the serum metabolomics approach can offer higher diagnostic performance by utilizing a single analysis in a cheaper, faster, non-invasive manner,

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potentially representing the ideal screening test [9]. Furthermore, as the metabolome provides unique information regarding the mechanisms underlying the disease onset and progression, a thorough investigation of the metabolomic fingerprint of CRC may provide crucial insights to enhance the understanding of the pathology, as well as to identify prognostic biomarkers and assess the severity of the disease [10]. Despite numerous studies available for CRC serum metabolomics profiling, they have yet to be conducted in clinical trial settings.

In addition, although many studies have been conducted focusing on CRC serum metabolomic profiling, only a few have focused on identifying serum metabolite biomarkers for colorectal polyp patients [11]. Most studies used patients with CRC as the experimental group and patients with a healthy colon as the control group. However, given that patients with colon polyps also have a high potential to develop the cancerous stage, their samples should also be included in the study and be considered the initiation phase (non-cancerous stage) CRC [11, 12]. Hence, this study analysed, summarized, and discussed potential predictive serum metabolites biomarkers that could be used for the detection of polyps and CRC. Moreover, their respective metabolic pathways were further discussed to give a better understanding of their involvement in the initiation and progression of polyps and CRC.

Materials and methods

This systematic review was prepared according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective of this review was to determine potential predictive serum metabolites as a screening biomarker for polyps and CRC. A complete search protocol was registered into PROSPERO (ID: CRD42023389940). Part of the protocol was amended as follows: (i) the addition of 'polyps' in the title, (ii) including colorectal adenoma/polyps as part of the methodological review, (iii) quality assessment using QUADOMICS tool, and (iv) analysis of pathways using MetaboAnalyst 5.0 software.

Search strategy

A literature search was performed to obtain a comprehensive finding via electronic databases, including PubMed, Web of Science (WoS), and Cochrane Library. The search strategy was designed by two reviewers (M.F.A.B. and A.M.N.) and conducted by all authors (M.F.A.B., A.M.N., C.S.F., and S.M.). Searched keywords included "metabolites" OR "metabolism product" OR "metabolic product" OR "metabolomics" OR "metabolome" OR "metabonome" AND "marker" OR "biomarker" OR "biological marker" OR "biological signature" AND "blood" OR "serum" OR "plasma" OR "circulating" AND "human" AND "diagnosis" OR "screening" OR "testing" OR "detection of cancer" AND "colorectal cancer" OR "colorectal carcinoma" OR "colorectal neoplasm" OR "colorectal adenocarcinoma" OR "colorectal tumour" OR "cancer of colorectal." Two reviewers (M.F.A.B. and A.M.N.) independently assessed the titles and abstracts of all abstracts as part of the primary screen and analysed the results. A secondary screening of titles and abstracts was then further conducted by two reviewers (S.M. and C.S.F.).

Eligibility criteria

Studies published between 1 January 2013 and 31 December 2023 were included to ensure that all of them were newly published evidence on potential serum biomarkers for CRC and polyp screening. The review was limited to studies that focused on serum samples from humans, was published in English, and addressed the findings of serum metabolite biomarkers in the detection of CRC and/or colorectal polyps using targeted metabolomics profiling.

Exclusion criteria

Review articles, conference abstracts, studies without a complete set of data, and articles that did not mention polyps, CRC, or serum metabolites in the title or abstract were excluded. In addition, the studies were limited to serum biomarkers as this type of sample is easily obtained and has been widely reported to be used as a CRC screening tool; hence, all other sources of CRC or polyp metabolite biomarkers, such as stool, urine, and biopsy tissues were excluded. Research studies using targeted metabolomics profiling were also excluded to standardize data analysis between collected data.

Quality assessment

The quality of each publication was evaluated by two independent reviewers (M.F.A.B. and A.M.N.) and was confirmed by two other authors (S.M. and C.S.F.). QUADOMICS, an adaption of a quality assessment tool for diagnostic accuracy studies (QUADAS), was used to assess the methodological quality of the selected studies. This tool is an upgraded version of QUADAS that was developed by considering the particular challenges when systematic reviews of "omics"-based techniques were being performed [13]. The quality of the studies was summarized by using the percentage of applied criteria scored positively.

Data extraction

All articles were screened by two authors (M.F.A.B. and A.M.N.), and any disagreement was overcome by a consensus or the involvement of two other authors (C.S.F. and S.M.). Data were extracted by two authors (M.F.A.B. and A.M.N.), followed by validation by other two authors (C.S.F. and S.M.). The articles/studies were selected based on the inclusion and exclusion criteria.

The following information was extracted from all included studies: first named author, year of publication, participant country, type of sample used, number of control participants, number of CRC and polyp patients, any other participant group used, number of significantly different metabolites, and type of analysis instrument.

Data synthesis

Identified serum metabolite biomarkers for polyps and CRC were extracted from the studies. Any unknown and unmatched metabolites reported by the included studies were removed from the analysis. Enrichment pathway analysis was conducted using MetaboAnalyst 5.0 for all metabolites detected for CRC and polyps. Further analysis was performed to identify the most commonly detected metabolites between studies associated with CRC and polyps, which could be used to differentiate between patients with CRC or polyps and patients with normal conditions.

Results

Studies selection

A PRISMA diagram of the studies selected for this systematic review is presented in Figure 1. The search strategy identified 644 suitable abstracts, from which 624 were excluded upon reviewing the title and abstract during the primary and secondary screening, as they did not meet the eligibility criteria. Full-text articles were obtained for 20 studies. A total of 10 papers [9, 11, 14–21] that examined potential serum metabolite biomarkers for CRC and/or polyps were included in this review for data extraction

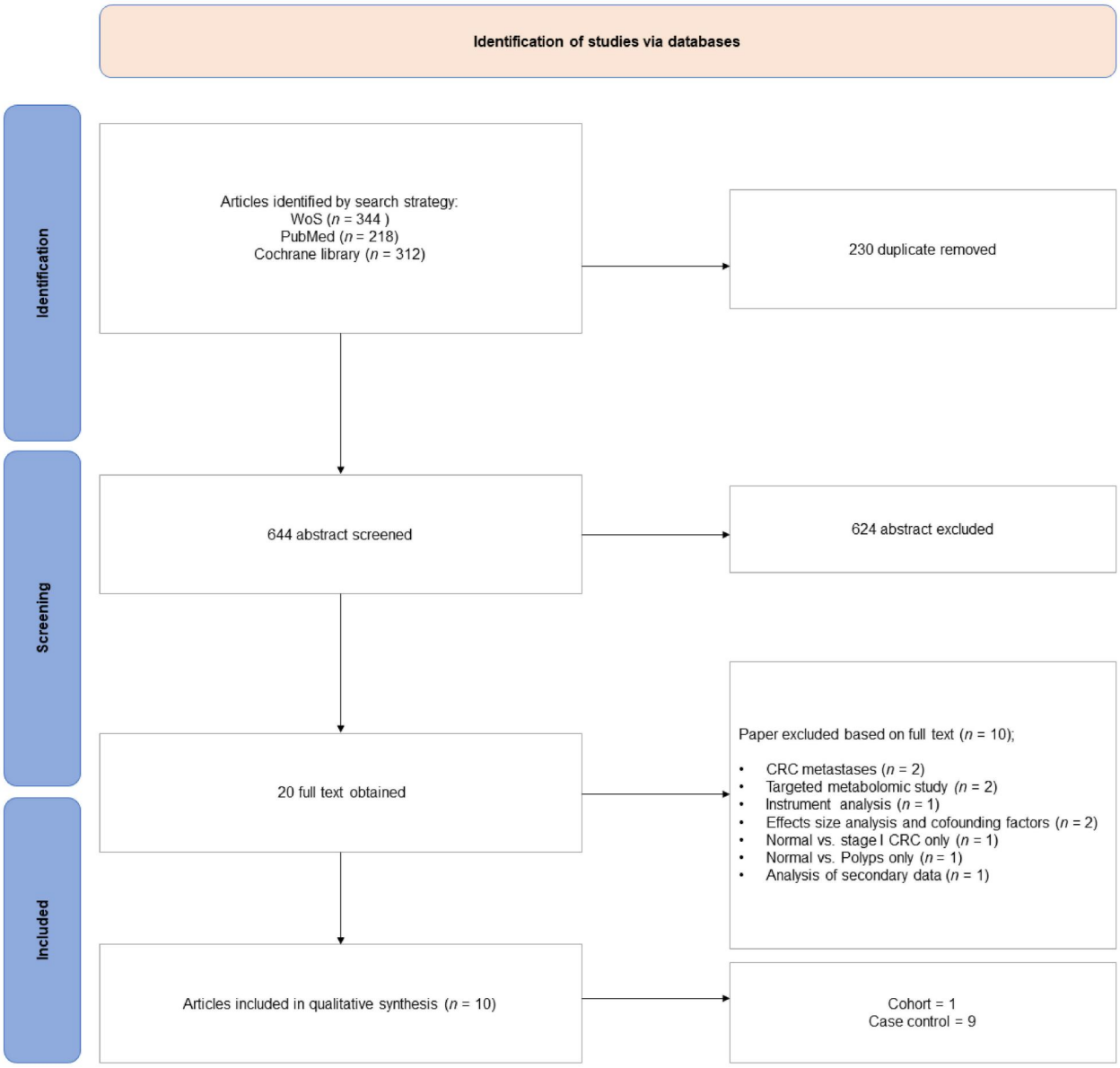

Figure 1. PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, CRC = colorectal cancer.

and analysis (Table 1). Only one of the studies [9] used the cohort sampling method, whereas the remaining nine studies [11, 14–21] used a case–control sampling method. The studies were conducted in Belgium, the USA, China, Japan, Malaysia, Italy, and Canada, with a range of 8–320 participants for each group using eight different analytical platforms, including GCxGC/TOF-MS, LC-MS, LC-QTOF-MS, GC-TOF-MS, UHPLC-MS/MS, GC-MS, H1-NMR, and CE TOF-MS (Table 1). Only four studies [9, 16, 20, 21] reported sensitivity and specificity of the suggested serum biomarkers for polyps and/or CRC (Table 2).

The quality of included studies

The quality assessment results for the individual studies were conducted using QUADOMICS. The detailed questions for all studies are shown in Supplementary Table S1. All studies included in this review met the inclusion criteria, and most of the items in QUADOMICS (>80% score) indicated that the overall quality of the included studies was good.

Altered metabolites associated with CRC and their metabolic pathways

All studies [9, 11, 14–21] reported a list of potential serum metabolites for CRC patients versus normal individuals. The differential serum metabolites associated with CRC identified by all studies were enriched into pathways (Table 1). The five most affected pathways in CRC are the urea cycle, glutathione metabolism, purine metabolism, glutamate metabolism, and ammonia recycling (Figure 2).

All significantly different serum metabolites that overlapped in more than two studies are listed in Table 3. A total of 28 metabolites were identified to be significantly different between CRC and normal individuals in two or more of the studies reviewed. From these metabolites, eight metabolites (tyrosine, lysine, cystine, arabinose, lactate, methionine, alanine, and valine) reported by more than three studies were further selected and were considered the most common serum metabolites that might be potentially associated with CRC. Further extraction included the regulation of these eight metabolites reported from respected studies under review (Table 4). The value of

Table 1. List of included studies on serum biomarkers for CRC and polyps

Authors (year)/country	Analysis instrument	No. of metabolites significantly different for CRC	No. of metabolites significantly different for polyps	Total no. of samples	No. of participants		
					Healthy control	CRC	Polyps
Bhatt *et al.* (2023)/Belgium [14]	GCxGC/TOF-MS	8	0	64	21	20	23
Zhang *et al.* (2021)/China [15]	LC-MS	9	–	148	50	98	–
Hashim *et al.* (2021)/Malaysia [16]	LC-QTOF-MS	11	–	100	50	50	–
Tan *et al.* (2013)/China [17]	GC-TOF/MS	20	–	203	102	101	–
Guo *et al.* (2023)/China [18]	UHPLC-MS/MS	20	20	30	14	8	8
Troisi *et al.* (2022)/Italy [9]	GC-MS	8	–	200	50	50	100
Gu *et al.* (2019)/China [19]	H1-NMR	24	24	110	38	32	40
Long *et al.* (2017)/USA [11]	LC-MS/MS	10	10	240	80	80	80
Uchiyama *et al.* (2017)/Japan [20]	CE TOF-MS	14	NR	175	60	59	56
Farshidfar *et al.* (2016)/Canada [21]	GC-MS	41	14	605	254	31	320

CRC = colorectal cancer, GCxGC/TOF-MS = two dimensional gas chromatography/time of flight-mass spectrometry, LC-MS = liquid chromatography-mass spectrometry, LC-QTOF-MS = liquid chromatography-time of flight-mass spectrometry, GC-TOF/MS = gas chromatography-time of flight/mass spectrometry, UHPLC-MS/MS = ultra high-performance liquid chromatography-mass spectrometry, GC-MS = gas chromatography-mass spectrometry, H1-NMR = hydrogen-1 nuclear magnetic resonance, CE TOF-MS = capillary electrophoresis time of flight-mass spectrometry.

Table 2. Studies that included the suggested predictive serum metabolites with sensitivity and specificity

Authors/year/country	Serum metabolites suggested for CRC	Serum metabolites suggested for polyps	Sensitivity (%)	Specificity (%)
Hashim *et al.* (2021)/ Malaysia [16]	Acetylcarnitine, hypoxanthine, xanthine, uric acid, methionine, tyrosine, citric acid, 5-oxoproline, pipecolic acid, LysoPE, LysoPC	–	70–90	70–90
Troisi *et al.* (2022)/Italy [9]	Galactose, 4-hydroxybenzyl alcohol, myristic acid, hydroxylamine, arabinose, guanine, fructose, tetraethylene glycol	–	98	100
Uchiyama *et al.* (2017)/ Japan [20]	Benzoic acid, octanoic acid, decanoic acid, histidine	–	100	98
Farshidfar *et al.* (2016)/ Canada [21]	Cystine, erythritol, glutamic acid, heptadecanoic acid, glyceric acid	Cystine, erythritol, glutamic acid, heptadecanoic acid, glyceric acid	85	86

CRC = colorectal cancer, LysoPE = Lysophosphatidylethanolamine, LysoPC = Lysophosphatidylcholines.

LogFC > 0.5 was considered upregulated, whereas LogFC < 0.5 was downregulated.

Altered metabolites associated with polyps and their metabolic pathways

Only four of the studies [11, 18, 19, 21] had detected serum metabolites for polyps. The differential serum metabolites associated with polyps identified by these studies were enriched into pathways (Table 1). Figure 3 presents the affected pathways for polyps versus normal tissues. The five most affected pathways in polyps are the urea cycle, glutamate metabolism, glutathione metabolism, arginine and proline metabolism, and carnitine synthesis (Figure 3).

All significantly different serum metabolites reported by more than two studies are listed in Table 5. In contrast with CRC, only two metabolites (lactate and glutamate) were identified to be significantly different in individuals with colorectal polyps, reported by two or more of the studies reviewed. Both lactate and glutamate were detected in the studies by Gu *et al.* [19] and Long *et al.* [11]. Gu *et al.* [19] reported that lactate and glutamate were upregulated in polyps compared to normal tissues, while Long *et al.* [11] did not include the regulation values for identified metabolites.

Discussion

In this study we reviewed 10 research studies on polyps and CRC serum metabolomics profiling in seven countries between January 2013 and December 2023, using eight different analysis platforms. We found that studies conducted in different populations, using different analysis platforms, exhibit a varied list of signature metabolites associated with polyps and CRC. The results suggested that lactate and acetate are commonly reported for polyps while tyrosine, lysine, cystine, arabinose, lactate, methionine, alanine, and valine are commonly reported for CRC.

The findings of the present systematic review confirmed the earlier reviews by Kim *et al.* [22] and Hashim *et al.* [23], in which different analytical platforms detect different altered metabolomes. The included studies [9, 11, 14–21] illustrated this fact despite analysing similar serum samples. The differences in the number of metabolites identified by these studies might be due to the distinctions in the handling techniques, separation methods, and detection using the different platforms, as suggested by Hashim *et al.* [23].

The studies that noted the differences in the list of altered serum metabolomes that were detected in the different populations for CRC and polyps were conducted in the following countries: the USA [11], China [15, 17–19], Japan [20], Malaysia

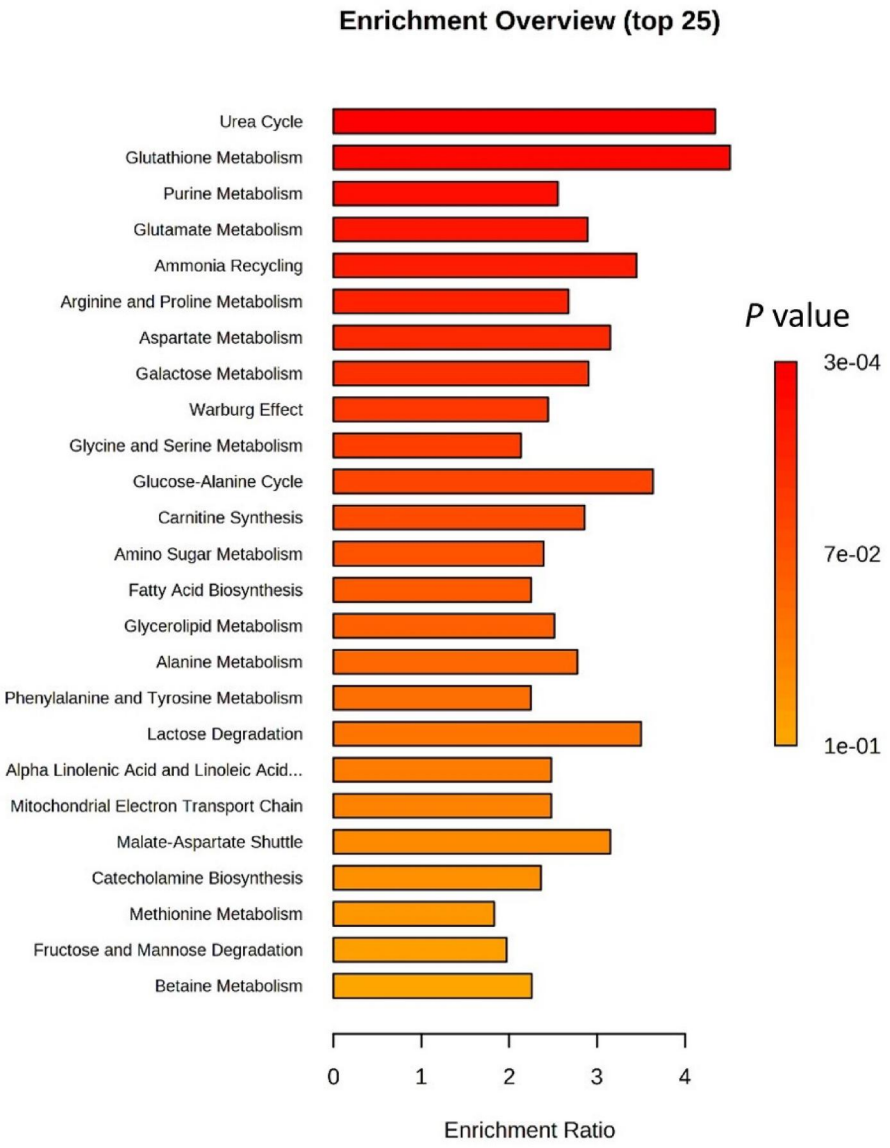

Figure 2. Affected metabolic pathways in colorectal cancer. The differential metabolites identified by all studies for colorectal cancer versus normal tissues under review were enriched into pathways using Metaboanalyst software (version 5.0; www.metaboanalyst.ca).

[16], Italy [9], Belgium [14], and Canada [21]. This is not surprising, as Hashim *et al.* [23] and Kastenmüller *et al.* [24] also reported that the identified metabolomes might be affected by genetics and environmental factors, such as nutrition and lifestyle.

Seven of the 10 reviewed studies have included research subjects with polyps in their study design. Although these studies used a group of patients with colorectal polyps as a part of their research participants, different studies had distinct experimental strategies. For example, Guo *et al.* [18], Gu *et al.* [19], Long *et al.* [11], and Farshidfar *et al.* [21] focused on the identification of serum metabolites for polyps and CRC by comparing them with metabolites presented in the control healthy group. However, Troisi *et al.* [9] and Bhatt *et al.* [14] assigned polyps and healthy patients as control samples to investigate CRC serum biomarkers, as they had suggested that the colorectal polyps were considered non-cancerous samples. In contrast, Uchiyama *et al.* [20] compared the difference of metabolites presented in control health samples with the combined samples of polyps and CRC by considering the colorectal polyps as stage 0 of CRC. Hence, only four studies [11, 18, 19, 21] reported a list of altered serum metabolites for polyps versus normal.

The present review identified that eight metabolites are mostly affected in CRC, i.e. tyrosine, lysine, cystine, arabinose, lactate, methionine, alanine, and valine. Tyrosine, arabinose, lactate, and methionine were reported to be upregulated [9, 16, 17, 19], whereas cystine, alanine, and valine were downregulated [17, 20]. However, the regulations for lysine remain uncertain. Lysine was detected to be upregulated by Tan *et al.* [17] but downregulated in CRC patients by Gu *et al.* [19]. The reason behind this finding is still unknown. According to Hashim *et al.* [16], the differences reported in serum metabolites, expression value, and the altered metabolic pathway might be caused by genetic and environmental factors. This hypothesis, however, requires further investigation.

For polyps, only two altered serum metabolites, lactate and glutamate, are commonly reported. Both were found to be upregulated in patients with colorectal polyps [19]. As only a few studies reported on them, further studies on altered serum

Table 3. Twenty-eight altered metabolites associated with colorectal cancer reported from at least two studies

Metabolite	Bhatt *et al.* [14]	Zhang *et al.* [15]	Hashim *et al.* [16]	Tan *et al.* [17]	Guo *et al.* [18]	Troisi *et al.* [9]	Gu *et al.* [19]	Long *et al.* [11]	Uchiyama *et al.* [20]	Farshidfar *et al.* [21]
Succinic acid		√							√	
Tyrosine	√		√	√			√			√
5-Oxoproline			√					√		
Hypoxanthine			√					√		
Xanthine			√					√		
Citric acid			√							√
Lysine			√	√			√			√
Glycine							√			√
Cystine				√					√	√
Ornithine				√	√					
Citrulline				√					√	
Arabinose				√		√				√
Fructose						√				√
Isoleucine							√			√
Lactate				√			√	√		
Alanine	√						√			√
Proline				√			√			
5-Oxoproline			√				√			
Glycerol				√			√			
Glutamate							√	√		
Methionine	√		√						√	
Threonic acid				√						√
Glutamine (Gln)				√			√			
Valine (Val)	√						√			√
Phenylalanine				√						√
Glycerol 3-phosphate									√	√
Inositol					√					√

√ = detected in the study.

Table 4. Regulation and LogFC value of eight most common significantly altered metabolites associated with colorectal cancer

Metabolite	Bhatt *et al.* [14]	Zhang *et al.* [15]	Hashim *et al.* [16]	Tan *et al.* [17]	Guo *et al.* [18]	Troisi *et al.* [9]	Gu *et al.* [19]	Long *et al.* [11]	Uchiyama *et al.* [20]	Farshidfar *et al.* [21]
Tyrosine	ND	–	↑ 13.05	↑ 1.15	–	–	↑1.19	–	–	ND
Lysine	–	–	–	↓ −8.14	–	–	↑−1.03	–	–	ND
Cystine	–	–	–	↓ −1.37	–	–	–	–	ND	ND
Arabinose	–	–	–	↑ 2.09	–	↑ >0.5	–	–	–	ND
Lactate	–	–	–	↑ 1.3	–	–	↑ 1.48	ND	–	–
Alanine	ND	–	–	–	–	–	↓1.17	–	–	
Methionine	ND	–	↑ 10.94	–	–	–	–	–	ND	–
Valine	ND	–	–	–	–	–	↓1.17	–	–	ND

FC = fold-change, ↓ = downregulated, ↑ = upregulated, ND = not determinable, – = not detected in the study.

metabolites for polyps are required. Since polyps could develop into cancer, it is essential to define the patients with colorectal polyps as a specific study group and identify the potentially altered serum metabolites that might be related exclusively to these patients.

The affected pathways may contribute to the altered metabolites associated with polyps and CRC. Tumorigenesis is associated with increased protein synthesis required for cell proliferation and metastasis. The increasing demands of energy by tumour cells will cause a nutrient-deprived condition, leading to an increased level of the urea cycle, glutathione metabolism, purine metabolism, glutamate metabolism, and ammonia recycling. These conditions indicate a high level of muscle proteolysis, generating a high amount of branched-chain amino acids (BCAAs). The BCAAs (such as valine) and other proteinogenic amino acids (such as methionine, alanine, and tyrosine) are crucial in cancer cell metabolism in nutrient-deprived conditions (Figure 4), as they will be oxidized via the citric acid cycle to provide a high amount of energy needed by the tumour cells [14, 23, 25–27]. We also found that glutathione metabolism was affected in CRC, which is similar to the result reported by Hashim *et al.* [23]. The increased metabolic activity of cancer cells led to the increased production of reactive oxygen species (ROS). ROS serves a significant function in the pathogenesis of cancer by activating signalling pathways that support cell proliferation, survival, and metabolic adaptation [28]. However, high levels of ROS may cause cell damage (Figure 5). Hence, tumour cells react by producing glutathione, an antioxidant, to prevent ROS from reaching toxic levels [23, 27, 28].

Furthermore, polyps are considered an early development of cell abnormality, which could lead to CRC. The five most affected pathways in polyps are the urea cycle, glutamate metabolism, glutathione metabolism, arginine and proline metabolism, and carnitine synthesis. Similar to tumours, polyps might be associated with increased protein synthesis required for cell proliferation. However, there is no information on the link between these metabolic pathways and polyps, which may differ from those associated with CRC. Our finding suggested that, although similar metabolic pathways could be affected in polyps and CRC, the expression level of each altered serum metabolite might slightly

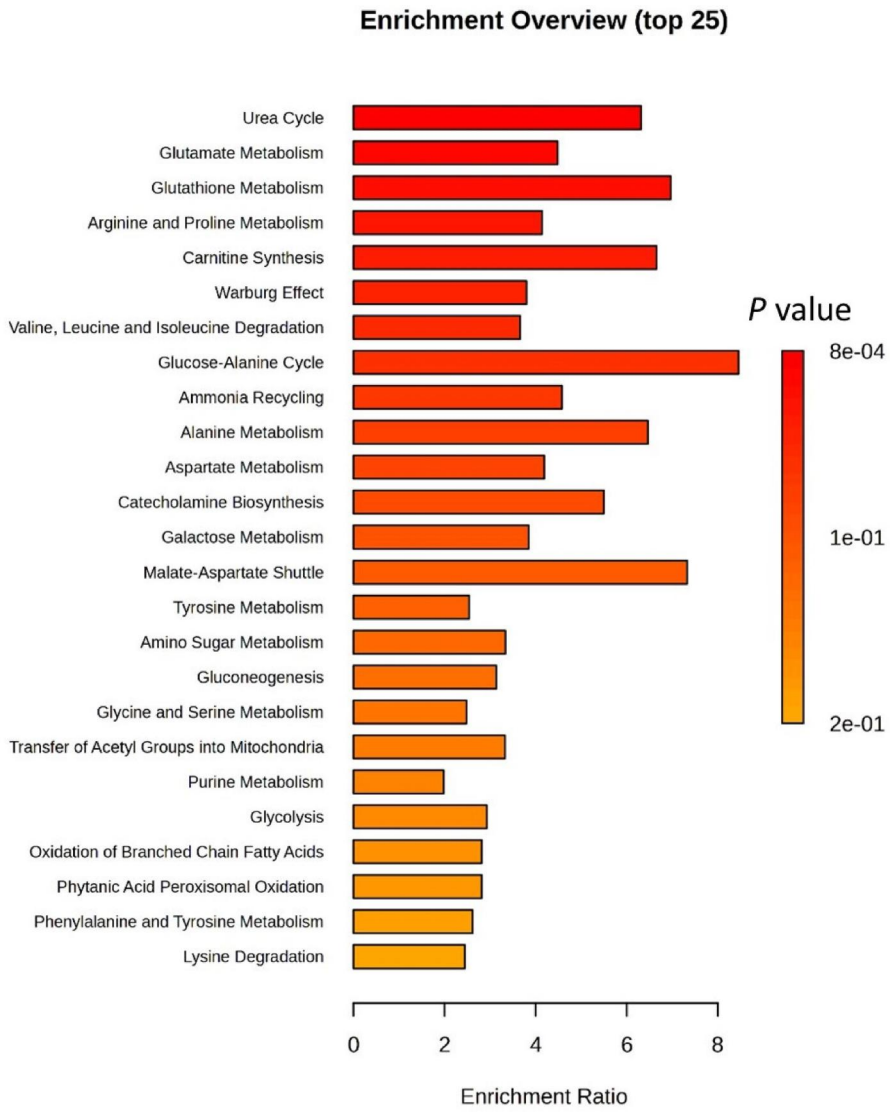

Figure 3. Affected metabolic pathways for the polyps. The differential metabolites identified by all studies under review for polyps were enriched into pathways using metaboanalyst software (version 5.0; www.metaboanalyst.ca).

Table 5. List of metabolites associated with polyps reported in more than two studies with regulation (LogFC) value

Metabolite (polyps vs normal)	Gu *et al.* [19]	Long *et al.* [11]	Farshidfar *et al.* [21]	Guo *et al.* [18]
Lactate	√	√	–	–
Glutamate	√	√	–	–
Regulation (LogFC value)				
Lactate	↑ 1.51	ND	–	–
Glutamate	↑ 1.41	ND	–	–

FC = fold-change, √ = detected in the study, – = not detected in the study, ND = not determinable, ↑ = upregulate.

differ between the two conditions. For example, Gu *et al.* [19] detected lactate for both polyps and CRC with a slight difference in the regulation/expression value.

As this review included only 10 studies that used different study populations with different analytical instruments, more studies are required to confirm the effect of populations on metabolomics profiles. This may contribute to the differences of a panel serum metabolites suggested as a potential biomarker for polyps and/or CRC from each included study. The population also plays an essential factor as it may signify differences in the sensitivity and specificity of each serum biomarker detected in different populations [26]. For example, Hashim *et al.* [16] conducted their study in Malaysia, and Farshidfar *et al.* [21] reported different values of sensitivity and specificity in Canada. It is quite challenging to determine whether the metabolite could be used as a standard biomarker for polyps and/or CRC with a constant high level of sensitivity and specificity in a different population. Thus, more experiments should be conducted to investigate and validate the sensitivity and specificity of identified serum metabolites in CRC and/or polyps among different populations. Moreover, further experiments are also needed to identify distinguishable serum metabolites associated with polyps and CRC

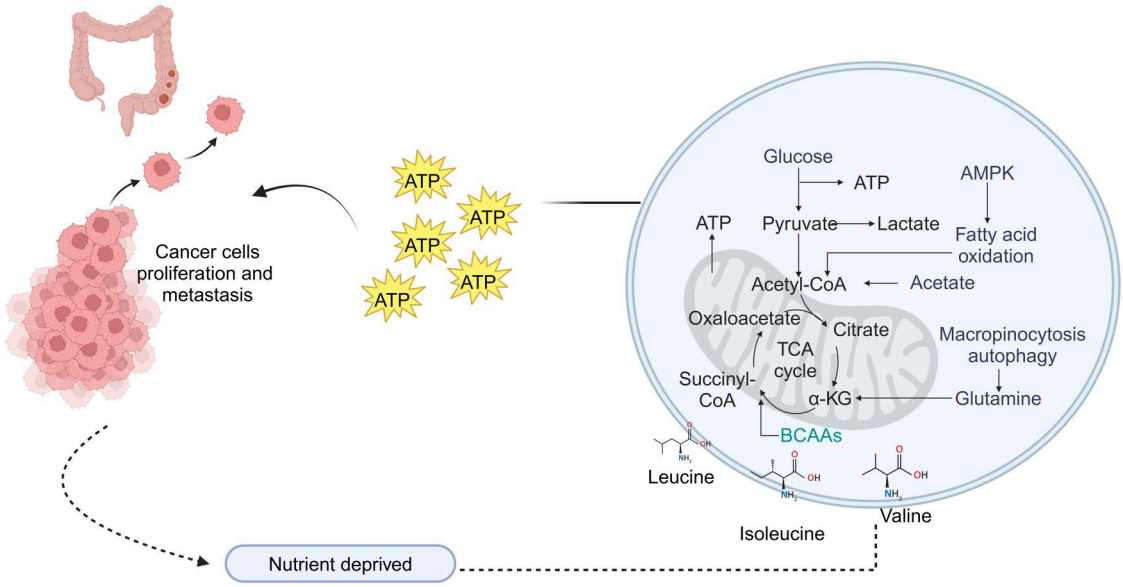

Figure 4. Cancerous cell metabolism during nutrient-deprived condition. AMPK = AMP-activated protein kinase, BCAAS = branched-chain amino acids, GLUT = glutathione, TCA = the citric acid, ROS = reactive oxygen species, ὰ-KG = alpha-ketoglutarate, ATP = adenosine tri-phosphate.

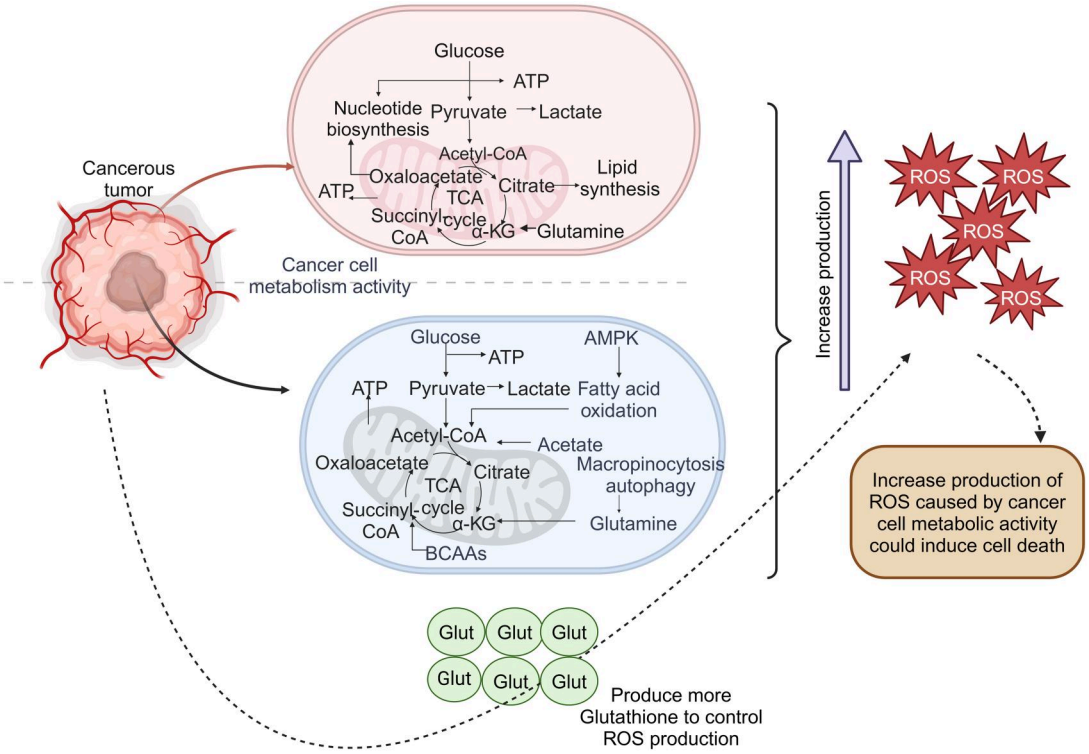

Figure 5. Glutathione production by cancer cells to avoid cell toxicity caused by ROS during metabolic activity. AMPK = AMP-activated protein kinase, BCAAS = branched-chain amino acids, Glut = glutathione, TCA = the citric acid, ROS = reactive oxygen species, ὰ-KG = alpha-ketoglutarate, ATP = adenosine tri-phosphate.

and investigate the differences in their altered pathways and other external factors, such as eating habits and patients' lifestyles, on the regulation level of serum metabolites detected.

This paper has a limitation. The scarcity of studies on serum metabolites for polyps led to insufficient data analysis in this review. The few published papers included in the present systematic review indicate an inadequate amount of research in this area. Although specific common metabolites were identified in this paper, further experiments are required to verify the most relevant serum metabolites in patients with polyps and CRC, perhaps with a standardized definition of research subjects, sample preparation, and analysis instrument.

Conclusions

Enrichment pathway analysis using data from all reviewed studies indicates that the urea cycle, glutathione metabolism, purine metabolism, glutamate metabolism, and ammonia recycling are the most affected pathways for CRC. In contrast, the urea cycle, glutamate metabolism, glutathione metabolism, arginine and proline metabolism, and carnitine synthesis are the most affected pathways for polyps. However, the altered serum metabolites in patients with polyps and CRC were identified to be different compared with those in healthy individuals among different studies. This might be due to the differences in study design, analytical instruments, study populations, and genetic and environmental factors.

Tyrosine, lysine, cystine, arabinose, lactate, methionine, alanine, and valine are the altered metabolites identified by three of the studies reviewed for CRC. Meanwhile, due to the limited number of studies that have included polyps in their study design, only two serum metabolites (lactate and glutamate) can be suggested for polyps. Further studies are required to determine the effects of different population, genetic, and environmental factors on the expression level of identified metabolites, followed by a clinical trial to validate whether these metabolites can serve as common biomarkers for polyps and CRC in different populations.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

Authors' Contributions

M.F.A.B. and A.M.N. conceived and designed the experiments, analysed and interpreted the data, and drafted the paper. S.M. and C.S.F. analysed and interpreted the data and drafted the paper. All authors read and confirmed the final version of this paper.

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Conflicts of Interest

The authors declare that they have no competing interests.

Data Availability

Not applicable.

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