Tyrosine, Phenylalanine, and Tryptophan in Gastroesophageal Malignancy: A Systematic Review

Tom Wiggins, Sacheen Kumar, Sheraz R. Markar, Stefan Antonowicz, and George B. Hanna

Abstract

Gastroesophageal cancer has a rapidly increasing incidence worldwide and reliable biomarkers are urgently required to facilitate earlier diagnosis and improve survival. The aromatic amino acids tyrosine, phenylalanine, and tryptophan represent potential biomarkers and their relation to gastroesophageal cancer will be evaluated in this review. An electronic literature search was performed to identify all published research relating to the measurement of tyrosine, phenylalanine, or tryptophan in the biofluids or tissues of patients with gastroesophageal cancer. Sixteen studies were included in this systematic review. Six studies investigated serum concentrations, which all found decreased concentrations of these aromatic amino acids, except one study that found increased phenylalanine. Five studies reported increased concentrations within gastric content of these patients and two reported increased urinary concentrations. Tissue concentrations of these aromatic amino acids were increased in three studies. Tyrosine, phenylalanine, and tryptophan represent potential biomarkers of gastroesophageal cancer, and further research is necessary to definitively establish the mechanism responsible for altered concentrations of these compounds in patients with gastroesophageal cancer. Cancer Epidemiol Biomarkers Prev; 24(1): 32–38. ©2014 AACR.

Introduction

The United Kingdom National Oesophagogastric Cancer Audit identified that there were 11,516 patients diagnosed with gastroesophageal cancer between April 2011 and March 2012 (1). Globally there are an estimated 482,300 new esophageal cancer cases per annum. Gastric cancer affects nearly one million people worldwide per year and is responsible for around 10% of total cancer-related deaths (2). There is significant geographical variation in the prevalence of gastric cancer with an incidence of up to 26.9 per 100,000 among males in Asia, compared with 3.4 per 100,000 among females in North America (3). The prognosis of gastroesophageal cancer is poor in Western countries as a result of the paucity of alarm symptoms in early stages of the disease resulting in late clinical presentation and delay in the institution of treatment (4). Overall 5-year survival rates also vary geographically with better oncologic outcomes in the Far East in part due to the existence of endoscopic or radiologic screening programs that facilitate early detection of cancer (5). The development of noninvasive, accurate biomarkers to determine gastroesophageal cancer risk could help facilitate earlier diagnosis and improve patient survival.

Amino acids are compounds that have been muted as potential biomarkers of malignant disease. A recent review demonstrated that tryptophan was the metabolite with the most frequently altered concentrations across several cancer types (6). Patients with esophageal cancer have reduced plasma levels of 14 separate amino acids, including tyrosine, phenylalanine, and tryptophan (7). Patients with cancer suffering with anorexia and malnutrition have the most distinctive changes in the plasma amino acid profile (7). Because of the obstructive nature of advanced esophageal cancer, up to 79% of patients develop a degree of malnutrition before diagnosis (8, 9). Aromatic amino acid metabolism (specifically tyrosine, phenylalanine, and tryptophan) may be dysfunctional in gastroesophageal cancer (7). Tryptophan and phenylalanine are both essential amino acids in the human diet. Tryptophan metabolism is linked to the production of serotonin. Phenylalanine is required for the production of the nonessential amino acid tyrosine. The production of tyrosine from phenylalanine was first discovered by Womack and Rose in 1934 (10). This conversion is catalyzed by the enzyme phenylalanine hydroxylase, which mainly functions in the liver, but has been shown to be active in other body tissues, including the kidney, pancreas, and brain (11). It has been shown that phenylalanine hydroxylase activity can be altered in inflammation or malignancy (12, 13). Tyrosine is broken down into several metabolites, including L-DOPA, pyruvate, fumarate, and phenol. Tyrosine is converted to phenol via the action of the enzyme tyrosine phenol-lyase (β-tyrosinase). This reaction was first discovered in bacterial cultures by Kakihara and Ichihara.
(14). Phenolic compounds are potential biomarkers of gastroesophageal cancer with altered concentrations observed within exhaled breath (15), urine (16) and gastric content (17).

Investigation of aromatic amino acid profiles may yield suitable clinical assays to assess a patient’s risk of gastroesophageal cancer. This systematic review will investigate the current published literature to evaluate concentrations of tyrosine, phenylalanine, and tryptophan within tissues or biofluids of patients with gastroesophageal cancer, and assess their potential as biomarkers of this disease.

Materials and Methods

A literature search (title and abstract) was performed using Ovid Medline (1948–2012), Embase (1974–2012), Web of Science, and PubMed electronic databases up to and including June 5, 2014. This search was used to identify relevant studies that had measured tyrosine, phenylalanine, or tryptophan within tissues or biofluids of patients with gastroesophageal cancer and compared levels with an appropriate control group. The search was undertaken using the terms tyrosine or phenylalanine or tryptophan and (cancer or malignancy or neoplasm) and (gastric or stomach or esophageal or esophageal) as well as the medical subject headings, tyrosine or phenylalanine or tryptophan and (stomach neoplasms or esophageal neoplasms). The electronic search was supplemented by a hand-search of published abstracts from relevant conference proceedings (2010–2013). Two reviewers (T. Wiggins and S.R. Markar) independently screened titles and abstracts of studies identified via the electronic search. Full texts were retrieved for all potentially relevant articles. Searching of reference lists of appropriate texts identified further potentially relevant studies. Inclusion criteria were any study measuring tyrosine, phenylalanine, or tryptophan in patients with gastroesophageal cancer via any appropriate analytic method comparing biologic samples from patients with cancer and suitable controls. Exclusion criteria were any studies without an appropriate control group or animal studies. Studies that reported the same patient population in multiple publications were also excluded, except for the most recent or complete publication.

The two reviewers independently extracted data from the selected studies, including number and types of specimen, analytic platform, and amino acid concentrations in cancer and control groups. The hypothesis under investigation was whether concentrations of these aromatic amino acids would be significantly different between cancer and control samples. The QUADAS-2 tool was used to assess the quality of the included studies (18). This model consists of four domains, including patient selection, index test, reference standard, and flow of patients through the study. The reference standard is defined as the best available method to establish the presence or absence of the target condition (19), which in this review was considered to be histologic confirmation of the diagnosis. Each domain is assessed in terms of bias and the first three are also assessed in terms of concerns regarding applicability.

Results

There were 16 studies that met our inclusion criteria for systematic review (see Fig. 1).

Summary table

Please see Table 1.

Study characteristics

Seven studies involved the investigation of patients with esophageal cancer, eight studies investigated patients with gastric cancer and one study investigated both cancer types. In total, there were 524 patients with gastric cancer and 296 patients with esophageal cancer included from these 16 studies. Six studies investigated blood levels of these aromatic amino acids (four esophageal cancer, one gastric cancer, and one for both cancers), five studies investigated gastric content (all patients with gastric cancer), two investigated urinary concentrations in patients with esophageal cancer, and three studies analyzed concentrations of these amino acids in cancer tissues (one esophageal and two gastric). Several analytic platforms were used, including LC/MS (n = 7), gas chromatography mass spectrometry (GC–MS; n = 3), nuclear magnetic resonance (NMR; n = 5), capillary electrophoresis mass spectrometry (CE–MS; n = 1), automated amino acid analyzer (n = 2), and chromatography (n = 1). Some studies used more than one analytic platform.

Quality assessment of studies

Details of the QUADAS-2 study quality assessment are shown in Supplementary Figs. S1 and S2. Unclear risk of bias in patient selection was recorded in all studies due to a lack of information regarding patient recruitment, as it was not specified whether consecutive patients were included or whether any patients were excluded. The risk of bias for the index test was unclear due to lack of information regarding blind or assessors. Several articles had a high risk of bias with regard to patient flow as not all of the controls received the reference standard investigation (histologic examination). Twenty-one percent of studies had an unclear or high risk of applicability concerns due to cancer and control groups not being appropriately matched.

Tyrosine

Tyrosine was measured in 13 of the studies included (five serum based, four gastric content, two urine based and two in tissue). Miyagi and colleagues (20) investigated concentrations of plasma-free amino acids in various cancer types using high-performance liquid chromatography electrospray ionization mass spectrometry. This study included 199 gastric cancer cases and 985 healthy controls. Results from this study showed a significantly decreased tyrosine concentration in gastric cancer cases compared with controls (p < 0.01). This difference was apparent in early (stage I) as well as late (stage IV) disease stage. Zhang and colleagues (21) showed that serum tyrosine levels were decreased in patients with esophageal cancer (n = 23) compared with healthy controls (n = 25; P < 0.002), a finding also reported by Norton and colleagues (P < 0.05; ref. 22). However, other studies by Zhang and colleagues (23) and Ikeda and colleagues (24) showed no significant difference in serum tyrosine levels in patients with esophageal and gastric cancer compared with controls.

Deng and colleagues (25, 26) have performed two studies to investigate levels of amino acids within gastric content. The initial study compared concentrations within gastric content of patients with gastric cancer (n = 33) to a control group (n = 68) using NMR and LC/MS. The median concentration of tyrosine in the cancer group was 54.9 ± 11.0 μg/mL, compared with 8.7...
Another study by the same group compared cases of early gastric cancer (EGC; \( n = 49 \)), advanced gastric cancer (AGC; \( n = 66 \)), and a control group of patients with nonneoplastic gastric disease (\( n = 70 \)). This study showed that median gastric content tyrosine concentrations in the EGC group was 19.4 \( \mu g/mL \) (5.8–72.4), compared with 18.3 \( \mu g/mL \) (6.4–52.3) in patients with AGC and 3.8 \( \mu g/mL \) (1.7–7.5) for the control group. An ROC curve analysis for the utilization of tyrosine concentrations to distinguish EGC from controls showed an AUC of 0.790 [95% confidence interval (CI), 0.703–0.877; \( P < 0.001 \)].

This finding of increased tyrosine levels within gastric content is supported by an early study by Abasov (27), who used chromatography to detect the presence of aromatic amino acids in the gastric content of gastric cancer cases (\( n = 100 \)). They detected tyrosine in 65% of cancer cases compared with 46% of controls. Segawa and colleagues (28) also showed that overall levels of amino acids (including tyrosine and phenylalanine) were higher in the gastric content of patients with gastric cancer (\( n = 16 \)) compared with controls (\( n = 40 \)).

Hasim and colleagues (29) investigated levels of tyrosine in the urine of patients with esophageal cancer (\( n = 108 \)) compared with controls (\( n = 40 \)) using NMR. They showed that tyrosine levels were increased within the urine of patients with esophageal cancer (correlation coefficient –0.32). Davis and colleagues (30) found increased tyrosine levels in the urine of patients with esophageal cancer (\( n = 44 \)) compared with healthy controls (\( n = 44 \)), although this difference did not reach statistical significance. This study also investigated urinary levels of tyrosine and tryptophan in patients with Barrett’s esophagus (\( n = 31 \)) against another healthy control group (\( n = 31 \)) but no significant differences were observed. Two studies investigated levels of tyrosine within gastric cancer tissue compared with normal controls. Wu and colleagues (31) used paired tissue samples (cancer and healthy mucosa) from 20 patients with esophageal cancer and used GC–MS to establish levels of tyrosine. This showed significantly increased levels of tyrosine in cancer tissue compared with normal mucosa. Hirayama and colleagues (32) used capillary electrophoresis mass spectrometry and showed that levels of tyrosine were significantly increased in gastric cancer tissues compared with normal tissue (\( P < 0.001 \)).
<table>
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<td>BE 3 HGD 9 HC 34</td>
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<td>hiatus hernia (n = 9)</td>
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<td>$^{a}$ (free trp levels)</td>
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<td>Tyr, Phe</td>
<td>Esophageal</td>
<td>Amino acid analyzer</td>
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<td>14</td>
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<td>Gastric</td>
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<td>Gastric</td>
<td>LC/MS</td>
<td>38</td>
<td>48 (BGD)</td>
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<td>68 (mix HC and BGD)</td>
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<td>Gastric</td>
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<td>40 (mix HC and BGD)</td>
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<td>Chromatography</td>
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<td>140 (HC + BGD)</td>
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<td>Tyr, Phe</td>
<td>Esophageal</td>
<td>NMR</td>
<td>108</td>
<td>40</td>
<td>$^{a}$</td>
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<td>Urine</td>
<td>Tyr</td>
<td>Esophageal</td>
<td>NMR</td>
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<td>44</td>
<td>$^{a}$</td>
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<td>Song et al. (34)</td>
<td>Tissue</td>
<td>Phe</td>
<td>Gastric</td>
<td>GC-MS</td>
<td>30</td>
<td>30</td>
<td>N/A</td>
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<tr>
<td>Wu et al. (31)</td>
<td>Tissue</td>
<td>Tyr, Phe</td>
<td>Gastric</td>
<td>GC-MS</td>
<td>20</td>
<td>20</td>
<td>$^{b}$</td>
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<td>N/A</td>
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<td>Tissue</td>
<td>Tyr, Phe, Trp</td>
<td>Esophageal</td>
<td>CE-TOF-MS</td>
<td>12</td>
<td>12</td>
<td>$^{b}$</td>
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</tbody>
</table>

Abbreviations: BE, Barrett's esophagus; CE-TOF-MS, capillary electrophoresis time-of-flight mass spectrometry; HC, healthy controls; N/A, not reported; Phe, phenylalanine; Trp, tryptophan; Tyr, tyrosine; $^{a}$, raised levels in cancer patients; $^{b}$, decreased levels in cancer patients; $^{-}$, no difference shown.

$^{a}P < 0.05$

$^{b}P < 0.001$
Phenylalanine

Phenylalanine levels were measured in 13 included studies (five blood-based studies, four gastric content–based studies, one urine based, and the three tissue studies). Miyagi and colleagues (20) and Norton and colleagues (22) showed that serum phenylalanine levels were decreased in patients with gastric and esophageal cancer, respectively. However, Zhang and colleagues (21) demonstrated patients with esophageal cancer to have raised serum phenylalanine levels compared with healthy controls \( (P = 0.004) \). Ikeda and colleagues (24) compared phenylalanine levels in patients with gastric and esophageal cancer \( (n = 15, n = 11) \), respectively with healthy controls \( (n = 12) \) but observed no significant difference. Naini and colleagues (33) also showed no significant change in plasma phenylalanine levels.

Deng and colleagues (25) demonstrated that median concentrations of phenylalanine in gastric content were \( 54.3 \pm 11.\mu g/mL \) in the gastric cancer group, compared with \( 8.8 \pm 2.1 \mu g/mL \) in the control group \( (P < 0.05) \). In a second study by Deng and colleagues (26), the AUC using gastric content phenylalanine concentrations to discriminate EGC cases from controls was \( 0.831 \) (95% CI, 0.750–0.911; \( P < 0.001 \)). The AUC for the AGC cases compared with controls was \( 0.858 \) (95% CI, 0.794–0.922; \( P < 0.001 \)). Abasov (27) showed that phenylalanine was detected in 80% of cancer cases and 56% of controls. Hasim and colleagues (29) observed increased phenylalanine concentrations in the urine of patients with esophageal cancer compared with controls \( (P < 0.001) \). However, Wu and colleagues (31) demonstrated no significant differences in phenylalanine concentrations between esophageal cancer tissue and normal mucosa. Song and colleagues (34) reported a trend toward increased phenylalanine concentrations in gastric cancer tissues but this observation was not statistically significant.

Tryptophan

Tryptophan levels were investigated in 10 studies (five blood based, four in gastric content, and one in tissue). Zhang and colleagues (23) measured fasting tryptophan levels in 67 patients with esophageal cancer and a control group, including 3 patients with Barrett’s esophagus, 9 patients with high-grade dysplasia, and 34 healthy volunteers. This study showed that tryptophan levels were significantly reduced in patients with esophageal cancer compared with controls \( (P = 3.2E−0.5; \text{fold change} = 1.2) \). This finding was supported by other groups, including Zhang and colleagues (21) and Naini and colleagues (33), who demonstrated decreased serum levels of tryptophan in these patients \( (Zhang \text{ VIP 3.55}, P = 0.000; \text{Naini} P < 0.05 \text{ for free tryptophan levels). Total tryptophan levels showed no significant change). Miyagi and colleagues (20, 22) also showed significantly decreased plasma tryptophan concentrations in gastric cancer cases compared with controls \( (P < 0.01) \). However, Ikeda and colleagues (24) found no significant difference in tryptophan between patients with esophageal or gastric cancer when compared with healthy controls.

Lian and colleagues (35) demonstrated tryptophan concentrations of greater than 6.0 mg/L were found within the gastric content of 52.6% of patients with gastric cancer \( (n = 38) \) compared with 22.9% of controls with BGD \( (n = 48; P < 0.05 \text{). This finding was further supported by Deng and colleagues (25), who showed that median concentrations of tryptophan in gastric content of patients with gastric cancer were \( 19.4 \pm 4.7 \mu g/mL \), compared with \( 2.7 \pm 1.0 \mu g/mL \) in controls \( (P < 0.05 \). The second study by Deng and colleagues (26) showed that the AUC for gastric content tryptophan concentrations was \( 0.819 \) (95% CI, 0.739–0.900; \( P < 0.001 \)) to discriminate gastric cancer from controls. Abasov (27) showed that tryptophan was found in 23% of cancer cases compared with 13% of controls. Hirayama and colleagues (32) found significantly increased tryptophan levels in gastric tissues compared with controls \( (P < 0.05 \).

Discussion

The results of this systematic review suggest that the three aromatic amino acids under investigation (tyrosine, phenylalanine, and tryptophan) are increased within the gastric content and tissues of patients with gastroesophageal cancer. Tyrosine and phenylalanine levels were also increased in the urine of these patients. The majority of studies investigating serum (or plasma) concentrations demonstrate that levels of these amino acids are decreased in the serum (or plasma) of patients with gastroesophageal cancer.

Malnourishment may also be a contributing factor to these reduced levels of plasma amino acids. Malnourished patients develop a hypermetabolic state with increased hepatic gluconeogenesis and protein catabolism. However, cachexia and malnourishment does not appear to be the primary factor contributing to the decreased serum amino acid concentrations in patients with gastroesophageal cancer; this hypothesis is supported by Miyagi and colleagues (20), who observed decreased plasma-free amino acid levels in both early-stage disease (stage I) as well as patients with stage IV disease. Kawamura and colleagues (36) have also demonstrated that in tumor-bearing rats, there is increased hepatic protein synthetic rates and increased muscle catabolism, particularly during later stages of disease. They concluded that development of cachexia in patients with cancer was not only related to reduced dietary intake but is linked to increased whole-body protein turnover; this particularly occurs during the late stages of disease in which skeletal muscle protein is mobilized for increased tumor synthesis. This increased protein demand in the tumor-bearing state reduces the availability of plasma amino acids (7). Increased demand and overutilization of amino acids by tumor tissue may account for the reduced concentration of serum amino acids (29). Certain amino acid transporters have been reported to be upregulated in cancer, in particular LAT1, which is involved in L-type amino acid transport (37). It has also been shown that blockade of amino acid transporters can cause apoptosis in certain cancer cell lines (38).

The changes in blood levels of phenylalanine are of particular interest. Two studies in this review showed reduced phenylalanine concentrations in patients with gastroesophageal cancer and another identified increased concentrations. Previous work has shown that activity of phenylalanine hydroxylase (which converts phenylalanine to tyrosine) is dysfunctional in inflammatory or malignant disease states (12, 13). This raises the possibility that blood phenylalanine levels could be altered in patients with gastroesophageal cancer due to reduced action of this enzyme. This reduction in enzyme activity may also account for the decreased tyrosine levels observed by Zhang and colleagues (21). However, the biologic mechanism...
responsible for these alterations in amino acid concentrations in patients with cancer remains unclear and further investigation is required to explore this relationship.

The increased levels of aromatic amino acids within the gastric content may be an especially important finding. The two studies by Deng and colleagues (25, 26) were both part of this review as only 6 cancer cases (from 33 total in the initial study, and 115 total in the second study) were included in both studies. In the second study, a logistic regression analysis was performed to establish the predictive values of candidate biomarkers for the detection of EGC. This identified four variables (age and elevated tyrosine, phenylalanine, and tryptophan levels in gastric content) as being significant for detection of EGC cases (26). Various potential mechanisms have been proposed for the increased concentrations of these aromatic amino acids within gastric content. One possibility involves increased production of enzymes, which degrade the basement membrane with extracellular matrix by invasive cancer cells (39), and specifically certain matrix metalloproteinase enzymes have been shown to be upregulated by aggressive cancer cells (40). This degradation may release aromatic amino acids into the gastric content causing increased concentrations of these compounds (25). Other postulated mechanisms to explain this phenomenon include increased protein synthesis within rapidly growing malignant tissues, thereby releasing these aromatic amino acids into the gastric content.

Aromatic amino acids within gastric content may be candidate biomarkers for gastroesophageal cancer. However, the retrieval of gastric content for analysis requires an invasive procedure either via endoscopy or nasogastric tube insertion. Therefore, the “gold-standard” investigation for gastroesophageal cancer remains endoscopy and histologic examination. Gastric content and tissue may be sampled as part of diagnostic endoscopy to allow supplementary amino acid profiling in early-stage gastroesophageal cancer. Furthermore, evaluation of amino acid concentrations in gastric content and tissue of patients undergoing multiple endoscopic tests (e.g., endoscopic ultrasound or repeat endoscopy) may allow serial measurements to monitor therapeutic response during neoadjuvant therapy. The effect of neoadjuvant therapy upon the amino acid profile as a marker of therapeutic response is an important area for future investigation.

These increased amino acid concentrations in gastric content are also important for the development of new biomarkers particularly given their link to phenol metabolism. Phenol production is linked to aromatic amino acid metabolism through the process of proteolytic fermentation. Specifically, tyrosine phenol-lyase is a bacterial enzyme involved in the conversion of tyrosine to phenol. It has been previously shown that phenols are a major product of tyrosine metabolism within the colon (41). Once tyrosine has been released into the gastric content, the action of tyrosine phenol-lyase from the microbiome could convert tyrosine to phenol causing increased concentrations within gastric content. This is in keeping with the findings of previous studies showing increased phenolic compound concentrations within gastric content of patients with gastroesophageal cancer (17). Increased phenol concentrations have also been observed in the exhaled breath of patients with gastroesophageal cancer (15). This raises the potential for phenol measurement within exhaled breath to be used as a surrogate marker of gastroesophageal cancer risk. Future studies may also help to definitively establish differences in the aromatic amino acid profile within the urine of patients with gastroesophageal cancer compared with controls. Serial urinary sampling could represent another noninvasive method for assigning risk of gastroesophageal cancer and monitoring therapeutic response. These methods could potentially be used for identifying at-risk individuals in need of urgent endoscopy, and thereby help in diagnosing gastroesophageal cancer at earlier disease stages. This could potentially increase the proportion of patients that are treated on an intention-to-cure basis if a sufficiently accurate clinical assay could be developed.

Conclusion

Tyrosine, phenylalanine, and tryptophan concentrations are altered within the biofluids and tissue of patients with gastroesophageal cancer; these compounds represent promising biomarker targets in gastroesophageal cancer, and hence further studies are needed to investigate whether the observed differences in tyrosine, phenylalanine, and tryptophan are cancer specific.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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