

Biochemical Transformation and Tumor Biomarkers in Colorectal Cancer: Advancements in Metabolic Profiling and Clinical Diagnostics

Erhan Oktay*

Turkish Armed Forces General Staff G.A.T.A. Command, Ankara, Turkey

*Corresponding author: Erhan Oktay, Turkish Armed Forces General Staff G.A.T.A. Command, Ankara, Turkey,

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ABSTRACT

Colorectal cancer (CRC) stands as the third most prevalent malignancy and the second leading cause of cancer-related mortality globally. Early detection remains the cornerstone of reducing mortality; however, current standard screening tools, such as colonoscopy and fecal immunochemical tests (FIT), face substantial limitations regarding invasiveness, costs, and patient compliance. While classical serum macromolecular tumor markers like Carcinoembryonic Antigen (CEA) are integrated into clinical surveillance, their poor diagnostic sensitivity and specificity prevent their efficacy as standalone early screening tools. This comprehensive review systematically evaluates the alterations in biochemical metabolism pathways and the clinical utility of classic tumor markers and emerging metabolic parameters for the non-invasive diagnosis and staging of colon cancer. A methodical review of peer-reviewed articles, clinical cohort data, and meta-analyses published up to 2026 was conducted using electronic engines including PubMed, Web of Science, and Google Scholar. Search queries combined keywords such as "colorectal cancer", "biochemical biomarkers", "metabolomics", "Carcinoembryonic Antigen", "Warburg effect", and "p53". Studies relying solely on tissue-based transcriptomics without serum or plasma validation were excluded. The metabolic reprogramming of colon cancer cells is heavily guided by the Warburg effect, which drives accelerated glycolysis, dysregulated lipid biosynthesis, and disrupted tricarboxylic acid (TCA) cycle intermediates.

Targeted metabolomics of platelet-rich plasma (PRP) and serum has unveiled major systemic shifts, including the elevation of specific carbohydrate metabolites (lactose, glycerol-3-phosphate, 2-hydroxyglutaric acid, isocitric acid) and marked depletions in specific amino acids (tryptophan, histamine). When evaluated in multi-analyte machine learning models, these panels yield diagnostic Area Under the Curve (AUC) scores between 0.96 and 0.97. In parallel, novel serum protein markers, such as Carbonic Anhydrase 1 (CA1) and Sphingomyelin Phosphodiesterase Acid Like 3A (SMPDL3A), display superb diagnostic synergy (AUC=0.917). While classical protein markers like CEA and CA 19-9 exhibit sensitivities below 53% for early disease stages, they remain vital for longitudinal monitoring, molecular profiling via circulating tumor DNA (ctDNA), and tracing targeted therapeutic resistance related to KRAS/NRAS/BRAF mutations. Integrating ultra-sensitive metabolic panels and novel specific proteins into blood-based screening algorithms marks a significant paradigm shift from anatomical screening to non-invasive molecular tracking. A multi-omics approach combining metabolic indicators with classical tumor markers presents the most powerful clinical pathway for the early detection, prognostic evaluation, and individualized therapeutic management of colon cancer.

Keywords: Colorectal Cancer; Biochemical Biomarkers; Carcinoembryonic Antigen (CEA); Metabolomics; Warburg Effect

Abbreviations: CA1: Carbonic Anhydrase 1; AUC: Under the Curve; SMPDL3A: Sphingomyelin Phosphodiesterase Acid Like 3A; PRP: Platelet-Rich Plasma; TCA: Tricarboxylic Acid; CEA: Carcinoembryonic Antigen; CRC: Colorectal Cancer; FIT: Fecal Immunochemical Tests; FOBT: Fecal Occult Blood Test; LC-MS: Liquid Chromatography-Mass Spectrometry; GC-TOFMS: Gas Chromatography-Time-of-Flight Mass Spectrometry; HK2: Hexokinase 2; PFK1: Phosphofructokinase 1; PKM2: Pyruvate Kinase M2; LDHA: Lactate by Lactate Dehydrogenase A; CTHRC1: Collagen Triple Helix Repeat Containing 1; IBD: Inflammatory Bowel Disease; MRD: Minimal Residual Disease

Introduction

Colorectal cancer (CRC) represents a paramount challenge to modern global healthcare systems. According to recent epidemiological profiles, it maintains its position as the third most frequent malignancy and the second primary driver of oncological deaths worldwide, with close to 1.9 million new cases recorded annually. The clinical trajectory of CRC is notoriously insidious, transitioning silently from benign adenomatous polyps to invasive adenocarcinoma over several decades. When diagnosed at an advanced or metastatic stage, the 5-year survival rate drops drastically, imposing an immense economic and social burden on healthcare infrastructures. Conversely, localized disease detected early correlates with highly favorable therapeutic outcomes, reinforcing the critical need for robust screening strategies. For decades, the clinical pathway for CRC screening and diagnosis has relied heavily on structural or fecal assays. Colonoscopy stands as the definitive gold standard for direct mucosal visualization and biopsy. However, its widespread utility in population-wide screening programs is hindered by its highly invasive nature, substantial financial costs, risk of bowel perforation, and low patient compliance. Non-invasive alternatives, such as the Fecal Occult Blood Test (FOBT) and the Fecal Immunochemical Test (FIT), offer improved screening compliance but are often limited by variable sensitivity for precancerous advanced adenomas and a propensity for false-positive results secondary to dietary factors or lower gastrointestinal tract bleeding [1-3].

To overcome these anatomical and compliance-driven limitations, clinical biochemistry has turned its focus to liquid biopsy platforms and blood-based biomarkers. Sinister transformations inside malignant cells alter systemic biochemical processes long before clinical symptoms like abdominal pain, anemia, or hematochezia manifest. Tumor cells, along with their altered tissue microenvironments, release macromolecular proteins, nucleic acids, and metabolic byproducts directly into the blood circulation. Historically, macromolecular serum markers such as Carcinoembryonic Antigen (CEA) and Carbohydrate Antigen 19-9 (CA 19-9) have been utilized to evaluate treatment efficacy and track disease recurrence. Nevertheless, their diagnostic sensitivity for early-stage asymptomatic CRC remains inadequate, frequently hovering below 53% [1-3]. This clinical review addresses this diagnostic gap by exploring the molecular pathways of CRC through the lens of metabolic reprogramming and advanced clinical biochemistry. By detailing the shifts driven by the Warburg effect, evaluating traditional tumor markers alongside emerging proteomics (e.g., CA1 and SMPDL3A), and discussing plasma metabolomics, this paper outlines a multi-analyte approach capable of transforming early detection and personalized oncological management.

Methods

To evaluate the biochemical parameters and tumor markers utilized in colon cancer diagnosis, a structured literature search was performed. Electronic archives including PubMed, Web of Science,

and Google Scholar were queried for high-impact peer-reviewed research articles, systematic reviews, multi-center cohort clinical trials, and meta-analyses published through early 2026. The search architecture utilized precise combinations of keywords linked by boolean operators: ("colorectal cancer" or "colon adenocarcinoma") and ("biochemical markers" or "metabolomics" or "tumor markers") and ("Carcinoembryonic Antigen" or "p53" or "Warburg effect" or "plasma serum proteomics"). The inclusion criteria focused tightly on clinical validation trials involving human plasma, serum, or platelet-rich plasma (PRP) samples, alongside clear diagnostic accuracy parameters such as Area Under the Curve (AUC), sensitivity, and specificity values [1,2]. Special attention was given to multi-omics validation frameworks combining liquid chromatography-mass spectrometry (LC-MS), gas chromatography-time-of-flight mass spectrometry (GC-TOFMS), and ultra-sensitive immunoassay protocols [3]. Studies limited strictly to animal models or those evaluating tissue transcriptomics without blood translation were excluded to maintain a firm focus on clinically viable, non-invasive diagnostic tools.

Results

Biochemical Metabolism Reprogramming in Colon Cancer the Warburg Effect and Glycolytic Up-Regulation

Malignant colon cells alter their internal metabolic networks to sustain rapid proliferation, a phenomenon known as the Warburg effect. Even in the presence of abundant oxygen, cancer cells bypass the highly efficient mitochondrial oxidative phosphorylation pathway in favor of accelerated glycolysis, rapidly converting glucose into lactic acid [4]. This metabolic shift is driven by the up-regulation of glucose transporters (primarily GLUT1) and key rate-limiting glycolytic enzymes, including Hexokinase 2 (HK2), Phosphofructokinase 1 (PFK1), and Pyruvate Kinase M2 (PKM2) [3,4]. The resulting accumulation of intracellular pyruvate is converted to lactate by Lactate Dehydrogenase A (LDHA). This process generates a continuous supply of Adenosine Triphosphate (ATP) and carbon skeletons necessary for synthesis pathways, while also acidifying the extracellular matrix to encourage tumor invasion and immune evasion.

[Normal Cells]: Glucose → Pyruvate → Mitochondrial TCA Cycle → ~36 ATP

[Warburg Effect]: Glucose → (HK2/PKM2) → Pyruvate → (LDHA) → Lactate + 2 ATP (Rapid)

Disruption of the Tricarboxylic Acid (TCA) Cycle and Amino Acid Pools: Metabonomic profiling of serum derived from colon cancer patients reveals significant disruptions in the tricarboxylic acid (TCA) cycle. Intermediates such as fumarate, succinate, and cis-aconitate are often depleted in circulating blood because they are diverted into pathways that support cellular building blocks. Concurrently, amino acid homeostasis undergoes dramatic changes. Tryptophan and 5-hydroxytryptamine (serotonin) levels are regularly depleted in the serum of CRC patients due to the overactivation of the indoleam-

ine 2,3-dioxygenase (IDO) pathway, an enzymatic system used by tumors to suppress local T-cell responses. Furthermore, targeted metabolomics demonstrates significant reductions in plasma histamine levels, an amino acid involved in modulating immune responses and mucosal barrier integrity within the gut [5-7].

Alterations in Lipid and Choline Metabolism: Rapidly dividing colon cancer cells require substantial lipid synthesis to construct new cellular membranes. Consequently, advanced lipidomic analysis reveals elevated levels of circulating free fatty acids, glycerol, and beta-hydroxybutyrate, alongside a distinct depletion of lysophosphatidylcholines (lysoPCs) in peripheral blood. Tumors aggressively consume lysoPCs from the bloodstream to fuel cell membrane expansion. Additionally, dysregulated choline metabolism leads to altered concentrations of phosphocholine and glycerophosphocholine, serving as direct biochemical indicators of high cellular turnover and advanced disease progression [1,4,6].

Evaluation of Classical Tumor Markers and Advanced Metabolic Parameters

To provide a clear, scannable overview of the diagnostic tools available for colon cancer management, the core parameters are categorized by their biochemical classification, central mechanisms, and diagnostic accuracy:

Carcinoembryonic Antigen (CEA) and CA 19-9: CEA remains the most widely recognized protein marker in colorectal oncology (Journal of WAOCP, 2009). It is an oncofetal cell-surface glycoprotein that plays a role in cellular adhesion and is shed into the peripheral blood by colorectal adenocarcinomas (PMC, 2020). However, because its baseline levels can be altered by non-malignant conditions such as smoking, inflammatory bowel disease (IBD), and liver cirrhosis, its early-stage diagnostic sensitivity is less than 53% [1]. Similarly, the sialylated oligosaccharide CA 19-9 shows limited early sensitivity, often remaining below 36%. Despite these screening limitations, longitudinal monitoring of CEA and CA 19-9 remains crucial; post-operative spikes in these markers serve as reliable early indicators of hepatic or pulmonary recurrence well before lesions are visible on structural imaging panels [7].

The CA1 and SMPDL3A Proteomic Panel: To address the limitations of classical markers, recent tissue-serum proteomics studies have identified novel diagnostic combinations (PubMed, 2026). Concurrently evaluating Carbonic Anhydrase 1 (CA1) and Sphingomyelin Phosphodiesterase Acid Like 3A (SMPDL3A) offers excellent CRC specificity. CA1 plays a role in cellular pH regulation, while SMPDL3A is involved in sphingolipid metabolism. During early colorectal carcinogenesis, their expression profiles shift predictably, and their combined evaluation yields an impressive AUC of 0.917 [6]. This performance provides an accurate non-invasive metric for distinguishing asymptomatic early-stage CRC from healthy controls [2,4,5].

Platelet-Rich Plasma and Serum Metabolomic Panels: The clinical application of untargeted and targeted metabolomics has significantly advanced early detection capabilities. Analyzing platelet-rich plasma (PRP) via ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) identified a unique 5-carbohydrate metabolite panel—consisting of lactose, glycerol-3-phosphate, 2-hydroxyglutaric acid, isocitric acid, and citric acid—that is markedly upregulated in CRC patients. When processed through machine learning classification algorithms (such as Random Forest and Support Vector Machines), this metabolic panel achieved an AUC of 0.961, outperforming traditional CEA and CA 19-9 tests. Furthermore, expanding this panel to encompass 26 endogenous metabolites linked to bile acid biosynthesis and taurine metabolism yielded an exceptional diagnostic accuracy of 92.5%, illustrating the power of metabolic footprints in early detection [4-6].

Discussion

The diagnostic framework for colon cancer is undergoing a major evolution, moving away from late-stage anatomical observation toward early-stage molecular and metabolic profiling [2]. The structural limitations of conventional tools like colonoscopies—such as high costs and low patient compliance—underscore the need for non-invasive, blood-based diagnostic options [3]. As detailed in the results, evaluating metabolic profiles offers a clear advantage for early screening. While traditional macromolecular protein markers like CEA and CA 19-9 are frequently absent or within normal ranges during stage I and II disease, cellular metabolic abnormalities manifest immediately upon malignant transformation to sustain tumor survival and proliferation [1]. However, translating these metabolic parameters into routine clinical practice requires addressing several confounding variables [4]. Because serum metabolomics reflects systemic processes, circulating metabolite levels can be influenced by metabolic comorbidities such as Type 2 Diabetes, obesity, liver disease, and alterations in the gut microbiome [2]. For instance, dyslipidemia can alter circulating free fatty acids and cholesterol fractions, potentially mimicking or masking CRC-specific lipid profiles [6]. To minimize these confounding effects, recent multi-omics strategies combine metabolic profiling with circulating cell-free DNA (cfDNA) methylation assays or circulating tumor DNA (ctDNA) analysis [1].

Integrating an 11-differential methylation site cfDNA profile with a 10-metabolite serum panel increased diagnostic performance to an AUC of 0.98, demonstrating that cross-validating independent biochemical pathways can virtually eliminate false-positive results [6]. Furthermore, liquid biopsies play a vital role beyond early detection, particularly in guiding targeted therapies and assessing prognosis [8-10]. Advanced molecular profiling of ctDNA fragments allows for the non-invasive tracking of somatic mutations within the KRAS, NRAS, and BRAF oncogenes. Detecting mutations within KRAS codons 12 or 13 via blood assays predicts immediate therapeutic resistance

to anti-EGFR monoclonal antibodies such as cetuximab and panitumumab, saving patients from ineffective interventions and related toxicities [8]. Additionally, emerging biomarkers like Collagen Triple Helix Repeat Containing 1 (CTHRC1)-which is induced by Transforming Growth Factor-beta (TGF-beta) within the tumor microenvironment-serve as strong indicators of treatment resistance and poor overall survival [1]. This underscores the value of multi-analyte blood panels that integrate metabolic indicators, mutated nucleic acids, and microenvironmental proteins to manage colon cancer comprehensively from initial screening through long-term therapeutic surveillance [8-10].

Conclusion and Recommendations

Colorectal cancer induces deep systemic changes, characterized by glycolytic acceleration, disrupted amino acid pools, altered lipid biosynthesis, and the shedding of specific tumor-associated proteins into the bloodstream. While traditional protein parameters like CEA and CA 19-9 lack the sensitivity required for early-stage screening, they remain essential tools for post-operative surveillance and monitoring disease recurrence. Advanced metabolic panels-such as the 5-carbohydrate PRP model-and novel proteomic signatures like the CA1/SMPDL3A panel offer non-invasive alternatives that can detect early malignant changes with high accuracy.

Based on these findings, the following actions are recommended for clinical research and healthcare implementation:

- 1. Development of Composite Screening Panels:** Transition from standalone biomarker screening toward integrated multi-analyte panels that combine classical markers (CEA) with highly sensitive metabolic parameters to improve early-stage detection rates.
- 2. Standardization of Pre-Analytical Protocol Designs:** Establish strict, global guidelines for collecting and processing blood samples (e.g., utilizing specialized platelet-rich plasma or dried blood spot sampling coupled with mass

spectrometry) to ensure reproducible metabolic measurements across clinical settings.

- 3. Routine Liquid Biopsy Integration:** Implement serial ctDNA and metabolic monitoring as standard clinical practice for post-resection patients to accurately identify minimal residual disease (MRD) and trace the development of targeted therapeutic resistance early.

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Erhan Oktay . Biomed J Sci & Tech Res



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