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Research Article

Serum Carcinoembryonic Antigen (CEA) and Tumor Characteristics Correlate with UBE2Q1 Protein Expression in Colorectal Cancer Patients

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ABSTRACT

Objectives: Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide, ranking third in men and second in women. The ubiquitin-conjugating enzyme UBE2Q1 has been reported to be overexpressed in colorectal tumors; however, its role in CRC pathogenesis and prognosis remains unclear. Carcinoembryonic antigen (CEA) is a well-established biomarker elevated in CRC, used to monitor treatment response and disease progression. This study aimed to investigate the association between UBE2Q1 gene expression and CRC prognosis by evaluating its correlation with serum CEA levels.

Methods: In this cross-sectional study, 48 CRC patients undergoing surgery at Faghihi Hospital, Shiraz University of Medical Sciences, were analyzed. Tumor and adjacent normal tissues were collected for UBE2Q1 expression analysis via Western blotting. Concurrently, serum CEA concentrations were measured using ELISA, and liver function tests were assessed using an autoanalyzer. Clinical and pathological data, including tumor size, lymph node involvement, and liver function tests, were also recorded.

Results: The cohort had a mean age of 57.2 ± 14.6 years, with equal gender distribution. Mean serum CEA was 2.35 ± 3.45 ng/mL, and UBE2Q1 expression was 5.80 ± 12.39 arbitrary units. Tumor size averaged 29.17 ± 46.13 cm^2; 21.4% had lymph node metastasis, and 70% exhibited well-differentiated pathology. Tumors were predominantly located in the rectum (35.7%) and colon (33.3%). A significant positive correlation was observed between serum CEA levels and UBE2Q1 expression (Spearman's $\rho = 0.38$, $p < 0.05$). UBE2Q1 expression also correlated significantly with alkaline phosphatase and AST liver enzymes ($p < 0.05$). No significant associations were found between UBE2Q1 expression and age, sex, or histopathological features, while serum CEA correlated with pathological differentiation.

Conclusion: UBE2Q1 protein expression is positively associated with serum CEA levels and certain liver function markers, suggesting its potential utility as a prognostic biomarker in CRC. Further studies are warranted to elucidate its mechanistic role and clinical applicability.

Keywords: Colorectal Neoplasms; Carcinoembryonic Antigen; Ubiquitin Conjugating Enzyme E2 Q1; Pathology

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Introduction

Colorectal cancer (CRC) ranks as the second most common cancer in women and the third in men worldwide. In 2012, approximately 614,000 women (9.2% of new cancer cases) and 746,000 men (10%) were diagnosed with CRC globally, with more than half of cases occurring in developed regions. The age-standardized incidence rate is higher in men (20.6 per 100,000) than in women (14.3 per 100,000), and most patients are diagnosed after age 50, with 75% of rectal and 80% of colon cancer patients over 60 years old at diagnosis (1).

Both genetic and environmental factors contribute to CRC etiology. The majority of CRC cases are sporadic, with approximately 75% of patients lacking a family history. However, individuals with a first-degree relative diagnosed between ages 50 and 70 have nearly double the risk, and this risk triples if the relative was diagnosed before age 50. The presence of two or more affected family members further increases the risk. These familial risks partly reflect low-penetrance genetic factors, and approximately 15–20% of CRC patients report a positive family history (2). Inherited CRC syndromes account for 5–10% of cases. Lynch syndrome, the most common hereditary syndrome, results from mutations in DNA mismatch repair genes, including MutL Homolog 1 (MLH1), MutS Homolog 2 (MSH2), MSH6, Postmeiotic Segregation Increased 2 (PMS2), and Epithelial Cell Adhesion Molecule (EPCAM). Defective mismatch repair leads to microsatellite instability (MSI), which is detectable via PCR, comparing tumor and normal DNA. Lynch syndrome diagnosis has evolved from clinical criteria (Amsterdam and Bethesda) to universal tumor testing for MSI and immunohistochemistry in patients under 70 years (3, 4).

Familial adenomatous polyposis (FAP), caused by mutations in the Adenomatous Polyposis Coli (APC) gene, which regulates WNT signaling, leads to numerous colorectal adenomas and early-onset CRC. Other inherited syndromes include MUTYH-associated polyposis, Peutz-Jeghers syndrome, juvenile polyposis, and inflammatory bowel disease-associated CRC (5).

CRC diagnosis arises from symptom evaluation or screening. Symptoms such as rectal bleeding, altered bowel habits, abdominal pain, fatigue, anemia, and weight loss have limited prognostic value but warrant further investigation. Colonoscopy remains the gold standard for diagnosis and screening, offering high accuracy, tumor localization, histological confirmation, and molecular profiling. Importantly, colonoscopy allows for therapeutic intervention via polypectomy, reducing CRC incidence and mortality (6–8). Despite initial lesion removal, patients remain at risk for new neoplasms due to biological and environmental factors (9).

Carcinoembryonic antigen (CEA) is widely used in CRC follow-up to detect recurrence. Measuring serum CEA is cost-effective and feasible in community settings compared to imaging modalities like CT scans (10). CRC develops through progressive mutations in genes such as p53, Mothers Against Decapentaplegic Homolog 4 (SMAD4), and Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), whose protein products are regulated by the ubiquitin-proteasome system (UPS) (11). The UPS controls protein degradation through a cascade involving ubiquitin-activating (E1), conjugating (E2), and ligase (E3) enzymes, culminating in proteasomal degradation. Dysregulation of UPS targets key cell cycle proteins and tumor suppressors, contributing to oncogenesis (12). For instance, APC mutations impair proteasomal degradation of β-catenin, resulting in unchecked Wnt signaling and cell proliferation in most CRCs (13, 14).

The UPS and autophagosomal-lysosomal system interact to maintain protein homeostasis, with shared ubiquitin signals directing substrates for degradation. Crosstalk between these pathways involves shared enzymes and receptors, including p62 and Neighbor of BRCA1 gene 1 (NBR1), and regulatory kinases such as Casein Kinase 2 (CK2) and p38 Mitogen-Activated Protein Kinase (MAPK) (15–17). UBE2Q1, an E2 ubiquitin-conjugating enzyme, is overexpressed in several cancers, including breast cancer, squamous cell carcinoma of the head and neck, and acute lymphoblastic leukemia (18), as well as CRC, but still remains unexplored.

Given the critical need for reliable biomarkers in CRC diagnosis and prognosis, investigating the relationship between UBE2Q1 expression and serum CEA levels, alongside pathological features, may enhance early detection and inform treatment strategies. Thus, our current study aimed to investigate the fundamental aspects underlying this phenomenon.

Materials and Methods

Collection of Tissue Specimens and Corresponding Clinicopathological Data

Colorectal tumor tissues were collected from patients at Shahid Faghihi Hospital, Shiraz. A total of 43 colorectal tumor specimens, along with adjacent normal tissues, were obtained either via needle biopsy (n = 12) or surgical resection (n = 31). Each case was accompanied by a concise clinical summary and pertinent examination data. The study cohort comprised individuals aged 25 to 81 years who underwent surgery for colorectal cancer treatment and had not received prior chemotherapy or radiotherapy. Tumor samples were excised from the medial margins, deliberately avoiding necrotic regions, while normal tissue specimens were harvested from the most distal resection margins. All tissue samples underwent hematoxylin and eosin (H&E) staining and were independently evaluated by experienced pathologists to confirm histopathological characteristics.

Following collection, tissues were promptly frozen in liquid nitrogen within one hour and stored at −70°C until further analysis.

The study was conducted in accordance with the ethical guidelines approved by the Ethics Committee of Shiraz University of Medical Sciences. All data derived from test results were anonymized to ensure patient confidentiality, with no personal identifiers disclosed. Strict adherence to confidentiality protocols was maintained throughout the study to protect the privacy and rights of all participants.

Protein Extraction and Western Blotting

Tissue samples, both normal and cancerous, were lysed in a buffer containing 150 mM sodium chloride, 1.0% NP-40 (v/v), 50 mM Tris (pH 8.0), and a protease inhibitor cocktail (Roche, Germany). Lysates were subjected to ultrasonication at 4°C for 30 seconds, followed by incubation at 4°C for 2 hours with continuous stirring. The samples were then clarified by centrifugation. Protein extraction from cultured cells employed the same protocol, except agitation was performed for 30 minutes at 4°C. Protein concentrations were determined using the Bradford assay.

For Western blotting, 30 µg of protein per sample was resolved using 12.5% SDS-PAGE (Mini-PROTEAN Tetra Cells, BioRad, USA) and transferred onto nitrocellulose membranes (PROTRAN, Whatman) at 25 V for 18 hours at 4°C. Membranes were blocked with 5% non-fat dried milk for 1 hour at room temperature, then incubated overnight at 4°C with a rabbit polyclonal antiserum (1:2000 in blocking solution) targeting the peptide ATDRLMKELRDIYRSQSF, corresponding to amino acids 252–269 of UBE2Q1 (19). After three washes with PBS-Tween, membranes were incubated with HRP-conjugated goat anti-rabbit IgG (Abcam, USA; 1:2500, 1 µg/ml in 2% BSA/PBS-T) at room temperature. Beta-actin (1:1000) was used as a loading control.

Protein bands were visualized using a chemiluminescent substrate (BioRad) and detected via X-ray film exposure. The relative expression of UBE2Q1 in colorectal tumors was calculated as the ratio of UBE2Q1 levels in malignant versus adjacent non-malignant tissues. Densitometric analysis was performed using Gel-Pro Analyzer software (version 6.0, Media Cybernetics), with actin signal intensity serving as the internal control.

Liver Function Assay

Liver function tests (LFTs), including serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, albumin, and globulins, were measured for all patients. Blood samples were collected under aseptic conditions via venipuncture and transferred to plain tubes. After clotting, the samples were centrifuged at 3000 rpm for 10 minutes to separate the serum. Biochemical analyses were performed using an automated analyzer (Roche, Hitachi 912 Chemistry Analyzer) based on the photometric method, following the manufacturer's instructions. All assays were performed in triplicate to ensure accuracy, and quality control samples were included in each batch of tests.

Serum Carcinoembryonic Antigen (CEA) Measurement

Serum CEA levels were measured using a commercially available ELISA kit (Monobind Inc., USA) according to the manufacturer's instructions. Blood samples were collected into plain tubes and allowed to clot at room temperature. The samples were then centrifuged at 3000 rpm for 10 minutes, and the separated serum was stored at -20°C until analysis. The ELISA assay was performed using a microplate reader (Stat Fax 2100, Awareness Technology Inc., USA) at a wavelength of 450 nm. Each sample was analyzed in triplicate. CEA concentrations were calculated based on a standard curve derived from known calibrators included in the kit. Internal quality control samples were incorporated in each run to ensure accuracy and reproducibility.

Statistical Analysis

The data were analyzed using SPSS version 16. The Kolmogorov-Smirnov test was employed to assess the normality of the data distribution. Given the non-normal distribution, the Spearman correlation test was utilized to investigate the associations between serum CEA levels, UBE2Q1 expression, and liver function tests among patients. Furthermore, the relationships between serum CEA levels and UBE2Q1 expression with demographic and histopathological variables were examined using the non-parametric Mann-Whitney and Kruskal-Wallis tests. Quantitative variables are presented as mean ± standard deviation (SD), while qualitative variables are reported as frequency, number, and percentage. A p-value less than 0.05 was considered statistically significant.

Results

Demographic and Clinicopathological Findings

In this study, 48 patients diagnosed with CRC were examined. The mean age of the participants was 58.14 ± 23.57 years, with an equal distribution of males and females. The average serum CEA level was 79.6 ± 55.3 ng/ml. Additionally, the mean expression level of the UBE2Q1 protein in cancerous cells was observed to be 39.12 ± 80.5 times greater than that in adjacent healthy tissue. The mean tumor size measured was 13.46 ± 17.29 cm^2. Lymph node involvement was present in 21.43% of the patients. Tumor localization included 15 cases (35.71%) in the rectum, 14 cases (33.33%) in the colon, and 13 cases (30.95%) in the sigmoid colon. The predominant tumor morphologies were ulcerative and

Table 1. Demographic and clinicopathological characteristics

Variable		Frequency N (%)
Gender	Male	24(50.0)
	female	24(50.0)
Lymph node involvement	Yes	22(78.57)
	No	6(21.43)
Pathological differentiation	Good differentiation	28(70.0)
	Medium differentiation	6(15.0)
	Poor differentiation	6(15.0)
Tumor location	Colon	14(33.33)
	Sigmoid	13(30.95)
	Rectum	15(35.71)
Tumor shape	Ulcerative	6(28.57)
	Infiltrative	5(23.81)
	Polypi	3(14.29)
	Mushroom shape	2(9.52)
	Circular ulcerative	1(4.76)
	Microscopic remains	1(4.76)
	Mushroom shape and Circular	1(4.76)
	Ulcerative and Infiltrative	2(9.52)

infiltrative, as detailed in Tables 1 and 2. Comprehensive data on liver function tests for the patients are also provided in Table 2.

Relationship between serum CEA levels and UBE2Q1 protein expression and liver function tests

Figure 1 presents the expression levels of UBE2Q1 protein in tumor and normal cells, normalized against the internal control β-actin. As shown, UBE2Q1 expression is markedly elevated in tumor cells compared to normal cells. In contrast, β-actin expression remains consistent across both tumor and normal cell samples, exhibiting no significant difference.

The associations between serum CEA levels and UBE2Q1 expression, as well as age, tumor size, and liver function test parameters, were evaluated using Spearman's correlation analysis. A statistically significant positive correlation was observed between serum CEA levels and UBE2Q1 protein expression (correlation coefficient, $r = 0.38$; $p = 0.001$), indicating a direct relationship between these variables. Furthermore, UBE2Q1 protein expression demonstrated significant positive correlations with alkaline phosphatase ($r = 0.50$; $p = 0.01$) and aspartate aminotransferase (AST) levels ($r = 0.42$; $p = 0.03$), suggesting an association between UBE2Q1 expression and these liver function markers.

Table 2. Mean and standard deviation of age, UBE2Q1 protein expression, CEA, and liver function tests

Variable	Mean ± SD
Age(years)	57.23 ± 14.58
UB2Q1 protein expression	12.39±5.8
CEA level (ng.ml)	6.79±3.55
Tumor size (Cm^2)	46.13±29.17
Total protein (T.Pro)	6.87 ±1.4
Albumin (Alb)	3.96. ± 0.73
Globulin (Glb)	2.92± 0.76
Albumin. Globulin(A.G)	1.4± 0.26
Aspartate transaminase (AST)	25.40 ± 15.73
Alanin aminotransferase (AlT)	24.44± 23.32
Alkaline phosphates (ALP)	187.7± 77.48
Total bilirubin (T.Bili)	0.89 ± 0.74
Direct bilirubin(D.Bili)	0.20 ± 0.13

Given the nonparametric distribution of the data, Spearman's rank correlation was employed for these analyses. Accordingly, Figure 2 depicts the relationship between UBE2Q1 and CEA based on ranked data, further illustrating the correlation between these two variables.

Association of serum CEA levels and UBE2Q1 protein expression with gender and histopathological characteristics of colorectal tumors

The mean expression level of UBE2Q1 protein was higher in women, whereas serum CEA levels

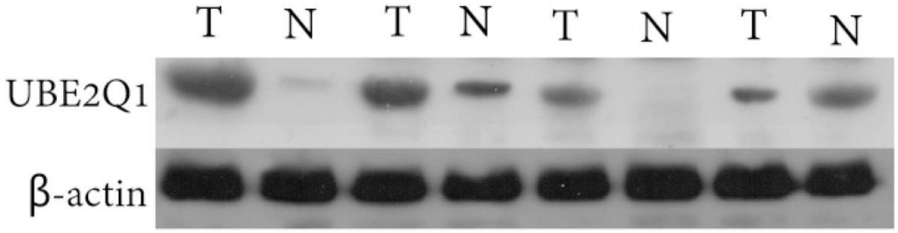

Figure 1. UBE2Q1 protein expression level in colorectal cancer cells (T: Tumor, N: Normal)

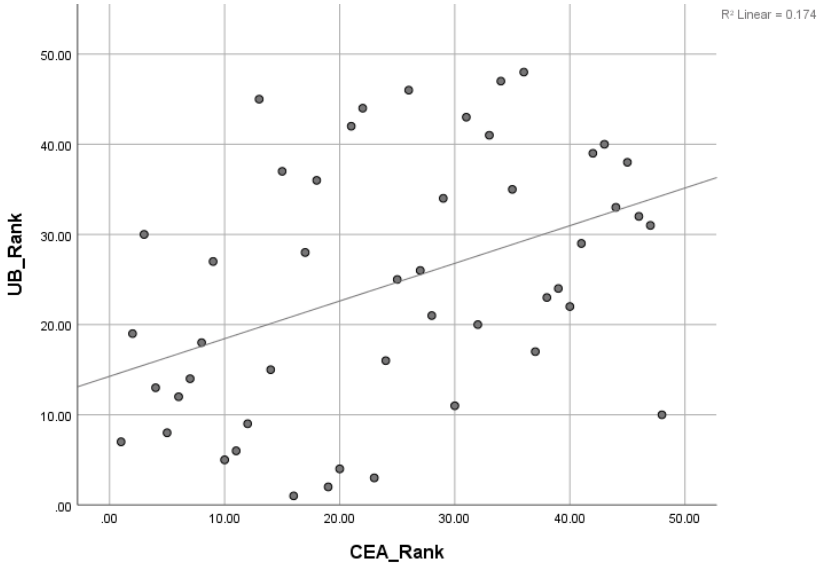

Figure 2. Correlation between UBE2Q1 and CEA

Table 3. Relationship between serum CEA levels and UBE2Q1 protein expression and liver function tests

	CEA	Age	Size	T.pro	Alb	A/G	Glb	ALP	AST	ALT	T.Bili	D.Bili
UBE2Q1	0.38*	-0.05	0.12	0.13	0.21	0.02	0.07	0.50*	0.42*	0.21	-0.37	-0.11
P. Value	0.007	0.75	0.26	0.57	0.60	0.92	0.75	0.01	0.03	0.30	0.09	0.62
CEA		0.001	-.04	0.19	0.22	0.10	0.08	0.07	0.12	-0.27	0.08	0.13
P. Value		0.99	0.83	0.39	0.31	0.66	0.72	0.74	0.58	0.19	0.73	0.55
Age			-0.2	0.16	0.19	0.24	0.03	0.04	-0.15	-0.03	0.23	0.08
P. Value			0.29	0.51	0.40	0.30	0.89	0.87	0.48	0.89	0.32	0.73
Tumor				0.10	0.05	0.05	0.01	0.36	0.25	0.10	-0.03	-0.01
Size				0.75	0.87	0.86	0.99	0.21	0.4	0.74	0.93	0.97

P value: *Statistically significant

were elevated in men; however, neither difference reached statistical significance (P = 0.50 and P = 0.29, respectively).

Contrary to expectations, both UBE2Q1 expression and serum CEA levels were higher in individuals without lymph node involvement, though these differences were not statistically significant (P = 0.57 and P = 0.67, respectively).

No statistically significant associations were observed between tumor status or tumor location and either serum CEA levels or UBE2Q1 protein expression (P > 0.05). Notably, the mean serum CEA level was higher in patients with poorly differentiated tumors compared to those with moderate or well-differentiated tumors; this difference approached but did not reach statistical significance when comparing all three groups (P = 0.06). However, the difference in mean serum CEA levels between the groups with good and poor differentiation was statistically significant (P = 0.03), indicating that poorly differentiated tumors are associated with elevated serum CEA levels. Similarly, UBE2Q1 protein expression was higher in poorly differentiated tumors relative to the other differentiation groups, although this difference did not attain statistical significance (P = 0.14) (Table 4, Figure 3).

Discussion

Despite considerable advancements in the diagnosis and treatment of colorectal cancer, it remains the third leading cause of cancer-related mortality among men and the second leading cause among women. The ubiquitination system constitutes a critical molecular mechanism implicated in the pathogenesis of this malignancy (20). Recent studies have reported elevated expression of the UBE2Q1 protein in human colorectal tumors; however, its precise role in colorectal cancer progression has not yet been elucidated (21). Additionally, carcinoembryonic antigen (CEA) protein levels are known to be elevated in colorectal and other cancers, serving as a biomarker for monitoring therapeutic response and resistance (22). Accordingly, this study aimed to investigate the association between colorectal cancer prognosis and increased UBE2Q1 protein expression by evaluating serum CEA protein levels.

In this study, data from 48 colorectal cancer patients (mean age: 57.23 ± 14.58 years; 50% female) were analyzed. The mean serum CEA concentration was 2.35 ± 3.45 ng/mL, and the mean UBE2Q1 protein expression level was 5.80 ± 12.39 (relative units). The average tumor size, measured

Table 4. Association of serum CEA levels and UBE2Q1 gene expression with gender and histopathological characteristics of colorectal tumors

		UBE2Q1	P-Value	CEA	P-Value
Gender	Male	8.26 ± 3.44	0.50	8.65±4.43	0.53
	female	15.30±8.16		4.42±2.68	
Lymph node involvement	Yes	8.13±3.58	0.57	5.49±3.53	0.61
	No	2.97±2.63		15.36±7.67	
Pathological differentiation	Good differentiation	14.29±7.27	0.14	8.37±3.99	0.06
	Medium differentiation	1.73±0.55		1.63±0.68	
	Poor differentiation	15.76±9.8		6.73±5.20	
Tumor location	Rectum	7.09±3.35	0.47	5.32±3.09	0.81
	Colon	19.45±11.35		10.19±4.38	
	Sigmoid	8.70±5.05		6.73±5.20	
Tumor shape	Ulcerative	15.38±8.04	0.45	5.90±3.68	0.98
	Infiltrative	1.58±0.65		16.78±13.06	
	Polypi	4.0±3.28		1.53±0.83	
	Mushroom shape	0.94±0.37		1.77±1.35	
	Circular ulcerative	3.31		0.90	
	Microscopic remains	1.71		0.80	
	Mushroom shape and Circular	7.85		2.00	
	Ulcerative and Infiltrative	1.19±0.28		1.00±0.71	

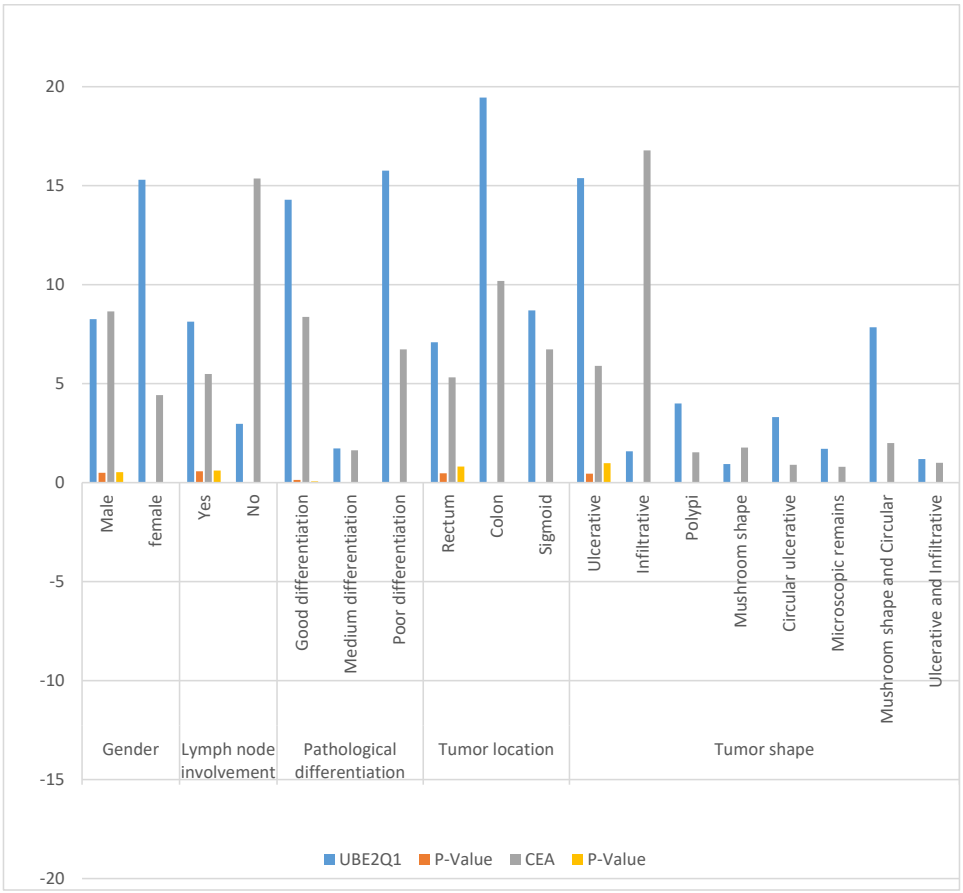

Figure 3. Mean serum CEA levels and UBQ2E1 gene expression according to gender variables and histopathological characteristics of colorectal tumors

post-surgical excision, was 29.17 ± 13.46 cm². Lymph node involvement was observed in 21.43% of patients, while 70% exhibited well-differentiated pathological features. Tumor localization was reported as 35.71% in the rectum and 33.33% in the colon. A statistically significant positive correlation was identified between serum CEA levels and UBE2Q1 protein expression (r = 0.38). Furthermore, UBE2Q1 expression correlated significantly with liver function markers alkaline phosphatase (r = 0.50, p = 0.01) and aspartate aminotransferase (AST) (r = 0.43, p = 0.03). No significant associations were observed between

serum CEA levels and tumor size, patient age, or liver enzyme levels. Given that liver enzyme abnormalities typically manifest in colorectal cancer patients with hepatic involvement, the absence of correlation between CEA and liver function tests may indicate minimal or absent liver metastasis within the studied cohort. Although UBE2Q1 expression was higher in patients without lymph node metastasis, those with poor pathological differentiation, and individuals with colon tumors compared to other groups, these differences did not reach statistical significance. Similarly, serum CEA levels showed no significant association with gender, lymph node status, tumor location, or tumor morphology.

Notably, however, CEA levels were significantly elevated in patients exhibiting poor pathological differentiation, suggesting a relationship between serum CEA concentration and more aggressive tumor phenotypes. Contrary to the present findings, Chang et al. reported a significant association between pathological differentiation grade and UBE2Q1 expression levels, noting increased expression concomitant with poorer differentiation (23). It is important to highlight that Chang et al. categorized UBE2Q1 expression dichotomously (high vs. low), whereas the current study quantified expression continuously. Both studies found no significant correlations between age, gender, and tumor size with UBE2Q1 expression. Previous investigations by Shafiee et al. (2013) (24), Chang et al. (2015) (23), Zhang et al. (2017) (25), and Topno et al. (2021) (26) have demonstrated elevated UBE2Q1 expression in colorectal, hepatocellular, and ovarian cancer cells relative to adjacent normal tissues. Notably, Chang et al. and Zhang et al. identified aberrant UBE2Q1 expression as a potential prognostic biomarker in hepatocellular carcinoma.

Multiple studies have established high serum CEA levels as prognostic indicators for colorectal cancer severity. This study corroborates these findings by demonstrating a positive and significant correlation between serum CEA levels and UBE2Q1 expression. Furthermore, UBE2Q1 expression was elevated in poorly differentiated tumor cells, supporting the hypothesis that heightened UBE2Q1 expression may serve as a prognostic biomarker in colorectal cancer.

The observed association between CEA secretion and UBE2Q1 expression may be attributable to the involvement of specific colorectal cancer cell lines, such as CACO-2, SW1116, and HT29. Trainer et al. (1988) reported elevated CEA levels in these and other colorectal cancer cell lines, including LS174T, SW403, LoVo, SW1463, SW1417, and SKC01 (27). Additionally, Shafiei et al. (2013) identified UBE2Q1 expression in multiple colorectal cancer cell lines, including HT29/219, LS180, SW742, CACO-2, HTC116, SW48, SW480, and SW1116. Ongoing research by Shafiei et al. aims to elucidate the relationship between UBE2Q1 expression and CEA secretion across these cell lines.

Several studies have explored the relationship between histopathological features of colorectal cancer and serum CEA levels. Consistent with the present findings, Jeon et al. (2013) (28) and Wu and Gu (2019) (29) reported that serum CEA levels increase with advancing tumor grade. Conversely, Siregar and Sibarani observed an inverse relationship, whereby less differentiated tumors exhibited lower serum CEA levels (30). Li et al. (2008) found no significant association between histopathological characteristics and serum CEA concentrations (31). Similar to the present study, Siregar and Sibarani (30), Jeon et al. (28), and Li et al. (31) reported no significant correlations between serum CEA levels and patient gender, tumor size, tumor location, or age.

Conclusion

In conclusion, this study demonstrates a direct and statistically significant association between serum CEA protein levels and UBE2Q1 protein expression in patients with colorectal cancer. These findings suggest that UBE2Q1 expression may serve as a valuable prognostic biomarker and inform therapeutic decision-making. Additionally, UBE2Q1 expression correlated significantly with alkaline phosphatase and AST levels but showed no significant relationship with age, gender, or histopathological parameters. Serum CEA levels were significantly associated with pathological differentiation, further underscoring their prognostic relevance.

Conflict of Interests

The authors declare no conflict of interest.

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Ethical Issues

The current study was ethically approved by the Ethics Committee of Shiraz University of Medical Sciences under the Ethics code of IR.SUMS.MED.REC.1400.618.

Availability of Data and Resources

This manuscript contains all data created and examined throughout this investigation. The corresponding author will provide datasets used or analyzed during the current work upon reasonable request.

Authors' Contributions

SR and DK were responsible for all of the experiments, data analysis, and figure preparation. SR and DK wrote the first version of the manuscript. SR,

DK, and SMS wrote the manuscript's second draft. SMS also reviewed and validated the manuscript. The manuscript proof was finally edited and completed by SMS. SMS also participated in the project design and contributed additional funding. All authors have read and agreed to the published version of the manuscript.

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