ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2024 August 26; 12(24): 5448-5635

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
August 26, 2024

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 August 26; 12(24): 5492-5501

DOI: 10.12998/wjcc.v12.i24.5492

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Correlation between TEX14 and ADAM17 expressions in colorectal cancer tissues of elderly patients and neoplasm staging, invasion, and metastasis

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single-blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade C

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Tomczyk M

Received: April 30, 2024

Revised: June 6, 2024

Accepted: June 19, 2024

Published online: August 26, 2024

Processing time: 71 Days and 18 Hours

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Abstract

BACKGROUND

Colorectal cancer (CRC) is one of the most frequently encountered malignant tumors in clinical settings. Proteins encoded by the testis-expressed gene 14 (TEX14) are imperative for spermatogenesis, necessitating intercellular bridges between germ cells. Anomalous expression of TEX14 has also been associated with the proliferation and differentiation of certain tumor cells. Recombinant A disintegrin and metalloprotease 17 (ADAM17) is known as a membrane-bound protease that regulates cellular activities and signal transduction by hydrolyzing various substrate proteins on the cell membrane. We hypothesize that TEX14 and ADAM17 may serve as potential biomarkers influencing the staging, invasion, and metastasis of CRC.

AIM

To probe the correlation between TEX17 and ADAM17 profiles in the CRC tissues of elderly patients and their association with CRC staging, invasion, and metastasis.

METHODS

We gathered data from 86 elderly patients diagnosed pathologically with CRC between April 2020 and December 2023. For each patient, one sample of cancer tissue and one sample of adjacent normal tissue were harvested. Real-time fluorescence quantitative PCR measured the mRNA profiles of TEX14 and ADAM17. Immunohistochemistry ascertained the positivity rates of TEX14 and ADAM17 expressions. Clinical pathological features of neoplasm staging, invasion, and metastasis were collected, and the association between TEX14 and

ADAM17 expressions and clinical pathology was evaluated.

RESULTS

The mRNA and expression profiles of TEX14 and ADAM17 were significantly elevated in CRC tissues. The positivity rates of TEX14 and ADAM17 proteins in CRC tissues were 70.93% and 77.91%, respectively. There were no significant differences in age, sex, pathological type, and tumor diameter between TEX14 and ADAM17-positive and -negative patients. Patients with higher tumor differentiation degree, deeper infiltration and TNM stages ranging from III to IV exhibited higher positivity rates of TEX14 and ADAM17. Patients with lymph node metastasis and distant metastasis showed higher positivity rates of TEX14 and ADAM17 than those without. Positive expressions of TEX14 and ADAM17 were highly correlated with tumor staging, invasion, and metastasis.

CONCLUSION

TEX14 and ADAM17 profiles were significantly elevated in the CRC tissues of elderly patients, and their high expressions were associated with tumor staging, invasion, and metastasis.

Key Words: Elderly patients; Colorectal cancer; TEX14; ADAM17; Staging; Invasion; Metastasis

Core Tip: This research retrospectively harvested clinical data from 86 elderly patients pathologically diagnosed with colorectal cancer to explore the impact of testis-expressed gene 14 (TEX14) and A disintegrin and metalloprotease 17 (ADAM17) expressions on tumor staging, invasion, and metastasis. The outcomes revealed high expressions of TEX14 and ADAM17 in tumor tissues, which were highly correlated with tumor staging, invasion, and metastasis. This suggests that TEX14 and ADAM17 could serve as effective biomarkers for diagnosing and evaluating the progression of CRC in elderly patients.

Citation: Chen G, Cong LH, Gu CJ, Li P. Correlation between TEX14 and ADAM17 expressions in colorectal cancer tissues of elderly patients and neoplasm staging, invasion, and metastasis. *World J Clin Cases* 2024; 12(24): 5492-5501
URL: https://www.wjgnet.com/2307-8960/full/v12/i24/5492.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i24.5492

INTRODUCTION

Colorectal cancer (CRC) ranks as the third most prevalent lethal malignancy in the world, causing approximately 900000 deaths annually and standing as the second leading cause of cancer-associated deaths worldwide[1,2]. The onset of CRC is linked with advanced age, with elderly individuals being more prone to CRC due to improper dietary habits, declining bodily functions, and factors such as mucosal and muscular atrophy of the colon, which dramatically increase the risk of intestinal mucosal cell mutations, stepping up the possibility of CRC[3]. With the recent advancements in medicine and the development of diagnostic and therapeutic techniques, the detection rate of CRC in its early stages has noticeably increased. Modern screening methods have proven effective in reducing the incidence and mortality rates of CRC[4,5]. Surgery remains the primary treatment modality for early-stage CRC, with tumor resection and lymph node clearance effectively extending the survival period of elderly patients[6]. Nevertheless, in reality, most elderly colorectal cancer patients are often ineligible for surgical treatment due to factors such as advanced age, underlying health conditions, or tumor progression.

Multiple biomarkers assume crucial roles in the occurrence and progression of CRC, as well as in the proliferation, invasion, metastasis, and apoptosis of tumor cells. Testis-expressed gene 14 (TEX14), a critical gene related to reproductive cell stability, influences intercellular bridge function. Its DNA methylation is linked to the development of early-onset familial breast cancer[7,8]. Recombinant A disintegrin and metalloprotease 17 (ADAM17) belongs to the metalloprotease superfamily, located on chromosome 2q24.3, possessing a structural domain with metalloenzyme activity. Tumor necrosis factor-alpha, epidermal growth factor receptor, and other cytokines are its common substrates, participating in the cleavage of various cell surface receptors, influencing cell growth, differentiation, and numerous physiological processes. In recent years, ADAM17 has been discovered to be a central regulatory hub in inflammation, immunity, and malignant tumor diseases, contributing to the occurrence and development of several solid tumors[9]. Wilkinson *et al*[10] found that TEX14 was highly expressed in endometrioid carcinoma tissue based on data from the Cancer Genome Atlas. However, the expression of TEX14 in CRC tissue remains unclear. Additionally, studies have shown that compared to the expression level in normal colonic mucosa, ADAM17 is upregulated in CRC tumor specimens, and inhibiting ADAM17 can significantly suppress tumor cell growth[11].

Based on this, we speculate that TEX14 and ADAM17 may similarly play crucial roles in the formation and progression of CRC in elderly individuals. We harvested cancer tissues and adjacent normal tissues from 86 elderly patients and conducted experimental research to investigate the correlation between TEX14 and ADAM17 expressions in CRC tissues

from elderly individuals and their association with tumor staging, invasion, and metastasis.

MATERIALS AND METHODS

Study participants and inclusion criteria

We retrospectively gathered data from 86 elderly patients diagnosed with CRC through pathological examinations between April 2020 and December 2023 for our research. The study population included 45 males and 41 females, with ages ranging from 60 to 78 (average 66.73 ± standard deviation [SD] 2.12) years. Pathological types were classified as follows: 33 cases of tubular adenocarcinoma, 27 cases of villous adenocarcinoma, and 26 cases of papillary carcinoma. The degrees of tumor differentiation were as follows: 34 cases of high differentiation, 25 cases of moderate differentiation, and 27 cases of poor differentiation. TNM staging consisted of 37 cases of stages I-II and 49 cases of stages III-IV. There were 53 cases with lymph node metastasis and 33 cases without it, as well as 46 cases with distant metastasis and 40 cases without it.

Inclusion criteria: Participants meeting the 8th edition colorectal cancer diagnostic criteria established by the American Joint Committee on Cancer[12] and clinically and pathologically diagnosed with CRC; first-time onset cases; age ≥ 60 years; complete clinical and pathological data; and no prior experiences of radiotherapy, chemotherapy, or other adjuvant treatments.

Exclusion criteria: Individuals with concurrent malignant tumor diseases; those with other digestive system diseases; individuals with hematological diseases or hemorrhagic disorders; those with infectious diseases; individuals with immune deficiencies or systemic immune diseases; or individuals on long-term immunomodulatory therapy.

Sample collection

Tissue samples from the tumors resected from the 86 patients, along with normal intestinal mucosal tissues approximately 5 cm away from the tumors, were harvested. Each sample was preserved in liquid nitrogen for freezing to await further testing. To ensure the accuracy of sample collection and diagnosis, the process was jointly completed by two experienced pathologists.

Clinical data collection

A clinical data collection form was designed to record all patient clinical characteristics, including age, sex, pathological type, tumor diameter, differentiation degree, TNM staging, depth of invasion, lymph node metastasis, and distant metastasis, among other baseline conditions.

Methods

Real-time fluorescent quantitative PCR: Appropriate amounts of tumor tissues and adjacent normal tissues were taken from liquid nitrogen, placed into a homogenizer, and thoroughly ground. After adding 1 mL of Trizol reagent, the samples were left to sit for 5 min at room temperature, followed by total RNA extraction from each tissue sample according to the instructions provided. Denaturing gel electrophoresis was used to evaluate RNA integrity and purity. RNA underwent reverse transcription into cDNA. RT-PCR was performed using the Bio-Rad CFX96 quantitative PCR system and SYBR Green, as instructed by the supplier. The PCR reaction conditions were as follows: 30 sec at 95 °C, 5 sec at 95 °C, 30 sec at 60 °C, and 10 sec at 73 °C for a total of 40 cycles. β-actin was used as the internal control for TEX14 and ADAM17. The relative mRNA profiles of TEX14 and ADAM17 were computed as per the $2^{-\triangle\triangle Ct}$ method. Specific primer sequences are listed in Table 1.

Immunohistochemistry and determination of outcomes: Appropriate amounts of tumor tissues and adjacent normal tissues were taken. After routine embedding in paraffin, the sections were dewaxed and dehydrated in gradient ethanol. After being blocked using 3% H_2O_2 for 10 min to get the endogenous peroxidase inactivated, the sections were treated with 0.01 mol/L sodium citrate buffer and microwaved at a pH of 6.0 for 15 min. The slices, sealed with 5% bovine serum albumin for 20 min, were incubated along with the primary antibodies anti-TEX14 and anti-ADAM17 (purchased from Abcam, Cambridge, United Kingdom) at 4 °C overnight. On the next day, the sections were incubated with goat anti-rabbit IgG (ab109489, 1:50; Abcam) for 20 min at room temperature. After washing with PBS, DAB was used for color development. After hematoxylin counterstaining, the sections were dehydrated and mounted for observation.

With PBS as a control, staining results were determined based on the staining of the tumor cell cytoplasm and cell membrane. Twenty high-power fields (× 400 magnification) were counted for immunohistochemical staining cells. The evaluation criteria were as follows: Staining area: 0 points for staining area below 10%, 1 point for 10%-25%, 2 points for 25%-50%, 3 points for 50%-75%, and 4 points for above 75%; staining intensity: 0 points for no staining, 1 point for pale yellow, 2 points for brownish-yellow, and 3 points for brown. The sum of the scores for staining area and staining intensity was adopted as the total score. A total score of 0 suggested negative, 12 points denoted weak positive (+), 3 points indicated positive (++), and a total score of 5 or more demonstrated strong positive (+++).

Statistical analysis

SPSS 22.0 software (IBM Corp., Armonk, NY, United States) was used for statistical processing and analysis. Quantitative data were presented as mean ± SD and assessed *via* *t*-test. Categorical data were represented as percentages, and χ^2 tests were conducted for comparison. Multifactor analysis was performed using logistic regression analysis, with statistical significance defined as $P < 0.05$.

Table 1 Primer sequences for each gene

Gene	Forward	Reverse
TEX14	ATGTCGGACATCGGAGACTG	CTGGTCTCCAAGTCGAAAG
ADAM17	CTGGCTGGCTCATCACATTC	CATGCCTGTAATCCCAGCAC
β-actin	AGAGCCTCGCCTTTGCCGATCC	CTGGGCCTCGTCGCCCACATA

ADAM17: A disintegrin and metalloprotease 17; TEX14: Testis-expressed gene 14.

RESULTS

Differences in TEX14 and ADAM17 mRNA profiles between CRC tissues and adjacent normal tissues

Compared to adjacent normal tissues, the mRNA profiles of TEX14 and ADAM17 in CRC tissues were significantly elevated ($P < 0.05$), as shown in Table 2 and Figure 1. These findings suggested that the *TEX14* and *ADAM17* genes may play a role in the occurrence and development of CRC, with their high expressions likely accelerating tumor growth and differentiation.

Divergence in TEX14 and ADAM17 protein expressions between CRC and adjacent normal tissues

Among the 86 cases of CRC tissues, 61 were positive for TEX14 and 25 were negative, while 67 cases were positive for ADAM17 and 19 were negative. Among the 86 cases of adjacent normal tissues, 23 cases were positive for TEX14 and 63 were negative, whereas 31 cases were positive for ADAM17 and 55 were negative. The positive profiles of TEX14 and ADAM17 in CRC tissues were significantly higher than those in adjacent normal tissues ($P < 0.05$). The positivity rate of TEX14 protein in CRC tissues was 70.93% (61/86), while the positivity rate of ADAM17 protein was 77.91% (67/86), as displayed in Table 3.

Correlation between TEX14 protein expression and clinical pathology

Patients positive for TEX14 and those negative for TEX14 exhibited no remarkable differences in age, sex, pathological type, and tumor diameter ($P > 0.05$). Among patients with high tumor differentiation, 85.29% were positive for TEX14. In patients with TNM stages III-IV, 81.63% were positive for TEX14. Among patients with lymph node metastasis, 83.13% were positive for TEX14. For patients with infiltration depths of T3 and T4, 80.49% and 87.50%, respectively, were positive for TEX14. Among patients with distant metastasis, 80.43% were positive for TEX14. Hence, we observed that patients with higher tumor differentiation and deeper infiltration displayed higher positivity rates for TEX14 ($P < 0.05$). Patients with TNM stages III-IV had a higher TEX14 positivity rate compared to those with stages I-II ($P < 0.05$). Patients with lymph node metastasis and distant metastasis exhibited higher TEX14 positivity rates than those without ($P < 0.05$), as denoted in Table 4. Our findings confirmed that the profile of the TEX14 protein was correlated with the clinical pathological characteristics of elderly patients with CRC, affecting tumor differentiation, infiltration depth, TNM staging, lymph node metastasis, and distant metastasis.

Correlation between ADAM17 protein expression and clinical pathology

Patients positive and negative for ADAM17 showed no significant differences in age, sex, pathological type, or tumor diameter ($P > 0.05$). Among patients with high tumor differentiation, 91.12% were positive for ADAM17. In patients with TNM stages III to IV, 87.76% tested positive for ADAM17. Among patients with lymph node metastasis, 86.79% were positive for ADAM17. For patients with infiltration depths of T3 and T4, 85.37% and 100%, respectively, were positive for ADAM17. Among patients with distant metastasis, 86.96% tested positive for ADAM17. Hence, patients with higher tumor differentiation and deeper infiltration exhibited higher positivity rates for ADAM17 ($P < 0.05$). Patients with TNM stages III-IV had a higher ADAM17 positivity rate than those with stages I-II ($P < 0.05$). Patients with lymph node metastasis and distant metastasis displayed heightened ADAM17 positivity rates than those without ($P < 0.05$), as illustrated in Table 5. From these results, it can be inferred that the expression of ADAM17 protein is linked to the clinical pathological characteristics of elderly patients with CRC. Moreover, positive expression of ADAM17 influences tumor differentiation, infiltration depth, TNM staging, lymph node metastasis, and distant metastasis.

Relationship between TEX14 and ADAM17 profiles and tumor staging, invasion, and metastasis

Using tumor TNM staging, invasion degree, and metastasis status of elderly patients with CRC as dependent variables, and TEX14 and ADAM17 expression as independent variables, the binary variable assignment table is illustrated in Table 6. Multiple logistic regression analysis was performed to examine the relationship between TEX14 and ADAM17 expressions and tumor staging, invasion, and metastasis. As evidenced by our research data, TEX14 positive expression was associated with higher TNM staging (OR = 3.343, 95%CI: 1.211-9.228, $P < 0.05$), deeper invasion (OR = 14.924, 95%CI: 2.152-103.491, $P < 0.05$), lymph node metastasis (OR = 5.018, 95%CI: 1.195-21.067, $P < 0.05$), and distant metastasis (OR = 6.203, 95%CI: 1.246-30.884, $P < 0.05$). Similarly, positive expression of ADAM17 was correlated with higher TNM staging (OR = 4.963, 95%CI: 1.546-15.930, $P < 0.05$), deeper invasion (OR = 6.593, 95%CI: 1.366-31.813, $P < 0.05$), lymph node metastasis (OR = 2.659, 95%CI: 1.067-6.628, $P < 0.05$), as well as distant metastasis (OR = 7.980, 95%CI: 1.651-38.584, $P <$

Table 2 Differences in TEX14 and ADAM17 mRNA profiles between colorectal cancer tissues and adjacent normal tissues

Group	*n*	TEX14 mRNA	ADAM17 mRNA
CRC tissues	86	1.61 ± 0.23	1.82 ± 0.29
Adjacent normal tissues	86	0.98 ± 0.13	1.00 ± 0.12
t value		22.114	24.230
P value		< 0.001	< 0.001

Data are mean ± standard deviation. ADAM17: A disintegrin and metalloprotease 17; CRC: Colorectal cancer; TEX14: Testis-expressed gene 14.

Table 3 TEX14 and ADAM17 protein profiles in colorectal cancer and adjacent normal tissues

Group	*n*	TEX14				ADAM17			
		(-)	(+)	(++)	(+++)	(-)	(+)	(++)	(+++)
CRC tissues	86	25 (29.07)	20 (23.26)	29 (33.72)	12 (13.95)	19 (22.09)	31 (36.04)	27 (31.40)	9 (10.47)
Adjacent normal tissues	86	63 (73.26)	17 (19.76)	6 (6.98)	0 (0)	55 (63.95)	18 (20.93)	13 (15.12)	0 (0)
χ^2 value		43.767				34.863			
P value		< 0.001				< 0.001			

Data are *n* (%). ADAM17: A disintegrin and metalloprotease 17; CRC: Colorectal cancer; TEX14: Testis-expressed gene 14.

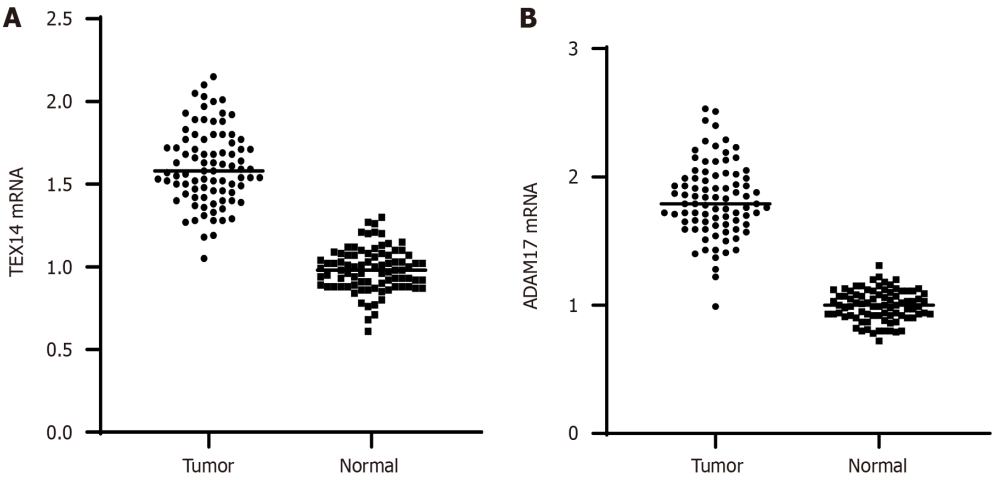

Figure 1 TEX14 (A) and ADAM17 (B) mRNA profiles in 86 cases of colorectal cancer tissues and adjacent normal tissues. ADAM17: A disintegrin and metalloprotease 17; TEX14: Testis-expressed gene 14.

0.05), as shown in Table 7. This indicates that high expressions of TEX14 and ADAM17 significantly influence tumor staging, invasion, and metastasis in elderly patients with CRC, promoting the malignant progression of tumors and contributing to advanced tumor TNM staging, aggravated invasion, and metastasis.

DISCUSSION

Due to the lack of specific symptoms in the early stages of CRC, most elderly patients are diagnosed at an advanced stage. This results in late tumor staging, deeper invasion, and conventional surgical treatment options often failing to achieve desirable outcomes, high surgical risks, poor postoperative recovery, and unfavorable prognosis. In clinical practice, it is necessary to combine the clinical and pathological characteristics of elderly patients to enhance treatment efficacy through adjuvant therapies such as chemotherapy, radiotherapy, and targeted therapy[13-15]. In advanced stages of CRC in elderly patients, tumor cell proliferation is rapid, and invasion and metastasis exacerbate, accompanied by uncontrolled apoptosis. Studies have suggested that various genes such as *STC1*, *AKR1B1*, and *EMP1* are overexpressed in invasive tumor clusters of CRC, affecting local invasion and patient prognosis[16]. Identifying biomarkers associated

Table 4 Association between the protein profile of TEX14 and clinical pathology

Pathological features		*n*	TEX14		X^2 value	*P* value
			Positive, *n* = 61	Negative, *n* = 25		
Age	≥ 65 years	54	36 (66.67)	18 (33.33)	1.279	0.258
	< 65 years	32	25 (78.13)	7 (21.88)		
Sex	Male	47	35 (74.47)	12 (25.53)	0.629	0.428
	Female	39	26 (66.67)	13 (33.33)		
Pathological type	Tubular adenocarcinoma	33	23 (69.70)	10 (30.30)	0.715	0.699
	Villous adenocarcinoma	27	18 (66.67)	9 (33.33)		
	Papillary carcinoma	26	20 (76.92)	6 (23.08)		
Tumor diameter	≥ 3 cm	46	30 (65.22)	16 (34.78)	1.565	0.211
	< 3 cm	40	31 (77.50)	9 (22.50)		
Differentiation degree	Low differentiation	27	15 (55.56)	12 (44.44)	6.602	0.037
	Moderate differentiation	25	17 (68.00)	8 (32.00)		
	High differentiation	34	29 (85.29)	5 (14.71)		
TNM staging	Stages I-II	37	21 (56.76)	16 (43.24)	6.327	0.012
	Stages III-IV	49	40 (81.63)	9 (18.37)		
Lymph node metastasis	Presence	53	43 (83.13)	10 (18.87)	6.972	0.008
	Absence	33	18 (54.55)	15 (45.45)		
Infiltration depth	T1 + T2	37	21 (56.76)	16 (43.24)	6.486	0.039
	T3	41	33 (80.49)	8 (19.51)		
	T4	8	7 (87.50)	1 (12.5)		
Distant metastasis	Presence	46	37 (80.43)	9 (19.57)	4.333	0.037
	Absence	40	24 (60.00)	16 (40.00)		

Data are *n* (%). TEX14: Testis-expressed gene 14.

with TNM staging, invasion, and metastasis in elderly patients with CRC is essential for enhancing tumor screening and disease assessment. This greatly aids in improving prognosis and increasing the expected survival duration for elderly patients.

TEX14, as a regulator of the PLK1 protein, is an important regulatory mediator of kinetochore structure, function, and chromosome segregation fidelity during mitosis[17]. Recent studies have revealed that TEX14-IT1 mediates the pro-proliferative and anti-apoptotic functions of transforming growth factor-beta in ovarian granular cells. This mechanism involves inducing the transcription of TEX14-IT1 in an AMAD4-dependent manner, exerting epigenetic regulatory effects [18]. Furthermore, in cancer, the TEX14 rs302864 site can interact with SEPT4 rs758377, influencing specific molecular subtypes of breast tumors, thereby augmenting the risk of breast cancer[19]. ADAM17, as a type of multi-domain transmembrane glycoprotein, participates in the formation and release of pro-tumor progression-related ligands, thus affecting the malignant progression of various tumors[20-22]. Previous studies have discovered that the expression level of ADAM17 is related to the ability of human umbilical vein endothelial cells to form capillary-like networks when co-cultured with fibroblasts in three-dimensional matrix gel and scaffolds. ADAM17 can participate in angiogenesis by modulating the activation of matrix metalloproteinase 2[23,24]. In CRC, FHL2 inhibits ADAM17 activity by regulating its plasma membrane localization. The interplay between FHL2 and ADAM17 in malignant colonic epithelial cells forms a complex that influences the occurrence and development of CRC[25].

Currently, there is scarce research on the functions of TEX17 and ADAM17 in the staging, invasion, and metastasis of CRC. To address this gap, our experiment explored these aspects. We found that TEX14 and ADAM17 expression levels in the tumor tissues of elderly patients with CRC were significantly higher than in adjacent normal tissues. High expression of TEX14 and ADAM17 was associated with tumor differentiation, TNM staging, invasion depth, lymph node metastasis, and distant metastasis in elderly patients, establishing them as independent risk factors affecting the staging, invasion, and metastasis of tumors. Our findings align with those of Kumar *et al*[26], who found that multiple biomarkers such as SVIP, BEND3, and TEX14 were abnormally expressed in breast cancer and could serve as efficacious indicators for early, non-invasive diagnosis and prognosis. Additionally, a study by Li *et al*[27] confirmed that exosomal ADAM17

Table 5 Correlation between ADAM17 protein expression and clinical pathology

Pathological characteristic		*n*	ADAM17		χ^2 value	*P* value
			Positive, *n* = 67	Negative, *n* = 19		
Age	≥ 65 years	54	44 (81.48)	10 (18.52)	1.077	0.299
	< 65 years	32	23 (71.88)	9 (28.13)		
Sex	Male	47	39 (82.98)	8 (17.02)	1.549	0.213
	Female	39	28 (71.79)	11 (28.21)		
Pathological type	Tubular adenocarcinoma	33	27 (81.82)	6 (18.18)	1.308	0.520
	Villous adenocarcinoma	27	19 (70.37)	8 (29.63)		
	Papillary carcinoma	26	21 (80.77)	5 (19.23)		
Tumor diameter	≥ 3 cm	46	38 (82.61)	8 (17.39)	1.270	0.260
	< 3 cm	40	29 (72.50)	11 (27.50)		
Differentiation degree	Low differentiation	27	20 (74.07)	7 (25.93)	10.079	0.006
	Moderate differentiation	25	15 (60.00)	10 (40.00)		
	High differentiation	34	32 (94.12)	2 (5.88)		
TNM staging	Stages I-II	37	24 (64.86)	13 (35.14)	6.418	0.011
	Stages III-IV	49	43 (87.76)	6 (12.24)		
Lymph node metastasis	Presence	53	46 (86.79)	7 (13.21)	6.336	0.012
	Absence	33	21 (63.64)	12 (36.36)		
Infiltration degree	T1 + T2	37	24 (64.86)	13 (35.14)	7.250	0.027
	T3	41	35 (85.37)	6 (14.63)		
	T4	8	8 (100.00)	0 (0)		
Distant metastasis	Presence	46	40 (86.96)	6 (13.04)	4.706	0.030
	Absence	40	27 (67.50)	13 (32.50)		

Data are *n* (%). ADAM17: A disintegrin and metalloprotease 17.

could accelerate the formation of pre-metastasis niches by strengthening CRC vascular permeability and promoting cancer metastasis. Previous studies may have already revealed the key roles of these two genes in the development of CRC, possibly associated with tumor growth, invasion, and metastasis. By comparing our research results, the exact mechanisms of action of these genes in the pathophysiological processes of CRC can be further validated. The outcomes of our experiment may be related to the following reasons: TEX14 may suppress apoptosis of tumor cells endogenously by affecting the mitosis process of CRC cells, accelerating cell proliferation, invasion, and metastasis, thereby bolstering CRC malignancy[28]. Furthermore, ADAM17, as a mediator in cell-matrix interactions, interacts with integrin α5, degrading the cell basement membrane and extracellular matrix. This interaction reduces the levels of adhesion molecules on the surface of CRC cells, impairing their function in cancer cell invasion and metastasis[29], ultimately exacerbating the malignant progression of tumors.

The clinical significance of these research findings is very important. By further investigating the relationship between the expression of TEX14 and ADAM17 in patients with CRC and metastasis, these genes could be utilized as potential therapeutic targets, providing a new direction for the treatment of CRC. However, this work also has certain limitations and shortcomings. Firstly, it is a retrospective study, which inherently has limitations. All data and information are derived from historical data of cases, which may result in incomplete information or selection bias, thus affecting the experimental findings. Additionally, this study included only 86 patients, which is a relatively small size, and all samples were sourced from a single hospital, which may introduce institutional bias, influencing the external validity and generalizability of the study outcomes. In the future, we will consider using carefully designed prospective studies combined with standardized data sampling to provide more robust evidence for our experimental results.

CONCLUSION

Overall, our findings corroborate the indispensable role of TEX14 and ADAM17 in the clinical diagnosis and prognosis assessment of elderly individuals with CRC. They can serve as effective biomarkers for predicting disease progression

Table 6 Binary variable assignment

Variable	Assignment	Outcomes
TNM staging	Stages I-II	0
	Stages III-III	1
Invasion	Infiltration depths T1 + T2	0
	Infiltration depths T3 + T4	1
Lymph node metastasis	Presence	1
	Absence	0
Distant metastasis	Presence	1
	Absence	0
TEX14	Positive	1
	Negative	0
ADAM17	Positive	1
	Negative	0

ADAM17: A disintegrin and metalloprotease 17; TEX14: Testis-expressed gene 14.

Table 7 Correlation between TEX14 and ADAM17 profiles and tumor staging, invasion, and metastasis

C	TEX14						ADAM17					
	B	SE	Wald	OR	95%CI	*P* value	β	SE	Wald	OR	95%CI	*P* value
TNM staging	1.207	0.518	5.429	3.343	1.211-9.228	0.020	1.602	0.595	7.249	4.963	1.546-15.930	0.007
Invasion	2.703	0.988	7.485	14.924	2.152-103.491	0.006	1.886	0.803	5.516	6.593	1.366-31.813	0.019
Lymph node metastasis	1.613	0.732	4.856	5.018	1.195-21.067	0.028	0.978	0.466	4.405	2.659	1.067-6.628	0.036
Distant metastasis	1.825	0.819	4.965	6.203	1.246-30.884	0.026	2.077	0.804	6.674	7.980	1.651-38.584	0.010

ADAM17: A disintegrin and metalloprotease 17; TEX14: Testis-expressed gene 14.

and prognosis in patients. In clinical practice, when treating elderly patients with CRC, it is essential to focus not only on common prognostic indicators and pathological results but also to strengthen the monitoring of TEX14 and ADAM17 markers. Future clinical research can further validate the value of these genes as potential diagnostic markers or therapeutic targets, providing new insights and possibilities for developing more effective treatment strategies.

FOOTNOTES

Author contributions: Chen G designed the research study; Chen G and Cong LH performed the research; Chen G, Gu CJ, and Li P analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of The Affiliated People's Hospital of Ningbo University (Approval No. 2020-NB-021032).

Informed consent statement: Patients were not required to provide informed consent for the study because the analysis used anonymous clinical data that were obtained after each patient agreed to the treatment through written consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No other data are available.

Country of origin: China

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S-Editor: Gong ZM
L-Editor: Filipodia
P-Editor: Che XX

REFERENCES

1 **Dekker E**, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet* 2019; **394**: 1467-1480 [PMID: 31631858 DOI: 10.1016/S0140-6736(19)32319-0]
2 **Baidoun F**, Elshiwy K, Elkeraie Y, Merjaneh Z, Khoudari G, Sarmini MT, Gad M, Al-Husseini M, Saad A. Colorectal Cancer Epidemiology: Recent Trends and Impact on Outcomes. *Curr Drug Targets* 2021; **22**: 998-1009 [PMID: 33208072 DOI: 10.2174/1389450121999201117115717]
3 **Kędzia-Berut R**, Berut M, Włodarczyk M, Włodarczyk J, Dziki Ł, Dziki A, Mik M. Colorectal Cancer: Is it Still a Disease of the Elderly? *Pol Przegl Chir* 2023; **96**: 41-45 [PMID: 38348978 DOI: 10.5604/01.3001.0054.0956]
4 **Betesh AL**, Schnoll-Sussman FH. Colorectal Cancer Screening in the Elderly. *Clin Geriatr Med* 2021; **37**: 173-183 [PMID: 33213771 DOI: 10.1016/j.cger.2020.08.012]
5 **Alswealmeen W**, Sadri L, Perrotti G, Heilman J, Bakshi K, Kim SY, Zebley DM, Fassler SA. Colorectal Cancer Screening in the Elderly: Is Age Just a Number? *Clin Colorectal Cancer* 2022; **21**: e113-e116 [PMID: 34955377 DOI: 10.1016/j.clcc.2021.11.011]
6 **Salibasic M**, Pusina S, Bicakcic E, Pasic A, Gavric I, Kulovic E, Rovcanin A, Beslija S. Colorectal Cancer Surgical Treatment, our Experience. *Med Arch* 2019; **73**: 412-414 [PMID: 32082011 DOI: 10.5455/medarh.2019.73.412-414]
7 **Chen J**, Haanpää MK, Gruber JJ, Jäger N, Ford JM, Snyder MP. High-Resolution Bisulfite-Sequencing of Peripheral Blood DNA Methylation in Early-Onset and Familial Risk Breast Cancer Patients. *Clin Cancer Res* 2019; **25**: 5301-5314 [PMID: 31175093 DOI: 10.1158/1078-0432.CCR-18-2423]
8 **Kim HJ**, Yoon J, Matsuura A, Na JH, Lee WK, Kim H, Choi JW, Park JE, Park SJ, Kim KT, Chang R, Lee BI, Yu YG, Shin YK, Jeong C, Rhee K, Lee HH. Structural and biochemical insights into the role of testis-expressed gene 14 (TEX14) in forming the stable intercellular bridges of germ cells. *Proc Natl Acad Sci U S A* 2015; **112**: 12372-12377 [PMID: 26392564 DOI: 10.1073/pnas.1418606112]
9 **Düsterhöft S**, Lokau J, Garbers C. The metalloprotease ADAM17 in inflammation and cancer. *Pathol Res Pract* 2019; **215**: 152410 [PMID: 30992230 DOI: 10.1016/j.prp.2019.04.002]
10 **Wilkinson M**, Sinclair P, Dellatorre-Teixeira L, Swan P, Brennan E, Moran B, Wedekind D, Downey P, Sheahan K, Conroy E, Gallagher WM, Docherty N, Roux CL, Brennan DJ. The Molecular Effects of a High Fat Diet on Endometrial Tumour Biology. *Life (Basel)* 2020; **10** [PMID: 32927694 DOI: 10.3390/life10090188]
11 **Dosch J**, Ziemke E, Wan S, Luker K, Welling T, Hardiman K, Fearon E, Thomas S, Flynn M, Rios-Doria J, Hollingsworth R, Herbst R, Hurt E, Sebolt-Leopold J. Targeting ADAM17 inhibits human colorectal adenocarcinoma progression and tumor-initiating cell frequency. *Oncotarget* 2017; **8**: 65090-65099 [PMID: 29029414 DOI: 10.18632/oncotarget.17780]
12 **Weiser MR**. AJCC 8th Edition: Colorectal Cancer. *Ann Surg Oncol* 2018; **25**: 1454-1455 [PMID: 29616422 DOI: 10.1245/s10434-018-6462-1]
13 **Itatani Y**, Kawada K, Sakai Y. Treatment of Elderly Patients with Colorectal Cancer. *Biomed Res Int* 2018; **2018**: 2176056 [PMID: 29713641 DOI: 10.1155/2018/2176056]
14 **Vacante M**, Cristaldi E, Basile F, Borzì AM, Biondi A. Surgical approach and geriatric evaluation for elderly patients with colorectal cancer. *Updates Surg* 2019; **71**: 411-417 [PMID: 30953329 DOI: 10.1007/s13304-019-00650-3]
15 **González-Senac NM**, Mayordomo-Cava J, Macías-Valle A, Aldama-Marín P, Majuelos González S, Cruz Arnés ML, Jiménez-Gómez LM, Vidán-Astiz MT, Serra-Rexach JA. Colorectal Cancer in Elderly Patients with Surgical Indication: State of the Art, Current Management, Role of Frailty and Benefits of a Geriatric Liaison. *Int J Environ Res Public Health* 2021; **18** [PMID: 34199923 DOI: 10.3390/ijerph18116072]
16 **Liu HT**, Chen SY, Peng LL, Zhong L, Zhou L, Liao SQ, Chen ZJ, Wang QL, He S, Zhou ZH. Spatially resolved transcriptomics revealed local invasion-related genes in colorectal cancer. *Front Oncol* 2023; **13**: 1089090 [PMID: 36816947 DOI: 10.3389/fonc.2023.1089090]
17 **Mondal G**, Ohashi A, Yang L, Rowley M, Couch FJ. Tex14, a Plk1-regulated protein, is required for kinetochore-microtubule attachment and regulation of the spindle assembly checkpoint. *Mol Cell* 2012; **45**: 680-695 [PMID: 22405274 DOI: 10.1016/j.molcel.2012.01.013]
18 **Li Q**, Huo Y, Wang S, Yang L, Li Q, Du X. TGF-β1 regulates the lncRNA transcriptome of ovarian granulosa cells in a transcription activity-dependent manner. *Cell Prolif* 2023; **56**: e13336 [PMID: 36125095 DOI: 10.1111/cpr.13336]
19 **Kelemen LE**, Wang X, Fredericksen ZS, Pankratz VS, Pharoah PD, Ahmed S, Dunning AM, Easton DF, Vierkant RA, Cerhan JR, Goode EL, Olson JE, Couch FJ. Genetic variation in the chromosome 17q23 amplicon and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 1864-1868 [PMID: 19454617 DOI: 10.1158/1055-9965.EPI-08-0486]
20 **Jiao X**, Yu W, Qian J, Chen Y, Wei P, Fang W, Yu G. ADAM-17 is a poor prognostic indicator for patients with hilar cholangiocarcinoma and is regulated by FoxM1. *BMC Cancer* 2018; **18**: 570 [PMID: 29776401 DOI: 10.1186/s12885-018-4294-9]
21 **Fang W**, Qian J, Wu Q, Chen Y, Yu G. ADAM-17 expression is enhanced by FoxM1 and is a poor prognostic sign in gastric carcinoma. *J Surg Res* 2017; **220**: 223-233 [PMID: 29180185 DOI: 10.1016/j.jss.2017.06.032]
22 **Lu HY**, Chu HX, Tan YX, Qin XC, Liu MY, Li JD, Ren TS, Zhang YS, Zhao QC. Novel ADAM-17 inhibitor ZLDI-8 inhibits the metastasis of hepatocellular carcinoma by reversing epithelial-mesenchymal transition in vitro and in vivo. *Life Sci* 2020; **244**: 117343 [PMID: 31978449 DOI: 10.1016/j.lfs.2020.117343]
23 **Göoz P**, Göoz M, Baldys A, Hoffman S. ADAM-17 regulates endothelial cell morphology, proliferation, and in vitro angiogenesis. *Biochem Biophys Res Commun* 2009; **380**: 33-38 [PMID: 19150341 DOI: 10.1016/j.bbrc.2009.01.013]
24 **Nakashima M**, Suga N, Ikeda Y, Yoshikawa S, Matsuda S. Relevant MicroRNAs of MMPs and TIMPs with Certain Gut Microbiota Could Be Involved in the Invasiveness and Metastasis of Malignant Tumors. *Innov Discov* 2024; **1**: 10 [DOI: 10.53964/id.2024010]

25 **Verset L**, Tommelein J, Decaestecker C, De Vlieghere E, Bracke M, Salmon I, De Wever O, Demetter P. ADAM-17/FHL2 colocalisation suggests interaction and role of these proteins in colorectal cancer. *Tumour Biol* 2017; **39**: 1010428317695024 [PMID: 28349819 DOI: 10.1177/1010428317695024]

26 **Kumar S**, Das A. Peripheral blood mononuclear cell derived biomarker detection using eXplainable Artificial Intelligence (XAI) provides better diagnosis of breast cancer. *Comput Biol Chem* 2023; **104**: 107867 [PMID: 37030103 DOI: 10.1016/j.compbiolchem.2023.107867]

27 **Li K**, Xue W, Lu Z, Wang S, Zheng J, Lu K, Li M, Zong Y, Xu F, Dai J, Yang Y, Sun J. Tumor-derived exosomal ADAM17 promotes pre-metastatic niche formation by enhancing vascular permeability in colorectal cancer. *J Exp Clin Cancer Res* 2024; **43**: 59 [PMID: 38413999 DOI: 10.1186/s13046-024-02991-3]

28 **Kou L**, Yang N, Dong B, Yang J, Song Y, Li Y, Qin Q. Circular RNA testis-expressed 14 overexpression induces apoptosis and suppresses migration of ox-LDL-stimulated vascular smooth muscle cells *via* regulating the microRNA 6509-3p/thanatos-associated domain-containing apoptosis-associated protein 1 axis. *Bioengineered* 2022; **13**: 13150-13161 [PMID: 35635088 DOI: 10.1080/21655979.2022.2070582]

29 **Machado-Pineda Y**, Cardeñes B, Reyes R, López-Martín S, Toribio V, Sánchez-Organero P, Suarez H, Grötzinger J, Lorenzen I, Yáñez-Mó M, Cabañas C. CD9 Controls Integrin α5β1-Mediated Cell Adhesion by Modulating Its Association With the Metalloproteinase ADAM17. *Front Immunol* 2018; **9**: 2474 [PMID: 30455686 DOI: 10.3389/fimmu.2018.02474]

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