해부 · 생물인류학 제 38 권 제 3 호
Anat Biol Anthropol Vol. 38, No. 3 (2025) pp. 263~268
https://doi.org/10.11637/aba.2025.38.3.263

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Original Article

CHEK1 Expression was Associated with the Prognosis in Colon Cancers

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Abstract : Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide, yet the molecular determinants of its progression are not fully understood. Although CHEK1 overexpression has been associated with poor prognosis in several malignancies, its role in CRC remains unclear. This study aimed to investigate the clinical and prognostic value of the CHEK1 gene in CRC. CHEK1 expression was analyzed across various cancer types, and its prognostic significance in CRC was further evaluated using data from The Cancer Genome Atlas (TCGA). Higher CHEK1 expression was associated with age in rectal cancer patients and correlated with early pathological stage, N0 stage, M0 stage, anatomic neoplasm type, and MSI status in colon cancer. Survival analysis revealed that higher CHEK1 expression was significantly associated with favorable prognosis in colon cancer. However, in rectal cancer, the association was not statistically significant, likely due to the small sample size. These findings suggest that CHEK1 may be potential as a prognostic biomarker in CRC, and further studies are warranted to elucidate its molecular mechanisms and prognostic implications.

Keywords : CHEK1, TCGA, Colon cancer, Rectal cancer

INTRODUCTION

In 2020, colorectal cancer (CRC) was diagnosed in approximately 1.9 million individuals worldwide, resulting in over 900,000 deaths. This makes CRC the second leading cause of cancer-related mortality globally, with incidence and mortality rates projected to rise due to aging populations and overall population growth [1,2]. The majority of CRC cases are sporadic, arising gradually through the adenoma-carcinoma sequence, although hereditary factors also play a key role [3]. Approximately 10% of adenomatous polyps progress to adenocarcinoma, with the risk increasing as polyp size enlarges [4]. This adenoma-carcinoma progression accounts for most CRC cases and is characterized by mutations in key driver genes such as APC, KRAS, and TP53 [5]. Despite extensive global research on the molecular mechanisms of CRC, further studies are required to fully elucidate its pathophysiology.

Checkpoint kinase 1 (CHK1) is a serine/threonine protein kinase encoded by the CHEK1 gene, located on chromosome 11q22-23 [6]. It was first identified in 1993 as a kinase regulating the G2/M cell cycle transition in response

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The author(s) agree to abide by the good publication practice guideline for medical journals.
The author(s) declare that there are no conflicts of interest.
Received: August 23, 2025; **Revised:** September 20, 2025; **Accepted:** September 23, 2025
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ISSN 2671-566X (Online)

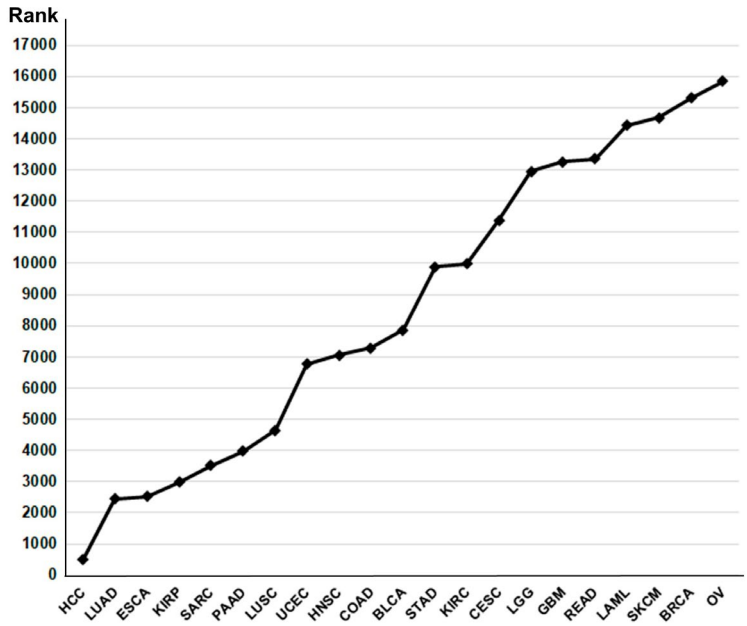

Fig. 1. The rank of survival value of CHEK1 in various cancers.

to DNA damage in fission yeast [7]. As a member of the CHK kinase family, CHK1 is activated by DNA damage and subsequently phosphorylates multiple downstream targets, thereby initiating a broad cellular response [8]. This response includes transcriptional regulation, modulation of energy metabolism, induction of cell cycle arrest or delay, promotion of DNA repair, and activation of cell death when damage is irreparable [8].

CHEK1 has been implicated in a wide range of diseases, particularly neoplastic conditions. Elevated CHEK1 expression has been associated with poor prognosis in several malignancies, including lung [9], ovarian [10], and breast cancers [11]. CHEK1 is suggested as one of CRC-related genes in colorectal cancer and its association with P53 was also suggested, however, it remains insufficiently understood [12-14]. Therefore, in this study, we investigated the clinical and prognostic significance of CHEK1 expression in CRC and explored its correlation with the expression of other genes using data from The Cancer Genome Atlas (TCGA) [15,16].

MATERIALS AND METHODS

We obtained primary data from The Cancer Genome Atlas (TCGA) portal (http://cancergenome.nih.gov) in February 2025. Prognostic *p*-value rankings for CHEK1 expression across cancer types were generated (Fig. 1). Among these, colon cancer and rectal cancer demonstrated the most promising associations and were selected for detailed analysis. A total of 440 colon cancer patients and 158 rectal cancer patients were included in the survival analysis.

Survival was defined as the interval from surgery to death. Overall survival was defined as the time between diagnosis and mortality. Data analysis was conducted using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA). Tumor staging followed the seventh edition of the American Joint Committee on Cancer (AJCC) TNM classification system. Clinicopathological variables—including age, sex, carcinoembryonic antigen (CEA) level, and pathological TNM stage—were analyzed using the chi-square test. Univariate survival analysis was performed using Kaplan-Meier curves with log-rank tests. A *p*-value of <0.05 was considered statistically significant.

RESULTS

To evaluate the clinical characteristics of expression, patients were divided into two subgroups according to the median values of CHEK1 expression. In colon cancer (Table

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Table 1. Clinical characteristics of CHEK1 gene in colon cancer.

	CHEK1				CHEK1		
	High (N, %)	Low (N, %)	*P*-value		High (N, %)	Low (N, %)	*P*-value
Age				T stage			
<65	83 (48.8)	87 (51.2)	0.667	T1	8 (72.7)	3 (27.3)	0.057
≥65	137 (50.9)	132 (49.1)		T2	43 (58.1)	31 (41.9)	
Gender				T3	150 (49.7)	152 (50.3)	
Female	108 (52.7)	97 (47.3)	0.314	T4	19 (37.3)	32 (62.7)	
Male	112 (47.9)	122 (52.1)		Histological type			
Lymphatic invasion				Colon adenocarcinoma	190 (50.8)	184 (49.2)	0.283
No	129 (53.1)	114 (46.9)	0.137	Colon mucinous adenocarcinoma	26 (43.3)	34 (56.7)	
Yes	69 (45.4)	83 (54.6)		MSI			
CEA				Indeterminate	0 (0)	2 (100)	0.001
≤5	96 (50.8)	93 (49.2)	0.130	MSI-H	50 (65.8)	26 (34.2)	
>5	37 (41.1)	53 (58.9)		MSI-L	36 (45.6)	43 (54.4)	
Venous invasion				MSS	130 (47.4)	144 (52.6)	
No	149 (51.4)	141 (48.6)	0.680	Colon polyps			
Yes	44 (48.9)	46 (51.1)		No	125 (51.7)	117 (48.3)	0.558
Pathologic stage				Yes	63 (48.5)	67 (51.5)	
Stage I	41 (56.9)	31 (43.1)		Anatomic neoplasm			
Stage II	93 (54.7)	77 (45.3)	0.022	Ascending colon	46 (54.1)	39 (45.9)	
Stage III	58 (46.0)	68 (54.0)		Cecum	42 (41.6)	59 (58.4)	
Stage IV	21 (34.4)	40 (65.6)		Descending colon	11 (57.9)	8 (42.1)	
M stage				Hepatic flexure	10 (37.0)	17 (63.0)	0.008
M0	174 (53.5)	151 (46.5)	0.006	Sigmoid colon	79 (54.5)	66 (45.5)	
M1	21 (34.4)	40 (65.6)		Splenic flexure	4 (57.1)	3 (42.9)	
N stage				Transverse colon	19 (50)	19 (50)	
N0	145 (56.4)	112 (43.6)					
N1	46 (44.2)	58 (55.8)	0.005				
N2	29 (37.2)	49 (62.8)					

1), CHEK1 expression has statistically significant relation with pathologic stage ($p=0.022$), M stage ($p=0.006$), N stage ($p=0.005$), MSI ($p=0.001$), Anatomic neoplasm ($p=0.008$). Although there was relation with T stage ($p=0.057$), it was not statistically significant. Specifically, CHEK1 levels were found to be high in MSI-H types, lower pathologic stages, M0 stage, and N0 stage. In rectal cancer (Table 2), higher CHEK1 expression has statistically significant relation with age ($p=0.031$). Although there was relation with gender ($p=0.091$), venous invasion ($p=0.088$), it was not statistically significant.

An overall survival analysis was performed to determine the prognostic value of CHEK1 in colon cancer (Fig. 2A) and rectal cancer (Fig. 2B). CHEK1 expression had statistically significant prognostic value (3038.83±214.48 vs. 2317.06±212.26 days, $\chi^2=11.74$, $p=0.001$) in colon cancer. Its expression tended to be associated with better prognosis, however, it did not get statistical significance in rectal cancer (3014.28±314.85 vs. 1675.21±186.19 days, $\chi^2=2.78$, $p=0.096$).

DISCUSSION

In this study, we investigated the clinical relevance of CHEK1 expression in colorectal cancer (CRC) and found

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Table 2. Clinical characteristics of CHEK1 gene in rectal cancer.

	CHEK1		
	High (N, %)	Low (N, %)	*P*-value
Age			
<65	44 (58.7)	31 (41.3)	0.031
≥65	34 (41.5)	48 (58.5)	
Gender			
Female	30 (42.3)	41 (57.7)	0.091
Male	48 (55.8)	38 (44.2)	
Lymphatic invasion			
No	40 (48.8)	42 (51.2)	0.437
Yes	24 (42.1)	33 (57.9)	
CEA			
≤5	31 (50)	31 (50)	0.644
>5	24 (54.5)	20 (45.5)	
Venous invasion			
No	52 (51.0)	50 (49.0)	0.088
Yes	12 (34.3)	23 (65.7)	
Pathologic stage			
Stage I	14 (46.7)	16 (53.3)	0.571
Stage II	25 (53.2)	22 (46.8)	
Stage III	20 (42.6)	27 (57.4)	
Stage IV	14 (58.3)	10 (41.7)	
M stage			
M0	59 (50)	59 (50)	0.181
M1	15 (65.2)	8 (34.8)	
N stage			
N0	41 (51.3)	39 (48.7)	0.331
N1	24 (55.8)	19 (44.2)	
N2	12 (38.7)	19 (61.3)	
T stage			
T1	5 (55.6)	4 (44.4)	0.116
T2	14 (50)	14 (50)	
T3	57 (53.3)	50 (46.7)	
T4	2 (16.7)	10 (83.3)	

that high CHEK1 expression is significantly correlated with favorable prognostic features. Moreover, higher CHEK1 levels were positively correlated with early pathologic stages, M0, N0 stage, and MSI-H status in colon cancer, and had a negative correlation with age in rectal cancer. Combining these statistics with the overall survival analysis in colorectal cancer, our findings challenge the conventional view of CHEK1 as a driver of tumor proliferation in CRC [17], suggesting a potentially tumor-suppressive role.

A key finding of this study was the association between high CHEK1 expressions and favorable clinical features in colon cancer, including early pathologic stage, N0, M0, and MSI-H status. These observations suggest that CHEK1 may be more actively expressed in the earlier stages of tumor development, where its role in maintaining genomic stability is most critical. As a central regulator of the DNA damage response (DDR) pathway, CHEK1 promotes cell cycle arrest and DNA repair in response to replication stress and genomic insults, thereby preventing the accumulation of mutations [18-20]. In tumors with MSI-H, which are characterized by increased DNA replication errors due to mismatch repair deficiency, this protective function of CHEK1 may be particularly important. Moreover, MSI-H subtypes are known to have more active immune surveillance and better prognosis [21], possibly reflecting a broader context in which high CHEK1 expression supports an anti-tumor environment. Notably, CHEK1 overexpression in MSI-H tumors may reflect the heightened DNA replication stress and mutational burden characteristic of mismatch repair deficiency. While MSI-H status itself is a well-recognized favorable prognostic factor, it remains unclear whether CHEK1 provides prognostic information beyond MSI-H. Evaluating CHEK1 expression after adjusting for MSI status would help clarify whether it simply mirrors MSI-H biology or represents an independent biomarker of tumor behavior. In addition, high CHEK1 levels might indirectly enhance immune visibility by stabilizing neoantigen-rich cells, thereby contributing to the more active immune environment observed in MSI-H tumors.

However, this pattern also raises the question of why more advanced tumors, which presumably experience greater replication stress, do not exhibit similarly elevated CHEK1 levels. One explanation may lie in the tumor's adaptation to bypass DDR signaling. As colorectal cancers progress, they may acquire mutations or epigenetic alterations that silence checkpoint pathways to enable unconstrained proliferation. This phenomenon has been reported in various malignancies and may reflect a selective advantage for clones that escape cell cycle control [22]. Therefore, lower CHEK1 expression in late-stage disease may not indicate reduced DNA damage, but rather the breakdown of genomic surveillance mechanisms that once restricted malignant progression. In our study, CHEK1 expression demonstrated significant correlations with several markers that are commonly implicated in colorectal cancer.

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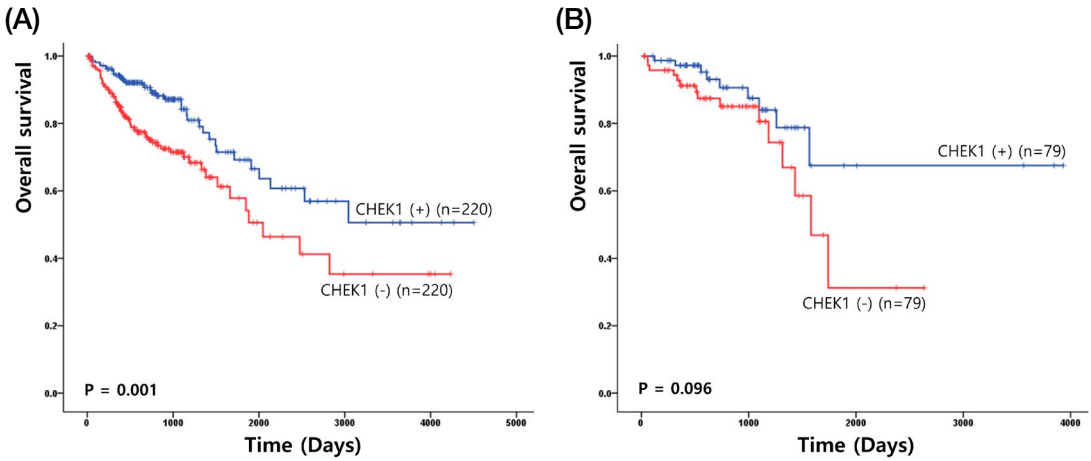

Fig. 2. Overall survival analysis in colon cancer (A) and rectal cancer (B).

CHEK1 was negatively correlated with CEA expression, a widely used supplemental biomarker that typically rises with tumor progression [23]. The inverse relationship between CHEK1 and CEA further supports the association between high CHEK1 expression and less advanced disease, reinforcing the hypothesis that elevated CHEK1 expression may reflect a more robust DNA damage checkpoint activity in tumors with relatively lower malignancy potential.

In the case of rectal cancer, the statistics showed a limited association between CHEK1 expression and clinicopathological variables. Among the examined categories, only age showed a statistically significant correlation with CHEK1 levels, and no meaningful association was observed in terms of survival outcomes. These findings suggest that the prognostic role of CHEK1 may differ between anatomical subtypes of colorectal cancer. However, given the relatively small sample, the role of CHEK1 expression in rectal cancer may still remain inconclusive therefore highlighting the needs for further investigation in larger cohorts.

Recent studies have highlighted the controversy surrounding the role of CHEK1 in colorectal cancer [24,25]. A recent article proposed similar prospects for CHEK1 as a prognostic indicator in CRC, supporting our observation that CHEK1 may play a protective role during early tumor development [24]. Conversely, previous work showed that inhibition of CHEK1 was related to poorer prognosis, indicating that loss of CHEK1 activity may promote tumor progression or treatment resistance [25]. Together, these findings underscore the complex and context-dependent role of CHEK1 in CRC biology.

CONCLUSIONS

As a result, this study identified a significant correlation between CHEK1 gene and colorectal cancer for the first time using TCGA data. It suggests that CHEK1 gene could be a potential biomarker or candidate for treating colorectal cancer. Overall, we emphasize the need for further studies for the molecular mechanisms and clinical characteristics of CHEK1 gene in colorectal cancer such as mediating *in vivo* and *in vitro* experiment results in larger samples. We demonstrate that CHEK1 gene may play a role in colorectal cancer progression and clinical features, opening the way for future research.

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