Expression of CASK Antibody in Non-Mucinous Colorectal Adenocarcinoma

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Abstract

Background: Colorectal cancers are one of the leading causes of cancer related morbidity and mortality worldwide. In Egypt was 4% in the year 2012 ranking as the sixth cancer in Egypt and representing 53% of GI malignancy. It is obvious that there is no single determining factor for the process of carcinogenesis or spread of colorectal carcinoma. There are many proposed contributing factors, including disturbances in Epithelial-Mesenchymal Transition (EMT) and loss of regulation of adhesion molecules and polarity proteins. Calcium/calmodulin-dependent serine protein kinase (CASK) belongs to the Membrane-Associated Guanylate Kinase (MAGUK) family. The role of CASK in Colorectal cancer hasn't been yet fully understood.

Aim of Study: To evaluate the expression of Calcium/calmodulin-dependent serine protein kinase (CASK) in non-mucinous colorectal adenocarcinoma and to evaluate its correlation with variable clinicopathological factors.

Material and Methods: It is retrospective descriptive study is conducted in the Department of Pathology, Faculty of Medicine, Suez Canal University Teaching Hospital. It include 42 archived paraffin blocks of non-mucinous colorectal adenocarcinoma of patients who underwent surgical excision without previous chemotherapy or radiation, 15 adenomatous polyps and 5 normal mucosa samples. The clinical and pathological data of studied patients are taken from medical records, pathology referral reports and pathology reports. Patients with incomplete data excluded from the study. Re-viewing the data of survival from the archived registry files at department of Oncology, Suez Canal University Teaching Hospital. Sections cut into 5um thick sections and mounted on positive charged slides for immunohistochemical staining using CASK Antibody (S56A-50): Mouse Monoclonal, Novus Biologicals, Catalogue no. NB1P1-47648. Staining intensity graded according to the Allred score on a 0-3 scale.

Data Analysis: The relation between CASK antibody staining intensity in the studied biopsies and other clinicopathological parameters including (age, gender, histopathological tumor features) was evaluated using Pearson’s X2 test. The level of statistical significance (p-value) was set at <0.05. All analyses were performed using the statistical package for social science (IBM SPSS) program (Ver. 19).

Results: The study revealed that CASK protein had mainly cytoplasmic and cytoplasmic-membranous pattern of expression. The CASK protein was overexpressed in the majority of CRC samples with 85.7% of cases showing moderate to strong expression, while only 14.3% of cases displayed minimal faint expression. On the other hand, CASK expression was low in the majority (53.3%) of adenoma samples. Additionally, adenomas with high grade dysplasia showed stronger staining intensity for CASK protein and higher percentage of positive cases than the ones with low grade dysplasia by IHC. As regard to the association between CASK protein overexpression and clinicopathological prognostic factors we found that CASK demonstrated significantly higher expression in tumor samples with early stages (I/II) rather than advanced stage (III/IV). Low grade tumors showed higher percentage of positive cases and stronger intensity of staining for CASK protein than high grade tumors. Expression of CASK protein showed no statistically significant correlation with patients’ gender or age respectively. There was also no significant correlation with tumor site, gross tumor size, histologic tumor border configuration, lymphovascular invasion or distant metastasis.

Conclusion: CASK protein was overexpressed in the majority of non-mucinous colorectal adenocarcinoma (CRC) cases with mainly cytoplasmic and cytoplasmic-membranous localization. However, its expression was significantly less in adenomas with a possible association with the grade of dysplasia; giving positive pattern in highly dysplastic cases suggesting a role in the progression of adenomas into carcinomas. CASK overexpression also associated with both TNM stage of tumors and their histologic grade. CASK was significantly overexpressed in early stage and low grade tumors rather than tumors with advanced stage and higher histological grades. This suggests that CASK protein is a good prognostic factor and might contribute in tumor confinement and localization.

Key Words: CASK – Cell-adhesion – Non-mucinous colorectal adenocarcinoma (CRC) – Colonic adenoma.

Introduction

COLORECTAL cancers are one of the leading causes of cancer related morbidity and mortality worldwide and on a national level as well. It is the third most common cancer globally and the fourth
leading cause of death [1]. In Egypt was 4% in the year 2012 ranking as the sixth cancer in Egypt and representing 53% of GI malignancy. Recent statistical data estimated the incidence of colorectal cancer among Egyptian males to 6.1% and slightly lower in females with a 5.2% incidence rate [2,3]. It is obvious that there is no single determining factor for the process of carcinogenesis or spread of colorectal carcinoma. There are many proposed contributing factors, including disturbances in Epithelial-Mesenchymal Transition (EMT) and loss of regulation of adhesion molecules and polarity proteins [4].

Calcium/calmodulin-dependent serine protein kinase (CASK) belongs to the Membrane-Associated Guanylate Kinase (MAGUK) family, which is characterized structurally by a tripartite domain structure: A Src homology 3 (SH3) domain, a domain with homology to the enzyme Guanylate Kinase (GUK), and a PDZ domain [5]. Its binding to syndecan-2 has been reported to mediate cell-cells adhesion and proliferation, which can contribute to tumorogenesis. CASK has also been reported to bind the cytoskeletal adapter protein EPB41 (Protein 4.1) linking both the extracellular matrix and the intracellular cytoskeleton and thus contributing to the regulation of epithelial cell polarity. Loss of cell polarity is a defining criterion of malignant neoplasms [6]. The role of CASK in Colorectal cancer hasn’t been yet fully understood. There is one study that linked CASK with the development and prognosis of colorectal cancer. This cannot be regarded as enough evidence to support or defy the fore mentioned hypothesis [7]. Based on the above mentioned functions of CASK in regulating both cell-cell interaction and cell polarity, we hypothesized that genetic errors involving the CASK encoding gene (Reelin) might participate in tumorogenesis, cancer spread and metastasis. The role of CASK in Colorectal cancer hasn’t been yet fully understood. There is one study that linked CASK with the development and prognosis of colorectal cancer. This cannot be regarded as enough evidence to support or defy the fore mentioned hypothesis.

In this study, we focused on studying the expression of CASK antibody in colorectal adenocarcinoma, its association with different prognostic factors mainly tumor stage, histological grade, vascular invasion and metastasis to evaluate its prognostic significance.

**Material and Methods**

It is retrospective descriptive study is conducted in the Department of Pathology, Faculty of Medicine, Suez Canal University Teaching Hospital. It include 42 archived paraffin blocks of non-mucinous colorectal adenocarcinoma of patients who underwent surgical excision without previous chemotherapy or radiation, 15 adenomatous polyps and 5 normal mucosa samples in period between January 2013 to January 2014. The clinical and pathological data including: Age, gender, site and size of the tumor, pathologic stage, grade, and metastasis will be taken from medical records, pathology referral reports and pathology reports. Patients with incomplete data will be excluded from the study. Reviewing the data of survival from the archived registry files at Department of Oncology, Suez Canal University Teaching Hospital.

**Immunohistochemistry staining:** Sections cut into 5μm thick sections and mounted on positive charged slides for immunohistochemical staining using CASK Antibody (S56A-50): Mouse Monoclonal, Novus Biologicals, Catalogue no. NB1-47648. Staining intensity graded according to the Allred score on a 0-3 scale as follows: 0 (absence of staining), 1 (weakly stained), 2 (moderately stained), 3 (strongly stained). The percentage of positive tumor cells scored as follows: 0 (absence of positive cells), 1 (<33% positive tumor cells), 2 (33-66% positive tumor cells), 3 (>66% positive tumor cells). The staining score calculated as the staining intensity score X the percentage score; ranging from 0 to 9 (absence, staining score=0; weak, 0<staining score≤4; strong, 5≤staining score≤9) using image analysis in counting staining score (Wei et al., 2014).

**Data analysis:**

The relation between CASK antibody staining intensity in the studied biopsies and other clinicopathological parameters including (age, gender, histopathological tumor features) was evaluated using Pearson’s χ² test. The level of statistical significance (p-value) was set at <0.05. All analyses were performed using the statistical package for social science (IBM SPSS) program (Ver. 19).

**Results**

**Demographic criteria of study population:**

The study involved 42 cases of non-mucinous adenocarcinoma, 15 cases of colorectal adenomas. 42 cases of non-mucinous adenocarcinoma included 40.5% male patients and 59.5% females with mean age of ±45 years. 15 adenoma cases included 53.3% males and 46.7% female patients with mean age ±47 years.
Histopathological features:

Histological subtypes of the adenomas group included tubulovillous subtype which represented the majority of cases (80%), while 13.3% of cases were of the tubular subtype and only 6.7% of the villous subtype (SD ±0.723). Cases with low grade dysplasia represented 53.3%, while 46.7% of cases showed high grade dysplasia with a SD ±0.516.

Out of the 42 CRC cases, 59.5% were of low grade while 40.5% of cases were of high grade with a Std. Dev. of ±0.497. Percentage of cases at TNM stage III was 16.7% cases of CRC were at stage I, 19% cases were stage II, 47.6% cases were stage III and 16.7% cases were stage IV. None of the studied tumors were at stage T1, while the majority of cases were diagnosed at advanced tumor (T) stage: 66.7% of examined samples were at pT3 and pT4. Metastatic deposits in lymph nodes were evident in 69.1% of cases, while 16.7% cases demonstrated evidence of distant metastasis. Lymphovascular invasion was assessed in 38.1% of cases. Lymphovascular invasion was associated with advanced tumor stage.

IHC expression of CASK protein:

The expression of CASK protein was evaluated by immunohistochemical technique on both CRC and adenomas samples. Normal colonic mucosa at the periphery of examined tumor sections were used as internal control.

Immunohistochemistry showed mainly cytoplasmic and cytomembranous pattern of expression for CASK protein, with focal localization at the basolateral borders of normal mucosa cells (internal control) which was given an IS of +1 and compared the IS of malignant cells accordingly. The ganglionic cells of the myenteric plexus between muscularis propria layers were positive for CASK and were used as an internal control as well Fig. (1).

The CASK protein was overexpressed in the majority of CRC samples with 85.7% of cases showing moderate to strong expression, while only 14.3% of cases displayed minimal faint expression. On the other hand, CASK expression was low in the majority of adenoma samples; 53.3% of cases showed low expression while only 6.67% showed strong expression. Pattern of staining showed no statistical significance in the adenomas group. No statistical significance was demonstrated between cytoplasmic staining pattern and either tumor TNM stage or grade (p-value >0.05). On the other hand, CASK expression was low in the majority of adenoma samples; 53.3% of cases showed low expression while only 6.67% showed strong expression. Pattern of staining showed no statistical significance in the adenoma group. No statistical significance was demonstrated between cytoplasmic staining pattern and either tumor TNM stage or grade (p-value >0.05). Membranous staining pattern showed a statistically significant relation with the TNM stage (p-value <0.05), with significantly higher expression in tumor samples with early stage tumors (I/II) as out of the 54.8% of cases with membranous pattern of staining for CASK protein, 28.6% were at early stages (I/II), while 38.1% were of advanced tumor stage (III/IV). Membranous staining pattern showed a statistically significant correlation with the TNM stage (p-value <0.05), with association with the early tumor stages. Tumor samples excised at an early stage mainly expressed CASK protein on their cytomembranes. Correlation between membranous expression of CASK protein and histologic grade of tumors revealed no statistical significance. Out of the 54.8% of cases with membranous expression of CASK, 38.1% were of low grade while 16.7% were of high grade.

Association of CASK with clinicopathological features of CRC:

Expression of CASK protein showed no statistically significant correlation with patients' gender or age respectively (p>0.05). There was also no significant correlation with tumor site, gross tumor size, histologic tumor border configuration, lymphovascular invasion or distant metastasis. The correlation of CASK expression with clustered TNM stage (stages I/II vs III/IV) was statistically significant (p<0.05), with significantly higher expression in tumor samples with early stages (I/II) rather than advanced stage (III/IV) (Table 2).

Low grade CRC samples that showed strong degree of CASK overexpression represented 33.3% out of the total number of cases Figs. (6,7), while
only 4.8% of cases with high grade carcinoma showed strong staining intensity Fig. (8). The correlation of CASK expression and histologic grade of differentiation was statistically significant \(p<0.05\) (Table 2), with low grade tumors showing higher percentage of positive cases and stronger intensity of staining for CASK protein expression than high grade tumors.

**Association of CASK and dysplasia in adenomas:**

Out of the examined adenoma specimens 53.3% showed low grade dysplasia Fig. (9), while 46.7% were of high grade Fig. (10). We measured the association between CASK protein overexpression and the degree of dysplasia. There was a reasonable association, where highly dysplastic adenomas showing stronger staining intensity and higher percentage of positive cases (Table 3).

Adenoma samples with high grade dysplasia that overexpressed CASK protein represented 33.3% Fig. (11), while only 13.3% of cases demonstrated low grade dysplasia and CASK overexpression Fig. (12).
Fig. (4): Low grade colorectal carcinoma section negative for CASK (IS=1), with inset higher magnification (X400) of a mild focal cytoplasmic stain (original magnification X100).

Fig. (5): Membranous pattern of staining of colon cancer with clear delineation of the cytomembranes, IS=2 (original magnification X400).

Fig. (6): Strong homogenous staining for CASK (IS=3) in low grade colorectal cancer cells. Inset higher magnification (X400) showing pure cytoplasmic pattern (original magnification X40).

Fig. (7): Higher magnification of low grade CRC formed of variable sized and shaped acini, IS=3 (original magnification X100).

Fig. (8): High grade colon adenocarcinoma with mild cytoplasmic stain (~ve), showing positive staining of normal glands on the right (internal control. Note the high nuclear atypia at high magnification (Inset) (original magnification X100).

Fig. (9): Tubular adenoma with low grade dysplasia in H & E stained section (original magnification X100).
CASK Expression in Non-Mucinous Colorectal Adenocarcinoma

Table (1): Pattern of staining (PS) for CASK protein in CRC and adenoma cases.

<table>
<thead>
<tr>
<th>CASK expression</th>
<th>Membranous stain</th>
<th>Cytoplasmic stain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>CRC N=42:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>% of total</td>
<td>45.2%</td>
<td>54.8%</td>
</tr>
<tr>
<td><strong>Adenomas N=15:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>% of total</td>
<td>60.0%</td>
<td>40.0%</td>
</tr>
</tbody>
</table>

p-value = *0.044.

Table (2): Association of CASK protein expression with clinicopathological features of CRC cases. N=42.

<table>
<thead>
<tr>
<th>Clinicopathological variant</th>
<th>CASK expression</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>TNM categories:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>0 (0%)</td>
<td>15 (35.7%)</td>
</tr>
<tr>
<td>III/IV</td>
<td>6 (14.3%)</td>
<td>21 (50.0%)</td>
</tr>
<tr>
<td><strong>Grades:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low grade</td>
<td>1 (2.4%)</td>
<td>24 (57.1%)</td>
</tr>
<tr>
<td>High grade</td>
<td>5 (11.9%)</td>
<td>12 (28.6%)</td>
</tr>
<tr>
<td><strong>Lymphovascular invasion:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>23 (54.8%)</td>
<td>3 (7.1%)</td>
</tr>
<tr>
<td>Present</td>
<td>13 (31.0%)</td>
<td>3 (7.1%)</td>
</tr>
</tbody>
</table>

Table (3): Association between degree of dysplasia and CASK protein expression in adenomas. N=15.

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>CASK expression</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Low grade:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>% of total</td>
<td>40.0%</td>
<td>13.3%</td>
</tr>
<tr>
<td><strong>High grade:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>% of total</td>
<td>13.3%</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

Discussion

Colorectal cancer is one of the leading causes of cancer related morbidity and mortality worldwide. It accounts for more than 9% of all cancer incidence. It is the third most common cancer globally and the fourth leading cause of death [2]. Research suggests that the process of colorectal carcinogenesis usually follows a succession of histologic changes called the adenoma-to-carcinoma sequence. This sequence involves the accumulation of a combination of abnormalities in the genome allowing uncontrolled proliferation, incapacity for apoptosis and ultimately invasive and metastatic propensity [8].

The aim of our study was to evaluate the expression of Calcium/calmodulin-dependent serine
protein kinase (CASK) in non-mucinous colorectal adenocarcinoma and its relation with clinicopathological variables of the disease (such as, tumor (T) stage, lymph node metastasis status, distant metastasis, lymphovascular invasion and grade of differentiation) with IHC staining.

The study was conducted at the Department of Pathology of Suez Canal University Teaching Hospital and included 42 non-mucinous CRC patients' samples and 15 adenomas biopsies.

CASK is expressed on the cell membranes of epithelial cells at different sites as in the choroid plexus epithelial cells, at synaptic junctions and hepatocytes. It was also found to be expressed in small and large intestinal epithelial cells; mainly at the baso-lateral regions of cell membranes and has been reported to mediate cell-cell adhesion and proliferation, which can contribute to tumorigenesis [5,9]. Our results showed that CASK protein was significantly overexpressed (p<0.05) in CRC compared with normal samples. We therefore think that CASK overexpression might be a participant in the pathogenesis of CRC. We observed that the majority (52.8%) of CRC samples showed both cytoplasmic and cytomembranous expression of CASK protein by immunohistochemistry, while only 20% of adenomas samples showed dual pattern of staining. This could suggest that besides CASK role in cell-cell interaction, its mobilization into the cytoplasmic pool might indicate it has a role in the control of cell growth and proliferation. Membranous staining pattern showed a statistically significant correlation with CASK protein overexpression (p<0.05). This membranous pattern of staining could support our observation that CASK is a good prognostic marker. CASK protein localization on the cytomembrane might contribute to better tumor cell cohesion, preserved architecture and polarity.

Our results are accordant with a previous study that used western blot and IHC technique to measure the expression of the CASK protein and its gene in 156 CRC tissue samples and compared it with its expression in 42 of normal and adenoma samples. Seventy three percent of their CRC samples displayed high expression while 84.2% of adenoma samples displayed low expression. Their results indicated that CASK was up-regulated in CRC compared with the other non-malignant tissue types [4,10,11].

We also demonstrated for the first time significantly high levels of expression within adenomas with high grade dysplasia. Such results are consistent with the adenoma-carcinoma model of CRC progression [6,12] and could indicate that CASK is involved along with other biomarkers in the progression of benign adenomatous polyps into highly dysplastic variant and then finally into invasive carcinomas.

CASK overexpression was significantly correlated with both TNM stage and grade of differentiation (p<0.05). We observed significantly higher expression in tumor samples with early stages (I/II) rather than advanced stage (III/IV) and with low grade tumors rather than high grade ones.

We suggest that CASK protein might be a marker of well-differentiated, less aggressive tumors and its overexpression might be suggestive of favorable prognosis. CASK protein mainly functions as cell-cell adhesion molecule and is involved in regulation of epithelial cell polarity [7]. This being said, CASK overexpression might contribute to better tumor cell-cell cohesion and preserved architecture of tumor cells and therefore lower tumor grade. Our results in this aspect are accordant with a previous study of CASK expression analysis in cell lines. They found that induced CASK overexpression, with the resulting increase in the level of CASK protein, lead to significant decrease in the rates of cell growth and proliferation, while inhibition of about 68% of endogenous CASK protein production resulted in significant increase of the cell growth rates. Together, from these results they concluded that CASK may play an important role in inhibiting cell growth and proliferation beside its role in cell-cell adhesion [8]. On the other hand, a previous study on CRC associated CASK overexpression with advanced tumor stage, unfavorable prognosis and poor survival [13]. This discrepancy might be due to the complexity of genetic factors involved in the pathogenesis of CRC and influencing its behavior. Different genetic profiles of populations of different ethnicities should be considered. The relatively small number of high grade CRC samples (17 cases) in our study might be a factor for limitation.

References


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تمثيل إنزيم كاسك في سرطان القولون والمستقيم الغير مخاطي

الخلايا العضلية: يعتبر سرطان القولون والمستقيم من أكثر أنواع السرطانات شeringاً في العالم. ويعتبر الرجال والنساء نسبياً على حد سواء، وذلك بسبب ارتفاع معدلات حدوث سرطان القولون فيما قبل سن الapphire، ولا يزال ذلك غير واضح، وقد يرجع ذلك إلى نقص الطعام أو نوعية الغذاء أو التعرض لبعض العوامل البيئية.

يقدر عدد حالات سرطان القولون في مصر في عام 2014 حوالي 218200. من بين كل 2500 إلى 5000 الذي يولد، أو سن سن، وقد شهدت حالات سرطان القولون وائد السرطان السائد في مصر من حيث الإصابة. وقد قدرت البيانات الإحصائية أن الإصابة بسرطان القولون والمستقيم بين الذكور في مصر وصلت إلى 6.1% مع ارتفاع معدل متوسط إنفاذ 2.5%.

ليس هناك جملة واحدة لدلالات الإصابة بسرطان القولون والمستقيم أو تطورها، ولكن هناك العديد من العوامل المساهمة بما في ذلك الإضطرابات الغذائية وطقس وظائف الخضروات والسبسيت. وتشير النتائج إلى أن الأنسجة خارج الخلايا، وتفاعلها مع المواد الرئيسة في عملية السرطان وانتشار الورم.

قائمة البروتينات هو مستقبل الCASK حيث يعتقد أنه يلعب دور في إرسال الخلايا وتنظيم حركتها، ومن ثم حدوت خلل في هذا البروتين على الحيوانات قد يساهم في إنشاء الورم وتطور ثانيات في مختلف أنحاء الجسم.

الهدف من إجراء البحث: دراسة مدى العلاقة بين تمثيل إنزيم الكاسك (CASK) وسرطان القولون والمستقيم وأهميتها كأحد العوامل المتميزة في تطور الورم.

الطريق والوسائل: هي دراسة وصفيةً، بالرغم من أن دراسة مدى العلاقة بين إنزيم الكاسك (CASK) وسرطان القولون والمستقيم (CASK) وأهميتها كأحد العوامل في تطور الورم عن طريق تحليل الصبغات المتميزة التي يبين درجة تأثر الجين المتميزة على تكوين الكاسك.

وقد تم إجراء البحث في قسم الباثولوجيا بجامعة القاهرة السور على حالات سرطان القولون والمستقيم الإkichكاملة. وبعد إجراء الحسابات الإحصائية، وجدنا أن الحد الأدنى المطلوب هو 15 حالة، فتم تقييم الورم عليها ودراستها. وقد شملت الدراسة عينة من 150 ورم مريضي بسرطان القولون والمستقيم الغير مخاطي، مع تقسيم عينة من 150 ورم مريضي بالقولون.

تم تحضير مقاطع من العينات وأغذاه بالزهورات والبوسين وفحصها مجهوراً، وتحضير مقاطع أخرى وصبها صبغة صبغة متميزة للكشف عن وجود الكاسك في نسيج الورم، امتصاصه داخل الخلايا، شدة الصبغ وعلاقته بالعوامل الإيككاملية والباثولوجية المتميزة في سرطان القولون والمستقيم.

وقد شملت مجموعة الدراسة نسبة 30% من الذكور و60% من الإناث، وweis بالسليمين بسرطان القولون مع مستويات غير معينة. وweis بالسليمين بسرطان القولون مع مستويات غير معينة.

وقد أظهرت الدراسة إرتفاعاً ملحوظاً في تمثيل الكاسك في الخلايا السرطانية مقارنة بالخلايا الطبيعية للقولون، وكذلك خلايا الأورام الغدي المحيطية. كما أن الدراسة أظهرت علاقة إيجابية بين تمثيل الكاسك وبين كلا من المرحلة المرتبطة ودرجة تميز الخلايا حيث أظهر الإرتفاع الملحوظ في مراحل الأورام، وكذلك مع درجة التمدد الأفقي للخلايا.

نستنتج من هذه الدراسة أن تمثيل إنزيم الكاسك يشبه بصورة واضحة في سرطان القولون والمستقيم وأنه من الممكن الاستعانة به كأحد المؤشرات الإيجابية في تطور الورم وانتشاره.