DOI: https://doi.org/10.54393/pjhs.v5i10.2016

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 10 (October 2024)

Original Article

OPEN ACCESS

Stanniocalcin 2 Expression: A Significant Marker in the Prognosis of Colorectal Carcinoma

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ARTICLE INFO

Keywords:
Lymph Node Metastasis, Tumor Progression, Colorectal Cancer, Perineural Invasion

How to Cite:
Zafar, S., Qamar, N., Shahid, M., Kamran, S., Sundus, S., & Aziz, Z. (2024). Stanniocalcin 2 Expression: A Significant Marker in the Prognosis of Colorectal Carcinoma: Prognosis of Colorectal Carcinoma. Pakistan Journal of Health Sciences, 5(10). https://doi.org/10.54393/pjhs.v5i10.2016

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Received Date: 15th August, 2024
Acceptance Date: 25th October, 2024
Published Date: 31st October, 2024

ABSTRACT

Colorectal Cancer (CRC) is one of the most common cancers worldwide and causes significant morbidity and mortality. Biomarkers that predict tumor behavior and prognosis were essential. Stanniocalcin-2 (STC2) was a glycoprotein hormone involved in tumor progression but its association with clinicopathological parameters in colorectal cancer needs to be studied. **Objective:** To evaluate the correlation of Stanniocalcin-2 expression with clinicopathological features of colorectal cancer including tumor grade, invasion, lymph node metastasis, perineural invasion, and disease prognosis. **Methods:** This retrospective observational study was conducted at Life Care Molecular and Polymerase Chain Reaction Lab Services, Karachi in collaboration with Fazaia Ruth Pfau Medical College. 60 paraffin-embedded blocks from colorectal cancer patients diagnosed between January 2020 and December 2022 were included. 10 colonic biopsies negative for malignancy were taken as controls. Immunohistochemically analysis of Stanniocalcin-2 was compared with clinicopathological parameters including tumor grade, invasion, lymph node status, and perineural invasion. Statistical significance was calculated at a 95% confidence level and 5% margin of error. **Results:** Stanniocalcin-2 was significantly associated with higher tumor grade, invasion, lymph node metastasis, and perineural invasion ($p<0.05$). Strong stanniocalcin-2 expression was associated with poor disease prognosis and aggressive tumor behavior. **Conclusions:** Stanniocalcin-2 was a poor prognostic marker in colorectal carcinoma and was linked to aggressive tumor features. Stanniocalcin-2 can be a useful biomarker to predict disease progression and treatment strategy.

INTRODUCTION

According to global statistics, Colorectal Carcinoma (CRC) has been listed as the fourth most prevailing cancer and third of all cancers in mortality [1]. Colorectal Cancer (CRC) poses a hazard to health and creates considerable societal consequences, accounting for approximately 10% of all new cancer cases [2]. However, recent research has shown that the incidence and mortality rates of CRC have reduced in some places while increasing in China [3]. In Pakistan, colorectal carcinoma is the fourth most common cancer in both sexes and all age groups with an incidence rate of 4.8%. The number of new cases in males with all age groups is 5.8%. The percentage of colorectal cancer before the age of 75 years is 11.5% for males and 12.3% for females. Likewise, 8.3% of males and 8.2 females have the risk of dying from this cancer before the age of 75 years (WHO Globocon 2020). Adopting Western dietary and lifestyle patterns, as well as the resulting changes in the gut microbiota, may contribute to the rising incidence of colorectal cancer [4]. It has been found that the five-year survival rate for localized CRC and CRC with distant metastasis is 90% and 14-70 % respectively. Presently, various prognostic factors like depth of tumor invasion, lymph node involvement, tumor grade, and lymphatic and venous infiltration as well as screening programs are in use for better clinical outcomes and improved survival rates. The main challenges faced by clinicians are local recurrence, distant metastasis, and aggressiveness of CRC which increases the rate of mortality. To minimize this

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high mortality rate of CRC, there is a dire need to design new techniques that should have the ability to predict tumor aggressiveness and metastasis and will improve the clinical outcome and management of CRC patients [5, 6]. Improving early detection and treatment, as well as minimizing the disease burden of CRC, is a major public health issue. The gut microbiota is critical to the development and progression of CRCs [7]. STC2 belongs to the glycoprotein hormone family, which is highly conserved and secreted. The term "Stanniocalcin" (STC) comes from the corpuscles of Stannius, the endocrine glands situated ventrally on the surface of the fish kidney [8, 9]. Human chromosome number 5 (5q35.2) expresses Stanniocalcin 2 (STC2) gene and in turn, this gene encodes a highly conserved glycoprotein named Stanniocalcin 2. This protein has some autocrine and paracrine capabilities and it is normally expressed in various tissues like the breast, pancreas, kidney spleen, lungs, intestines, and brain. This protein has many physiological functions like cellular calcium/phosphate homeostasis. STC2 upregulates Cyclin-dependent kinase 2 and 4 (CDK2 and CDK4) and enhances angiogenesis to protect cells against oxidative stress or glucose deprivation. Furthermore, it down-regulates cell cycle inhibitors p16 and p21 and activates pAKT and pERK1/2 signaling pathways resulting in increased cell viability and survival during cell exposure to unfavorable environments [9]. Stanniocalcin 2 (STC2) was discovered in mice and humans by searching for sequences identical to Stanniocalcin [10]. Over-expression and upregulation of STC 2 are found in various tumors of the head and neck, GIT, lung, liver, kidney, brain, and breast. Increased expression of STC2 is well correlated with aggressiveness, distant invasion, and poor prognosis in all such tumors [11]. Recent research indicates that STC2 plays a significant role in cancer formation, specifically colorectal carcinoma [12].

In this study, immunohistochemically analysis investigated the strength and proportion of STC 2 in various histological grades of 60 CRC patients.

METHODS

This study was conducted at the Life Care Molecular and Polymerase Chain Reaction (PCR) Lab Services, Karachi from January 2020 to December 2022 in collaboration with Fazaia Ruth Pfau Medical College Karachi. It was a retrospective observational study with immunohistochemical analysis with a 95% confidence level and a 5% margin of error. After obtaining approval from the Ethical Committee of Fazaia Ruth Pfau Medical College, Ref no: FRPMC/001/IRB/19 and Ref no: LCMB/001/IRB/24 of Lifecare Molecular Lab. This study's outcome variable includes the presence of carcinoma infiltration into the biopsies. To calculate the sample size, use proportions or prevalence of cancer cases (for example, the proportion of cancerous to non-cancerous biopsies resected). Using the formula for comparing proportions was the most popular way of calculating sample size in clinical research with proportions. According to a 2019 analysis, the prevalence of colorectal carcinoma in Pakistan is approximately 4.9% [13] with taking 6% margin of error 95% confidence interval and a 10% dropout rate was 60. The equation for sample size was using a single proportion formula:

$$n = \frac{Z2 \times Px(1-P)}{d2}$$

60 selected paraffin blocks were selected which were obtained from the biopsy samples of patients with clinically and diagnostically proven colon and rectum cancer received at Life Care Molecular Lab in collaboration with Fazaia Ruth Pfau Medical College, Karachi. All biopsy specimens showed all layers of intestinal mucosa with varying degrees of cancer infiltration. 10 cases of colonic biopsies were also included which were negative for any malignancy as negative controls. "Demographic details of all patients were retrieved and maintained Diagnostic details including radiological and ultra-sonographic details of all patients were collected. Histopathology of all intestinal biopsies was performed on H and E-stained slides to identify the degree of tumor infiltration and invasion. At least five sections were taken from each paraffin block from all biopsies to carry out routine stain (H and E) and immunostaining for Stanniocalcin 2.04 mm thick sections were obtained from all intestinal biopsies.04 mm thick sections were obtained from all intestinal biopsies. Tissue sections were mounted on positively charged slides followed by routine deparaffinization and antigen retrieval by automated water bath (Cyto test, China). An unlabeled primary antibody was added which bound with a specific antigen on the tissue. Another labeled antibody (secondary) which was already conjugated with an enzyme (HRP) was added which binds to the antigen-antibody complex just to amplify the detection level compared with direct staining methods. A colored (brown), insoluble precipitate at the antigenic sites was formed by the conjugation of the enzyme (HRP) and a substrate (H2O2) using a chromogen, DAB (3, 3'-diaminobenzidine), (Thermal Fischer Scientific, USA). Positive expression was indicated as the brown coloration of tumor cells that were easily visualized and photographs were taken by using light microscopy (Leica 2500 optical microscope, GmBH Germany). All slides were examined by two consultant histopathologists. The STC2 staining score was computed using the method introduced by Zhang ZH et al [14]. The percentage positivity of the stained tumor cells and the staining intensity were assessed as follows: <5%, scored 0; ≥5 to <25%, scored 1; ≥25 to <50%, scored 2; ≥50 to <75%,

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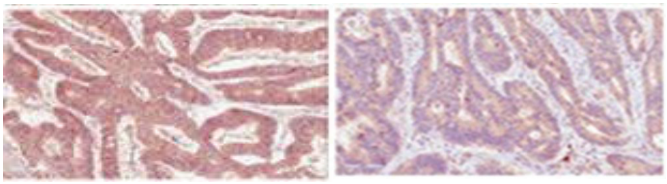
scored 3; and ≥75%, scored 4. Staining intensity was graded as follows: score 0=no staining; score 1 = mild staining; score 2=moderate staining; and score 3=intense staining [5]. Cancer cells showing STC2 expression were counted as the percentage of cells with positive staining by counting at least 100 cells using a scale of 1-4 where 5-10 % cancer cells as 1+, 11-40 % cancer cells as 2+, 41-70 % cancer cells as 3+, 71-100 % cancer cells as 4+ [15]. All statistics analyses were performed on SPSS version 22. Qualitative Variables such as tumor grade, STC2 score, lymph node metastasis, and perineural invasion will be summarized as frequency and percentages and Quantitative Variables like age and tumor size will be summarized as Mean ± Standard Deviation. The Chi-square Test will be used to evaluate associations between qualitative variables like STC2 expression and categorical clinicopathological features such as tumor grade, lymph node metastasis, and perineural invasion. The p-value <0.05 was set as the level of significance.

RESULTS

Out of 60 cases, 32 (53%) were male patients with a median age of 60 to 70 years while 28 (46%) were female patients with a median age of 70 years. No statistically significant relationship was found between age, sex, and STC 2 expression as shown in Table 1. CRC shows various gross and morphological appearances including fungating, ulcerating, or infiltrative but none of them shows any significant association with STC 2 expression as seen in Table 2. Significant association present between histopathological features of CRC and STC 2 expression. Tumor grade, T-stage, lymph node involvement, distant metastasis, Duke Stages, and lymph-venous and perineural invasion as shown in Table 3. The different clinicopathological parameters used in this study were: Tumor staging and grading, Tumor invasion, Lymph node metastasis, perineural invasion, Disease Progression, and Prognosis. Tumor grading was based on the Gleason scoring system which divides tumors into three types depending on their level of differentiation; well-differentiated, moderately differentiated, and poorly differentiated. The biopsy specimens were analyzed through histopathological methods in an attempt to categorize the tumors. Well, if we look at the level of differentiation and the structure of cells studied under the microscope, they meet all the requirements of grading CRC according to standardized norms. Staging of tumors was according to the Duke staging system, it's measured in terms of the extent of tumor penetration into the bowel wall, involvement of regional lymph nodes, and distant metastasis. The invasion was described in the TNM system and was evaluated by the T system degree of penetration into the intestinal wall. Lymph Node Metastasis can be evaluated in the N staging system in TNM system. The architecture of the biopsy tissue section was analyzed histologically to see how far the cancer had spread to the perineural region. In tissue sections, pathologists look for cancer cells that invade nerves. Out of 60 cases of CRC included in this study, 15 cases (25.1%) had negative staining, 34 cases (56.6 %) showed mild positive staining, and 11 cases (18.3%) showed intense positivity. Strong positive staining (+3) in Invasive adenocarcinoma and weak positive staining (+1) in well-differentiated adenocarcinoma of colorectal cancer is illustrated in figure 1.



(Brown Color Staining) = Strong Positive (+3) Invasive Adenocarcinoma (Poorly Differentiated)

(Slight Brown Color Staining=Weak Positive (+1) Well Differentiated Adenocarcinoma

Figure 1: Immunohistochemically Analysis of Stanniocalcin Expression

The data reveal no significant association between STC 2 expression and gender (p=0.117) or age (p=0.095). The distribution of Stanniocalcin 2 (STC 2) expression based on age and sex are shown in table 1.

Table 1: Association between Age, Gender and STC 2 Expression

Age and Gender Distribution	Number of Patients N (%) / Mean ± SD		Stanniocalcin 2 Expression			p-Value
			Negative	Mild Positive	Strong Positive	
Gender						
Male	32 (53%)		12	14	6	0.117
Female	28 (46%)		8	15	5	
Age						
>50 Years	63 ± 7	50 (83%)	14	27	9	0.095
<50 Years	44 ± 5	10 (16%)	3	5	2	

Various gross appearances of Colorectal Cancer (CRC) such as fungating, ulcerating and infiltrative do not show a significant association with STC 2 expression (p=0.139), as shown in table 2.

Table 2: Association between Gross Appearance of CRC and Stanniocalcin 2 Expression

Gross Appearance	Number of Patients N (%)	Stanniocalcin 2			p-Value (Chi-Square Test)
		Negative	Mild Positive	Strong Positive	
Fungating	22 (36%)	5	15	2	0.139
Ulcerating	28 (46%)	10	14	4	
Infiltrative	10 (16%)	1	3	6	

Associations between histopathological features of CRC and STC 2 expression are presented significantly. Tumor grade, T-stage, lymph node involvement, distant metastasis, Duke Stages and lympho-venous and perineural invasion all demonstrate significant statistical associations (p<0.001), as shown in table 3.

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Table 3: Association between Histopathological Characteristics and STC 2 Expression

Histopathological Feature	No of Patients N (%)	Stanniocalcin 2			p-Value (Chi Square Test)
		Negative	Mild Positive	Strong Positive	
Tumor Grade					
II	50 (83%)	10	35	05	<0.001
III	10 (17%)	01	07	02	
T-Stage					
T2	05 (9%)	03	02	00	0.004
T3	40 (66%)	12	22	06	
T4	15 (25%)	01	06	08	
Lymph Node Involvement					
N0	28 (46%)	11	14	03	0.001
N1(Up to 3 LN)	20 (33%)	04	13	03	
N2 (≥ 4 LN)	12 (21%)	02	04	06	
Distant Metastasis					
Mx	48 (80%)	-	-	-	0.001
M1	12 (20%)	00	02	10	
Duke Stages					
B1	01 (2%)	00	00	-	<0.001
B2	28 (46%)	10	14	04	
C1	02 (3%)	00	01	01	
C2	26 (43%)	02	15	09	
D	03 (5%)	00	01	02	
Lympho-Venous Invasion					
Negative	42 (70%)	15	27	00	<0.001
Positive	18 (30%)	00	06	12	
Perineural Invasion					
Negative	48 (80%)	16	29	03	<0.001
Positive	12 (20%)	00	04	08	

DISCUSSION

In Pakistan, various statistical data collected from different regions have shown a 4-7% prevalence rate of colorectal carcinoma [16]. Genetic as well as cultural and environmental factors play a significant role in the development and pathogenesis of colorectal carcinoma. Consumption of high quantities of red and smoked meat in multiple ethnic groups in Pakistan was the main cause of this fatal disease [17]. According to the American Cancer Society, 106,970 new cases of colon cancer and 46,050 new cases of rectal cancer were expected to be diagnosed as colorectal carcinoma in the USA in 20203 and expected deaths by this disease would be 52550 in 2023. (ACS 2020). In Pakistan, various statistics have shown prevalence rate of colorectal carcinoma in adolescents, adults, middle-aged age, and senior citizens was found to be as 5.2%, 7.4%, 4.9%, and 4.4% respectively [18]. Although, in the past various studies have been done on STC2 expression all of them were based on genetic analysis and gene slicing of STC2 in colorectal carcinoma showing inhibition of tumor cell viability, infiltration, and metastasis. A few studies based on immunohistochemistry have been performed in recent years to demonstrate the immunohistochemical expression of STC2 about different clinicopathological features of colorectal carcinoma. Since all these studies prove the importance of STC2 in the prognosis and management of CRC, it compares these results with the results of those studies. In this study, it found that overall 74.9% of cases were STC2 positive in which (56.6 %) showed mild positive staining 11 cases (18.3%) showed intense positivity, and 25.1% were negative. Almost similar results were seen in studies like Galal RS *et al.*, which showed 28.3% negativity, 53.3% low-grade positivity, and 18.3% high-grade positivity. While Zheng *et al.*, showed 24.35% negativity with 75.6% positivity in his study [4]. No significant statistical association was seen among age and gender distributions (p=0.117, p=0.095). Zheng *et al.*, and Galal RS *et al.*, have the same insignificant association (p>0.005) [4, 5]. A significant association was found between tumor grade and STC2 expression (p=0.001). In CRC, tumor grade and stage were two important prognostic factors [19, 20]. Galal RS *et al.*, also a significant relation between tumor grade and STC2 (p=0.004), while Zheng et al., showed no significant association (p=0.205) [4, 5]. Lymph node involvement was also an important prognostic factor in the management and survival of patients. This study shows a significant relationship between lymph node involvement and STC2 expression (p=0.001) while Zheng *et al.*, and Galal RS *et al.*, also show the same results [4, 5]. This study also shows a significant association with distant metastasis (p=0.001) while Zhang also shows similar results [11]. This study showed a significant association between lymph vascular and perineural invasion (p=0.001) Similar results were also found in a study by Galal RS *et al* [5].

CONCLUSIONS

This study reveals a definite association of immunohistochemical expression of Stanniocalcin 2 (STC2) with potent clinicopathological criteria such as tumor grade and invasiveness. These results infer that STC2 could play a role in determining the aggressiveness of CRC tumors. This evidence indicates that STC2 could be used to predict a prognosis; nonetheless, further clinical investigation with larger samples based on different populations was required to use it safely in clinical application for early diagnosis and treatment planning.

Authors Contribution

Conceptualization: SZ, NQ, ZA
Methodology: NQ, MS
Formal analysis: SZ, MS
Writing, review and editing: SK, SS, ZA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

DOI: https://doi.org/10.54393/pjhs.v5i10.2016

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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