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Association of Esophageal Adenocarcinoma With B-catenin

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Abstract

Background-Aims: Esophageal cancer is the ninth most prevalent cancer and the sixth leading cause of cancer-related deaths globally. The development of esophageal adenocarcinoma is strongly linked to the expression of β-catenin and E-cadherin. The primary goal of this study is to explore the relationship between esophageal adenocarcinoma and β-catenin. The expression levels of β-catenin and E-cadherin could serve as valuable biomarkers for diagnosing and treating esophageal adenocarcinoma, potentially enhancing patient outcomes

Methodology: In this particular quantitative research, a total sampling of the eligible anonymous esophagectomy specimens from 71 patients with esophageal adenocarcinoma was studied to investigate the association of esophageal adenocarcinoma with β-catenin

Results: The coefficient of the variable had a positive sign, which implied that the percentage of the existence of β-Catenin Immunohistochemistry tended to increase with the increase in the

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percentage of E-Cadherin Immunohistochemistry. Also, it could be concluded that gender substantially did not affect the response rate.
Conclusions: Targeting the concurrent regulation of β-catenin and E-cadherin could offer a promising therapeutic approach for treating adenocarcinoma. This is because the simultaneous dysfunction of these proteins, hyperactivation of β-catenin and the loss of E-cadherin, are key factors driving the aggressiveness and metastasis of adenocarcinoma.

Keywords: b-catenin, Wnt, E-Cadherin, adenocarcinoma, oesophagus

1. Introduction

1.1 Background

Oesophageal cancer (EC) is ranked as the ninth most common type of cancer and the sixth leading cause of cancer-related death worldwide. Most studies show that men have a 2-3 times higher mortality and incidence of esophageal cancer in comparison to women. Esophageal cancer begins when abnormal cells begin to grow in the muscular tube of the esophagus (Sheikh et al., 2023; Stabellini et al., 2022).

The two main histopathological subtypes of oesophageal cancer are Oesophageal Adenocarcinoma (OAC), which is mainly located in the lower part, and Esophageal Squamous Cell Carcinoma (ESCC), placed throughout the esophagus (King et al., 2021). OAC is the prevailing EC subtype and, in most instances, is thought to get developed by a precursor lesion that is called Barrett's Esophagus (BE) (Photo 1)

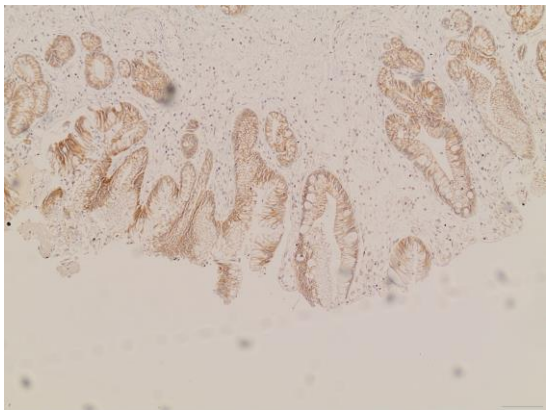

Photo 1. Barrett's Esophagus (x10)

Esophageal adenocarcinoma accounts for the majority of esophageal cancer in Western countries. Despite improvements in treatments, the prognosis of patients with EC remains poor, with a global 5-year survival rate of approximately 20.5% (Gen et al., 2024).

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OAC is considerably associated with the expression of β-catenin and E-cadherin. β-catenin is a multifunctional protein with a central role in normal homeostasis. Its abnormal high expression leads to various diseases including cancer. E-cadherin is substantially a trans membrane protein which is actually entailed in the maintenance of cell adhesion and cell polarity maintenance, and it is found in nearly all epithelial cells (Gao et al., 2017). It is 120-KD calcium-dependent and has been shown to be regulated by the rate of necrosis of invasive tumors. A loss of E-cadherin expression correlates with enhanced tumor cell motility and invasion. (Na et al., 2020; Fernando et al., 2018).

Wnt serves as the primary regulator of β-catenin, which is a group of 19 glycoproteins that are involved in the regulation of both β-catenin-dependent (canonical Wnt) and β-catenin-independent (non-canonical Wnt) signaling pathways. The Wnt signaling pathway plays a crucial role in the development of esophageal cancer. In addition, activation of Wnt/β-catenin is linked to a poor prognosis in patients with this particular type of cancer (Chu et al, 2022; Yu et al., 2021). E-cadherin, a protein involved in cell adhesion, is known to have reduced expression in cases of esophageal cancer, contributing to lymph node metastasis. β-catenin, as a key component of the Wnt signaling pathway, interacts with E-cadherin at the cell membrane, where the complex of these two proteins could assist in stabilizing cell adhesion (Shah & Kazi, 2022).

E-cadherin is an essential protein involved in the process of cell adhesion, and its expression is crucial for maintaining cellular structure. It is well-established that a decrease in E-cadherin expression contributes significantly to lymph node metastasis in esophageal cancer. β-catenin, a key regulator within the Wnt signaling pathway, interacts with E-cadherin at the cell membrane. The complex formed between these two proteins plays a vital role in stabilizing cell adhesion and maintaining the integrity of the epithelial cell layer (Zhao et al, 2022; Su et al., 2015).

Esophageal adenocarcinoma is typically diagnosed at advanced stages, often when the disease has already spread. Despite recent improvements in treatment strategies, the clinical outcomes for these patients remain unsatisfactory. This is largely due to the fact that reduced E-cadherin expression is closely associated with more advanced tumor stages, leading to poorer prognosis in individuals with esophageal adenocarcinoma (Ribatti et al., 2020).

The main aim of the present study is to investigate the association of esophageal adenocarcinoma with β-catenin. Consequently, it is of crucial importance to explore the underlying molecular markers in order to enhance patient outcomes.

1.2 Rationale

The specific research could provide valuable insights into the molecular mechanisms of EAC, potentially identifying β-catenin and E-cadherin as key players in its pathogenesis. Furthermore, β-catenin and E-cadherin expressions could serve as biomarkers to guide the diagnosis and treatment of esophageal adenocarcinoma, potentially improving patient outcomes (Dourakis et al., 2024; Tan et al., 2016).

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1.3 Objectives

The primary objectives of this particular study are: a) to assess the role of b-catenin, E-cadherin and Wnt signaling pathway apropos esophageal adenocarcinoma and b) to investigate any correlations between β-catenin and E-cadherin, and c) to explore whether the proteins b-catenin and E-cadherin can be used as potential biomarkers for early detection or as a therapeutic target.

1.4 Hypothesis for the study

The study hypothesizes that β-catenin and E-cadherin dysregulation could be associated with the initiation or progression of esophageal adenocarcinoma. Specifically, this dysregulation could involve the overexpression or abnormal activation of β-catenin, in conjunction with altered or reduced expression of E-cadherin. These changes might disrupt cellular adhesion and contribute to the activation of the Wnt signaling pathway, promoting uncontrolled cell proliferation, invasion, and tumor growth.

1.5 Research Questions

The following research questions are concentrated on exploring the role of β-catenin and E-cadherin in esophageal adenocarcinoma as well as understanding the biological role of β-catenin and E-cadherin in cancer progression and their clinical relevance.
a) Is there a significant association between β-catenin and E-cadherin in esophageal adenocarcinoma tissue samples?
b) How does the expression of β-catenin correlate with the clinical features of esophageal adenocarcinoma?
c) Could β-catenin and E-cadherin expression levels serve as potential biomarkers for the early detection or prognosis of esophageal adenocarcinoma?

2. Methodology

2.1 Ethical considerations

The specific study was carried out in accordance with the standards of conduct and ethics of the Research Ethics Committee of the Medical School of Athens of the National and Kapodistrian University of Athens (NKUA) in Greece, which gave its approval for the Research Protocol. The Research Ethics Committee of the Medical School of Athens (EKPA) also approved the publication of the present study.

2.2 Study design

The research concerned biomedical data and was based on statistical analysis to examine any differences between parameters. This quantitative research used comparative and correlational statistical methods. In this research we had 2 types of immunohistochemistry. β-catenin was examined as independent and E-cadherin as dependent in Regression Analysis.

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In this particular quantitative research, the researcher made use of the One-Way Analysis of Variance (ANOVA), one (1) Regression Analysis, T-Tests and Chi-Square Tests,which assessed the association of the 2 variables; that is to say, the 2 particular proteins, β-catenin and E-cadherin. The variables were numerical, specifically nominal, ordinal and scale.

It was based initially on a literature review and then on the experimental results that was available after diaphragmatic esophagectomies.

2.3 Study settings

The present data came from anonymous esophagectomy specimens from patients with esophageal adenocarcinoma. The specimens that were used for this study are archival material from the settings of the First Laboratory of Pathological Anatomy, Medical School of Athens (EKPA) in Greece. The present study was conducted at the facilities of the First Laboratory of Pathological Anatomy, Medical School of Athens (EKPA).

2.4 Participant characteristics

The present study used a total sampling of the eligible anonymous esophagectomy specimens from patients (n=71) with esophageal adenocarcinoma, with or without previous treatments, during the study period.

The study took place between the years 2023-2025 and the patients consisted of male and female adults between 47 and 94 years of age (the median age was 67,08 years). With regard to the sample, fewer females were included than males, as the proportion of men was 83,1% (59 people) and women was 16,9% (12 people).

2.5 Research Methods

The histological and immunohistochemical study was performed on tissue sections fixed in 10% aqueous neutral formalin solution and embedded in paraffin blocks (*Paraplast*) at 55^0C. From each case, 4 μm thick sections were cut with a microtome (*Finesse ME, Thermoshandon, Runcorn, UK*), spread in a water bath (*Tissue Bath, P/S, NBIT Y2K, Chicago 47, USA*) adjusted to 60^0 C and then plated on electrostatically charged slide slides, to prevent detachment of the sections during processing. Subsequently, the sections were placed in a dry heat oven for 1 hour at 60^0 C to stabilize the tissues, melt the paraffin, followed the Hematoxylin-Eosin staining (Photo 2) and then continued with the immunohistochemistry process (Hinton et al., 2019).

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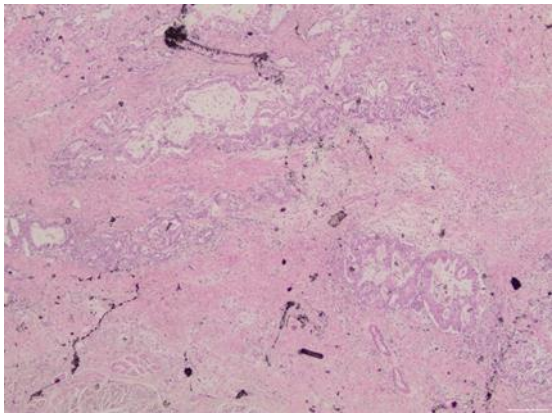

Photo 2. Gastroesophageal junction adenocarcinoma (x10) with Hematoxylin-Eosin stain

Deparaffinization and hydration of the sections was performed at high pH [*EnVision FLEX Target Retrieval Solution High pH* (*50x*)] for both markers (*β-catenin, e-cadherin*).

The binding of endogenous peroxidase activity was performed by placing the sections in a 0.3% H_2O_2 solution at room temperature and in the dark environment for 15 minutes, followed by washing with Tris solution [*EnVision FLEX WASH BUFFER (20x)]* for 5 minutes.

Then, the Sequenza immunohistochemistry device (*Thermoshandon, Runcorn, UK*) was used using cover-plates technology, which was based on the capillary effect and ensured staining with the minimum amount of reagent and protection of the samples from drying.

The antibodies used in the study were:
1) Beta-Catenin, clone 14 (*BioSB, 5385 Hollister Ave #108, Goleta, CA, USA*). The antibody was prediluted (*RTU*) and the incubation time was 30 min.
2) E-Cadherin, clone (*NCH-38*) (*DAKO*). The antibody was prediluted (*RTU*) and the incubation time was 30 min.
Then, the Ready-to-Use EnVision FLEX/HRP complex (*EnVision FLEX+, Agilent DAKO*) was placed at room temperature for 30 minutes and the sections were washed with Tris solution for 10 minutes.
The peroxidase activity, which contributed to the enhancement of the immunoreaction signal, was marked by placing a solution of 3,3′, diaminobenzidine tetrahydrochloride chromogen (*DAB Chromogen, EnVision FLEX, Agilent, DAKO*). DAB in the presence of peroxidase was localized at the antigen-antibody sites and provided intense and stable gray staining.

The solution was prepared at least for 15 minutes before use, by placing and stirring 1-2 drops (*40-100 ul*) of DAB chromogen in 1 ml of DAB substrate solution (*DAB Substrate, EnVision FLEX, Agilent, DAKO*). The sections were placed in the chromogen for 6 minutes, in the dark environment and at room temperature, followed by rinsing with Tris solution for 10 minutes and

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running tap water for another 10 minutes. Then, the sections were placed for counterstaining in fresh Gill's hematoxylin solution (*BIOGNOST, Medjugorska 59, 10040 Zagreb, Croatia*,) for 1 minute.

The sections were dehydrated by successive immersions in ethanol solutions (ascending alcohols) 70^0C, 80^0C, 96^0C and 100^0C for 1 minute and room temperature xylene for 2 minutes. The technique was completed by covering the sections with the special mounting material Entellan (*Sigma-Aldrich, Queens Road, Teddington, Middlesex, UK Ref.# 1.07961.0500*) and placing a coverslip.

As breast cancer is highly correlated with the two proteins, b-catenin and E-cadherin, it was used as a positive control for both markers, in order to determine the intensity of the staining (Photo 3).

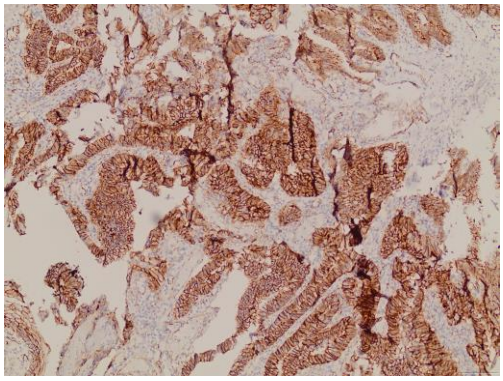

Photo 3. Membranous staining e-cadherin. adenocarcinoma of gastroesophageal junction (x10)

As negative control, the technique that was based on the lack of addition of antibody was applied. This particular technique demonstrated that the results were neither false positive nor negative. Thus, in Lab Photos 4,5,6 and 7, the positive described intensity, which was +++, while in the negative indicator, there was absence of intensity.

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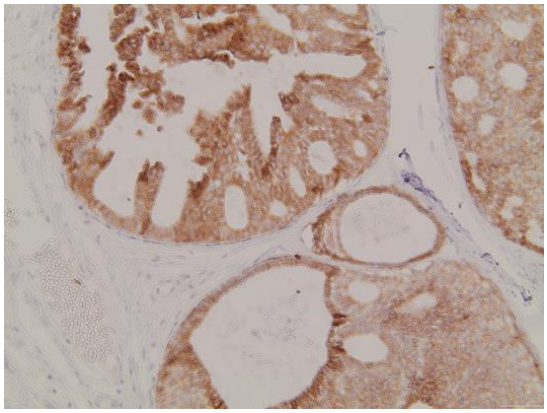

Photo 4. β-catenin indicator+ (x10)

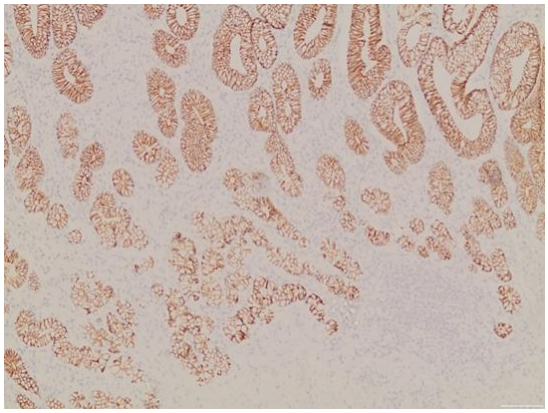

Photo 5. E-cadherin indicator+ (x10)

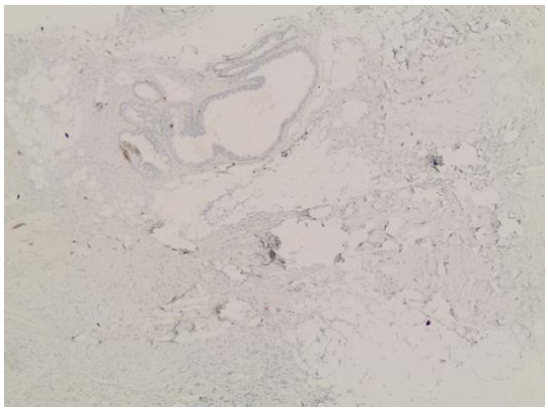

Photo 6. β-catenin indicator- (x10)

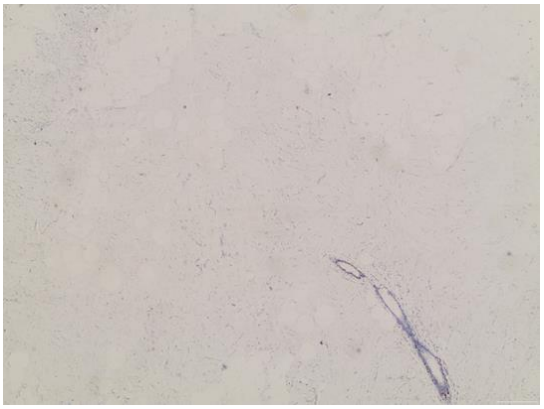

Photo7. E-cadherin indicator- (x10)

2.6 Statistical analysis

The examination of the research objectives was performed via One Way ANOVA and 1 (1) Regression Analysis to analyze and interpret the correlations. As far as the definition of the reliability of statistics, the internal consistency was very good with a Cronbach's Alpha coefficient of 0,782 (Torisson et al., 2016).

In the current quantitative research, the researcher made use of the One-Way Analysis of Variance (ANOVA), one (1) Regression Analysis, T-Tests as well as Chi-Square Tests which assess the association of the 2 variables, b-catenin and E-cadherin. The variables were numerical, specifically nominal, ordinal and scale.

All the assumptions were investigated in detail. Descriptive analysis and frequencies were appropriately carried out. The statistical significance test result was set at $p<0.05$ and all

statistical analyses concerning all raw data were conducted using SPSS Statistical Package for Windows (version 28.0) (Pocevičiūtė et al., 2022).

3. Results

The Cronbach's Alpha coefficient, as a measure of the reliability and consistency strength of the present study, was 0,782 (Torisson et al., 2016). At first, a One-Way ANOVA was carried out. In the ANOVA table it was observed that the statistical significance approaches 0 (sig.≈0=0.000) that was sig.<0.05, whic meant that the model was statistically significant and had the ability to explain the related variables.

Table 1: Anova analysis to assess the difference between E-Cadherin and b-Catenin

ANOVA[a]						
Model		Sum of Squares	df	Mean Squares	F	Significance
1	Regression	9485,792	1	9485,792	52,747	0,000[b]
	Residuals	12408,575	69	179,834		
	Total	21894,366	70			
a. Dependent Variable: E-Cadherin Immunohistochemistry%						
b. Predictor: (Constant): B-Catenin Immunohistochemistry%						

In the following table of correlations, the multicollinearity assumption was checked, as it was critically considered through the correlation coefficients of the independent variable, since all correlations between the variables (Pearson correlations) were less than 0.8 (<0.8). Additionally, the statistical significance (p value) in the correlation was p<0.05) with a correlation rate of the variables r_1=0.658. Therefore, the investigation between the variables was very good.

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Table 2: The correlation coefficients between B-Catenin and E-Cadherin

Correlations			
		E-Cadherin Immunohistochemistry%	B-Catenin Immunohistochemistry %
Pearson Correlations	E-Cadherin Immunohistochemistry %	1,000	0,658
	B-Catenin Immunohistochemistry %	0,658	1,000
Sig. (1-tailed)	E-Cadherin Immunohistochemistry %	.	0,000
	B-Catenin Immunohistochemistry %	0,000	.
N	E-Cadherin Immunohistochemistry %	71	71
	B-Catenin Immunohistochemistry %	71	71

In the following table of Coefficients, it was initially examined that through the criteria for the multicollinearity assumption, the tolerance should have values greater than 0.1 and the VIF should have values less than 10, for each variable, which was the case. In this particular table, sig. indicated the statistical significance of the variable in predicting the dependent variable. Here it was observed that sig≈0<0.05. From the column Unstandardized coefficients B, could be interpreted the contribution of the variable with statistical significance less than 0.05 in the model. The coefficient of the variable had a positive sign, which implied that the percentage of the existence of B-Catenin Immunohistochemistry tended to increase with the increase in the percentage of E-Cadherin Immunohistochemistry. More specifically, holding all other variables constant, B-Catenin Immunohistochemistry was predicted to increase by 1.578 percentage points.

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Table 3: Prediction of B-Catenin Immunohistochemistry

Coefficients											
Model		Unstandardized Coefficients		Standardized Coefficient	t	Sig.	Coefficients			Collinearity Statistics	
		B	Std. Error	Beta			Zero Class	Partial	Part	Tolerance	VIF
1	(Constant)	18,081	2,853		6,337	0,000					
	B-Catenin Immunohistochemistry %	1,578	0,217	0,658	7,263	0,000	0,658	0,658	0,658	1,000	1,000
a. Dependent Variable: E-Cadherin Immunohistochemistry %											

The condition of extreme values was considerably examined so that the particular model could be analyzed correctly. It was required that be as few cases as possible with Mahalanobis. Distance >15. The mean value of this was at 0.986 with a variation of 1.576 and a maximum value reaching 6.701. This meant that there were no any case from the 71 cases with Mahal. Distance > 15 which was acceptable, since the maximum would be 6.701+0.986=7.687. Cook's Distance should be <1 as well as Centered Leverage Value should also be < 0.2, which were definitely met.

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Table 4: The Residuals Statistics

Residuals Statistics[a]					
	Minimum	Maximum	Mean Value	Variance	Number
Predicted Price	21,24	65,42	35,28	11,641	71
Std. Predicted Value	-1,207	2,589	0,000	1,000	71
Standard Error	1,604	4,444	2,144	0,690	71
Adjusted Predicted Value	21,64	66,08	35,33	11,720	71
Residuals	-16,237	39,030	0,000	13,314	71
Std. Residual	-1,211	2,910	0,000	0,993	71
Stud. Residual	-1,232	2,945	-,002	1,005	71
Deleted Residual	-16,824	39,958	-,051	13,642	71
Stud. Deleted Residual	-1,237	3,126	,008	1,028	71
Mahal. Distance	0,015	6,701	0,986	1,576	71
Cook's Distance	0,000	0,103	0,012	0,020	71
Centered Leverage Value	0,000	0,096	0,014	0,023	71
a. Dependent Variable: E-Cadherin Immunohistochemistry %					

Independent Samples T-Test compared the Mandard response rate between the two genders. The p-value (0.036) was less than 0.05, so the hypothesis of equal variance was rejected. This meant that the variances between men and women differed significantly and the hypothesis of unequal variance must be examined. It is observed that the t was 1.505, the degrees of freedom were 18.423, while the sig. was 0.149. Therefore, the p-value was greater than 0.05, so there was no statistically significant difference in the response rate between men and women. Although men seemed to have a higher average in the Mandard response rate compared to women (1.42 vs 0.75), this difference was not statistically significant, so it could not be concluded that gender substantially affected the response rate.

Immunohistochemistry E-cadherin had an average of 35.28% while the average for B-Catenin was 10.90%. This difference indicated that on average the first group had a higher value than the second. The standard deviation of the first variable was 17.685% which showed a greater variation around its average, while the second variable had a standard deviation of 7.378%. The standard error of the mean was 2.67% for the first variable and 1.09% for the second.

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Table 5: T-Test shows differences between 2 variables

Paired Samples T-Test					
		Mean Term	N	Standard Deviation	Mean Standard Error
Pair	E-Cadherin Immunohistochemistry %	35,28	71	17,685	2,670
	B-Catenin Immunohistochemistry %	10,90	71	7,378	1,090

According to X^2 test analysis, the value of Pearson Chi-Square was 141.278 with 99 degrees of freedom and p-value 0.003<0.05, so it could be inferred that there was a significant relationship between the 2 variables. The value of the Likelihood was 91.665 with p-value 0.687>0.05, for this reason it was not statistically significant. The value of Linear-by-linear association was 17.371 and p-value 0.000<0.05, so there was a significant linear relationship between the 2 variables. It should also be mentioned that the 119 positions in the table had expected values less than 5 due to the sample size (71 people), while only one was exactly 5.

Table 6: Significant linear relationship between the 2 variables

Chi-Square Tests			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	**141,278[a]**	**99**	**0,003**
Likelihood Ratio	**91,665**	**99**	**0,687**
Linear-by-Linear Association	**17,371**	**1**	**0,000**
N of Valid Cases	**71**		
a. 119 cells (99,17%) have expected count less than 5. The minimum expected count is 0,02.			

4. Discussion

Esophageal adenocarcinoma is strongly associated with the expression of β-catenin and the transmembrane protein E-cadherin. β-catenin plays a pivotal role in intracellular signaling, particularly through the Wnt signaling pathway, which is essential in the development and progression of esophageal cancer (Zhang & Wang, 2020). Over recent decades, a growing body of research has highlighted the significant role of Wnt/β-catenin signaling not only in the initiation of cancer but also in various other critical processes, such as tumor growth, dormancy, immune evasion, metastasis, and the maintenance of tumor stem cells. These findings have

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contributed to a deeper understanding of the molecular mechanisms that drive esophageal cancer and underscore the potential of targeting this signaling pathway for therapeutic interventions (Yao et al., 2011).

In the particular study of 71 samples from patients with esophageal adenocarcinoma, with or without previous treatments, it can be indicated that the percentage of the existence of β-Catenin Immunohistochemistry tends to increase with the increase in the percentage of E-Cadherin Immunohistochemistry (Borcherding et al., 2018). More specifically, keeping all other variables constant, β-Catenin Immunohistochemistry is predicted to increase by 1.578 percentage points.

The results show that the 2 groups have a statistically significant difference in their means and the low value of p (0.000), allowing us to reject the null hypothesis H0, that is, there is no difference between the means. In addition, we can conclude that the 2 groups differ significantly in terms of the characteristic measured, which is their quota in the existence of adenocarcinoma. The correlation coefficient is 0.658, which means that there is a relatively high positive correlation between the 2 variables, namely, when one increases the other tends to increase as well. Therefore, it is shown that in this study there is a simultaneous increase in the β-Catenin and E-Cadherin proteins.

β-catenin serves a central role as an adaptor protein, connecting E-cadherin to the actin cytoskeleton, which is essential for maintaining cell-cell adhesion. Furthermore, B-catenin remains a component of vital importance in the Wnt signaling pathway, where it influences various cellular processes, including gene expression and cell behavior (Shenoy, 2019).

Wnt/β-catenin signaling is also crucial in regulating tumor immunology. A study by Spranger et al. (2015) involving the analysis of 266 metastatic human cutaneous melanoma samples demonstrated that the activation of β-catenin within the tumor cells primarily inhibits the infiltration of T cells into the melanoma tumor microenvironment. This suggests that intrinsic β-catenin activation could serve as a key resistance mechanism against T cell-based immuno-oncology therapies, potentially limiting the effectiveness of these treatments in targeting the tumor.

Apropos the limitations of the present research, it should be mentioned that the number of samples was small. This means that the conclusions that were obtained based on the specific data could be restricted concerning their contribution to future therapies. That's why it is of vital importance that research be continued in larger sample size (Serdar et al., 2020).

Nevertheless, β-Catenin and E-Cadherin are related to cell adhesion and have an important role in the development and progression of adenocarcinoma (Lin et al., 2023). Normally, β-catenin is attached to E-cadherin outside the cell and maintains cellular cohesion. More specifically, β-catenin is the main regulator of the Wnt pathway, which is a pathway for functions, such as cell proliferation and migration, and therefore also in carcinogenesis with its dysfunction, as

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examined here in the specific study of 71 patients. Wnt signaling pathway is directly related to β-catenin and when activated it results in the accumulation of β-catenin in the cell nucleus **(**Photo 8), resulting in the transfer of oncogenes and the development of aggressive tumors (Ma et al., 2023; Pai et al., 2017). For this reason, Wnt pathway through β-catenin is an important therapeutic target.

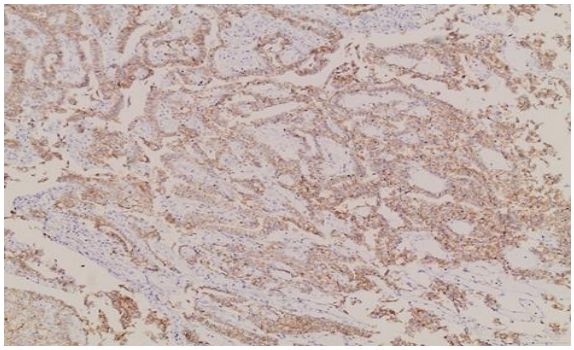

Photo 8. Moderately differentiated esophageal adenocarcinoma with positive nuclear expression, β-catenin in the nucleus of the tumor cells (x10)

5. Conclusions

The simultaneous regulation of these 2 proteins, β-Catenin and E-Cadherin, would be an interesting therapy for the treatment of adenocarcinoma as their simultaneous dysfunction, hyperactivation of β-catenin and loss of E-cadherin, are responsible for the aggressiveness and metastasis of adenocarcinoma respectively. Inhibition of Wnt b-catenin pathway could lead to the restoration of E-cadherin, so it is significant in the near future that the scientific community aim to create an effective treatment that can simultaneously regulate these 2 proteins.

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