Assessment of ERB in Cancer Colon and Its Clinical Relationship in Egyptian Patients

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Abstract: Background: Colon cancer is one of the leading causes of worldwide morbidity and mortality. Estrogen receptor ß (ERß) in particular is abundantly expressed in the gut. Colon cancer tissue often displays a loss of ER expression, and tumors with a more severe loss of expression are associated with poorer prognosis. Aim of the work: Assessment of ERb in cancer colon and its clinical relationship in Egyptian patients. Patient and method; the study included 40 subjects who are attending Ain Shams University hospitals which were divided into 2 groups:-**Group A:** Included 30 patients with colorectal carcinoma proved by endoscopy and histopathological examination (*with or without metastases).* **Group B**: Included 10 patients who undergo colonoscopy as part of routine investigation eg; (piles, fissures, IBS….etc). They were subjected to full medical history, clinical examination &lab investigations. Colonoscopic examination was done for Group A subjects and biopsies were taken from both malignant tissue and also from normal mucosa. For Group B subjects, the biopsies were taken from their colonic mucosa. Detection of Estrogen receptor βeta assay in malignant and normal colonic mucosa by immuno histochemistry was also done. **Results**: As regard the clinical picture it was found that there was a statistically significant difference between CRC group and control group in relation to anorexia and weight loss as nearly 100% of patients with CRC experienced weight loss. In the CRC group, 24 patients had adenocarcinoma (9 well differentiated adenocarcinoma, 9 moderate differentiated adenocarcinoma, 5 poor differentiated adenocarcinoma and 1pappilary adenocarcinoma). Two patients had non Hodjkin lymphoma, 3 had mucoid carcinoma and one patient had GIST. ERβ was negative in 24 (80%) and positive in 6. In the control group 5 patients had features of non specific colitis, 3 had bilharzial hyperplastic polyps. One patient had an adenomatous polyp and one patient had IBD. ER**β** was positive in all the control group except for three patients (1 with IBD. 1 with non specific colitis, 1 with Hyperplastic polyps). Our study showed that there was a statistically significant difference between patients and control groups regarding the ER-beta in the unhealthy mucosa. We have also found no significant correlation between ER**β** and gender but there was a statistically significant difference between patients who were positive for ER-beta and negative for ER-beta regarding the age. We also found that there was no statistically significant difference between malignant mucosal tissue and ER-beta expression. **Conclusion:** ER**β** mediated functions, in part, could be a potential mechanism by which estrogens alter susceptibility for colon cancers. The potential clinical significance is that ERβ may mediate chemopreventive effects for estrogens in the colon and selective ERβ ligands might be a colon cancer prevention strategy. The protective effects of estrogen replacement therapy against colon cancer may be mediated by ER**β.**

[Mohsen M. maher, Wael A. Yousry, Wesam A. Ibrahim, Hesham H. Radwan and Khaled Amr. **Assessment of ERB in Cancer Colon and Its Clinical Relationship in Egyptian Patients.** *Life Sci J* 2014;11(11):814-822]. (ISSN:1097-8135). http://www.lifesciencesite.com. 146

Key words: colorectal cancer, estrogen receptor **β**

1. Introduction:

Colon cancer is one of the leading causes of worldwide morbidity and mortality. In the US, approximately 140,000 new cases and 50,000 deaths are registered each year. In Europe, each year about 213,000 new cases and 110,000 deaths are reported, respectively [1].

Colorectal cancer in Egypt has no age predilection and more than one-third of tumors affects young population. The high prevalence in young people can neither be explained on a hereditary basis nor attributed to bilharziasis. The disease usually presents at an advanced stage, and predisposing adenomas are rare. Similarity of the data from different centers suggests that this picture of colorectal cancer is typical for Egyptian patients[2].

Sex hormones are thought to play a role in the development of colorectal cancer. Several sex hormone receptors, including androgen, progesterone, and estrogen receptors, are expressed in the digestive tract. These receptors are proteins that upon activation by a sex hormone, bind to DNA and regulate important cellular functions [3].

ERs are widely expressed in different tissue types, however there are some notable differences in their expression patterns: The *ERα* is found in endometrium, breast cancer cells, ovarian stroma cells, and the hypothalamus[4]. In males, *ERα* protein is found in the epithelium of the efferent ducts [5]. The expression of the *ERβ* protein has been documented in kidney, brain, bone, heart, lungs, intestinal mucosa, prostate and endothelial cells[6]. Estrogen receptor ß

(ERß) in particular is abundantly expressed in the gut. Colon cancer tissue often displays a loss of ER expression, and tumors with a more severe loss of expression are associated with a poorer prognosis. Earlier studies have shown that ERß may influence tumor growth and progression by inducing apoptosis, preventing metastasis, and regulating inflammation. Certain single neucleotide polymorphisms in the promoter region of the gene encoding ERß influence the protein's function in clinically relevant ways which predispose to colon cancer.[3]

Many studies indicate that estrogen replacement therapy (ERT) exerts a protective role against colon cancer in postmenopausal women [7].Several epidemiologic, clinical, and experimental evidences showed that E2 confers protection against prostate and colon cell proliferation[8,9].

ERβ is expressed in the human colon and activates a specific signal transduction pathway that controls apoptosis in the colon and works by being activated by estradiol and more recently found to possibly be activated by Quercetin[10]. Quercetin activates the ERβ along with the apoptotic cascade when caspase-3 is present by the phosphorylation of P38 kinase[11]**.** In colon cancers and tumors ERβ and its pathway have been proven to be significantly decreased thus allowing the tumors to thrive.[12]

Aim of the work:

Assessment of ERb in cancer colon and its clinical relationship in Egyptian patients.

2. Patients and Methods

The study was done at Ain Shams University hospitals after approval of the ethical committee and informed written consent. It included 40 subjects which were divided into2 groups:-

Group A:

Included 30 patients (22 males & 8 females) with colorectal carcinoma proved by endoscopy and histopathological examination (*with or without metastases).*

Group B:

Included 10 patients (5males &5 females) who underwent colonoscopy as part of routine investigation eg; (piles, fissures, IBS….etc).

These patients were selected from internal medicine, surgery and endoscopy departments.

The 40 patients were subjected to full medical history taking, clinical examination, lab investigations including complete blood picture,liver and kidney function tests, serum electrolytes, ESR,tumour markers assay including: CEA, CA19.9, α fetoprotein. Abdominal ultrasound and pelviabdominal CT were also done to detect metastasis.

Colonoscopic examination was done for **Group A** and biopsies were taken from malignant tissue as well as from normal mucosa of the same case. Also Colonoscopy was done for **Group B** and biopsies were taken from their unhealthy colonic mucosa.

Biopsies were subjected to histopathological examination and immune histochemical assay for estrogen receptor βeta in malignant and normal colonic mucosa.

Exclusion criteria

Patients with liver cell failure,renal failure, chest or cardiac problems were excluded from the study.

Histopathological Evaluation

Colonic biopsies were formalin fixed and paraffin embedded then sections were cut from the block 5 microns thick for H&E staining and histopathological examination.

Immunohistochemistry

Another section was cut from each case on poly L-lysine coated slides for immunostaining with ERβ using Streptavidine Biotin Peroxidase.Immunological detection was achieved with the commercially available monoclonal antiboby for Estrogen receptor βeta *(BIO GENEX) Ab LOT: AR3850307 REF: AR385- 5R.*The super sensitive antibodies had been optimally diluted by BIO GENEX and were ready for use without further dilution.

The Horseradish Peroxidase kits (DAB Kits) was prepared by adding 2 drops to one vial (2.5 ml) of substrate and mixed well. This solution remains stable for 8 hours at room temperature.

The tissue sections were not allowed to dry out during the rehydration and staining procedures.

The procedure was accomplished as described by the manufacturers.

1-All sections were parafinised in the oven at 57°c over night and rehydrate using xylem for 20 minutes, washed by absolute alcohol and distilled water.

2-Sections were treated for antigen removal using high power oven. Sections then left 20 minutes to cool and washed by distilled water.

3-Application of blocking reagent: Two drops of prepared peroxidase kit were put to cover each slide and were incubated at 10 minutes at room temperature and were rinsed twice with buffer (phosphate buffered saline PBS).

4-Application of primary antibody: Two drops of mouse IgG1133 were put on each slide and were incubated at room temperature for 45 minutes.

5-Applicatiion of Iink: Appropriate volume of ink was used to cover the specimens according to tissue size (usually 2 drops) incubated at room temperature for 20 minutes and rinsed well with buffer.

6-Application of Label: Two drops of label (streptavudine) were added on the specimen

and incubated at room temperature for 20 minutes and washed by buffer PBS.

7-Application of substrate solution:Appropriate volume of DAB –chromogen were put and left at room temperature for 10 minutes, or until acceptable colour intensity has been reached and washed by distilled water.

8- Counter staining procedure: All slides were immersed in a bath of Mayer's hematoxylin for 1-5 minutes according to the strength of hematoxylin used, the slides were rinsed under tap water.

Assessment

Positive immunostaining were considered as brown nuclear staining of epithelial cells.

Statistical analysis:

Data was analyzed using Statistical Package for Special Science (SPSS) software computer program version 15.

Data was described as **mean ± standard deviation (SD)** for quantitative (Numerical) variables and as **frequency & percentage** for qualitative (Categorical) variables.

Independent Student's t test was used for comparison of quantitative variables among two independent groups.

Chi-square test (or **Fisher's exact test** when appropriate) was used for comparison of distribution of qualitative variables among different group. Significance levels: $p>0.05$ non significant (NS), $p<0.05$ significant (S) and $p<0.01$ highly significant (HS).

3. Results:

Results of the study were shown through from tables (1-12) & figures (1-2).

Demographic data:

Table (1) Comparison between patient and control groups as regards sex and age

		Patients (n=30)		Control (n=10)		X^2	p	Sig
		No.	%	No.	%			
Sex	Male	22	73.3	5	50	1.861	0.172	NS
	Female	8	26.7	5	50			

Age	Patient (n=30)	Control (n=10)	t	p	Sig
	61.97±6.45	35.90±6.90	10.880	**0.000**	S

Clinical data:

Table (2) Comparison between the patients and the control groups regarding clinical picture

		Patients (n=30)		Control (n=10)		X^2	P	Sig
		No.	%	No.	%			
DM	Negative	22	73.3	7	70	0.042	0.838	NS
	Positive	8	26.7	3	30			
HTN	Negative	18	60	7	70	0.320	0.572	NS
	Positive	12	40	3	30			
Smoking	Negative	14	46.7	6	60	0.533	0.358	NS
	Positive	16	53.3	4	40			
Family History	Negative	23	76.7	8	80	0.048	0.601	NS
	Positive	7	23.3	2	20			
Anorexia	Negative	12	40	9	90	7.519	**0.007**	S
	Positive	18	60	1	10			
Weight Loss	Negative	0	0	9	90	34.839	**0.000**	S
	Positive	30	100	1	10			
Constipation	Negative	16	53.3	2	20	3.367	0.069	NS
	Positive	14	46.7	8	80			
Diarrhea	Negative	23	76.7	5	50	2.540	0.111	NS
	Positive	7	23.3	5	50			
Bleeding per rectum	Negative	18	60	5	50	0.307	0.580	NS
	Positive	12	40	5	50			
Abdominal pain	Negative	15	50	3	30	1.212	0.233	NS
	Positive	15	50	7	7			
Abdominal mass/Ascites	Negative	27	90	10	100			
	Positive	3	10	0	0			

Laboratory data:

Table (3) Comparison between patients and control groups regarding laboratory parameters

	Patient (n=30)	Control (n=10)	t	P	Sig
WBCs	6.28±1.94	5.15±1.15	1.731	0.092	NS
Hb	7.54±1.44	10.74±1.20	-6.296-	**0.000**	**S**
PLT	163.77±67.52	166.50±48.23	-0.118-	0.907	NS
ALT	64.67±25.17	47.20±13.12	2.089	0.043	NS
AST	71.47±21.48	45.30±12.19	3.641	**0.001**	**S**
ALB	3.31±0.71	3.92±0.63	-2.396-	**0.022**	**S**
ALP	186.57±178.60	86.00±7.54	3.076	**0.005**	**S**
S.creat	1.54±0.73	0.63±0.51	3.642	**0.001**	**S**
Urea	49.97±20.52	24.10±5.45	6.274	**0.000**	**S**
Na	132.80±8.18	136.90±4.36	-1.506-	0.140	NS
K	4.16±0.70	4.01±0.51	0.623	0.537	NS
RBS	159.23±95.11	104.10±12.24	3.099	**0.004**	**S**
ESR	60.30±49.81	21.40±25.37	3.208	**0.003**	**S**
CEA	136.00±157.98	105.50±171.08	.522	0.606	NS
CA19.9	316.45±704.14	178.50±285.86	.532	0.599	NS
Alfa-Feto	223.03±312.14	225.67±264.03	-.023	0.982	NS

Table (4) Ultrasonographic findings among patients group

Patient (n=30)		**No.**	**%**
Pelvi-Abdominal U/S	**Normal**	16	53.3
	HSM	5	16.7
	HM	5	16.7
	MHFL	3	10
	SHFL	1	3.3

HSM: hepatosplenomegaly. **HM:** hepatomegaly
MHFL: multiple hepatic focal lesions**. SHFL:** solitary hepatic focal lesion

Table(5): Pathological and endoscopic characteristics of patients group

Patient (n=30)		**No.**	**%**
Healthy mucosa histology	**Normal**	**30**	**100**
	Abnormal	**0**	**0**
Unhealthy mucosa histology	**Well-diff. Adenocarcinoma**	**9**	**30**
	Mod-diff. Adenocarcinoma	**9**	**30**
	Poor-diff. Adenocarcinoma	**5**	**16.7**
	Papillary Adenocarcinoma	**1**	**3.3**
	Mucoid Carcinoma	**3**	**10**
	G.I.S.T	**1**	**3.3**
	Non-Hodjkin lymphoma	**2**	**6.7**
Site of abnormal mucosa	**Caecum**	**5**	**16.7**
	Transverse colon	**1**	**3.3**
	Descending colon	**8**	**26.7**
	Sigmoid colon	**12**	**40.0**
	Rectum	**4**	**13.3**
Duke Stage	**Stage B**	**21**	**70**
	Stage C	**4**	**13.3**
	Stage D	**5**	**16.7**

Table (6): Pathological characteristics of control group

Control (n=10)		**No.**	**%**
Unhealthy mucosa histology	**Non-specific colitis**	5	50
	Hyperplastic polyp (bilharzial)	3	30
	Adenomatous polyp	1	10
	IBD (UC)	1	10

Table (7): Comparison of ER-beta between patients and control groups:

		Patients (n=30)		Control (n=10)		X^2	p	Sig
		No.	%	No.	%			
ER-beta (healthy mucosa)	Negative	10	33.3					
	Positive	20	66.7					
ER-beta (Unhealthy mucosa)	Negative	24	80	3	30	8.547	**0.006**	**S**
	Positive	6	20	7	70			

Table (8): Comparison of ER-beta (unhealthy mucosa) between Different duke stages in patients group

		ER-beta negative (n=24)		ER-beta positive (n=6)		X^2	P	Sig
		No.	%	No.	%			
Duke Stage	Stage B	16	66.67	5	83.33	1.503	0.472	NS
	Stage C	3	12.50	1	16.67			
	Stage D	5	20.83	0	0			

Table (9) Comparison of ER-beta (unhealthy mucosa) between sites of abnormal mucosa in patients group

		ER-beta negative (n=24)		ER-beta positive (n=6)		X^2	p	Sig
		No.	%	No.	%			
Site of abnormal mucosa	Caecum	5	20.83	0	0	3.177	0.529	NS
	Transverse colon	1	4.17	0	0			
	Descending colon	5	20.83	3	50			
	Sigmoid colon	10	41.67	2	33.33			
	Rectum	3	12.50	1	16.67			

Table (10) Comparison of ER-beta (unhealthy mucosa) between unhealthy mucosa histology in patients group

		ER-beta negative (n=24)		ER-beta positive (n=6)		X^2	p	Sig
		No.	%	No.	%			
Unhealthy mucosa histology	Well-diff. Adenocarcinoma	8	33.33	1	16.67	7.778	0.255	NS
	Mod-diff. Adenocarcinoma	6	25	3	50			
	Poor-diff. Adenocarcinoma	5	20.83	0	0			
	Papillary Adenocarcinoma	1	4.17	0	0			
	Mucoid Carcinoma	1	4.17	2	33.33			
	G.I.S.T	1	4.17	0	0			
	Non-Hodjkin lymphoma	2	8.33	0	0			

Table (11) Comparison of ER-beta (unhealthy mucosa) between unhealthy mucosa histology in control group

		ER-beta negative (n=3)		ER-beta positive (n=7)		X^2	p	Sig
		No.	%	No.	%			
Unhealthy mucosa histology	Non-specific colitis	1	33.33	4	57.14	3.016	0.389	NS
	Hyperplastic polyp (bilharzial)	1	33.33	2	28.57			
	Adenomatous polyp	0	0	1	14.29			
	IBD (UC)	1	33.33	0	0			

Table (12): Comparison of Age and laboratory parameters among patients grouped according to the ER-beta (unhealthy mucosa)

	ER-beta negative (n=24)	ER-beta positive (n=6)	t	p	Sig
Age	60.75±6.18	66.83±5.49	-2.198	**0.036**	**S**
WBCs	6.41±2.06	5.75±1.34	.739	0.466	NS
Hb	7.42±1.41	8.03±1.60	-.927	0.362	NS
PLT	152.25±59.02	209.83±85.08	-1.957	0.060	NS
ALT	61.87±20.92	75.83±38.40	-1.225	0.231	NS
AST	69.96±21.46	77.50±22.46	-.764	0.452	NS
ALB	3.23±.76	3.65±.37	-1.941	0.069	NS
ALP	203.25±195.98	119.83±40.59	1.926	0.064	NS
S.creat	1.53±.70	1.57±.92	-.098	0.922	NS
Urea	49.13±21.89	53.33±14.83	-.443	0.661	NS
Na	132.50±8.77	134.00±5.73	-.396	0.695	NS
K	4.17±.73	4.13±.64	.103	0.919	NS
RBS	158.00±97.68	164.17±92.40	-.140	0.890	NS
ESR	64.42±52.65	43.83±35.10	.902	0.375	NS
CEA	143.63±157.48	105.50±171.08	.522	0.606	NS
CA19.9	352.43±778.40	178.50±285.86	.532	0.599	NS
Alfa-Feto	222.38±328.17	225.67±264.03	-.023	0.982	NS

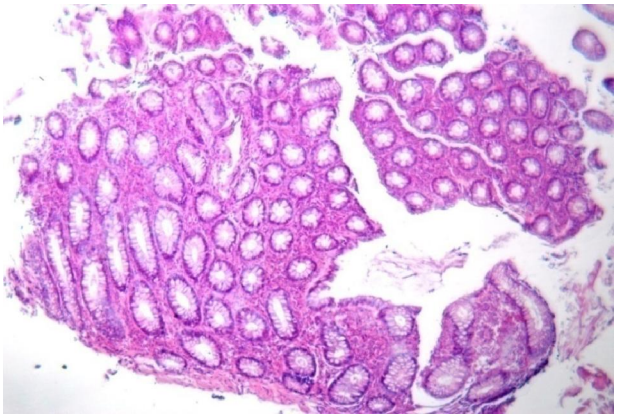

Figure 1: Showing normal colonic mucosa

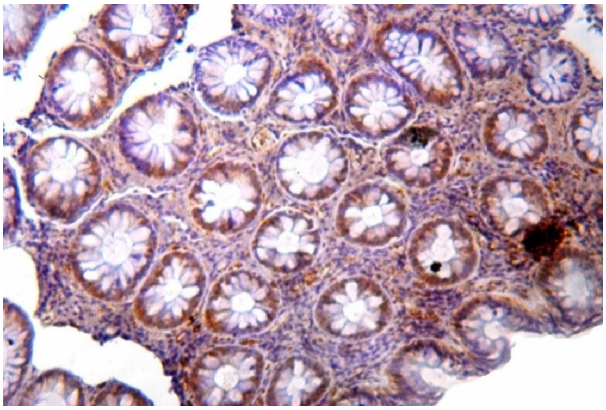

Figure 2: A Positive nuclear staining pattern is seen with immunohistochemistry staining using streptavidine biotine and DAB chromogranim

4.Discussion:

Colon cancer is the most frequent neoplasia of the intestine. Estrogen has been implicated in the development and progression of colon cancer. Also sex-specific differences have been suggested to be involved in the process. Previous studies have shown that estrogen beta receptor to be the dominant receptor type in normal colonic tissue and its down-regulation along with the progression of colorectal cancer. The presence of estrogen receptors and products of estrogen-related genes in the colon suggests that estrogens have direct effects on the colonic tissue. However, the specific effect of estrogens on a normal colon and the role in the colon carcinogenesis are far from clear [13,14].

In this study, we aimed at assessment of ERb in cancer colon and its clinical relationship in Egyptian patients. We included 40 patients and divided them into two groups: **Group A** comprised 30 patients (22 males & 8 females) with colorectal Carcinoma (CRC). **Group B (control)** included 10 patients (5males and 5 females) with colonoscopic and biopsy findings other than CRC. Demographic data showed no statistically significant difference as regards sex (p 0.172) but there was statistically significant difference as regards age (p 0.000). This matches with other studies were they showed that 50% of the population at 70 years of age will develop a polyp of which 5% are expected to develop into adenocarcinomas and patients with HNPCC develop polyps that often progress to cancers because of defective DNA mismatch repair genes that result in increased mutation rates[15].

As regards the clinical picture the study showed that there was a statistically significant difference between group (A) and group (B) in relation to anorexia and weight loss (*P*-value. 007 and.000) respectively and nearly 100% of patients of group (1) experienced weight loss, which goes with what **Kenneth *et al.*** and **Argiles *et al.*** concluded regarding the Cancer cachexia syndrome in patients with colonic and pancreatic cancers[16,17].

As regards laboratory investigations the study showed that there was a statistically significant difference between patients and control groups as regards Hb, AST, Alb, ALP, serum creatinine, urea, RBS and ESR which could be explained by the clinical condition of malignant process and presence of metastasis.

Colonoscopic and histopathological examination of patients of group A showed that 24 patients had adenocarcinoma (9 well diff adenocarcinoma, 9 moderate diff adenocarcinoma, 5 poor diff asenocarcinoma, 1pappilary adenocarcinoma) 2 patients had non Hodgkin lymphoma, 3 had mucoid carcinoma and one patient had GIST (Gastro intestinal Stromal Cell Tumour). As regards Duke staging, 21 patients were classified as Duke B, 4 as Duke C and 5 patients as Duke D. As for group B, 5 patients had nonspecific colitis, 3 hyperplastic bilharzial polyps, 1 adenomatous polyp and 1 IBD (ulcerative colitis).

When comparing ER-beta between patients(A) and control(B) groups in both healthy and unhealthy mucosa there was a statistically significant difference between patients and control groups regarding the ER-beta in the unhealthy mucosa (P-value.006). This is going with another study which showed prominent expression of ER**β** in colonic superficial epithelium, denoting that ER**β** has a significant role in differentiation. In the hyperproliferative state, a progressive accumulation of somatic mutations occurs in the stem cells, which have a long residence period in the mucosa. This cumulative damage may contribute to the development of a malignant phenotype that possesses a growth advantage over other stem cells within the crypt.ER **β** is now believed to have a protective role against colon cancer development, loss of ER **β** is correlated with loss of differentiation. At the luminal surface of the colon, senescent epithelial cells are normally eliminated by apoptosis[18].

Comparison of ER-beta in the unhealthy mucosa in different duke stages in unhealthy mucosa biopsies in the patients group, showed that there was no statistically significant difference between different duke stages (*P* –value.472) which may indicate that the expression of ER **β** doesn't affect the progression or staging of the malignant process neither affects its prognosis.

Comparison of ER- **β** in the unhealthy mucosa in different sites in patients group showed that there was no statistically significant difference (*P*-value.529) between site of abnormal mucosa and ER-beta expression which indicates that there is no certain predilection of expression of ER- **β** along different areas of colonic mucosa. Also, comparison of ER-beta expression in the unhealthy mucosa histology in patients group showed that there was no statistically significant difference (*P*-value. 255) in the expression of ER **β**.

These results are in accordance with what **Li-Qun *et al.*** concluded that there was no statistically significant correlation between ER**β** expression and clinicopathologic features, including Duke's types, lymph node metastasis and differentiation. When studying 40 CRC cases, 10 colonic adenomas, and 10 normal colon mucosa biopsies their study used RT-PCR amplification for detection of ERβ as well as ERα which showed that ERα and ERβ mRNA were both expressed in CRC, semiquantitative RT-PCR revealed there was no statistical significance in ER**β** mRNA level between CRC tissue and paired normal colon tissue. Immunohistochemical results showed that some sections were only cytoplasmically stained. The previous study included cytoplasmic staining of ERβ as an indicator of positivity however in our study we used only the nuclear staining as a sign of positivity with regards to Duke staging[19]. Our findings were also opposed by the data retrieved from **Jassam *et al.*** study that showed a correlation between loss of ER**β** expression and type of Dukes' stage[20]. **Foley *et al.*** reported that western blot analysis revealed very low levels of ERβ protein in tumor and normal colon tissue. However, malignant colon tissue showed a selective loss of ERβ protein expression when compared to normal colon tissue in the same patient. A post transcriptional mechanism may account for the decrease of ERβ protein expression in CRC tissue[21].

Another reason is the different expressions of ERβ isoforms in CRC. There are at least 5 different ERb isoforms, which show different amino acid sequences at the COOH terminus and are differently expressed in tumor cell lines. **Campbell-Thompson *et al.*** and **Witte *et al.*** showed that ERβ was the predominant ER subtype between human colon and that the decreased levels of ERb1 and ERb2 mRNA were associated with colonic tumorigenesis in females. Their data suggested that there was a change in the relative expression of ERb isoforms[22,23].

On the other hand our work was in accordance with the work done by **Eugene *et al.*** which was done on 11 patients, five males and six female patients with CRC who have demonstrated that ER**β** protein expression is markedly and specifically reduced in colon cancers compared to adjacent normal colon in

vivo, regardless of gender. However in their work they used solely the RT-PCR for detection of ER**β** and no immunohistochemistry. The lack of difference in ERβ mRNA expression between normal and malignant samples supports a posttranscriptional mechanism for this ERβ protein down-regulation incolon cancer, suggesting that the ER-α: ER-β ratio at the mRNA level is not useful as a marker for this disease[24].

So, according to our study and given the high incidence of colon cancer in the aging population and high mortality rates for advanced disease, new prevention strategies are needed. A possible protective effect for estrogens on colon cancer risk has been suggested by numerous epidemiological and experimental studies. Several epidemiologic studies have shown that colon cancer might be influenced by steroid hormones[25] and estrogen use might be associated with a low risk of colon cancer[26].

Estrogens are used for the reduction of post menopausal symptoms and for preservation of bone mineral density. Epidemiological studies suggest that combined estrogen and progestogen hormone replacement therapy reduces the incidence of colorectal cancer (CRC) in postmenopausal women[27-29].

Conclusion:

ER**β** mediated functions, in part, could be a potential mechanism by which estrogens alter susceptibility for colon cancers. The potential clinical significance is that ERβ may mediate chemopreventive effects for estrogens in the colon and selective ERβ ligands might be a colon cancer prevention strategy. The role of estrogen and antiestrogens in the pathogenesis of colorectal cancer holds significant public health interest and has yet to be fully elucidated.

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10/25/2014