Value of estrogen receptor β expression in normal colon mucosa and colorectal cancer: an immunohistochemical analysis

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Abstract
Estrogens (ER) have a protective role against colorectal carcinoma (CRC). Reduction of death from CRC has been observed in women (30%) as compared to men (7%) in particular with the users of oral contraception and in those women treated with Hormone Replacement Therapy (HRT). The aim of this study is to analyze the expression of estrogen receptor β (ERβ) in normal colonic mucosa and in CRC. The archival material of formalin-fixed-paraffin embedded tissue sections of 10 cases of normal colonic mucosa and 25 specimens of CRC were utilized in this study. An immunohistochemistry using avidin-biotin immuno-enzymatic technique (ABT) for the expression of ERβ primary mouse monoclonal antibody was performed. ER is expressed in 3 out of 10 cases of normal colonic mucosa. CRC revealed different levels of ERβ expression regardless of patient age, gender, grade, invasion, or lymph node status. ERβ positive immunostaining is more common in well differentiated tumors and in lower stage of disease than in poor differentiated one and advanced stage of CRC. The immunopositivity of ERβ in CRC is seen in 56% of cases, whereas its negativity is 44%.

Keywords: ERβ, normal colon mucosa, colon cancer, immunohistochemistry

Introduction
Estrogen receptor β (ERβ) is the predominant ER that is expressed in the normal colonic epithelial cells; yet its expression is progressively decreased in adenomas and CRC in relation to the disease aggressiveness and significantly reduces the risk of colon cancer [1-6]. Data was obtained demonstrating a reduction of CRC risk by 33% in women taking Hormone Replacement Therapy (HRT) as compared to non-users [7]. However, the protective effect of ER was not correlated to the duration of HRT and only dosage related [8].

Loss of ERβ expression is associated with advanced stage of CRC and higher degrees of dedifferentiation, suggesting its role in maintaining dedifferentiation and regulating cell proliferation [9,10]. Studies reported that tamoxifen or raloxifene treatment can inhibit proliferation of colon cancer cells, and raloxifene can reduce proliferation of CRC cells expressing ERβ, but raloxifene has little effect on the growth of CRC cells do not expressing ERβ [11,12]. These data suggested that ERβ may have preventive or therapeutic potential in CRC, and these effects may be attributable to the ability of estrogens to regulate micro RNA expression and mismatch repair gene activity via ERβ, and these mechanisms may be the basis for the anti-cancer effects in colorectal cells [1,13]. Additionally, studies evaluated the association between the users of soy foods, that are the main sources of phytoestrogens (estrogens agonists) and the reduced CRC risk [14,15]. Also, several epidemiological studies reported a reduction in CRC risk associated with the consumption of isoflavones (found in legumes such as soy) and lignans (found in grains, seeds, nuts, fruits, and vegetables) [16,17]. Two case-control studies suggest that lignans may be protective against polyps [18,19]. As well as, there is a protective effect of estrogens against the development of adenomatous polyps the mostly precede CRC [20]. This was evidenced by administration of diet enriched with phytoestrogens cumestrol, which is potent ERβ agonist, to ovariectomized Apc female mice induced a reduction of adenomatous polyps occurrence [8].

ERβ expression in the colon is associated with regulation of important prognostic markers as thymidylate synthases, survivin,
telomerase, and Apc [21,22]. Additionally, multiple review articles indicated that loss of ERβ expression is a common step in the development of CRC [23]. This study will try to analyze the levels of ERβ expression in the tissues of normal colon mucosa and CRC.

Materials and methods
Setting and specimens
This study was performed on tissue sections including 10 biopsies of normal colonic mucosa that were used as a control and for the comparison of immunohistochemical expression of ERβ with overall 25 specimens of CRC. Majority of specimens were colonic biopsies which were obtained endoscopically in the surgical endoscopic unit in patients who were suspected clinically and radiographically to have CRC. The study was conducted in the Department of Pathology at Arar Central Hospital, Arar City, Saudi Arabia, through the period from 2010 to 2014. All the clinicopathological data of patients including age, gender, histological tumor types, degree of differentiation, and depth of invasion, associated lymph node status, and staging were reviewed from patient’s medical records and pathology reports. Colorectal carcinoma was identified pathologically as malignant glands that were eliciting desmoplastic and inflammatory reactions.

Immunohistochemical examination and interpretation
All specimens were previously fixed in 10% formalin solution and prepared for the immunohistochemical procedure using the avidin-biotin immuno-enzymatic technique (ABT). The principal steps are as follows; selected blocks were cut into 5 micron sections, deparaffinized in xylene, rehydrated in different grades of alcohol and rinsed in Tris-buffered saline (TBS). Antigen-retrieval was done using water bath microwave. The sections were incubated in 5% normal rabbit serum and incubated with anti-ERβ primary mouse monoclonal antibody (dilution 1:35; clone PPG5/10; Dako company). The slides were visualized using 3, 3′-diaminobenzidine (DAB). Meyer’s hematoxylin was used as counter stain. Positive control of normal colonic mucosal tissue was used with each run of immunostain. After completion of the immunohistochemical staining, the cases were examined microscopically for the localization of the antibody. The colon cancer cells were positive by nuclear staining for the used antibody and the degree of immunoreactivity in the targeted cells was evaluated [10]. ERβ immunoreactivity was evaluated according to the following scales: Negative for ERβ immunoreactivity, if less than 10% of the tumor cells nuclei showed positive staining; moderate expression with positive staining of 10-50% of the cells nuclei and high or strong positive staining in >50% of cancer cells [24,25].

Statistical analysis
Statistical analysis of this study was undertaken using SPSS computer software (SPSS Version 16 for Microsoft Windows), appropriate statistical tests were used for comparison between the two study groups. Results were considered to be statistically significant at p<0.05.

Results
Clinicopathological findings
This study encompassed of 10 biopsies of normal colon mucosa (Figure 1), majority of them were from normal mucosa adjacent to cancerous areas, whereas the others were obtained from endoscopy done for nonmalignant cases, and 25 specimens of CRC which were taken from suspected patients with malignancy. The clinicopathological findings of CRC cases were shown in (Table 1); majority of patients were above 50 years and they were men. 10 out of the 25 CRC specimens were colectomy specimens, whereas the remaining 15 cases were endoscopic biopsies. Majority of these specimens were obtained from rectosigmoid region. Four cases were mucinous carcinoma (Figure 2), and the rest 21 were conventional adenocarcinoma. Malignant involvement of pericolic lymph nodes was observed in 2 cases among the colectomy specimens, whereas the other 8 cases were free from malignancy. Regarding the histological grading 7 cases were well-differentiated, 11 moderately-differentiated (Figure 3), and 7 cases were poorly differentiated carcinoma.

ERβ expression
By using avidin-biotin immuno-enzymatic technique (ABT), ERβ positive immunoreactivity was seen in 3 out of 10 cases of normal colonic mucosa (Figure 4 and Table 2). In some sections there were also high cytoplasmic immunopositivity in the normal colonic mucosa in conjunction to the nuclear immunostaining of ERβ protein. Also, some stromal cells and lamina propria lymphocytes revealed variable positive immunoreactions to ERβ protein. In concern to CRC cases ERβ immunopositivity was observed in 14 (56%) out of 25 cases, which was distributed as follow; 5 out of 7 cases were well-
Table 1. Clinicopathological parameters of CRC cases and their relations to ERβ immunoreactivity.

| Parameter          | N  | ERβ negative | ERβ positive | P value |
|--------------------|----|--------------|--------------|---------|
| Age (years)        |    |              |              |         |
| <50                | 3  | 3(12%)       | 0            | >0.05   |
| ≥50                | 22 | 8(32%)       | 14(56%)      |         |
| Sex                |    |              |              |         |
| Male               | 18 | 8            | 10           | <0.05   |
| Female             | 7  | 3            | 4            |         |
| Tumor type:        |    |              |              |         |
| Mucinous           | 4  | 2            | 2            | >0.05   |
| Conventional       | 21 | 9            | 12           |         |
| adenocarcinoma     |    |              |              |         |
| Duck's stage       |    |              |              |         |
| A                  | 4  | 1            | 3            |         |
| B                  | 3  | 1            | 2            | <0.05   |
| C                  | 2  | 2            | 0            |         |
| D                  | 1  | 1            | 0            |         |
| LN status          |    |              |              |         |
| Negative           | 8  | 3            | 5            | >0.05   |
| Positive           | 2  | 2            | 0            |         |
| Histological grade:|    |              |              |         |
| Well differentiated | 7  | 2            | 5            |         |
| Moderately         | 11 | 3            | 8            | >0.05   |
| differentiated      |    |              |              |         |
| Poorly differentiated| 7 | 6            | 1            |         |

Immunoreactivity of ERβ, positive immunoreactivity was insignificantly correlated with age of patients, histological tumor types, lymph node status, and the histological grade of tumors, whereas its immunostaining was significantly correlated with patient gender and cancer stage.

Table 2. ERβ immunoreactivity in tissue of normal colonic mucosa and CRC.

| Parameter          | N  | ERβ positive | ERβ negative | P value |
|--------------------|----|--------------|--------------|---------|
| Normal mucosa      | 10 | 3(30%)       | 7(70%)       | >0.05   |
| CRC                | 25 | 14(56%)      | 11(44%)      |         |

(Figures 2 and 3), while the other 2 cases were negative, 8 out of 11 were moderately differentiated CRC (Figures 5 and 6), while the other 2 cases were negative, 8 out of 11 were moderately differentiated CRC (Figures 7 and 8), while the other 3 cases of were negative (Figure 9), and one out of 7 cases of poorly differentiated CRC revealed moderate degree of immunostaining for ERβ (Figure 10). In addition to the above findings, cancer cells which invaded the perineural tissue exhibited high...
Figure 6. Well differentiated infiltrating CRC exhibiting high nuclear immunoreactivity for ERβ (DAB 100X).

Figure 7. Moderately differentiated CRC revealing high nuclear immunostaining for ERβ (DAB 200X).

Figure 8. Moderately differentiated infiltrating CRC Duck’s stage C revealing mild degree of nuclear immunoreactivity for ERβ (DAB 200X).

Figure 9. Moderately differentiated infiltrating CRC revealing negative nuclear immunoreactivity for ERβ (DAB 200X).

Figure 10. Poorly differentiated infiltrating CRC revealing high degree of nuclear immunoreactivity for ERβ (DAB 400X).

Figure 11. Moderately differentiated infiltrating CRC with perineural invasion revealing high degree of nuclear and cytoplasmic immunoreactivity for ERβ (DAB 200X).

Figure 12. Poorly differentiated infiltrating CRC revealing high degree of nuclear immunoreactivity for ERβ (DAB 400X).

Figure 13. Moderately differentiated infiltrating CRC involved by malignant deposits.

Discussion
ERβ is abundantly expressed in the normal colon, progressively decrease in adenomas and CRC in relation to the disease aggressiveness and its deficiency enhances intestinal tumorigenesis in ApcMin/+ mice, an animal model [24]. So, loss of ERβ is a common step in the development of CRC and involved by malignant deposits (Figure 13). In some cases of CRC, ERβ was expressed in cytoplasm of the cancer cells, and in vascular endothelia.

degree of immunoreactivity to ERβ protein (Figure 11). Majority of cases of well-differentiated CRC and moderately differentiated cases showed variable degrees of expression to ERβ protein, and most cases of poorly differentiated CRC were negative for ERβ protein immunostaining (Figure 12). In the same theme, ERβ was not expressed in lymph nodes that
its presence in the colon has a protective effect [13]. This is evidenced by several immunohistochemical studies which reported that estrogen receptor was present in normal human colon and CRC tissues, and CRC development when concerned with a markedly reduced ERβ expression seems to be related to the worsening of CRC stage and grade [5,25,26]. In the same theme the expression rate of ERα was about 20-40%, but the expression of ERβ was higher than 65% [27-31].

In this study ERβ expression with varying levels of positive immunostaining seen in 3 out of 10 cases among the normal colonic mucosa, also observed in some stromal cells, lamina propria lymphocytes, and neural tissue. In concern to ERβ immunostaining in CRC cases, its lower expression was observed among high grade CRC cases than in lower grade and its immunoreactivity was lacked in cases with lymph nodes metastasis than in lymph nodes which were free from malignant involvement. Also, the intensity of staining was higher expression in well-differentiated tumors than in poor differentiated one, yet one case with perineural invasion was positive for ERβ.

Many published studies since the discovery of ERβ in 1997 indicated that ERβ was distributed in the human tissues and more expressed in the normal colonic epithelium, suggesting that estrogens may play an important role in the growth of normal colonic mucosa [31,32]. In addition to the above estrogen β receptor considered the dominant receptor type in normal colonic tissue and its down-regulation may be linked to the progression of colorectal cancer [33]. In the same theme a previous study revealed high nuclear immunoreactivity of ERβ in all epithelial cells of normal colon lining epithelia, where as in colon cancer, ERβ expression was lost in 21% of samples irrespective of patient age or gender. Loss of ERβ with increased Dukes' stage suggests that it may be affording a protective effect against colon carcinogenesis. Its presence may be a favorable prognostic marker in this disease and could explain the protective effect of estrogens against colon cancer development [5].

Regarding our findings of ERβ immunostaining in CRC cases, these findings are not in parallel with a study done by Rudolph et al., [6], who observed insignificant different levels of ERβ in relation to tumor differentiation, but there was a higher expression in relation to a higher stage of CRC. Also, similar findings found by Fang et al., [5]. This discrepancy may be related to the large numbers of surgical specimens that were collected by first authors which were 1564 cases, whereas the collected cases for the second one were from 423 CRC patients. On the other hand many previous studies with small samples that ranged from 11 to 92 cases revealed a parallel findings with our results [5,10,34-36]. In our study the percentage of ERβ positive immunoreactivity for CRC cases was 56%, and the remaining 44% cases were lacked ERβ immunoexpression. This finding was in near to results reported by Rudolph et al., [6], who found ERβ positive immunoreactivity including moderate and high levels in 67.6%, and the negative expression was seen in 32.4%.

In this study, there was insignificant correlation between ERβ expression and some of the clinico pathological variables, including age, differentiation, and lymph node status, whereas there was a significant correlation with patient gender and Duke's stage. The lacking of significant correlation may be attributable to the small sample size, and a large sample size may investigate a more significant relationship between ERβ expression and other clinicopathological features.

Our study had certain weakness and strengths. The weakness was relating to the lack of funding to perform this study on large samples and lacking of publications that were discussing the expression ERβ on other tissues such as neural tissue, stromal cells and lymphocytes. One of the strengths was related to the including of this small samples of material to different stages and differentiation of CRC.

Conclusion
ERβ is detected with variable degrees of immunoreactivity in tissues of both normal colonic mucosa and CRC, so the use of selective ERβ agonists as phytoestrogens may become of significant value in preventative measures of CRC.

Competing interests
The authors declare that they have no competing interests.
## Authors’ contributions

| Authors’ contributions | TMMH | AMSH | MMM |
|------------------------|------|------|-----|
| Research concept and design | ✓    | ✓    | ✓   |
| Collection and/or assembly of data | ✓    | ✓    | ✓   |
| Data analysis and interpretation | ✓    | ✓    | ✓   |
| Writing the article | ✓    | ✓    | ✓   |
| Critical revision of the article | ✓    | ✓    | ✓   |
| Final approval of article | ✓    | ✓    | ✓   |
| Statistical analysis | ✓    | ✓    | ✓   |

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