Expression of Estrogen Receptors (Alpha and Beta) in Pre-Malignant & Malignant Colorectal Lesions Using Immunohistochemistry and PCR Techniques

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ABSTRACT

Colorectal cancer (CRC) is one of the most common malignant neoplasms in Egypt. Adenomatous polyps and inflammatory bowel diseases (IBD) are considered the commonest pre-malignant lesions for CRC. A possible protective effect for estrogens on CRC risk has been suggested by numerous epidemiological and experimental studies.

Aim of work: to assess the expression of estrogen receptors (alpha and beta) in pre-malignant & malignant colorectal lesions.

Patients and methods: The 45 patients studied were divided into 4groups; CRC group (15patients), IBD group (10patients), adenomatous polyps group (10 patients) and control group (10 patients). Endoscopic guided biopsy was done from the colonic lesions the nearby normal colonic mucosa (in the first three groups) and from the control group. Estrogen receptors (alpha and beta) expression in the biopsies has been assessed by immunohistochemical staining and RT-PCR.

Results: all the studied biopsies have shown negative expression of estrogen receptors alpha and beta by both techniques doubting the proposed protective effect of estrogen and estrogen ligands in the protection against CRC and prevention of premalignant lesions.

Key words: Estrogen receptors – CRC – IBD – Adenomatous polyps – RT-PCR - Immunohistochemistry

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LIST OF ABBREVIATIONS

- **ACF**: Aberrant crypt foci
- **ACG**: American collage of gastroenterology
- **AF**: activation functions
- **AFAP**: attenuated familial adenomatous polyposis
- **AJCC**: American joint committee on cancer
- **AP-1**: activator protein-1
- **APC**: attenuated adenomatous polyposis coli
- **5-ASA**: 5-aminosalicylic acid
- **CBC**: Complete blood count
- **CD**: Crohn's disease
- **CEA**: carcinoembryonic antigen
- **CIN**: chromosomal instability
- **COX-2**: cyclo-oxygenase 2
- **CRC**: colorectal cancer
- **CT**: computerized tomography
- **DALM**: dysplasia-associated lesions or masses
- **DBD**: DNA binding domains **DCBE**: double contrast barium enema
- **DCC gene**: deleted in colon cancer
- **E_1**: estrone
- **E_2**: estradiol
- **E_3**: estriol
- **ER**: estrogen receptors
- **ERα**: Estrogen receptor Alpha
- **ERβ**: estrogen receptor Beta

- **ERE**: estrogen receptor-E2
- **ESR**: erythrocyte sedimentation rate
- **FAP**: familial adenomatous polyposis
- **FCC**: familial colorectal cancer
- **FIT**: fetal immunohistochemical staining
- **FOBT**: fecal occult blood testing
- **GAPDH**: Glyceraldehyde 3-phosphate dehydrogenase
- **GIT**: gastrointestinal tract
- **hMLH1**: human mutL homolog 1
- **hMSH2**: human mutS homolog 2
- **HNPCC**: hereditary non polyposis colorectal cancer
- **hPMS**: human postmeiotic segregation
- HRT: hormone replacement therapy
- **Hsp**: heat-shock proteins
- **IBS**: irritable bowel syndrome
- **IL**: interleukin
- **IPAA**: ileal pouch–anal anastomosis
- **IRA**: ileo-rectal anastomosis
- **JPS**: Juvenile polyposis syndrome
- **kDa**: kilo Dalton **IBD**: inflammatory bowel disease
- **LBD**: Ligand binding domain
- **MAP**: MUTYH-associated polyposis
- **MDM2 ligase**: murine double minute 2 ligase
- **MMR genes**: mismatch repair genes
- **MORE**: Multiple Outcomes of Raloxifene Evaluation
- **MSI**: microsatellite instability

- **NCI**: national cancer institute
- **NF-κB**: nuclear factor kappa-light-chain-enhancer of activated B cells
- **NO**: nitrous oxide
- **NSAIDs**: non steroidal anti-inflammatory drugs
- **PJS**: Peutz–Jeghers syndrome
- **PR**: progesterone receptors
- **PSC**: primary sclerosing cholangitis
- **UC**: ulcerative colitis
- **RER**: replication error
- **RT-PCR**: real time polymerase chain reaction
- **SERMs**: Selective estrogen receptor modulators
- **Sp-1**: stimulating protein-1
- **TGF-B**: transforming growth factor B
- **TNF:** tumour necrotic factor
- **TSG**: tumour suppressor gene
- **WHI**: Women's Health Initiative
- **WHO**: World heath organization

INTRODUCTION

Colorectal cancer (CRC) constitutes 9.4% of all cancer worldwide. It is ranked as the 4th most common cancer site for males after lung, prostate and stomach cancer, and the 2nd for females after breast cancer ***(WHO, 2006)***.

The incidence of CRC is increasing globally; worldwide an estimated 1 million cases of CRC were diagnosed in 2002, accounting for more than 9% of all new cancer cases ***(Jemal et al., 2009)***.

In Egypt, according to National Cancer Institute (NCI) statistics, in males CRC ranks the sixth most common cancer after bladder, liver, NHL, lung and leukemia, while in females it ranks the fifth common caner after breast, non Hodgkin lymphoma, leukemia and liver cancer. The median age of CRC cases in Egypt is 48 years for both males and females ***(Elattar, 2005)***.

CRC is more common in men than women, the difference being more striking amongst pre-menopausal women and age-matched men ***(Wong et al., 2005)***. A possible protective effect for estrogens on CRC risk has been suggested by numerous epidemiological and experimental studies ***(Ries et al., 2000; Campbell et al., 2001 and Terry et al., 2002)***.

The anti-estrogen (tamoxifen) in cancer breast is associated with increase the risk of CRC. Patients with Estrogen receptors (ER) expression are suggested to have a better survival rate ***(Slattery et al., 2000)***.