Y. Niv [2011] Med. Hypotheses Res. **7**: 35–37.

CLINICAL VIEWPOINT

Estrogen Receptor β May Be a Tumor Suppressor Gene in Colorectal Cancer of Inflammatory Bowel Disease Patients

Yaron Niv*

Department of Gastroenterology, Rabin Medical Center, Tel Aviv University, Israel

Abstract. Gender effect on the incidence and prognosis of colorectal cancer (CRC), sporadic and on the back ground of inflammatory bowel disease, is unique by protecting women till the age of menopause. This protection disappears in older women and cancer risk becomes similar to men. There are two types of estrogen receptors, ERα and ERβ. ERα is a nuclear receptor for 17β-estradiol, and presented in the female reproductive system. ERβ is found in the colon. It was demonstrated that silencing of ERβ by mutation or by promoter methylation increased proliferation and carcinogenesis. Furthermore, Malignant colon tissue showed a selective loss of ERβ protein expression when compared to normal colon mucosa in the same patient, and loss of ERβ expression in CRC is associated with more advanced staging. Long standing ulcerative colitis or Crohn's colitis patients are in danger of developing CRC. The potential role of ERβ as a tumor suppressor gene in CRC of colitis patients has never been investigated. Proving this hypothesis and finding a way to induce ERβ expression in these patients by an agent that will not attached to ERα and induces estrogen feminine side effects in men, will be a potential therapy preventing development of CRC.

* **Correspondence:** Dr. Yaron Niv, Department of Gastroenterology, Rabin Medical Center, 39 Jabotinski Street, Petach Tikva 49100, Israel. TEL : 972-3-9377237. FAX: 972-3-9210313. E-MAIL: yniv@clalit.org.il. nivyaron@013.net.il

Received on 04-21-2008; accepted on 07-17-2011.

1. Introduction

Gender effect on the incidence and prognosis of colorectal cancer (CRC) is unique by protecting women till the age of menopause [1]. This protection disappears in older women and become similar to men. The cause for gender differences is unknown and seldom investigated in depth. Sex hormones are frequently blamed for gender dependant change in disease prevalence, most of the time without any scientific evidence. Estrogen receptor beta (ERβ) is abundant on colonic mucosa of men and women and may be activated by estrogen in younger women. We hypothesize that ERβ is a tumor suppressor gene (TSG) for CRC, and that finding a way to activate this gene without activating estrogen receptor alpha (ERα) will be protective against CRC without estrogen side effects. This strategy may be important for patients with long standing ulcerative colitis for prevention of dysplasia and cancer development.

2. Clinical Studies of Gender Difference in CRC

Almost million cases of CRC are diagnosed every year all over the world, and almost half million patients die of this devastating disease every year. According to the CORI database, an American endoscopy data base of 75 American medical centers, men have a greater risk of polyps (with OR of 1.5) and tumors (OR of 1.4) than women [1]. Interestingly, women have a greater risk of developing pure right-sided polyps (with OR of 1.2) and tumors (OR of 1.6) than men. In the California registry of 52,882 patients with metastatic CRC, younger women lived longer than men, 17 months in average in comparison with 14 months, but older women lived less than men. These results were highly significant. We evaluated prospective colonoscopy studies for screening CRC and early detection of polyps in the average-risk, asymptomatic population [2]. The maximal detection rates of adenomas, advanced adenomatous polyps and CRCs were higher in men than in women. Adenoma detection rate of 35.7% vs 15.5%, advanced adenomatous polyp detection rate of 10.3% vs 4.8%, and CRC detection rate of 1% vs 0.48%. Similarly, gender differences in CRC incidence was evaluated in inflammatory bowel disease (IBD) patients [3]. A population base of 7607 IBD patients were followed for 44 years in Sweden, all together 171,000 person-years of follow-up. They found 196 new cases of CRC, 123 in men and 73 in women. Men had 60% higher risk of CRC, 8.3% vs 3.5%. Again, this observation hold only for patients younger than 45 years. Thus, the incidence of adenomatous polyps, advanced adenomatous polyps and CRC is lower in younger women than men, in cases of sporadic CRC and in CRC occurring in long standing IBD, also survival in metastatic CRC is better in younger women than men [4]. These differences disappear after the age of 45; thus, estrogen may be protective. Then, it was found that hormone replacement therapy protected against CRC and decreased the incidence in 66% after 15 years of therapy [5].

3. Estrogen Receptor β and CRC

There are 2 types of estrogen receptors, ERα and ERβ. ERα is a nuclear receptor for 17β-estradiol, on chromosome 6q25, and presented in the female reproductive system. ERβ, on chromosome 14q23, is found in the colon. It was demonstrated that silencing of estrogen receptor β (ERβ) by mutation or the promoter methylation increased proliferation and carcinogenesis [6]. ERβ is abundantly expressed in normal colonic mucosa, but declines in CRC paralleling the tumor's dedifferentiation [7]. Malignant colon tissue showed a selective loss of ERβ protein expression when compared to normal colon mucosa in the same patient [8]. Loss of ERβ expression in CRC is associated with more advanced staging [9].

4. Estrogen Receptor β Is a Tumor Suppressor Gene in CRC

Loss of ERβ in knockout mice leads to colonic mucosa hyper-proliferation and disordered apoptosis [10]. Activation of ERβ induced apoptosis in COLO205 and LoVo CRC cell lines [11,12]. ERβ, located especially in epithelial cells at the bottom of the mucosal crypt may play an important role in the growth and regeneration of normal colonic mucosa, as well as being a tumor suppressor gene in CRC, directs neoplastic cells toward apoptosis and prevents proliferation. This theory is not supported by a recent paper suggests that ERβ acts as colon tumor promoter, and raloxipene as an antagonist to ERβ provides protection against colon carcinogenesis [13]. Since several ERβ isoforms were described, it left to be investigated if a specific isoform is more responsible than others for protecting against CRC [14].

5. Conclusions

Long standing ulcerative colitis or Crohn's colitis patients are in danger of developing CRC. The potential role of ERβ as TSG in CRC of colitis patients has never been investigated. Proving this hypothesis and finding a way to induce ERβ expression in these patients by an agent that will not attached to ERα and induced estrogen feminine side effects in men, will be a potential maintenance therapy preventing development of CRC.

References

1. **McCashland TM, Brand R, Lyden E, de Garmo P** [2001] CORI Research Project. Gender differences in colorectal polyps and tumors. Am J Gastroenterol 96: 882-886.
2. **Niv Y, Hazazi R, Levi Z, Fraser G** [2008] Screening colonoscopy for asymptomatic population; a meta-analysis. Dig Dis Sci 53: 3049-3055.
3. **Söderlund S, Granath F, Broström O, et al. Karlén P, Löfberg R, Ekbom A, Askling J** [2010] Inflammatory bowel disease confers a lower risk of colorectal cancer to females than to males. Gastroenterology 138: 1697-1703.
4. **Hendifar A, Yang D, Lenz F, Lurje G, Pohl A, Lenz C, Ning Y, Zhang W, Lenz HJ** [2009] Gender disparities in metastatic colorectal cancer survival. Clin Cancer Res 15: 6391-6397.
5. **Long MD, Martin CF, Galanko JA, Sandler RS** [2010] Hormone replacement therapy, oral contraceptive use, and distal large bowel cancer: a population-based case-control study. Am J Gastroenterol 105: 1843-1850.
6. **Rakoff-Nahoum S, Medzhitov R** [2007] Regulation of spontaneous intestinal tumorigenesis through the adaptor protein MyD88. Science 317: 124-127.
7. **Konstantinopoulos PA, Kominea A, Vandoros G, Sykiotis GP, Andricopoulos P, Varakis I, Sotiropoulou-Bonikou G, Papavassiliou AG [2003]** Oestrogen receptor beta (ERbeta) is abundantly expressed in normal colonic mucosa, but declines in colon adenocarcinoma paralleling the tumour's dediff erentiation. Eur J Cancer 39: 1251-1258.
8. **Foley EF, Jazaeri AA, Shupnik MA, Jazaeri O, Rice LW** [2000] Selective loss of estrogen receptor beta in malignant human colon. Cancer Res 60: 245-248.
9. **Jassam N, Bell SM, Speirs V, Quirke P** [2005] Loss of expression of oestrogen receptor beta in colon cancer and its association with Dukes' staging. Oncol Rep 14: 17-21.
10. **Wada-Hiraike O, Imamov O, Hiraike H, Hultenby K, Schwend T, Omoto Y, Warner M, Gustafsson JA** [2006] Role of estrogen receptor beta in colonic epithelium. Proc Natl Acad Sci USA 103: 2959-2964.
11. **Qiu Y, Waters CE, Lewis AE, Langman MJ, Eggo MC** [2002] Oestrogeninduced apoptosis in colonocytes expressing oestrogen receptor beta. J Endocrinol 174: 369-77.
12. **Hsu HH, Cheng SF, Wu CC, et al.** [2006] Apoptotic eff ects of overexpressed estrogen receptor-beta on LoVo colon cancer cell is mediated by p53 signalings in a ligand-dependent manner. Chin J Physiol 49: 110-116.
13. **Janakiram NB, Steele VE, Chinthalapally VR** [2009] Estrogen receptor-β as a potential target for colon cancer prevention: chemoprevention of azoxymethane-induced colon carcinogenesis by raloxifene in F344 rats. Cancer Prev Res 2: 52-59.
14. **Campbell-Thompson M, Lynch IJ, Bhardwaj B** [2001] Expression of estrogen receptor (ER) subtypes and ER beta isoforms in colon cancer. Cancer Res 61: 632-640.

Conflicts of interest statement: There is no conflict of interest to declare.