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Molecular Pathways: Estrogen Pathway in Colorectal Cancer

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Abstract

Worldwide colorectal cancer (CRC) has a higher incidence rate in men than in women, suggesting a protective role for sex hormones in the development of the disease. Preclinical data supports a role for estrogen and its receptors in the initiation and progression of CRC and establishes that protective effects of estrogen are exerted through ERβ. Hormone replacement therapy (HRT) in postmenopausal women as well as consumption of soy reduces the incidence of CRC. In the Women's Health Initiative (WHI) trial use of HRT in postmenopausal women reduced the risk of colon cancer by 56% (95% CI, 0.38 to 0.81; P=0.003). A recent meta-analysis showed that in females, consumption of soy reduced the risk of colon cancer by 21% (95% CI, 0.03 to 0.35; P=0.026).

In this review, utilizing the preclinical data, we translate the findings in the clinical trials and observational studies to define the role of estrogen in the prevention of CRC. We hypothesize that sometime during the tumorigenesis process ERβ expression in colonocytes is lost and the estrogen ligand, HRT or soy products, exerts its effects through preventing this loss. Thus in the adenoma to carcinoma continuum, timing of HRT is a significant determinant of the observed benefit from this intervention. We further argue that the protective effects of estrogen are limited to certain molecular subtypes.

Successful development of estrogen modulators for prevention of CRC depends on identification of susceptible CRC population(s). Thus research to better understand the estrogen pathway is fundamental for clinical delivery of these agents.

Keywords

estrogen; colorectal cancer; pathways; outcome; incidence

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BACKGROUND

Age is the strongest risk factor for colorectal cancer (CRC), with 90% of cases and 94% of deaths reported in individuals older than 50 years. Yet the incidence is lower in females across all age groups.[1] This epidemiological observation can be explained by differences in the CRC related risk factors between men and women such as obesity, smoking, dietary exposures, and physical activity. However, persistence of the gender differences across several decades, in different racial groups, and across the world suggest that sex hormones (estrogen and progesterone) play a role in the pathogenic pathways of CRC and this role is most likely protective.

Additionally, studies of relationship between gender and mortality of CRC consistently show lower mortality for females, especially pre-menopausal females. Epidemiologic studies over several decades suggest a decline in mortality of females attributed to use of hormone therapy.[2,3]

Protective role of the estrogen pathway in development of colon cancer has been studied and established in animal models. In several studies, exposure of ovariectomized rats to estrogen reduced the rate of colon tumors by 71% even in the presence of an ERα knockout.[4,5] Additionally, in the $Apc^{Min/+}$ mice ovariectomy resulted in an increased number of polyps, while replacement of estrogen in these mice reduced the number of polyps to the baseline values.[6]

Over the last two decades use of Hormone replacement therapy (HRT) provided the opportunity to discover the role of this intervention in prevention and outcome of CRC. Data from multiple prospective and retrospective cohorts support a protective role for HRT in the development and outcome of colon cancer.

Experience with soy products complements the hypothesis that estrogens have a protective effect against CRC. Lower incidence of CRC in Asians is attributed to high soy content. In animal models genistein, estrogen in soy, inhibits colon cancer cell proliferation and enhances apoptosis through interaction with several pathways. [7,8] The estrogen pathway has the potential to be targeted for preventive and therapeutic strategies in CRC, therefore, its role and relationship with other pathways warrant further investigation. In this review, we will provide comprehensive evidence on the role of estrogen and progesterone and how their signaling pathways play a critical role in CRC development and outcome.

Molecular effects of estrogen and progesterone in CRC

Estrogens are members of steroid hormone family and are traditionally associated with the female reproductive development. The most abundant and most potent estrogen in humans is 17β-estradiol (E2). Other natural estrogens include estrone (E1) and estriol (E3), metabolites of E2. The estrogen receptor recognizes a molecule as estrogen based on its 3D configuration and charge, but preferentially binds E2 over E3 (2X) and E1 (3X).[9] Estrogen production and metabolism is tissue specific and is different in colon compared to breast tissue. In colon 17βHSD2 and 4 convert E2 to E1, which is antiproliferative in human colon cancer cell lines.[10,11]

The discovery of different estrogen receptors (ER) have revealed their significant role in tissue types other than the female reproductive tract including the gastrointestinal system.[12] Estrogens regulate these cellular effects through their intracellular receptors, ERα and ERβ. The two receptors are coded for by separate genes, *ESR1* (ERα) and *ESR2* (ERβ), with each gene producing different receptor isoforms from alternative splicing, resulting in three ERα and five ERβ variants. The two receptors share DNA homology, co-receptors and

downstream signaling, however, their dissimilarities dictate the differences observed in their effects.[13] Estrogen interacts differently with ERα and ERβ downstream pathways.[14] The differences in the downstream signaling of these two receptors may explain their distinctive intracellular effects. Furthermore, it has been demonstrated that the biological response of activated ERα and ERβ is dependent on the ratio of ERα to ERβ in the cell, and that ERβ inhibits transcriptional activity of ERα.[15] The intracellular effects of estrogen are exerted through two main pathways: *genomic* and *non-genomic*.

Genomic effects of estrogen in CRC: an activated ER, activates gene transcription through either direct interaction with specific DNA sequences known as estrogen response elements (ERE) or other transcription factors such as c-Jun and/or c-Fos, resulting in transcription (Figure 1). While interaction of both ERs with ERE is similar, ERα interacts with other transcription factors such as c-Jun and c-Fos of the activating protein-1 complex (AP-1) and SP1, while ERβ's interaction with these transcription factors is less significant. [13] In the case of AP1, it has been shown that binding of E2 to ERα results in transcription activation and to ERβ inhibits transcription through diversion of estrogen away from the ERα pathway.[16,17]

Genomic effects can also be seen in a ligand independent manner, where ERs are phosphorylated through an activated kinase pathway in the absence of the estrogen ligand (Figure 1). As an example, EGFR can activate the Ras/Raf/MAPK pathway, which in turn will phosphorylate the ER, resulting in dimerization and ligand independent activation of gene expression.[18,19]

The genomic mediated effects of estrogen results in activated transcription of a wide array of genes including genes involved in angiogenesis such as VEGF, cellular adhesion such as cadherins and laminins, and proliferation and apoptosis including the TGFβ family.

Non-genomic effects of estrogen in CRC: In addition to genomic effects, estrogen and its receptors can activate several signaling pathways without direct interaction with DNA, resulting in modulation of additional cellular processes. Transmembrane ERs have been shown to activate diverse intracellular pathways, including protein kinase C (PKC)[20], intracellular Ca^{2+}[21,22], cytosolic cAMP[23], nitric oxide[24], and MAPK[25] (Figure 1). For example, transmembrane ERα signaling through PI3K can result in cell proliferation and survival, while transmembrane ERβ signaling cause the influx of Ca^{2+} in the cell, resulting in suppression of protein kinase C (PKC) signaling (Figure 1). An additional role of ERβ is through modulation of cell cycle control through interactions with c-Myc, cyclin D1[26] and cyclin A[27] resulting in inhibition of cell cycle progression.

In both normal and cancerous colonocytes, ERα expression levels remain low. [30] In contrast, ERβ is the predominant ER in the normal colon[28,29] with higher expression level in the ascending colon.[30] Expression level of ERβ in tumor tissue compared to normal colon mucosa is decreased and correlates with stage of the disease. [31,32]

Hartman et al showed that transfection of SW480 cell lines with ERβ resulted in inhibition of proliferation and cell cycle arrest. SW480 xenographts with ERβ expression had 70% reduction in the tumor weight.[33] Furthermore knock out of ERβ in $Apc^{Min/+}$ mice results in a dramatic increase in the polyps and addition of E2 treatment did not prevent development of polyps in these mice.[34]

Edvardsson had shown that transfection of colon cancer cell lines with ERβ affects the MAPK signaling pathway.[35] Furthermore, ERβ results in down regulation of IL6, and thus reducing inflammation.[35] Giroux et al, postulate that the effects of ERβ in $Apc^{Min/+}$ mice are through modulation of TGFβ signaling pathway.[34]

Several studies support the cross talk between Wnt/β-Catenin signaling and ERα. In one experiment, ERα transfection of SW480 and HCT116 resulted in activation of Wnt signaling and addition of an ER antagonist resulted in deactivation of the pathway. Moreover, in this experiment adding an antibody against β-Catenin resulted in activation of ERE in an estrogen dependent manner.[36]

Despite the established cellular role for the ERs in CRC, the exact role of estrogen in CRC remains unclear. Effects of estrogen on colonocytes may be related to the direct effects of the estrogen ligand and its interaction with the receptors (*directly related to ligand*) or changes in the ERs ratio and function independent of the ligand (in*directly related to ligand*). For example, the rise in the incidence of colon cancer after menopause in women, when circulating amount of estrogen ligand is decreased, could be related to the loss of cell cycle regulatory effects of ERβ (*directly related to ligand*); Or that the decrease in the endogenous estrogen level at the time of menopause results in a change in the ratio of ERs (*indirectly related to ligand).* In fact, in animal models the transcriptional activity of ERs changes over time and is influenced by estrogen level.[37] In APC mouse models, E2 treatment results in an increase in the ratio of ERβ and protection against colon cancer.[6] Therefore, it is likely that HRT in women protects against colon cancer through an increased ratio of ERβ. As ERβ expression decreases throughout the process of tumorigenesis the timing of HRT to prevent loss of ERβ is critical.[38]

As for estrogen metabolism, polymorphism in the metabolic pathway of estrogen may result in higher level of E2 and lower level of E1 in colonocytes, thereby stimulating growth. The expression level of 17β-HSD2 and 17β-HSD4 is lower in colon cancer than normal colon tissue, resulting in lower levels of E1 in the tumor. The imbalance in the level of the estrogen metabolites can result in an increase in proliferation or decrease in apoptosis. [10,11,39] In a recent study, Level of E2 was higher in cohort of Chinese men with colon cancer compared to controls, in this population combination of genetic variations in the ESR2 and E2 level was predictive of the risk of colon cancer, where in the group with high E2 level and CT/TT genotypes of ESR2 risk of colon cancer was 2.3 (95% CI, 1.4–3.9) compared to those with low level of E2 and CC genotype.[40]

The literature from soy supports that use of isoflavons, a strong ERβ agonist, in DLD-1 human colon cancer cell line, resulted in G2 cell cycle arrest. Use of Soy Isoflavons after silencing of ERβ in this cell line failed to suppress G2 arrest.[41] Pintova et al. had shown that genistein, reduces proliferation in HT29, DLD1, and RKO cell lines through inhibition of Wnt/beta-catenin pathway.[42] While these finding are exciting, results of a meta-analysis of relationship between use of soy and risk of colorectal cancer in humans suggests that the protective effects of soy are limited to females.[43] Thus suggesting that effects of soy depend on the endogenous estrogen level through altering estrogen metabolism.[44] Furthermore, use of soy isoflavons in rats resulted in increased expression of ERβ and decreased expression of ERα in osteocytes; exposure of colonocytes to soy may also result in increased expression of ERβ.

In addition to estrogen, the steroid hormone progesterone has been shown to play a distinct role in the regulation of the normal female reproductive function and regulating the bone matrix, but further has anti-estrogen effects in other tissue types.[45] Cellular effects of progesterone are mediated through a similar pathway as the ER, where progestins bind either progesterone receptor (PR) A or B and mediate transcription through interaction with progesterone response elements (PRE). The only prominent non-genomic effect of progesterone that is reported is a rapid and transient activation of the MAPK pathway.[46] The observed cellular effects of progesterone are largely attributed to its ability to oppose the action of estrogen, causing an inhibition of ER expression and through abrogating the

induction of estrogen related genes.[47] Cellular effects of progesterone in colonocytes have been minimally studied. In mammary cells, interception of the progesterone receptor by progesterone results in up regulation of EGFR and Wnt-1.[48–50] In animal breast cancer models, combination of estrogen and progesterone results in increased amphirgulin and augmented proliferation compared to estrogen alone. Assuming that EGFR and Wnt-1 can be up regulated in colonocytes, endogenous progesterone may have a proliferative effect on the colonocytes. These finding are presumably, fitting the interactions of progesterone with ERα and interactions between ERβ and progesterone are unexplored. Medroxy progesterone, the progesterone formulation in HRT, has direct inhibitory effect on colon cancer cell lines, supporting the observation that HRT is protective against colon cancer.[50]

Epidemiologic Data

The results of the Women Health Initiative (WHI) study raised the awareness of the scientific community about the interactions between sex steroids and incidence and outcome of colon cancer. One limitation of the WHI study is that colon cancer was not the primary endpoint of the study and therefore the number of CRC in the study was small (122 during the trial and 263 during and after follow-up), making the data hypothesis generating. Hartz et al. published an analysis inclusive of all WHI enrollees and its observational cohort and found that use of any form of HRT reduces the risk of colon cancer by 30% (95% confidence interval, 0.62 to 0.80; P<0.01) and the risk of rectal cancer by 43% ($p < 0.0001$).[51]

Since the publication of WHI results, several observational studies have examined the role of HRT in the incidence and outcome of colon cancer. Table 1 summarizes the data from few selected observational studies. The majority of these studies suggest that the use of HRT reduces the incidence of colon cancer[52–55], however, this finding is not confirmed in other studies.[52,53,56,57] It is important to point out that these studies are planned and analyzed over several decades, with different formulations of hormones being used by participants. There is a large variation in the timing of start of these hormones after menopause and duration of hormonal use. It is unknown whether they are used to alleviate symptoms of menopause or for other reasons. More importantly due to the observational nature of these studies, compliance with the treatment and indication for treatment is unknown. Furthermore, in all these studies, prior use of hormonal therapy (post menopausal or contraceptives) may have resulted in a difference in the observed outcome. Although, statistical methods are used to adjust for these variations, one should not ignore the potential role of bias in the results given the multitude of underlying factors.

In addition, four studies evaluated the role of hormones in mortality from colon cancer in patients who were diagnosed with colon cancer while on HRT. All these studies reported that HRT reduces the risk of death from colon cancer (table 1).[58–61] However, Newcomb evaluated the risk of death in patients with colon cancer who were users of HRT and found that HRT doesn't reduce the risk of death from colon cancer (HR= 1.09, CI 0.81–1.47).[62] These results further support a role for estrogen in reducing the mortality of colon cancer.

CLINICAL-TRANSLATIONAL ADVANCES

Although the estrogen pathway is not the central pathway in CRC, it plays an important role in the initiation and progression of the disease. Despite expression of ERβ in normal colonocytes, none of the existing colon cancer cell lines express sufficient amount of ERβ; thus suggesting that loss of expression of ERβ is part of the tumorigenesis process. This review establishes that the estrogen receptors play a major role in the fate of the colonocytes and ligands maintain the receptors balance.

WHI and observational cohorts collectively support that HRT, estrogen surrogate, reduces the risk of developing colon cancer. Nevertheless, the degree of risk reduction differs among individuals, likely, based on the activated pathways leading to CRC. In the WHI study colon cancer in the hormone replacement group seemed to be more advanced and had a higher number of positive lymph nodes, suggesting that tumors developing while on HRT appear to be biologically more aggressive.[63] Interestingly, in the observational studies, obesity and smoking were associated with lesser degree of benefit from HRT. These phenotypic features are linked to aberrant activation of the pathways that are independent from estrogen pathway and thus HRT may be less effective in preventing the tumors driven by these ER independent pathways. For example, obesity results in hyperinsulinemia which in turn results in PI3K activation and increased risk of CRC.[64] As shown in figure 1, there is no relationship between PI3K and ERβ (Fig. 1), therefore estrogen may not protect against PI3K driven tumors. Additionally, smoking is linked to increased risk of MSI high tumors, and HRT does not decrease the risk of MSI high tumors, which emphasizes that HRT may be effective in molecularly defined populations.[65,66]

In WHI study, women older than 60 years on HRT had lesser degree of CRC risk reduction, suggesting that timing of start of HRT (shorter interval from menopause) may play a crucial role in its protective effects on colon cancer. Based on the existing preclinical evidence, early start of HRT prevents changes in the ratio of the receptors and results in lower rate of CRC through maintaining ERβ receptors. Furthermore, it is likely that start of estrogen before activation of the aberrant pathways will prevent CRC, while if the precancerous process is already initiated and ERβ is lost estrogens will not be able to reverse the process.

Besides HRT, high estrogen content of soy is implicated to be protective against CRC. However, recent evidence suggests that higher soy consumption is protective against colon cancer only in females.[43]

To maximize the benefit of estrogen for prevention of CRC, exploring the phenotypic and molecular subgroups of the individuals who achieve maximum benefit from this intervention is essential. Until then, use of estrogens for prevention of colon cancer should remain investigational.

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Translational relevance

Use of estrogens for prevention of colon cancer is an attractive concept in women, however, the increased rates of cardiovascular events with HRT, limit use of these agents in clinical practice.

While there are no clinical data to prove that ERβ modulation reduces the incidence of colon cancer, preclinical models of ERβ modulation are promising. In the study by Schleipen, treatment of ovariectomized rats by ERβ agonists or genistein increased the apoptosis and reduced proliferation in the ileum and colon, further supporting the role of these agents in the prevention of colon cancer.[67] Also Giroux et al. showed that ERβ agonist treatment reduces the number of small intestinal polyps in $Apc^{Min/+}$ males and females.[68] Though development of selective ERβ modulators has proven to be very challenging, two agents are currently in phase III and IV trials. MF101 and raloxifen are being studied for their effects on menopausal symptoms and osteoporosis respectively.[69,70] Long-term follow up will show if any of the agents in clinical development have an effect on the incidence of colon cancer in women. The challenge is that benefit from these agents happens primarily in the presence of ERβ, thus secondary prevention in patients who express ERβ, is the most logical first step to test the clinical efficacy of these agents.

We conclude by stating that although estrogen modulation has a role in CRC prevention, the burden is on investigators to identify the appropriate population and product to move the field forward.

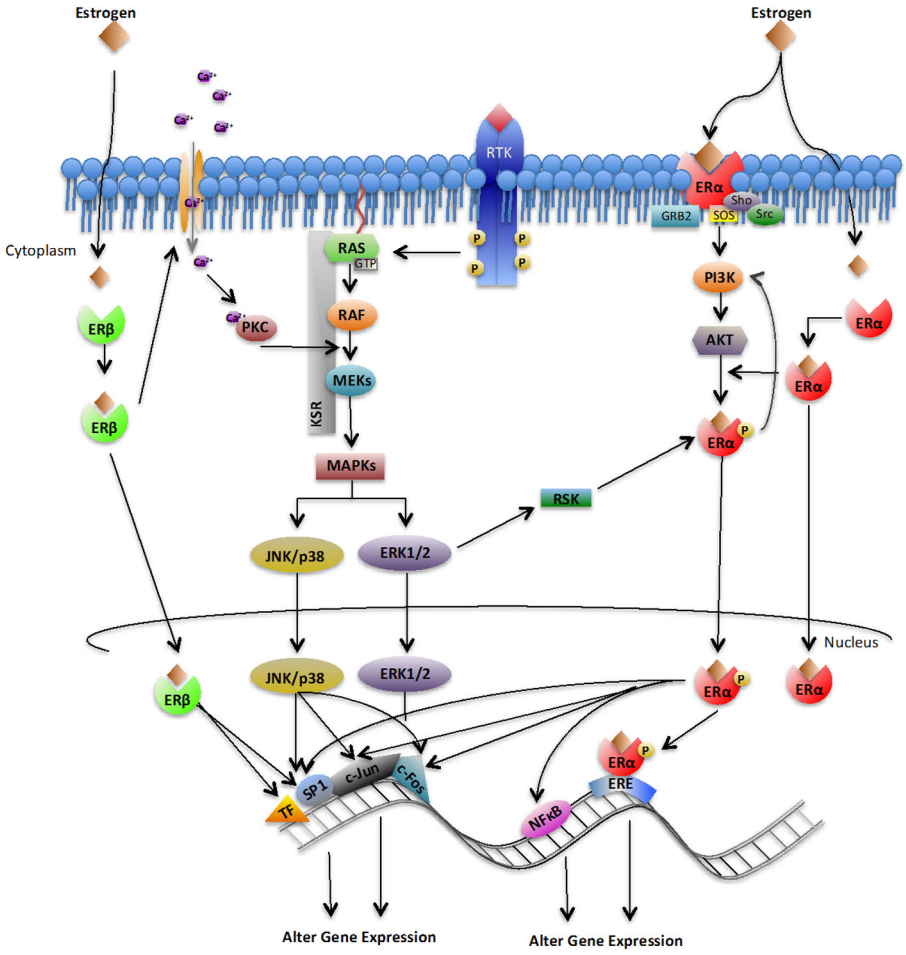

Figure 1.

Intracellular effects of estrogen are exerted through two main pathways, genomic and non-genomic. Interaction of the estrogen receptor and ligand with DNA, through estrogen response elements (ERE) or other transcription factors such as C-Fos/C-Jun/AP1, results in transcriptional alteration of genes and is the main genomic mechanism of estrogen in cells. The genomic effects can also be achieved from interactions of the receptor, without the ligand, through ligand independent pathways, where ERs are phosphorelayted through activated kinase pathway.

The non-genomic effects are achieved through several intracellular pathways, including protein kinase C (PKC), Intracellular ca++, Cytosolic CAMP, Nitric oxide, and MAPK.

Abbreviations: ER, estrogen receptor; ERE, estrogen receptor element; ERK, extracellular signal-regulated kinase; MAPK, mitogen activated protein kinase; NFkB, nuclear factor kappa-light-chaine-enhancer of activated B-cells; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; RTK, receptor tyrosine kinase; TF, transcription factor.

Table 1

Selected observational studies assessing the interactions between HRT and incidence and mortality of colorectal cancers.

Study (pub year)	Risk	Product	M Age	CRC	HR (95% CI) [P-Value]
French E3N prospective cohort (2012)[52]	I	E	51.1	525	0.72 (0.56 – 0.94) [S]
French E3N prospective cohort (2012)[52]	I	E + P	56		1 (0.83 – 1.21)
Cancer Prevention Study II nutrition Cohort (2009)[53]	I	E	61&66	776	0.76 (0.59 – 0.97)[0.01]
Cancer Prevention Study II nutrition Cohort (2009)[53]	I	E + P	57&59		0.84 (0.54–1.30) [0.72]
UK General Practice Research Database (GPRD) (2007)[56]	I	E	60.5		1.18 (0.72 1.92) [0.77]
UK General Practice Research Database (GPRD) (2007)[54]	I	E + P	60.5		0.56 (0.35–0.87)
European Prospective Investigation into Cancer and Nutrition[57]	I	HRT	49.7	1186	1(0.86–1.16) [0.06]
Nested Case Control (2012)[55]	I	HRT	73.8	4708	0.81 (0.73–0.91) [0.001]
Cancer Prevention Study II (1995)[58]	M	HRT	65.8	897	0.71 (0.63–0.81) [0.001]
Utah, California, and Minnesota Cancer Registry Data[59]	M	HRT			0.4
Seattle HMO Database[60]	M	HRT		699	0.41
Nurses Health Study[61]	M	HRT	63	834	0.64

Abbreviations, I: Incidence, M: Mortality, E: estrogen, P: Progesterone, HRT: hormone replacement therapy.