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Estrogen and Colon Cancer

Cancer is the second leading cause of death for both males and females of all races. Colon cancer is the most common type of gastrointestinal cancer. Excluding skin cancers, colorectal cancer is the third most common cancer diagnosed in both men and women in the United States. It is also the third leading cause of cancer-related deaths in the United States when men and women are considered separately, and the second leading cause when both sexes are combined. Gender seems to be an additional factor in this multifactorial disease. But what is the exact role of sex hormones in colon cancer development? This is what SJSM students found out:

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Estrogen and Colon Cancer

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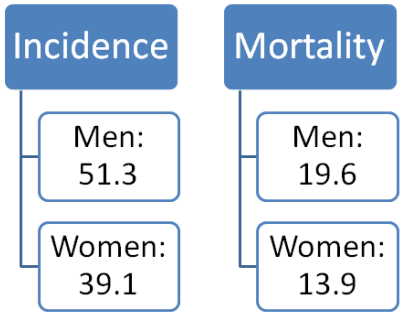
Introduction

Colon cancer has been increasing in prevalence over the past decades and it has been discovered that estrogen (E2) plays a seemingly controversial role in the development of the disease. In order to gain a holistic understanding of the causative and protective influences of estrogen, the mechanisms of action of this hormone have been discussed here.

Demographics

- **Prediction:** Approximately 138,830 individuals will be diagnosed with colon cancer and 50,310 will succumb to it annually between 2014 and 2016.
- As of January 1st, 2012, there were approximately 1.2 million Americans living with the disease.
- It is currently expected that 5% (1 in 20) Americans will be diagnosed with this neoplasia in their lifetime.
- 90% of newly diagnosed cases and 93% of colon cancer-related deaths occur in individuals 50 years of age or older (ACS 2014).

Figure 1: Colon Cancer Incidence and Mortality Rates



Per 100,000 per year, age adjusted.

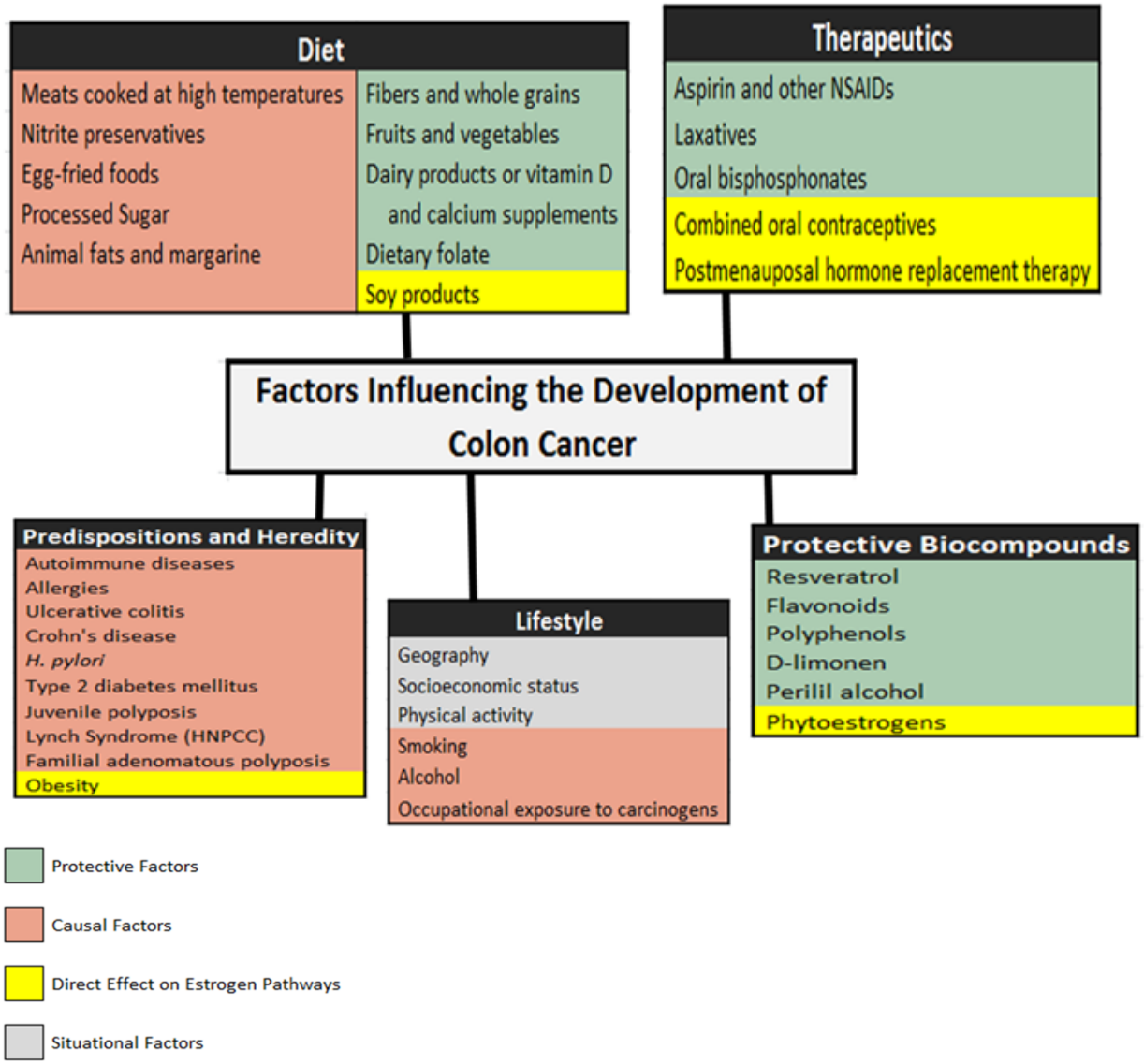
Overall survival rates among women:

- Those diagnosed between the ages of 18 and 44 lived approximately 17 months longer than men of the same cohort.

- Women diagnosed after the age of 44 showed a life expectancy of about 7 months less than men in the comparative age range. (Hendifar et al. 2009).

Influential Factors

Figure 2: Factors Influencing Development of Colon Cancer

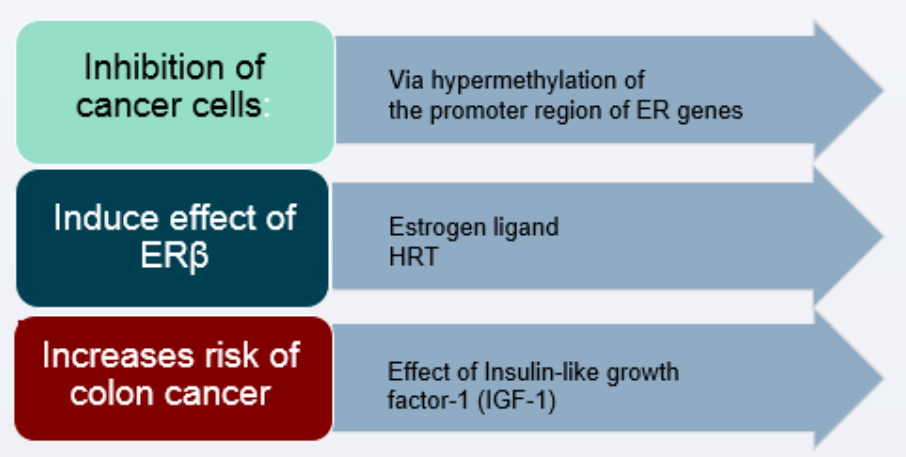


Animal Models

- The study of Apc (Min/+) mice lacking estrogen receptor α (ERα) demonstrated an increased colon tumor burden and multiplicity when compared to wild-type mice (Burn & Korach 2012).

- This resulted in the suppression of the Wnt−β-catenin signaling pathway and tumorigenesis. Suggesting that ERα has a suppressing effect on this pathway.
- Apc (Min/+) mice where an ERβ-selective agonist diarylpropionitrile was administered: - Important decrease in polyp multiplicity was detected (Burn & Korach 2012).
- Estrogen under certain circumstances may play a mitogenic role, possibly once a tumor is formed (Williams et al. 2016).

Figure 3: Estrogen Effects in Animal Models



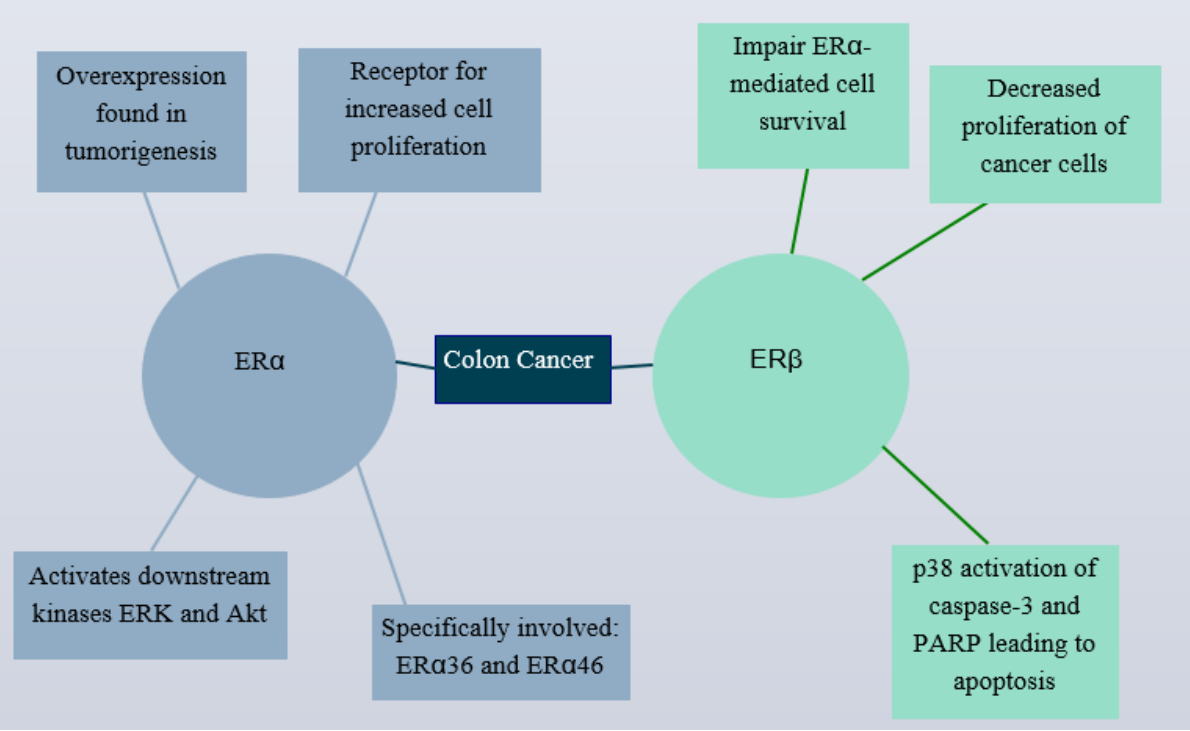
MECHANISMS OF ESTROGEN RELATED COLON CANCER

Associative Effects of Estrogen in Colon Cancer

- ERα and ERβ are the two receptors that have been shown to be associated with both causal and protective aspects of colon cancer.
- Both of these estrogen receptors are expressed in the mucosa of the colon, both have definitive pathways for pro-apoptotic and cell proliferation.
- Perhaps ERα is responsible for proliferation of carcinogenic cells in the colon via an impact on the balance of pro- and anti-apoptotic pathways as well as having an influence on cyclin D1 to allow progression in the cell cycle (Caiazza et al. 2015).
- Overall the ERβ receptor has been shown to inhibit the proliferative effects of ERα (Lopez-Calderero et al. 2014).
- The evidence has shown that when there is a disruption between the balance of the ERβ and the ERα, there is colonic tumorigenesis as compared to a normal balance between the two estrogen receptors (Caiazza et al. 2015).
- ERα has been shown to activate downstream kinases including ERK and Akt, and activation of the colonic mRNA leading to tumorigenesis (Sokolosky & Wargovish 2012).

- Expression levels measured by real-time PCR showed overexpression of ER-α36 and ER-α46 variants in different types of carcinogenic colon tissue compared to normal tissue (Jiang et al. 2008).
- For further study on ERα and colon cancer, a more standardized measurement should be used, as different techniques showed different levels of the estrogen receptor and its associated subtypes.

Figure 4: Roles of ERα and ERβ in Colon Cancer



Protective Effects of Estrogen in Colon Cancer

Figure 5: ER Expression in Colon Cancer

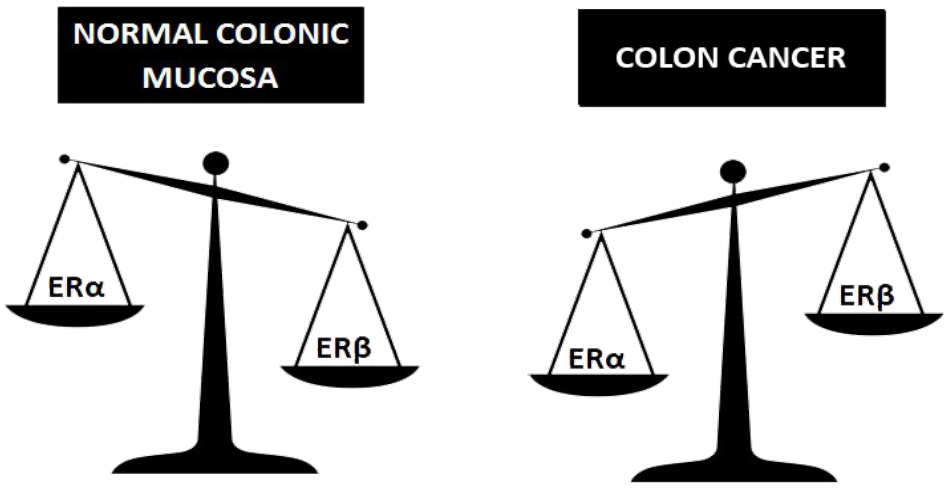
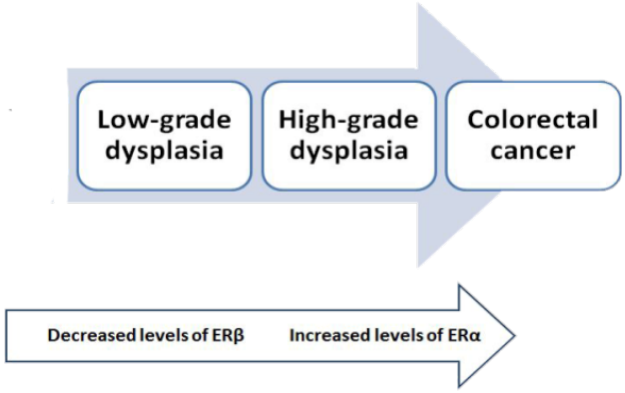


Figure 6: Change in ER Expression in Disease Progression

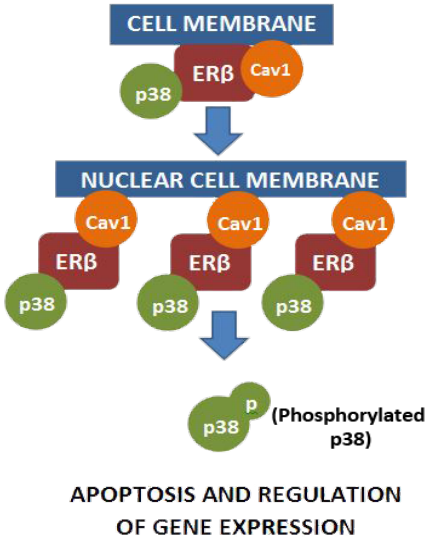


Estrogen plays a protective role in the progression of colon cancer via ERβ-linked inhibition of cell proliferation by the following mechanism:

- ERβ is the predominant ER subtype in the human colon.
- Decreased ERβ1 (ERβwt) and ERβ2 (ERβcx) are associated with colonic tumorigenesis in women (Barzi et al. 2013).
- ERβ expression is significantly lower in colon cancer cells than in normal colonic epithelium (Burn & Korach 2012).

- E2 stimulation causes ERβ to undergo de-palmitoylation in parallel to an increased association of receptor to caveolin-1 and p38 (Marino et al. 2014).
- Association between ERβ-caveolin-1 and p38 activates downstream pro-apoptotic cascade involving the cleavage of caspase-3 and of its main substrate poly-(ADP-ribose) polymerase (PARP) (Marino et al. 2014).
- ERβ activation of p38-MAPK pathway leads to increased expression of ERβ itself by genomic and non-genomic mechanisms, leading to a self-perpetuating cycle (Marino et al. 2014).

Figure 7: E2 Stimulation of ERβ



CONCLUSION

These pharmaceutical agents may have a potential protective role in colon cancer in conjunction with ERβ

Raloxifene

- may be an agonist to ERβ in colon cancer cells
- suppresses colon adenocarcinoma formation
- modulates immune signaling and decreases stem-like cells
- exposed tumors showed increased apoptotic cells

Aspirin

- reduces inflammation of colon, known risk factor for colon cancer
- inhibits COX-2, which is an enzyme responsible for inflammation
- high doses reduce incidence of colon cancer by 26%
- low doses reduce long-term incidence of colon cancer as well as mortality rates, without gastrointestinal toxicity

It is a challenging task to use the estrogenic agents or SERMs in prevention and treatment of colon cancer. Apart from the adverse effects of these agents, a decline in ERβ status in colon cancer is an important concern. In such circumstances, ERβ agonist many not work effectively. Nevertheless, development of selective ERβ modulators is a promising area. A precise understanding of ERβ signaling in colonic tissue will greatly progress our therapeutic strategies.

Abbreviations used- E2: 17β-Estradiol; ER: Estrogen receptor; APC: Adenomatous polyposis coli; Min: Multiple intestinal neoplasia; HRT: Hormone replacement therapy; ERK: Extracellular signal-regulated kinase; Akt: Protein kinase B/serine-threonine kinase; p38: p38 mitogen-activated protein (MAP) kinase; PARP: Poly(ADP-ribose) polymerase; Cav1: Caveolin-1; SERMs: Selective estrogen receptor modulators.

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