Colorectal Cancer (CRC) in Women — Screening and Prevalence

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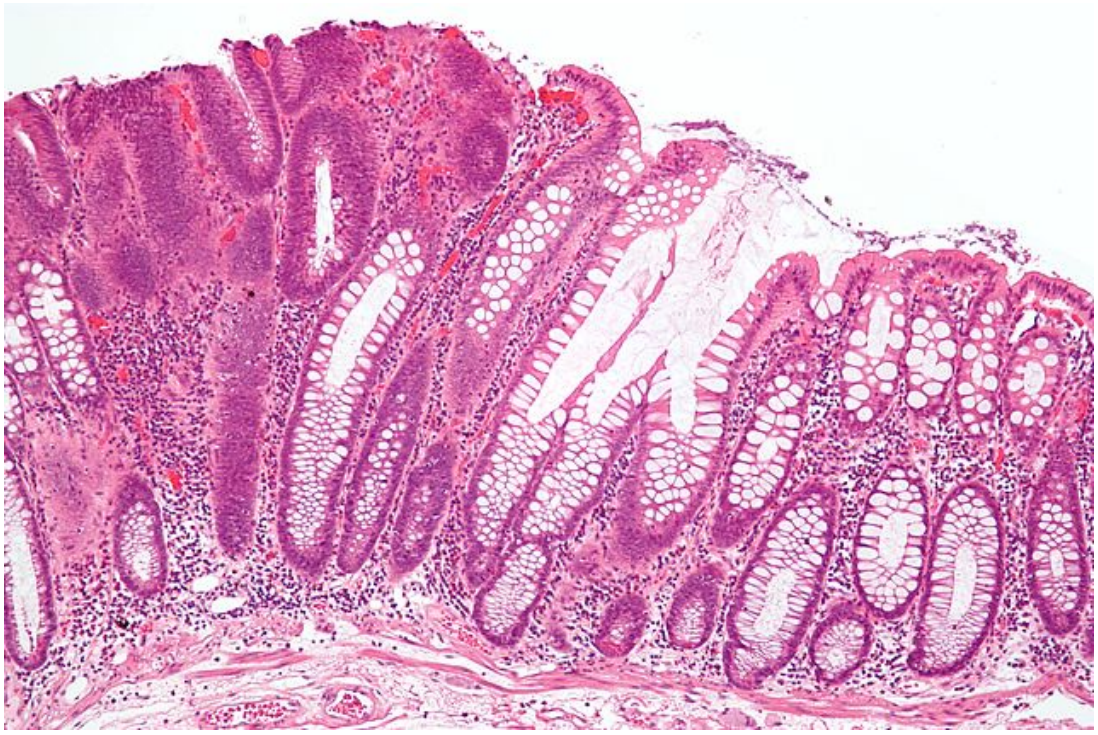
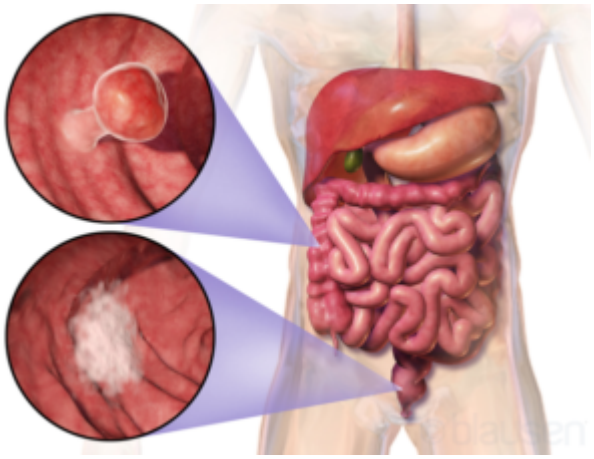
Colorectal cancer is a common malignancy in women that arises from precancerous lesions that undergo a prolonged transition before they evolve into overt carcinoma. The transition from normal mucosa to a precursor lesion to overt cancer occurs over a period of 10–20 years. This understanding of the pathogenesis of colorectal cancer is important as it implies colorectal cancer can be detected and possibly prevented in an early stage when it is curable. One method of preventing colorectal cancer in women is hormone replacement therapy.



Overview of Colorectal Cancer in Women



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Colorectal cancer is believed to arise from a **precancerous lesion known as an adenomatous polyp**. The transition from adenoma to carcinoma is the main pathological mechanism of carcinogenesis in colorectal cancer. Approximately 95% of colorectal carcinomas arise from the precancerous polyps. Thus, the detection and removal of polyps reduce the risk of colorectal cancer.

Adenomatous polyps can be tubular (80%), villous (10%) or tubulovillous (10%) in configuration. The risk of colorectal cancer in women received special attention because of **two important observations:**

First, **the risk of colorectal cancer in premenopausal women was significantly lower compared to men** who are age-matched.

Second, preliminary studies have shown an **increased risk of colorectal cancer in menopausal women** which approaches the risk of colorectal cancer in age-comparable men.

Epidemiology of Colorectal Cancer in Women

Colorectal cancer is the **second most common type of cancer in women,** preceded only by breast cancer. The **mortality rate** of colorectal cancer in women is **quite high**, 14.6 per 100,000. Additionally, colorectal cancer is considered the third leading cause of new cancer and cancer death among women in the United States.

The estimated incidence of colorectal cancer in women is around 41 new cases per 100,000. The last decade has seen an increasing trend in the diagnosis of colorectal cancer, most likely due to the more frequent screening programs and the increased detection of precancerous lesions such as adenomatous polyps.

African American women have a higher risk of colorectal cancer compared to white or American Indian women. Hispanic women have the lowest risk of colorectal cancer with an estimated incidence of 28.4 per 100,000. The mortality rate of colorectal cancer is highest in African American women and lowest in Hispanic women.

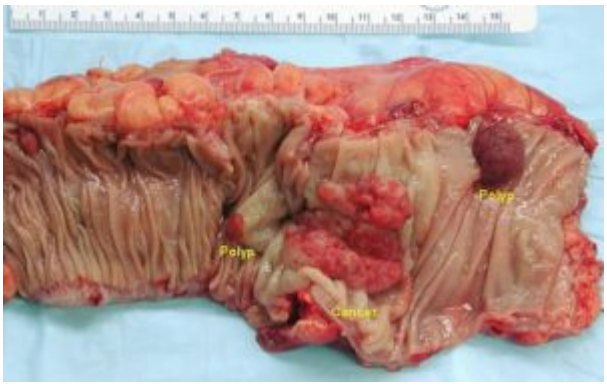
Pathophysiology of Colorectal Cancer in Women

While the estimated incidence of colorectal cancer in women is around 41 per 100,000, the estimated incidence in men is around 51 per 100,000. Similarly, the **mortality rate**

of colorectal cancer in men is significantly higher compared to women of similar age and ethnicity. Because of these gender differences, it has been suggested that **female reproductive hormones might play a protective role** against colorectal cancer.

Malignant polyps in women most commonly **occur in the descending colon and sigmoid colon**. The second most common site for colon cancer in women is the cecum and ascending colon. The remainder of colorectal cancers occurs in the transverse colon or the flexures.

Approximately 70% of colorectal cancers in women arise from a **precancerous adenomatous polyp**. The remaining 30% arise from the serrated pathway which is characterized by the formation of **serrated polyps**. These polyps show mutations in the genetic and epigenetic loci responsible for the encoding of BRAF. **Genetic BRAF mutations** occur spontaneously in these precancerous lesions. Epigenetic abnormalities of the same gene, i.e., CpG island methylation, for example, are also associated with serrated polyps and an increased risk of cancer.



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Regardless of the pathway of colorectal cancer formation, it is still believed that the transition from normal mucosa to a precancerous lesion to **overt cancer takes 10–20 years**. Therefore, chemoprevention is a hot topic of research and we will focus on the potential role of hormone replacement therapy as a chemoprevention agent for colorectal cancer in women.

Early Studies of the Efficacy of Hormone Replacement Therapy for the Prevention of Colorectal Cancer in Postmenopausal Women

The Women's Health Initiative conducted a study in 2002 that aimed to evaluate the benefits and risks of administering combined hormone replacement therapy "estrogen plus progestin" to postmenopausal women.

This study showed clear evidence of a **decreased risk of colorectal cancer in women who received hormone replacement therapy**. Additionally, the risk of invasive colorectal cancer was also significantly decreased in the treatment group compared to the placebo group. Women with invasive colorectal cancer in both groups had a similar location, grade and histologic features of their tumors.

This study also showed that the administration of **estrogen alone, to women who**

have undergone a hysterectomy, did not have any protective effect against colorectal cancer. One problem with this study was a contradictory observation in women with established metastatic colorectal cancer who had to worsing of their disease when they received combined hormone replacement therapy.

From 2002–2010, five more major studies were conducted to further evaluate the role of hormone replacement therapy as a potential chemo-preventative agent against colorectal cancer in postmenopausal women.

These studies were more specifically geared to answer the question of **whether combined hormone replacement therapy is effective in lowering the risk** of colorectal cancer in postmenopausal women or not. **Four out of these five studies showed a clear reduction** in the risk of colorectal cancer in postmenopausal women receiving hormone replacement therapy compared to those who did not.

Mechanism of Chemoprevention for Colorectal Cancer by Hormone Replacement Therapy

Basic scientific research was required to better understand how and why hormone replacement therapy is protective against colorectal cancer.

This research aimed to answer three main questions:

1. Why is the risk of colorectal cancer in premenopausal women lower than postmenopausal women?
2. Why is the risk of colorectal cancer in women with no metastatic colorectal carcinoma clearly lowered with combined hormone replacement therapy but increased in women with established metastatic disease?
3. Why is progestin needed for estrogen to have an effect in lowering the risk of colorectal cancer?

To answer the **first question**, a group of researchers evaluated the differences between colorectal precancerous lesion characteristics in premenopausal versus postmenopausal women. It was noted that the abundance of microsatellite instability was significantly lower in precancerous lesions from premenopausal women compared to postmenopausal women.

Therefore, it was hypothesized that **women with high microsatellite instability are at an increased risk of colorectal cancer** compared to those with low microsatellite instability.
To answer the **second question**, postmenopausal women who received combined hormone replacement therapy and who had tumors with a low microsatellite instability index had a 40% reduction in colorectal cancer risk.

On the other hand, those who had a high microsatellite instability index did not benefit from the treatment. Therefore, it was suggested that **women with established metastatic colorectal cancer are harmed by hormone replacement therapy** possibly due to an impaired response to estrogen when the cells have a high microsatellite instability index.

Finally, to answer the **third question,** cellular studies were performed. It was noted that **progestin acts synergistically with estrogen to increase the efficacy of estrogen as a chemo-preventative agent against colorectal cancer**.

References

Barnes, E. L. and M. D. Long. 2012. “Colorectal cancer in women: hormone replacement therapy and chemoprevention.” Climacteric. 15(3): 250-255. Available at: http://dx.doi.org/10.3109/13697137.2012.659450

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