CLINICAL RESEARCH

Review Article

Hormonal Protection against Colon Cancer in Women Aged 50 and Over More Efficient than Screening Colonoscopy

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ABSTRACT

Screening colonoscopy for early detection of colon cancer needs an alternative. These are available for women after menopause with hormone replacement for primary colon cancer prevention.

This also applies to the development of polyps, which are classified as precursors of colon cancer.

Substituted estrogens provide cancer protection through various mechanisms of action. This includes avoiding chronic inflammation in the intestines, which in the long term increases the risk of cancer. Hormonal substitution causes more lactobacilli in the intestine. These displace other risky bacteria, but also viruses and fungi. This protection applies especially to the lower intestinal sections with a high lactobacilli colonization. This is based on the anatomical proximity to the vaginal microbiome with many lactobacilli.

In the fertile phase, women have plenty of protective lactobacilli due to their endogenous estrogen supply from the ovaries. This no longer applies after menopause. This is reversible through estrogen replacement.

Anti-inflammation to protect against colon cancer corresponds to recommendations from US specialist societies. But Ass and COX 2 inhibitors, as anti-inflammatory drugs, have risks such as bleeding and kidney damage. On the other hand, estrogen substitution transdermally in low doses has no risks in healthy women.

Colon cancer protection through estrogen substitution after menopause also comes about through the preservation of beta-estrogen receptors. Otherwise these will disappear due to estrogen deficiency. These receptors have antiproliferative and thus tumor-protective properties. In addition, there is apoptosis promotion. The intestinal walls are equipped with beta estrogen receptors.

When there is a lack of estrogen, the alpha estrogen receptors dominate. These have proliferation-promoting properties. This, combined with other risk factors, can lead to colon cancer.

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These biologically based aspects are confirmed in studies. A US study from 2013 came to the conclusion: Hormone replacement for 9-14 years halves the risk of colon cancer (RR 0.49). Other studies quickly confirmed this. This is accompanied by reduced overall mortality. The same applies to breast cancer according to a study in Finland. The risk of breast cancer is halved with hormone replacement.

Hormone substitution cannot and will not compensate for a risky lifestyle. This also applies to colon cancer risk factors.

Product information/short synopsis

Screening colonoscopy is hardly efficient and needs an alternative.

Keywords: Colon Cancer - Early Detection, Colon Cancer Prevention, Estrogen for Cancer Protection, Cancer after Menopause.

INTRODUCTION

When it comes to early detection of colon cancer, screening colonoscopy is "reflexively" thought of, but up to what age? A US cross-sectional study [1] with subjects over 75 years old (n= 7067), in a 13-year period (1/2009 -1/2022). The average age was 78 years and 56% were women.

The result in brief: colonoscopies were carried out too often despite life expectancy of less than 10 years (estimated using tool [2]). Normal findings were found in 57%, non-advanced intestinal polyps in 37% and advanced neoplasms in just under 6%. The diagnosis of colorectal cancer was made in 15 people (0.2%). Of these, 10 subjects did not want treatment because their expected life expectancy was less than 10 years.

This was compared to adverse events per 1,000 within the first 10 days after colonoscopy, with a frequency of almost 14%.

The conclusion of the study authors: the indication for early detection should not be based on age, but rather on life expectancy and health status. Because there are fewer findings of clinical relevance, complication rates are very important.

This means that screening colonoscopy can only be carried out after a great deal of effort. Health status via clinical examination and estimated life expectancy with the use of tools must be clarified in advance.

That speaks for an alternative approach. Hormonal prevention of colon cancer and therefore fewer polyps as precancerous lesions [3]. This can be implemented on the basis of evident study results.

According to guidelines, screening colonoscopy should begin at the age of 50 due to the significantly increasing incidence of colon cancer. When it comes to basic hormonal competence, this makes women "prick up their ears". This is the time when ovarian function ceases or menopause begins around 50 years.

The question may arise here: does this also apply to men?

These do not have typical symptoms with the onset of testosterone deficiency. That is why the problem of the increasing risk of colon cancer is hardly recognized or misunderstood. The result is a lack of larger studies on this topic.

It should be remembered that testosterone has 19 carbon atoms and is metabolized to estrogen by splitting off 1 carbon atom. This metabolite with 18 carbon atoms is clinically effective in men. If this estrogen is not further metabolized due to liver cirrhosis, then gynecomastia and other feminization phenomena occur due to remaining high estrogen levels in the serum.

Colon cancer protection from menopause onwards through lactobacilli maintenance

The development of colon cancer, particularly in the rectum and descending colon, is often preceded by chronic inflammation over a long period of time. These are classified as cancer triggers. Local lactobacilli maintenance counteracts this from the menopause onwards as follows:

Lactobacilli, gram-positive rod-shaped bacteria, can break down carbohydrates into lactic acid. They colonize the digestive tract and especially the vaginal walls. The prerequisite for this is that cells there have stored sufficient carbohydrates. Fermentation to lactic acid to generate energy for the lactobacilli creates acidic vaginal secretions with a pH of around 4.5.

This metabolism has the peculiarity that energy is created from carbohydrates without oxygen and this turns into 90% lactic acid (lactate). The latter can be classified as a "protective product" against bacteria, viruses and fungi. This is where the oncological aspect begins: pathological pathogens are

destroyed or kept "in check".

The result is less inflammation in the vaginal area. Evolution has set up the high number of lactobacilli there as a "protective shield". If possible, no ascending inflammation should occur in the uterus, fallopian tubes and therefore also in the free abdominal cavity. This prevention of acute abdomen is not necessary for men because they do not have free access to the abdominal cavity from the outside.

Lactobacilli protection has been known since 1890. The Leipzig gynecologist Albert Döderlein (named "Döderlein bacteria" after him). observed in women who developed puerperal sepsis immediately after birth (usually fatal) that no "rod-shaped" bacteria were present in the vaginal secretion. Even back then, this was easily visible under the microscope.

Today we know that in addition to pH around 4.5, lactobacilli also produce bactericins and H2O2 to defend against inflammation.

Preventative colon cancer oncology rarely thinks about lactobacilli

Lactobacilli can "migrate" from vaginally via the anus into the rectum (anatomically quite a short distance). The further the colon regions are from the anus, the lower the lactobacilli concentrations are.

If this is the case, then women of fertile age without menstrual cycle problems and therefore a good supply of estrogen from the ovaries should develop fewer distal colon cancers than men of the same age.

There is currently a German study (1) with the following results:

Fewer colorectal cancers in women under 50 than in men of the same age

Data from a German study show that women up to 49 years of age are less affected by the increasing incidence of early-onset colorectal cancer than men of the same age, expressed in AAPC (differential annual percentage changes).

It was shown in a table (1) that up to the age of 49, the frequency of tumors in the distal colon increases more in men than in women: 0.95 to 0.55. For T3 stage cancers the gender difference was 1.07 to 0.22 and for rectal cancer it was 68.73 to 35.59. .

This confirms the lactobacilli aspects above: there are clear gender differences when tumors are located proximally.

Given the short anatomical distance from the introitus vaginae to the anus/rectum, it should be borne in mind that lactobacilli make up over 80% of the pathogens in vaginoma and reach numerous distal sections of the intestine.

If the estrogen deficit is counteracted with hormone replacement after menopause, hormonal protection against inflammation is maintained, also with the effect of a 20% to 50% lower risk of colon cancer [2,3].

Why estrogens from the menopause onwards to prevent colon cancer?

Colon cancer screening achieved 2.1% lower mortality from this cancer in German women in 10 years [4]. Over a period of 10 years, this was particularly true for distally located cancers. This is significant given that mortality from this cancer is around 40%. With breast cancer, the risk of death is less than 20% and this is spread over a much longer period of time. This hormonal alternative has many additional benefits, but colonoscopy can have considerable risks, depending on the experience of the person performing it.

In 100 screening colonoscopies, 1 overt cancer is currently discovered. These account for around 10% of all newly discovered colon cancers per year in Germany. With current screening, 5-6 fewer colon cancer deaths per 100,000 per year can be achieved [4].

Start hormonal cancer prevention at the right time

After menopause, the frequency of colon cancer increases significantly when there is an estrogen deficit. This is biologically plausible due to previously protective endogenous estradiol from the ovaries. This can also be achieved with exogenous estradiol from menopause onwards.

If the application is chosen appropriately (transdermal if possible), small doses of estradiol are sufficient to reduce the risk of cancer. This effect occurs essentially through anti-inflammatory effects that counteract the development of cancer.

The concept of the guidelines from the American College of Gastroenterology and US Multi Society Task Force on Colorectal Cancer [5]: ASA and COX-2 inhibitors should

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be given preventively, i.e. anti-inflammatory drugs. This is recommended for several years, e.g. B. when multiple polyps are discovered. This should be weighed up very critically compared to ASA bleeding and kidney damage induced by COX-2 inhibitors.

These problems do not occur with substituted estradiol and the risk of VTE is hardly worth mentioning with transdermal estradiol application. This way the first liver passage is avoided and the coagulation system is not activated.

Another US guideline points out that estrogen deficiency leads to more or less severe chronic infections in the colon and that the result is more frequently diagnosed colon cancer [6].

In addition, there is another efficient hormonal cancer protection, which is also effective in relation to the risk of breast cancer (the Finland study will be discussed later). With substituted estradiol, beta estrogen receptors are preserved from the menopause onwards, which are otherwise reduced under estrogen deficiency. These receptors have antiproliferative and tumor protective properties via the promotion of apoptosis. The colon walls are equipped with beta receptors [7]

Without estrogen substitution, postmenopausal alpha estrogen receptors with cell proliferating properties dominate. This has clinical relevance.

Little is known about studies on hormonal colon cancer prevention

A US study in women after menopause who used HRT for 9-14 years showed a halved risk of colon cancer (RR 0.49) [2]. Another study confirmed this [8]). This also applies to the use of combination pills [9]. This results in reduced overall mortality [10].

The above receptor mechanism of action also applies to breast cancer. According to nationwide Finnish data, HRT halves the risk of dying from breast cancer for at least ten years [11]. Bias problems were not found in discussions at international congresses.

Previous US trial data with inappropriate HRT

HRT for cancer prevention is successful if MPA is not used as a progestin. When it is metabolized, biologically active estrogen intermediates are formed. These have a proliferative effect and thus promote cancer, depending on the individual concentration of these metabolites.

When conjugated estrogens are used in large-scale studies in the USA, it is a "hormone mixture" with several steroids from mare urine, some of which are not found in humans and can promote cancer.

These two hormones have not been prescribed in Germany for decades. No large HRT studies are being carried out with the hormones now used in Germany or the EU (especially estradiol). This would hardly be affordable given 10 years and longer observation periods. The pharmaceutical industry is not interested in this. Because of "horror reports" from the WHI study, HRT use has fallen from 50% to less than 20% since 2002. Only one group of women was unimpressed by hormone bashing. 80% or more of female gynecologists and the partners of gynecologists continue to use HRT (representative survey by K. Bühling/University Hospital Hamburg-Eppendorf, on behalf of the German professional association of gynecologists).

Hormones cannot "compensate" for a risky lifestyle

In women of fertile age who smoke heavily, their ovarian function is reduced. If the latter is eliminated by taking combination pills, this will also reduce the risk of cancer in these women [2]: This must be weighed up against the higher risk of VTE.

Obesity is becoming increasingly common in all age groups of women. This is associated with more inflammation problems. This group is known to be at high risk of colorectal cancer. Even younger, obese women have a higher risk of colonoscopy.

Disturbed intestinal microbiome is currently causally confirmed as a cancer risk

At the beginning of 2023, a study from China (n = 18,400) [12-15] confirmed that altered intestinal microbiomes in the sense of bacterial imbalance can be classified as the cause of cancer.

The conclusion of the study authors: with this causality, the intestinal flora can be classified as an efficient factor for cancer prevention in the future.

Lactobacilli promote physiological intestinal flora, but need sufficient lactate in the intestinal cells for their own nutrition. This works better with HRT and explains the cancer protection.

SUMMARY

The halving risk of colorectal cancer in women after menopause with HRT for 10 years or longer is not achieved with screening colonoscopy. The hormonal mechanism of action includes sufficient maintenance of lactobacilli, which act against pathogenic germs and thus reduce the risk of chronic intestinal inflammation as a cancer risk. In addition, there is hormonal maintenance of beta-estrogen receptors. These have antiproliferative and apoptosis-promoting properties.

HRT transdermal has hardly any risks in healthy women. This also applies to thromboembolic events, because the liver first pass effect is avoided and therefore no activation of the coagulation system.

In addition to the oncological benefit, there are many additional benefits of HRT, such as a halved risk of osteoporosis.

Studies have proven that hormonal primary prevention of colon cancer is evident. Implementation requires biological-rational advice on hormone replacement. This co-indication is more efficient than screening colonoscopy because there are hardly any risks and many additional benefits.

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