Int J Clin Exp Med 2017;10(1):174-178
www.ijcem.com /ISSN:1940-5901/IJCEM0038229

*Review Article*

# Elevated levels of estrogens as a risk for colorectal carcinoma in patients with liver cirrhosis

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Received August 19, 2016; Accepted November 4, 2016; Epub January 15, 2017; Published January 30, 2017

**Abstract:** Colorectal carcinoma is one of the most fatal cancers, but to date, the underlying mechanisms are not entirely understood. Recent epidemiological studies and clinical trials have begun to provide insights into the links between estrogens and colorectal carcinoma. The results obtained from established animal models indicated that abnormal high levels of estrogens promote the tumorigenesis of colitis-associated carcinoma. Estrogens regulate biological events mainly through two distinct receptors (Erα and Erβ). After combined with the receptor, estrogens translocate to nucleus and act as transcription factors to modulate several signaling pathways. Since organ destruction and parenchymal loss result in hormone inactivation disorder, patients with liver cirrhosis always have high levels of endogenous estrogens, which are the predominant causes of liver palm, spider angioma, gynecomastia, and testis atrophy. Meanwhile, several population-based studies confirmed that patients with liver cirrhosis face higher risks of colorectal carcinoma compared to general population. Although the influencing factors may be complicated, the high level of endogenous estrogens has been proposed as an important pathogen. Several studies, with the particular focus on menopause women, provided some contradictory results that estrogens may protect patients from cancers. However, the low levels of endogenous estrogens of menopause women, administration route, and the composition of drugs could lead to different conclusions. The exact effect of estrogens on the pathogenesis of colorectal carcinoma of a patient with liver cirrhosis is only just starting to be dissected.

**Keywords:** Estrogen, liver cirrhosis, colorectal carcinoma, menopause, polyp

## Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide, where it represents the leading cause of cancer-related death [1]. Although epidemiologic studies have identified many risk factors for CRC [2], the pathogenesis of CRC is still debated.

Accumulating evidence suggests that estrogens may play an important role in the malignant transformation of CRC. Increased levels of endogenous estrogens may enhance the incidence of CRC [3-5]. Results obtained from established animal model further support this view [6]. Estrogens can promote the colonitis-related CRC development by impairing the mucosal response to inflammatory damage.

In addition to hepatocellular carcinoma (HCC), patients with liver cirrhosis (LC) face a dramatically increased risk of developing CRC [7-11]. Meanwhile, it is well-known that high levels of endogenous serum estrogens can be detected in cirrhotic patients because of inactivation disorder. These patients exhibit gynecomastia and testis atrophy [12]. Moreover, spider nevi and palmar erythema are also two prominent features of estrogen effects. However, the exact relationship between CRC and estrogens in patients with LC remains largely unknown.

## The risk of CRC in patients with LC

It is well recognized that HCC is more common in males than in females [1]. Meanwhile, more than 80% of patients who develop HCC have cir-

rhosis [13]. Furthermore, CRC also seems more frequently in patients with LC compared to the general population [7-11]. The risk of CRC in patients with LC was four times higher than that of the general population [8]. Furthermore, Naveau et al. [9] demonstrated that liver cirrhosis is an independent risk factor for colorectal adenomatous polyps, a pre-cancerous lesion of CRC. The prevalence of colorectal adenomatous polyps was greater in patients with LC than in those patients without.

Unfortunately, how LC, as an independent risk factor, affects the pathogenesis of CRC and colorectal adenomatous polyps have not been well elucidated. A well-known fact is that most patients with LC exhibit increased endogenous estrogen levels. Male patients with cirrhosis have hyperestrogenism, which may lead to gynecomastia and testicular atrophy [12]. LC also has a close relationship with menstrual irregularity, increased the frequency of spontaneous abortion, and early menopause in female patients [14]. Hormonal imbalance provides a possible explanation for why cirrhotic patients have an increased risk of CRC.

## The role of estrogens in CRC

Estrogens regulate several critical biological events in both male and female. However, hyperestrogenism may cause many diseases. Previous studies indicated that the risk of CRC is proportional to the level of endogenous estrogens [3-5]. A study found that a high endogenous level of estradiol (E2) was associated with a 1.5-fold increased risk of CRC, after adjustment for other colorectal carcinoma risk factors [4].

Recently, a study reported that risks of colorectal carcinoma increase in direct proportion to elevated levels of estrogen [3]. Another study focusing on the relationship between the reproductive factors and risks of CRC further supported the contribution of sex hormones to the colorectal tumorigenesis. It suggested that postmenopausal women have a high risk of CRC after aberrant exposure to endogenous estrogen [5]. Consistent with previous evidence, a group, making use of established animal models, suggested that estrogens can promote the development of polyps and the tumorigenesis of colitis-associated cancer [6]. Another experiment of breast cancer indicated that the direct effect of estrogen and progesterone on malignant cells can drive the dissemination of cancer [15].

Although additional validations are still required, several molecular mechanisms have been proposed to explain why estrogens are associated with increased risks of CRC. Estrogen regulates the tumorigenesis of CRC by two distinct estrogen receptors (Erα and Erβ) [6]. When E2 binds the receptor, they form homo- or heterodimers and translocate from the cytoplasm to the nucleus where they act as transcription factors. The estrogen receptors, Erα and Erβ, are products of different genes localizing on different chromosomes, and with distinct expression patterns. They can mediate different effects of estrogens and have pleiotropic effects on cancer development [16]. Erα can promote tumorigenesis by aggravating inflammation, whereas, Erβ has inflammation-independent effects [6]. In vitro studies, estrogen can serve as a regulator of mitosis of the colorectal epithelium [17-26]. Estradiol enhances the expression of mitogen-activated protein kinase cascade, a key pathway in the stimulation of DNA and protein synthesis that can induce cell growth and proliferation [19, 22]. Also, reduced enzyme-mediated inactivation of estradiol has been observed in colorectal carcinoma tissues as compared to normal tissues, suggesting that malignant colorectal carcinoma cells may be exposed to high levels of endogenous estradiol [21, 26].

LC is characterized by architectural changes, which contribute to the loss of abnormal liver functions including protein synthesis and hormone inactivation. In addition to HCC, patients with LC face a higher risk of CRC than the general population. Based on the evidence mentioned above, we hypothesize that elevated level of endogenous estrogens may serve as an important risk factor for CRC (**Figure 1**).

## Potential mechanism

Chronic hepatitis is one of the major public health problems worldwide. Especially in China, there are about 20 million hepatitis B virus (HBV)-infected patients [27]. About 10-20% of these cases will progress to cirrhosis [28]. The levels of endogenous estrogens elevate significantly because of aberrant inactivation.

Since the underlying mechanisms are largely unclear, no special attention has been paid to

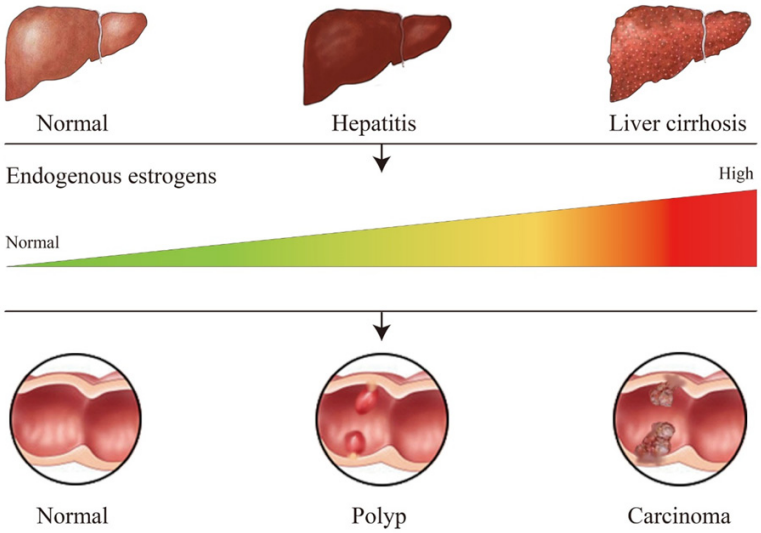


**Figure 1.** Liver cirrhosis promotes the tumorigenesis of CRC. Liver with chronic injury progresses to cirrhosis through the hepatitis-fibrosis-cirrhosis sequence. The levels of endogenous estrogens increase significantly at the end stage of the lesion. The cirrhotic patients showed increased risk for CRC. The aberrant levels of endogenous estrogens may play an important role in the malignant transformation of CRC.

the potential pathogenicity of abnormal estrogen. Fortunately, recent studies start to concern about risks for malignant neoplasms in cirrhotic patients. The published literature indicated that these patients face a higher risk of CRC as compared to general population. Although there is no substantial evidence, epidemiological studies confirmed the close relationship between the high levels of estrogens and the pathogenesis of CRC.

Nevertheless, some elaborate studies also provided an opposite view that female sex hormones may protect patients from CRC [29]. In those great random placebo-controlled trials, the combination of estrogen and medroxyprogesterone acetate (MPA) reduced the incidence rate of colon carcinoma by 37% as compared to placebo at five years follow-up [30, 31]. Treatment with estrogens alone did not significantly affect the risk of colon carcinoma development [32, 33].

We proposed here two different explanations for why the oral therapy showed a protective effect against CRC. First, the prescription was composed of estrogen and progesterone. Estrone, rather than estradiol, was the main component of estrogens [26]. It can decrease the proliferative response in colonic epithelial cells, whereas estradiol has the opposite role [19, 26]. Meanwhile, estrone can protect ovariectomized mice from carcinogen-induced colon carcinoma [34]. However, the estradiol-treated mice showed a dramatic 10-fold increased the risk for polyp compared to placebo-treated mice [6]. Second, these elaborate studies mainly focused on postmenopausal women, in which female hormone may fall to a very low level. Meanwhile, the estrogen-to-proestrogen and the estrogen-to-testosterone ratios decrease significantly compared to women of childbearing age. These changes may contribute to the disturbance of internal microenvironment and the pathogenesis of many diseases. Oral administration of female hormone may help to control homeostasis and decrease the risk of CRC.

Despite the recent advances in our understanding of the important biological role of estrogen, the exact effect of estrogen on the pathogenesis of CRC in patients with liver cirrhosis is only just starting to be dissected. From a clinical perspective, an understanding of the relationships among estrogen, cirrhosis, and the carcinogenesis of CRC is essential in guiding cirrhotic patients' management and for offering new therapeutic strategies.

## Acknowledgements

This study was supported by grants from the National Natural Science Foundation of China (No. 81300347), the Natural Science Foundation of Jiangxi Province, China (No. 20132BAB205037, 20151BAB215008, 20151BBG70200), and Foundation of Jiangxi Educational Committee (No. GJJ14192), Foundation of Health and Family Planning Commission of Jiangxi Province (No. 20155592, 20155103, 20161086, 20161093).

## Disclosure of conflict of interest

None.

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