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Serum Level of Sex Hormones in Women With Colon Cancer in Northern Iran

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ABSTRACT

Background: The incidence of colorectal cancer (CRC) is lower among women than among men in all age groups, and higher estradiol exposure in women is thought to have a protective role. This study aimed to investigate the relationship between sex hormones and the risk of CRC in women.

Materials and Methods: This study explored the relationship between the risk of CRC and estradiol, testosterone, progesterone, and sex hormone-binding globulin (SHBG) concentrations in non-current users of exogenous hormones. Multivariate conditional logistic regression models were applied to calculate odds ratios and 95% confidence intervals to estimate the association between circulating sex hormone levels and CRC.

Results: Median levels of estradiol and SHBG were found to be significantly high in women with CRC but circulating levels of progesterone in patients were significantly lower than those in controls. No correlation was observed between estradiol, testosterone, progesterone, and SHBG and CRC after adjusting for age and menopausal status.

Conclusion: Based on current findings, relationships between CRC risk and the levels of progesterone, testosterone, and SHBG seem unlikely. Future studies may be required to elucidate the association between estradiol levels and CRC risk in women using greater sample sizes and well-defined boundaries.

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Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women. Incidence rates are approximately 3-4-fold higher in men than in women. According to GLOBOCAN 2020 data, more than 1.9 million new CRC cases and 935,000 deaths were estimated to occur in 2020 [1]. Overall, CRC ranked third in incidence in 2020, but the second leading cause of cancer-related deaths [1]. Different factors are involved in the occurrence and development of CRC, including familial history, ethnicity, age, gender, smoking, alcohol consumption, weight, physical activity, and mutations in *APC*, *MLH1*, *MSH2*, *MSH6*, *KRAS*, *BRAF*, and *SMAD4* genes [2].

Men are more likely to develop CRC, and sex differences are reported concerning the type of disease, location, mortality, and response to adjuvant chemotherapy [3-6]. These findings support the role of sex hormones in the etiology of CRC. Differences in lifestyle and socioeconomic factors can moderately explain the sex differences in CRC, but hormonal factors also play an effective role in the occurrence of this difference [3]. Numerous studies have identified that sex hormones increase tumor development in different types of cancers, including breast, ovary, endometrium, glioblastoma, prostate, and thyroid [7-9]. While hormone replacement therapy (HRT) is related to an increased risk of breast, ovary, and endometrium cancers, no significant association is found between HRT and colorectal, stomach, and lung cancers [10]. This suggests the probable role of estrogen in reducing the risk of colorectal, stomach, and lung cancers.

Steroid hormones, estrogen, and androgen play major roles in the physiology and development of hormone-dependent tissues. There is evidence to suggest that high estrogen levels throughout pregnancy and/or exogenous hormone therapy, such as oral contraceptives and postmenopausal hormone therapy, are linked to a lower risk of CRC in women [6]. High estrogen levels in women are believed to have a protective role in the development of CRC, and the incidence rate of this cancer is low in women [11]. Estrogen acts via binding to its corresponding estrogen receptors, α (ERα) and β (ERβ), and also regulates transcription activity following activation and nuclear translocation. ERβ participates in the regulation of DNA repair, increases apoptosis, decreases cell proliferation, and reduces tumor formation and development [12]. It is a dominant receptor in both normal colonic mucosa and CRC epithelial cells [13, 14]. Lower levels of ERβ expression are reported in colon tumor tissue compared to normal tissue in the pre-cancerous phase of colon carcinogenesis and sporadic CRC and familial adenomatous polyposis syndrome [15, 16].

The role of testosterone as a contributing factor in the formation of colon cancer tumors remains controversial. Some studies have demonstrated that testosterone develops colonic adenomas and carcinomas, and may be a tumor-promoting factor at an early stage of CRC. Therefore, reduction of testosterone can protect against adenoma development [17]. An opposite association was detected between the ratio of estradiol to testosterone and CRC in postmenopausal women [18], and circulating testosterone levels were found to be positively related to CRC risk in Japanese postmenopausal women [19]. Epidemiological data from the UK Biobank indicated no association between testosterone levels and risk of CRC in women [20]; however, a cohort study showed a positive association between circulating testosterone levels and CRC risk in women [19].

Inconsistent results have also been found in terms of sex hormone-binding globulin (SHBG) and CRC risk. The UK Biobank described no differences in the associations between SHBG and CRC risk in analysis stratified by menopausal status [20]. However, an observational analysis reported that higher SHBG concentrations are associated with greater CRC risk in women [21]. The role of progesterone in the development of CRC is not fully understood. Progesterone receptor (PR) A or B interaction may activate epidermal growth factor receptor and Wnt-1 pathways in colonocytes and apply proliferative effects that disagree with the effect of estrogen [22]. In addition, experimental modeling of colon cancer estradiol and progesterone are believed to be necessary to reduce colon cancer cell proliferation and induce apoptosis through estrogen receptor β activation [23]. Based on animal experiments, progesterone signaling was found not to be involved in the initiation and progression of colon carcinogenesis [24]. The inhibitory effects of progesterone on CRC cell proliferation are exerted via upregulation of DNA damage-inducible protein α (GADD45α) and activation of the JNK pathway that triggers G1-phase arrest of cell cycle progression and apoptosis induction [25].

To provide more conclusive evidence for the association between endogenous concentrations of circulating sex hormones and colon cancer, we conducted a case-control study in women with CRC. We measured their circulating concentrations of estradiol, testosterone, progesterone, and SHBG.

Materials and Methods

This was a case-control study conducted at the Comprehensive Cancer Center, Sari City, Iran. The required sample size was calculated using STATA software, version 17, with parameters set at α=0.05, 1-β=0.95, Mean±SD values (0.91±1.2 and 0.4±0.21), based on data from the Abbasi Natajomrani study [26]. The initial calculation yielded 75 participants per group. To account for a potential 10% dropout rate, the study enrolled 82 individuals in the case group and 84 in the control group.

The case group consisted of patients with a confirmed CRC diagnosis, based on endoscopic findings and pathological examination, and none of the patients had received any treatment prior to enrollment. The control group included individuals who underwent colonoscopy for anemia evaluation or routine screening purposes and had normal colonoscopy findings in the oncology clinic. In addition, they had no family history of CRC among first-degree relatives and were not using any hormonal medications. The sampling methods in both groups were convenience-based.

All procedures involving human participants were conducted in accordance with the ethical standards of the institutional Ethical Committee and conformed to the ethical norms and standards in the 1964 Declaration of Helsinki. Ethical approval was received from Mazandaran University of Medical Sciences, and all participants signed consent forms before interviewing and sample collection. Various clinicopathological parameters, such as gender, age, histological grade, lymphatic and vascular invasion, depth of invasion, and tumor type, were recorded.

Some inclusion and exclusion criteria were established in this study. The inclusion criteria for CRC patients were not using exogenous hormones as medication and no chemotherapy regimen. Women with histological findings on colonic polyps and those with CRC in first-degree relatives were excluded from the study.

Blood sample

Blood samples were collected from the patients using tubes containing a clot activator. All serum samples were prepared by centrifuging the clotted whole blood (5 mL) at 800 g for 20 min. The serum was then transferred to sterile cryotubes and stored at -80 ˚C.

Enzyme-linked immunosorbent assay

Circulating sex hormones (estradiol, progesterone, testosterone, and SHBG) were measured by immunoenzymatic assay using a commercially available (direct enzyme-linked immunesorbent assay) Enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions. A competitive immunoenzymatic colorimetric method was used for quantitative determination of 17β-Estradiol, testosterone, and progesterone concentrations in sera (DiaMetra, Milano, Italy). A direct ELISA was conducted to measure SHBG expression levels (DiaMetra, Milano, Italy). The absorbance was measured spectrophotometrically at 450 nm wavelength in a microplate reader Synergy™ HTX Multi-Mode Microplate Reader (BioTek; USA) equipped with specialized Gen5 software, version 2.09, (BioTek; USA). A standard curve was constructed by plotting absorbance values versus estradiol, progesterone, testosterone, and SHBG concentrations of the standards.

Statistical analysis

Differences between the two qualitative variables were tested using chi-square or Fisher's exact test. The Mann-Whitney U test and t-test were used to compare the mean age of women and hormone levels between the two groups. Odds ratios (OR), 95% confidence intervals, and significance (P) values were reported. P<0.05 were considered statistically significant.

Results

The mean age in the case group (57.84±11.27 years) was significantly higher than the control group (41.38±11.66 years) (P<0.0001). The study population was categorized into menopausal and non-menopausal people. There was a significant difference between the two groups in terms of menopausal status (P<0.0001).

Table 1 presents quartiles 1, 2, and 3 of estradiol, progesterone, testosterone, and SHBG concentrations in patients and controls. The cases had significantly higher estradiol levels than controls (median 28.345 pg/mL vs 17.550 pg/mL; P=0.0001). Serum progesterone concentrations were significantly lower in women with CRC than those in healthy controls (median 0.310 ng/mL vs 0.885 ng/mL; P=0.0001). Similar to estradiol, the median levels of SHBG were found to be significantly higher in women with CRC (75.665 nmol/L) compared with healthy women (31.09 nmol/L) (P<0.0001). No sig-

Table 1. Estradiol, progesterone, testosterone, and SHBG levels in study groups

Groups	Percentile	Estradiol (pg/mL)	Progesterone (ng/mL)	Testosterone (ng/mL)	SHBG (nmol/L)
Case	25th	18.705	0.2	0.2	34.145
	50th	28.345	0.31	0.2	75.665
	75th	125.675	0.938	0.2	130.842
Control	25th	9.76	0.200	0.2	20.292
	50th	17.55	0.885	0.2	31.09
	75th	43.332	5.052	0.2	47.65
P		<0.0001	<0.0001	>0.99	<0.0001

SHBG: Sex hormone-binding globulin.

Table 2. Odds ratios for associations between circulating estradiol, progesterone, and SHBG concentrations in CRC patients and healthy controls

Variables		No. (%)		P	Unadjusted OR (95% CI)	Age-adjusted OR (95% CI)
		Case	Controls			
Estradiol	≥ Normal value	52(63.4)	36(45)	0.027	0.472 (0.252, 0.886)	0.793 (0.365, 1.725)
	< Normal value	30(36.6)	44(55)			
Progesterone	≥ Normal value	70(87.5)	76(92.7)	0.303	1.81 (0.625, 5.238)	0.671 (0.198, 2.266)
	< Normal value	10(12.5)	6(7.3)			
SHBG	≥ Normal value	76(92.7)	72(87.8)	0.431	0.568 (0.196, 1.644)	0.407 (0.114, 1.467)
	< Normal value	6(7.3)	10(12.2)			

Abbreviations: OR: Odds ratio; SHBG: Sex hormone-binding globulin; CRC: Colorectal cancer.

nificant differences were observed between testosterone levels and CRC (P>0.99).

Considering different levels of sex hormones in menopausal and non-menopausal women, the participants were classified into two groups: Higher hormone levels than normal values and lower levels (hormones that showed a significant difference between the two groups). Based on the kit's instructions, estradiol levels <60 pg/mL were considered the reference range in postmenopausal women, and levels 30- 350 pg/mL were considered borderline in non-menopausal women. A higher number of women with low estradiol levels were observed in controls compared with cases (P=0.027).

Low endogenous estradiol levels in women might exert a protective effect against CRC; OR value for estradiol level was 0.472 (95% CI, 0.886%, 0.252%) (Table 2); however, this association disappeared after adjusting for age as a confounding factor. No significant relationship was found after age-adjustment as a confounding factor in logistic regression analysis. Post-menopausal women had a progesterone reference range of 0.1- 25 ng/mL, and a progesterone level <1 was considered borderline in menopause women. As shown in Table 2, the number of people with progesterone levels less than the reference range was high in the case group, but this relationship was not significant even after age adjustment as a confounding factor. No statistically significant difference in SHBG levels was evident between the case group and control groups when stratified by hormone levels (Table 2).

Discussion

In the current study, the median values for estradiol and SHBG were higher, and progesterone levels were significantly lower in patients with CRC; however, logistic regression analysis showed no significant correlation between CRC and serum levels of estradiol, testosterone, progesterone, and SHBG after age-adjustment and menopausal status stratification. Our findings are con-

sistent with other studies that assessed the relationships between endogenous sex hormone levels and CRC. The New York University Women's Health Study included 148 women who developed CRC and 293 matched controls, in which a hazard ratio of 1.8 was reported for the highest vs lowest quartile of estrone. The study found a positive correlation between circulating estrone levels and the risk of CRC. A non-significant inverse association between SHBG levels and CRC was also observed [27]. Lin et al. investigated total testosterone, SHBG, and the ratio of estradiol to testosterone in 293 cases with CRC and showed no association between circulating sex hormones and CRC in women; only the ratio of estradiol to testosterone was in reverse association with CRC after adjustments for all factors. They reported an inverse association between the ratio of estradiol to testosterone and CRC in postmenopausal women [6].

A large-scale observational analysis showed little association between the risk of CRC and circulating levels of total testosterone and SHBG. In fact, a high risk of CRC was observed in women with high testosterone levels; however, pleiotropic effects led to conflicting outcomes. SHBG levels were observed to be highly associated with CRC risk in multivariable Cox proportional hazards models, but this was not confirmed by Mendelian randomization analyses [21]. In a nested case-control study, no significant positive association was observed between estrone concentrations and CRC in European postmenopausal women with CRC (odds ratio per log2 1-unit increment = 1.17; odds ratio quartile 4-quartile 1 = 1.33. No significant associations were observed between testosterone, progesterone, and SHBG concentrations and CRC risk. Similarly, no clear associations were identified between circulating sex hormones and the risk of CRC [28]. Previously, in a follow-up cohort study, positive associations were detected between circulating testosterone levels and risk of CRC (OR=2.10). No relationship was observed between CRC and circulating estradiol, SHBG, and progesterone levels [19]. Other published data did not report any significant associations between endogenous sex hormones and CRC risk [29, 30]. In contrast, the results from the Women's Health Initiative Clinical Trial of 401 postmenopausal women with CRC showed that estrone, free estradiol, and total estradiol were inversely related to CRC. Higher concentrations of SHBG were associated with an increased CRC risk. These findings provided further evidence indicating that endogenous levels of estrogens decrease the risk of CRC and could play a protective role against CRC in postmenopausal women [31]. This result is inconsistent with a prospective cohort of postmenopausal women in which a positive association was reported between endogenous estradiol levels and risk of CRC [32]. It was suggested that CRC may be developed through at least two independent biological pathways [32]. Possible clarifications for these inconsistencies include different laboratory methods and various confounder adjustment strategies. Most studies performed adjustments for several variables, including obesity, smoking, alcohol intake, and physical activity [33-35] as confounding factors that distort the association between sex hormones and CRC. The majority of women in WHI-OS (60%) [32] and 40% of women in the studies carried out by Clendenen et al. and Lin et al. [6, 27] were overweight and obese. The current study relied solely on mean body mass index (BMI) values of 27.1±5.82 kg/m^2. Different results may also arise from various laboratory methods (RIA, LC-MS/MS, and chemiluminescence) and high laboratory error rates that lead to biased estimates of the association.

The analysis of estrogen and CRC risk depends on the form of estrogen in the body; during women's reproductive years, estradiol is at its highest levels, and estrone is the only type of estrogen in postmenopausal women. In a study by Murphy et al., total estradiol concentrations did not significantly differ between cases and controls. However, estrone levels and free estradiol, calculated based on total estradiol and SHBG concentrations, were statistically different between the two groups [31]. Interestingly, Clendenen et al. observed a positive relationship between circulating estrone and CRC risk when both age-matched non-menopausal and postmenopausal women were included and menopausal status was ignored [27]. Partial positive associations between estrone and CRC risk were statistically detected in overweight and obese (BMI ≥25 kg/m^2) women compared with those with lower BMI in the subgroup analysis of stratified BMI [27]. BMI is a crucial consideration in developing CRC through biological non-hormonal pathways, including insulin and IGF-I. BMI regulates adipose tissue to catabolize the androgens to estrogen in postmenopausal women and provides a causative pathway of CRC [27]. A prospective study of postmenopausal women reported a lower risk of CRC with a higher estrone level >60 pg/mL, which is significantly higher than the reference range of 32 pg/mL [27]. Short-term use of hormone therapy (estrogen + progestin) was reported to be associated with a decreased risk of CRC in postmenopausal women, but later a positive association was seen between endogenous estradiol and CRC in a case-cohort study [32]; These conflicting outcomes can be explained in part by some evidence: Exogenous estrogen exposes the liver to a large amount of estrogen and downregulates CRC- related hepatic proteins, oral

contraceptives mainly consist of estrone rather than estradiol which has antiproliferative on colon cancer cells [32], and possible protective effect of progesterone on CRC risk [32]. Our findings indicated no association between endogenous progesterone and CRC risk, and were consistent with other reports [36]. However, we cannot rule out the role of exogenous progestin in CRC risk through PR or other steroid receptors [37]. Murphy et al. adjusted confounding factors, including exogenous hormone, which is an exclusion criterion, but isoflavones and phytoestrogens intake were not calculated [31]. In postmenopausal women, a meta-analysis suggested that soy or isoflavone consumption increases serum estradiol levels [36]; however, no association was detected between soy isoflavones and CRC risk. In postmenopausal women, there was a non-significant association between the risk of CRC and circulating estradiol, SHBG, and progesterone concentrations. Subgroup analyses for dietary isoflavones intake showed that increased levels of circulating SHBG, and not estradiol, were associated with an increased risk of CRC in women with low intake of total isoflavones (OR=2.05) [19]. Unlike our findings, Murphy et al. observed a positive association between SHBG concentrations and CRC risk that may be independent of estrone and estrogen levels and suggested a new pathway that could be related to the development of CRC [31].

Conclusion

In conclusion, our study does not indicate any evidence of an overall association between CRC risk and serum levels of progesterone, testosterone, and SHBG. Further investigations may be required to verify the association between estrogen levels and CRC risk in women using a greater sample size in which estrogen types (estrone and estradiol) with defined boundaries are considered.

Ethical Considerations

Compliance with ethical guidelines

The study protocol was approved by the Research Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran (Code: IR.MAZUMS.IMAMHOSPITAL.REC.1399.081).

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Authors contribution's

Data collection: Ramin Shekarriz and Niloofar Sadeghi; Methodology, data curation, and data analysis: Reza Alizadeh-Navaei; Investigation: Akbar Hedayatizadeh-Omran and Omolbanin Amjadi; Writing: Omolbanin Amjadi; Supervision: Adele Bahar and Ramin Shekarriz; Supervision: Adele Bahar and Ramin Shekarriz; Project administration, review, and editing: Akbar Hedayatizadeh-Omran; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interests.

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