Sex Hormone and Colorectal Cancer: The Knowns and Unknowns

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ABSTRACT

Sex hormones have been suggested as a contributor to gender disparity in incidence and mortality of colorectal cancer, but previous observational studies on endogenous sex hormones and colorectal cancer risk have led to contradictory results. Leveraging the large-scale UK biobank resource, Dimou and colleagues performed both observational and Mendelian randomization (MR) analyses to investigate the association of serum testosterone and sex hormone binding globulin concentrations with the risk of colorectal cancer. Although the findings provide little evidence for independent roles of the hormones in colorectal cancer, further interrogation of possible mediating effects of sex hormones on the causal pathways of colorectal cancer could deepen our understanding of colorectal cancer etiology and improve tailored prevention. While MR analysis is useful for inferring causality in observational studies, the current null results should be interpreted with caution because of insufficient statistical power and predefined assumptions of linearity. Moreover, given the widespread use of testosterone supplementation in older men to restore age-related decline of endogenous concentrations, large and long-term randomized controlled trials are required to clarify the effect of testosterone on colorectal cancer risk, which would provide critical evidence for health decision making.

See related article by Dimou et al., p. 1336

Men tend to have higher incidence and mortality rates in colorectal cancer than women (1). The underlying mechanisms of this gender disparity are still unclear, but sex hormones have long been postulated as an explanation. Men treated with androgen deprivation therapy were at a higher risk of colorectal cancer (2), and women receiving hormone replacement therapy (HRT) had lower risk of colorectal cancer (3, 4) and adenoma (5). Moreover, higher levels of endogenous testosterone were associated with a lower risk of colorectal cancer in men (6), but an increased risk in postmenopausal women (7), suggesting sex-specific effects of testosterone on colorectal cancer development. Our recent study also found a suggestive positive association between free testosterone and risk of advanced adenoma in postmenopausal women (8). However, some other studies (9, 10), together with the complementary observational and Mendelian randomization (MR) analyses by Dimou and colleagues in this issue of the Journal, indicated that endogenous levels of testosterone were not associated with colorectal cancer risk.

The major strengths of the study by Dimou and colleagues included the large sample size, adjustment for a wide range of covariates, and detailed sensitivity analyses. Because testosterone may exert adverse metabolic effects in women by influencing fat mass expansion and distribution, insulin signaling, and lipid metabolism (11), it is not unexpected that the results of observational analysis were null after adjusting for various covariates including body mass index and markers of inflammation and glycemic pathways. It seems reasonable when the purpose of Dimou and colleagues was to identify independent effects of sex hormones beyond known risk factors. However, there remains the possibility that testosterone plays a role in colorectal carcinogenesis as a mediator in the relationship of obesity, physical activity, or other factors with colorectal cancer risk. This is in accordance with the findings of Dimou and colleagues in MR analysis showing a positive association between testosterone and colorectal cancer in women, although pleiotropy may exist.

Dimou and colleagues also found higher sex hormone binding globulin (SHBG) concentrations in relation to an increased risk of colorectal cancer in women in observational analysis, consistent with a prior analysis in Women's Health Initiative clinical trial study (12). In the other three studies reporting no association in postmenopausal women, the numbers of patients with colorectal cancer were relatively small ($n < 200$) and the statistical power might be limited (6, 7, 13). It is noteworthy that a recently published study in UK Biobank (14) and a case–control study nested in four U.S. prospective cohorts (6) both reported an inverse association between SHBG levels and colorectal cancer risk in men. Unlike the analysis by Dimou and colleagues, these two studies did not adjust for total testosterone, CRP, IGF-1, or HbA1c. SHBG can regulate sex hormone bioactivity through binding to circulating testosterone and estradiol (15). Moreover, a low SHBG level is a marker of insulin resistance (16), and experimental evidence suggests that SHBG may suppresses inflammation and lipid accumulation in macrophages and adipocytes (17). Therefore, although Dimou and colleagues did not observe an independent association between SHBG and colorectal cancer in men, the possibility of SHBG as a protective mediator in colorectal cancer pathogenesis cannot be excluded. In a recent observational study, higher SHBG concentration were associated with lower risk of conventional adenomas, particularly advanced adenomas (8).

As for MR analysis, although it is useful to address reverse causation and residual confounding within observational studies, the variance explained by the selected genetic variants for total testosterone was only 8.0% in women and 9.1% in men; for free testosterone was 3.9% in women and 4.2% in men; and for SHBG was 3.1% in both women and

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men (data from the response of Dimou and colleagues during revision). Also, the genetic-predicted levels may not extend to low or high enough concentrations for identifying an association. One of the major dilemmas inherent in MR studies is low statistical power (18). Therefore, future MR studies powered by large-scale genome-wide association studies of sex hormones are important to provide causal evidence. Furthermore, the relationship between sex hormones and colorectal cancer might not be linear, and nonlinear MR analysis is useful to characterize the shape of the association.

Regarding endogenous estrogens, several observational studies have evaluated the association with colorectal cancer risk but yielded conflicting results. Two studies reported a positive association between estrogens and colorectal cancer in postmenopausal women (13, 19), while others found null (6, 7) or inverse associations (12). Reasons for the inconsistency remain unclear, but may be partly attributed to the different assay methods. It has been noted that radioimmunoassay is less specific than LC/MS-MS and therefore the estrogen levels measured by radioimmunoassay are likely to be overestimated (12, 13), while electrochemiluminescence is not sufficiently sensitive to detect low concentrations (7). Because the majority of postmenopausal women in UK biobank had estradiol levels below the detection limit of chemiluminescent immunoassay, Dimou and colleagues were unable to estimate the association between endogenous estradiol and colorectal cancer risk. Future large-scale observational and MR studies, together with laboratory evidence, are required to elucidate the roles of estrogens in colorectal neoplasia.

It is noteworthy that in the past decade, millions of older men have turned to testosterone replacement therapy for sexual health and vitality, among whom 28% received a new prescription without a prior endogenous testosterone measurement (20). Safety concerns were raised when two early retrospective studies reported a positive association between testosterone use and an increased risk of cardiovascular disease (20), whereas the Testosterone Trials and recent meta-analyses of randomized controlled trials (RCT) generally found no increase in cardiovascular adverse events (21). To date, no RCTs have been designed to evaluate colorectal cancer risk with testosterone use. On the other hand, evidence from two RCTs of menopausal HRT, namely, the Heart and Estrogen/Progestin Replacement Study and the Women's Health Initiative, have shown that estrogen plus progestin could reduce colorectal cancer incidence compared with placebo (3). This is in agreement with observational studies which have fairly consistently suggested a benefit of HRT on colorectal cancer risk (3).

In conclusion, although Dimou and colleagues did not provide evidence regarding independent associations of endogenous testosterone and SHBG with colorectal cancer risk, further interrogation of possible mediating roles of sex hormones in the causal pathways underlying specific exposures and colorectal cancer may shed light on the etiology of colorectal cancer and have implications for tailored prevention. Given the widespread use of testosterone supplementation, large and long-term RCTs are also required to ascertain the effect of exogenous testosterone on colorectal cancer in men with repeated measurements of endogenous testosterone, which would provide critical evidence for improving health decision making.

Authors' Disclosures

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