

Sex Hormones and Colorectal Cancer: What Have We Learned So Far?

Jennifer H. Lin, Edward Giovannucci

Correspondence to: Jennifer H. Lin, PhD, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave, Boston, MA 02215 (e-mail: jhlin@rics.bwh.harvard.edu) or Edward Giovannucci, MD, ScD, Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115 (e-mail: egiovann@hsph.harvard.edu).

The androgen dependence of prostate cancer has led to therapeutic strategies designed to lower androgen levels to treat this cancer. Circulating male hormones including the principal androgen, testosterone, are synthesized primarily in the testes and also in the adrenal glands and peripheral tissues. In most prostate cancer patients, treatment with gonadotrophin-releasing hormone agonists or orchidectomy effectively inhibits testicular androgen synthesis and lowers plasma testosterone levels close to the detection limit of most conventional assays, leading to a reduction in plasma levels of prostate-specific antigen and tumor regression. However, the treatment also comes with several adverse effects and, over time, a subset of tumor cells survives in the androgen-depleted environment and becomes resistant to the therapies.

Although colorectal cancer is generally not considered to be a hormone-related malignancy, accumulating evidence has suggested that sex hormones are relevant to its development. Over the past three decades, epidemiological studies in women have consistently shown that an increase in female hormones such as estrogens and progestin as a result of pregnancy or use of exogenous steroid hormones is associated with a lower risk for developing colorectal cancer (1–3). In support of these results, the Women's Health Initiative estrogen plus progestin clinical trial reported an approximately 40% lower risk for colorectal cancer in the treatment group as compared with the placebo group (4,5). By contrast, the other Women's Health Initiative trial did not demonstrate a lower risk of colorectal cancer among hysterectomized women treated with estrogen alone (6,7). Two recent observational studies also found no reduced risk for colorectal cancer incidence among postmenopausal women with higher circulating levels of estradiol and estrone (8,9). These observations seem to suggest that progesterone, but not estrogen, may be the key candidate for reduction of colorectal cancer risk in women. Because the endogenous synthesis of sex hormones and their activation of transcription in target tissues are determined by biosynthetic enzymes, metabolizing enzymes, and steroid receptors, genetic and epigenetic modifications of the genes for these proteins may also affect the risk of cancer associated with sex hormones.

Little is known about the association between sex hormone levels and colorectal cancer risk in men. Two observational studies have supported the hypothesis that lower androgenicity may increase men's risk of developing colorectal cancer (10,11). An increase (≥ 23) in the number of CAG repeats in the gene for the androgen receptor, which is related to lower transcriptional activation by the androgen receptor and thus lower androgenic action in tissues, was associated with elevated risk of colon cancer (10). An inverse association with

borderline statistical significance was observed between plasma dehydroepiandrosterone sulfate and colon cancer risk (11). These preliminary data await confirmation in large prospective cohort studies.

In this issue of the *Journal*, Gillessen et al. (12) present an interesting evaluation of the association between androgen deprivation therapies and subsequent risk of developing colorectal cancer in 107859 prostate cancer patients aged 67 years or older in the Surveillance, Epidemiology, and End Results–Medicare database beginning in 1993. As of 2004, they identified 2035 patients who subsequently developed colorectal cancer. Patients who received treatment with gonadotrophin-releasing hormone agonists or orchidectomy had a 30%–40% increased risk of developing colorectal cancer relative to those who did not have the therapies. The observed associations were not modified by tumor location and grade.

The authors also reported a dose–response trend of increased colorectal cancer risk with longer duration of the anti-androgen therapies. The increased risk appeared to arise relatively quickly, perhaps as early as within one year, suggesting that hormones may influence relatively late processes of carcinogenesis. The risk appeared to increase across years of duration of treatment, but the cut point for the upper category was only “greater than 2 years,” so it is not known whether risk would increase further with longer treatment. A meta-analysis of five prospective studies in postmenopausal women (3) found no additional reduction in the risk of colorectal cancer with longer duration of hormone therapy use (ie, ≥ 5 years) as compared with shorter exposures (< 5 years).

Medical history and several lifestyle and dietary factors have a potential role in colorectal cancer development and may confound the associations observed by Gillessen et al. For instance, patients who receive gonadotrophin-releasing hormone agonist injections may have more medical health-care contacts and are thus more likely to receive screening examinations by colonoscopy or sigmoidoscopy as well as other physical checkups. The authors have prudently addressed these issues with adjustment for screening examinations received after diagnosis of prostate cancer, obesity diagnosis, and incident diabetes in their models. In this study population, patients with androgen-deprivation therapies were more likely to have advanced prostate cancer. Conceivably, these patients might be more physically inactive and might engage in fewer outdoor activities and thus may potentially have lower vitamin D, all of which have been associated with an increased risk of colorectal cancer (13). The authors have additionally adjusted for prostate tumor grade and stage as a proxy for lifestyle or dietary factors that potentially differ in patients who did or did not receive anti-hormone therapy.

The mechanisms underlying the inverse association between androgen levels and colorectal cancer risk in men are unclear. Findings from laboratory studies in male rodents have suggested that androgens inhibit colorectal tumor growth, likely through the activation of androgen receptor signaling pathway. Male rats with azoxymethane-induced cancers of the colon have increased colonic tumorigenesis following castration (13) but have reduced formation of aberrant crypt foci and tumors when treated with the potent androgen dihydrotestosterone (14,15). Treatment of nude mice with dihydrotestosterone also resulted in growth inhibition of xenografts of colorectal adenocarcinoma where expression of androgen receptor was present (16). It has further been shown in human colon cancer cell lines that activation of the ligand-bound androgen receptor results in the suppression of β -catenin transcription, leading to decreased expression of β -catenin target oncogenes, including cyclin D1 (17).

Obesity has been consistently associated with increased colorectal cancer risk in men. Hyperinsulinemia and insulin resistance may be causally linked to obesity and colorectal cancer development (18). Obese men also tend to have lower androgen levels (19). Treatment with testosterone reduces insulin resistance in men (20), suggesting a role of androgens in promoting insulin sensitivity. Thus, insulin resistance as a consequence of anti-androgen therapies is another plausible mechanism for the elevated colorectal cancer risk. Interestingly, although obesity has been also associated with an increased risk of colorectal cancer in women, the magnitude of the association is substantially stronger in men (21). A plausible explanation for this sex difference is that obesity is associated with lower testosterone levels only in men. However, because the finding in the study by Gillessen et al. is limited to the relatively immediate effects of very low testosterone levels, further research is needed to evaluate whether moderate differences in androgen profiles over longer time scales, as associated with obesity, are associated with colorectal cancer risk in the general male population.

Although some subgroups of prostate cancer patients will benefit overall from androgen deprivation therapies, the medical side effects and effects on quality of life are important considerations (22). The findings of Gillessen et al. suggest that an elevated risk of colorectal cancer may be an additional consideration to weigh in the risk vs benefit profile. Their findings also reinforce the need for routine screening for colorectal cancer and the adoption of lifestyle practices such as physical activity that may help to counter some of the drawbacks of anti-androgen therapies.

References

1. La Vecchia C, Franceschi S. Reproductive factors and colorectal cancer. *Cancer Causes Control*. 1991;2(3):193–200.
2. Fernandez E, La Vecchia C, Balducci A, Chatenoud L, Franceschi S, Negri E. Oral contraceptives and colorectal cancer risk: a meta-analysis. *Br J Cancer*. 2001;84(5):722–727.
3. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med*. 1999;106(5):574–582.
4. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321–333.
5. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med*. 2004;350(10):991–1004.
6. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701–1712.
7. Ritenbaugh C, Stanford JL, Wu L, et al. Conjugated equine estrogens and colorectal cancer incidence and survival: the Women's Health Initiative randomized clinical trial. *Cancer Epidemiol Biomarkers Prev*. 2008;17(10):2609–2618.
8. Gunter MJ, Hoover DR, Yu H, et al. Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. *Cancer Res*. 2008;68(1):329–337.
9. Clendenen TV, Koenig KL, Shore RE, Levitz M, Arslan AA, Zeleniuch-Jacquotte A. Postmenopausal levels of endogenous sex hormones and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2009;18(1):275–281.
10. Slattery ML, Sweeney C, Murtaugh M, et al. Associations between ERalpha, ERbeta, and AR genotypes and colon and rectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14(12):2936–2942.
11. Alberg AJ, Gordon GB, Hoffman SC, Comstock GW, Helzlsouer KJ. Serum dehydroepiandrosterone and dehydroepiandrosterone sulfate and the subsequent risk of developing colon cancer. *Cancer Epidemiol Biomarkers Prev*. 2000;9(5):517–521.
12. Gillessen S, Templeton A, Marra G, Kuo Y-F, Valtorta E, Shahinian VB. Risk of colorectal cancer in men on long-term androgen deprivation therapy for prostate cancer. *J Natl Cancer Inst*. 2010;102(23):1760–1770.
13. Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. *Gastroenterology*. 2013;138(6):2029–2043. e10.
14. Izbicki JR, Hamilton SR, Wambach G, et al. Effects of androgen manipulations on chemically induced colonic tumours and on macroscopically normal colonic mucosa in male Sprague-Dawley rats. *Br J Cancer*. 1990;61(2):235–240.
15. Pereira MA, Khoury MD. Prevention by chemopreventive agents of azoxymethane-induced foci of aberrant crypts in rat colon. *Cancer Lett*. 1991;61(1):27–33.
16. Stebbings WS, Vinson GP, Farthing MJ, Balkwill F, Wood RF. Effect of steroid hormones on human colorectal adenocarcinoma xenografts, of known steroid-receptor status, in nude mice. *J Cancer Res Clin Oncol*. 1989;115(5):439–444.
17. Chesire DR, Isaacs WB. Ligand-dependent inhibition of beta-catenin/Tcf signaling by androgen receptor. *Oncogene*. 2002;21(55):8453–8469.
18. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. *Gastroenterology*. 2007;132(6):2208–2225.
19. Kapoor D, Malkin CJ, Channer KS, Jones TH. Androgens, insulin resistance and vascular disease in men. *Clin Endocrinol (Oxf)*. 2005;63(3):239–250.
20. Marin P, Krotkiewski M, Bjorntorp P. Androgen treatment of middle-aged, obese men: effects on metabolism, muscle and adipose tissues. *Eur J Med*. 1992;1(6):329–336.
21. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. *Am J Clin Nutr*. 2007;86(3):556–565.
22. Loblaw DA, Mendelson DS, Talcott JA, et al. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. *J Clin Oncol*. 2004;22(14):2927–2941.

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Affiliations of authors: Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (JHL); Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, MA (EG); Harvard Medical School, Boston, MA (EG); Department of Nutrition and Department of Epidemiology, Harvard School of Public Health, Boston, MA (EG).