

Does Androgen Deprivation Therapy for Prostate Cancer Increase the Risk of Colorectal Cancer?

Colorectal cancer (CRC) is the third most common cancer in the United States.¹ The causality of CRC is multifactorial and includes genetic factors, lifestyle factors (diet, physical activity, smoking, alcohol consumption), obesity, metabolic syndrome, and sex hormones. In the study by Lu and colleagues published in this issue of *Cancer Control*, Swedish patients with prostate cancer were followed-up and an increased risk of CRC was observed in patients diagnosed with prostate cancer after 1980, which is when the use of androgen deprivation therapy (ADT; bilateral orchiectomy and gonadotropin-releasing hormone [GnRH] agonists) increased in Sweden.^{2,5} No increased risk of CRC was found in patients treated with estrogen therapy. Thus, Lu and colleagues concluded that ADT might be a causal factor for the increased risk of CRC seen in this cohort of patients. The similar but stronger and dose-dependent effect of ADT associated with an increased risk of CRC was also found by Gillissen et al.⁶

Treatments for prostate cancer include active surveillance, radical prostatectomy, radiotherapy, or hormone therapy. ADT is a first-line treatment option for men with metastatic prostate cancer because it suppresses the binding of androgen to the androgen receptor. In Sweden, hormonal treatment for prostate cancer has changed over time²⁻⁵; up until the 1980s, estrogen therapy was the predominant hormonal therapy prior to the introduction of ADT.²

Animal studies have demonstrated that androgen may have a protective effect against colorectal carcinogenesis; by contrast, androgen deprivation may promote it. Evidence indicates that activating androgen receptors represses Wnt/ β -catenin/T-cell factor signaling in colon cancer cells and is associated with a decreased risk of CRC.⁷ This process may influence competition among androgen receptors and T-cell factors for β -catenin binding; by contrast, administering antiandrogen therapy may instead reverse it. In fact, the expression levels of androgen receptors in CRC are lower than those found in samples of normal mucosa.⁶ Furthermore, testosterone deficiency has been linked to an increased risk of metabolic syndrome, diabetes, and cardiovascular disease in men⁸⁻¹⁰; in addition, strong risk factors for CRC include obesity, hyperinsulinemia, type 2 diabetes, and metabolic syndrome.¹¹⁻¹⁶ Research has also indicated that visceral

adiposity accumulating during the short-term use of ADT is correlated with resistance to insulin (within 3 months for some cases) and increasing levels of circulating insulin.¹⁷

Although clinical recommendations for CRC screening among patients with prostate cancer receiving ADT may be unnecessary at this time, health care professionals should be aware of the association between ADT and CRC in this patient population. It may be advisable for physicians to order relatively inexpensive laboratory studies (eg, fecal occult blood test) and suggest lifestyle modifications and early treatment options for lipid disorders in their patients with prostate cancer receiving ADT.

Anna Martling, MD, PhD

Professor
Department of Molecular Medicine and Surgery
Karolinska Institutet
Stockholm, Sweden
anna.martling@karolinska.se

References

1. American Cancer Society. *Cancer Facts & Figures 2015*. Atlanta: American Cancer Society; 2015.
2. Giertz G. Urology in Sweden: 1940-1990 [in Swedish]. *Sydsven Medicinhist Sällsk Arssk*. 1996;(suppl 21):1-284.
3. McLeod DG. Hormonal therapy: historical perspective to future directions. *Urology*. 2003;61(2 suppl 1):3-7.
4. Adolfsson J, Garmo H, Varenhorst E, et al. Clinical characteristics and primary treatment of prostate cancer in Sweden between 1996 and 2005. *Scand J Urol Nephrol*. 2007;41(6):456-477.
5. Cox RL, Crawford ED. Estrogens in the treatment of prostate cancer. *J Urol*. 1995;154(6):1991-1998.
6. Gillissen S, Templeton A, Marra G, et al. Risk of colorectal cancer in men on long-term androgen deprivation therapy for prostate cancer. *J Natl Cancer Inst*. 2010;102(23):1760-1770.
7. Chen SY, Wulf G, Zhou XZ, et al. Activation of beta-catenin signaling in prostate cancer by peptidyl-prolyl isomerase Pin1-mediated abrogation of the androgen receptor-beta-catenin interaction. *Mol Cell Biol*. 2006;26(3):929-939.
8. Teoh JY, Chan SY, Chiu PK, et al. Risk of acute myocardial infarction after androgen deprivation therapy for prostate cancer in the Chinese population. *BJU Int*. 2014. Epub ahead of print.
9. Teoh JY, Chiu PK, Chan SY, et al. Risk of new-onset diabetes after androgen deprivation therapy for prostate cancer in the Asian population. *J Diabetes*. 2014. Epub ahead of print.
10. Zhao J, Zhu S, Sun L, et al. Androgen deprivation therapy for prostate cancer is associated with cardiovascular morbidity and mortality: a meta-analysis of population-based observational studies. *PLoS One*. 2014;9(9):e107516.
11. Cowey S, Hardy RW. The metabolic syndrome: a high-risk state for cancer? *Am J Pathol*. 2006;169(5):1505-1522.
12. Stepien M, Rosniak-Bak K, Paradowski M, et al. Waist circumference, ghrelin and selected adipose tissue-derived adipokines as predictors of insulin resistance in obese patients: preliminary results. *Med Sci Monit*. 2011;17(11):PR13-PR18.
13. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. *Am J Clin Nutr*. 2007;86(3):s836-s842.
14. Esposito K, Chiodini P, Capuano A, et al. Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis. *Endocrine*. 2013;44(3):634-647.

15. Stocks T, Lukanova A, Bjørge T, et al; Metaboli Syndrome Cancer Project Me-Can Group. Metabolic factors and the risk of colorectal cancer in 580,000 men and women in the metabolic syndrome and cancer project (Me-Can). *Cancer*. 2011;117(11):2398-2407.
16. Aleksandrova K, Nimptsch K, Pischon T. Influence of obesity and related metabolic alterations on colorectal cancer risk. *Curr Nutr Rep*. 2013;2(1):1-9.
17. Harrington JM, Schwenke DC, Epstein DR, et al. Androgen-deprivation therapy and metabolic syndrome in men with prostate cancer. *Oncol Nurs Forum*. 2014;41(1):21-29.