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Colorectal Cancer: The Last Nail in the Coffin for Androgen Deprivation Therapy for Prostate Cancer?

In this issue of *Cancer Control,* the *Special Report* by Lu and colleagues suggests that androgen deprivation therapy (ADT) may be associated with an increased incidence of colorectal cancer (CRC). We elected to publish this provocative paper for 2 reasons: (1) It supports the results of an analysis of Surveillance, Epidemiology, and End Results Program data with the weight of a Swedish cancer registry, which includes all cases of prostate cancer diagnosed since 1958 in Sweden,[1] and (2) it is a reminder that some common and presumably innocuous interventions may have long-term complications. The association of CRC and ADT may, in fact, be the last nail in the coffin for the use of ADT in individuals with recurrences of prostate-specific antigen and without imaging evidence of metastatic disease. In these settings, the use of ADT does not improve survival rates, but its use has been associated with other serious complications, including the loss of libido, hot flashes, fatigue, sarcopenia, osteoporosis, diabetes, and an increased risk of infarction in the setting of coronary artery disease.[2,3]

A hypothesis suggested by Lu and colleagues is the possibility that estrogen therapy, which was widely used in Sweden prior to the introduction of gonadotropin-releasing hormone therapy, could reduce the risk of CRC. Undoubtedly, this article will elicit controversy, and Lu and colleagues have thus detailed the limitations and weaknesses of their *Special Report*.

The authors use 3 sources of information: (1) a Swedish cancer registry initiated in 1958 that includes nearly all cases of cancers diagnosed in Sweden, (2) a Swedish patient registry that began in 1964 for 2 counties and was then extended to the entire country in 1987 and includes surgical (but not medical) treatments, and (3) the Swedish total population registry that includes demographic data for the entire Swedish population since 1961. Prior to 1980, Swedish patients with prostate cancer were treated with estrogen therapy but with orchiectomy, gonadotropin-releasing hormone therapy, or other treatments after 1980.[4-7] Furthermore, the patient registry did not cover the entire Swedish population until 1987, so the authors infer that it is unclear whether patients underwent prostatectomy or orchiectomy prior to that date. It is also unclear how many patients received radiotherapy in lieu of prostatectomy or how many experienced a recurrence following local treatment and underwent ADT as secondary treatment. Thus, the authors divided patients from the registries into 2 cohorts, ie, those diagnosed between 1960 and 1980 and those diagnosed between 1981 and 2008. Finally, no consideration was given to the fact that male life expectancy — and, hence, the possibility to diagnose new cases of CRC — has increased in Sweden since 1958.[8]

Despite these limitations, the incidence of CRC in Swedish men with prostate cancer has increased since 1980 and the results of this *Special Report* suggest that ADT is a likely culprit of this increase. Thus, we felt that these conclusions were important and robust enough to justify the publication of this *Special Report* by Lu and colleagues in the hopes that we can open a lively debate of the issue.

Is this study practice changing? Definitely not. It presents one more reason to avoid the use of ADT when it is not indicated, but it does not offer reasons to avoid ADT in conditions in which there are evidence-based benefits to this type of treatment. Such situations include using ADT as initial treatment for patients with metastatic prostate cancer in combination with radiotherapy in patients with locally advanced disease or in those at high risk of recurrence, as well as adjuvant treatment following prostatectomy in patients with involved pelvic lymph nodes.[3]

This *Special Report* is a reminder of the need to monitor long-term treatments throughout a patient's lifetime, and this is particularly true of therapeutic options that may appear innocuous but may cause unwanted long-term consequences. Currently, vitamin D deficiency is considered to be the cause of a variety of conditions, including cancer, hematological disorders, and bone and cardiovascular diseases.[8] As clinicians, we would be well advised to monitor the long-term effects of ongoing vitamin D supplementation. In yet another example of the importance of monitoring long-term treatments, we now know that vitamin E supplementation might have facilitated the development of prostate and lung cancers — the exact types of cancer it was purported to prevent[9]! With the rising life expectancy of the global community (the global life expectancy has increased by 6 years since 1990[8]), clinical epidemiology has become an invaluable instrument to detect the long-term effects of medical intervention.

This *Special Report* is also an opportunity to revisit a turning point in the management of prostate cancer.

Since the 1984 report of the Leuprolide Study Group suggesting that ADT in combination with leuprolide and a daily dose of 3 mg of diethylstilbestrol (DES), a synthetic estrogen, were comparable treatment options for the management of metastatic prostate cancer,[10] estrogen therapy was all but banned from US practice. In our opinion, this approach might have been premature and ill advised. Estrogen therapy is associated with an increased risk of deep venous thrombosis (DVT), whereas leuprolide use increases the incidence of hot flashes[10]; however, at the time, the cost of estrogen was less than 1% of the cost of leuprolide. Furthermore, a study comparing leuprolide with a daily dose of 1 mg DES was never performed. Some evidence suggests that 1 mg and 3 mg DES may be equivalent but that the lower dose may be associated with a lower risk of DVT.[11] Finally, estrogens do not cause many of the complications of gonadotropin-releasing hormone therapy, such as loss of libido, osteoporosis, and hot flashes.[2,3] It may be too late to advocate a return to estrogen therapy, but the results from the *Special Report* by Lu and colleagues suggest that estrogen therapy might have had an additional advantage over ADT and that promoting the economic considerations of leuprolide might have trampled science and patient safety.

We must be skeptical about some of the study conclusions. For example, no biological or epidemiological evidence supports the claim that prostatectomy may have caused the incidence of CRC to increase. It is impossible to accept this conclusion without knowing how many patients received radiotherapy, hormonal therapy, or both following prostatectomy.

Some readers may question our decision to publish this *Special Report* despite its methodological flaws. As the editors of *Cancer Control*, we are privileged to place the importance of information over academic purity. Despite its flaws, we felt that the conclusion that ADT was associated with an increased risk of CRC was justified and robust, and, as such, the results of this *Special Report* are relevant to all health care professionals involved in the management of prostate cancer.

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