Risk of Colorectal Cancer by Subsite in a Swedish Prostate Cancer Cohort

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Background: The relationship between sex hormone–related treatment for prostate cancer and the risk of colorectal cancer is controversial.

Methods: A prostate cancer cohort was initiated from the Swedish Cancer Registry of patients diagnosed between 1961 and 2008. Patients diagnosed with prostate cancer between 1961 and 1980 were generally treated with estrogen. The cohort diagnosed between 1981 and 2008 was further divided into 3 subcohorts of orchiectomy, prostatectomy, and other treatment. Standardized incidence ratios (SIRs) for developing colorectal adenocarcinoma were estimated and 95% confidence intervals (CIs) were used to compare relative risk among these patients and the general male population.

Results: Of 601,542 person-years of follow-up, 1,698 cases of colorectal adenocarcinoma were identified. Compared with the general male population, no association was detected in the cohort diagnosed between 1961 and 1980, whereas an increased risk of colorectal adenocarcinoma was observed among patients diagnosed with prostate cancer who received treatments other than estrogen. Following bilateral orchiectomy, the SIR was 1.30 (95% CI: 1.14–1.47); after prostatectomy, the SIR was 1.22 (95% CI: 1.04–1.43); among those who received treatment other than estrogen, the SIR was 1.37 (95% CI: 1.29–1.45). The increased risks were more apparent in cases of adenocarcinoma of the distal colon and rectum than in the proximal colon.

Conclusions: Patients with prostate cancer undergoing bilateral orchiectomy, prostatectomy, or other treatments, including antiandrogen therapy and radiation, may be at increased risk for colorectal adenocarcinoma.

Introduction

The role of the influence of sex hormones in the etiology of colorectal cancer (CRC) deserves attention, particularly regarding potential differences between the locations of such cancer. Based on separate embryological origins, and thus potentially divergent causal pathways, the colorectal intestine is often divided into the proximal colon (cecum, ascending colon, and transverse colon), distal colon (descending colon and sigmoid colon), and rectum. Accumulating evidence from epidemiological studies has demonstrated the differences in risk-factor profiles between men and women of cancers in the colorectal subsites with regard to dietary factors,1-4 obesity,5 and physical activity.6,7 The incidence of cancer of the proximal colon is 10% to 20% higher in women than in men at all ages, whereas men have a higher incidence of cancer in the distal colon and rectum.8,9 It is possible that sex hormones could differently influence cancers of the proximal colon, distal colon, and rectum. Epidemiological studies in women have shown that higher levels of the female sex hormones estrogen and progesterone are associated with a lower risk of developing CRC, particularly when exogenous steroid hormones are used,10,11 but few studies have associated sex hormones with risk of colorectal adenocarcinoma by subsite in men.12,13

Previously, hormone therapy was a major treatment approach for prostate cancer, although hormone therapy does produce adverse events.14-16 Estrogen therapy and androgen deprivation therapy (ADT; including orchiectomy and gonadotropin-releasing hormone [GnRH] agonists) are 2 types of sex hormone therapies used in patients with prostate cancer. Theoretically, patients with prostate cancer treated with sex hormones may constitute an ideal natural human model for evaluating the association between external sex hormones and the risk of CRC. In 2010, a study found that patients with prostate cancer receiving ADT...
had an increased risk of CRC compared with patients not receiving ADT.17 Due to confounding by indication, this association is still controversial. Further studies comparing patients with prostate cancer and the general population may provide more evidence.

Methods
Because of the nature of Swedish national health registries (see below for a detailed description of each registry used), we were able to identify all of the patients diagnosed with prostate cancer in Sweden between 1961 and 2008 and followed them up to the development of a second adenocarcinoma in the colon or rectum. The patients with prostate cancer were grouped into 4 treatment cohorts.

The aim of this study was to determine whether prostate cancer treatments, particularly sex hormone therapy, were associated with risk for CRC. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Data Sources
This study was based on data from 3 nationwide Swedish population-based registries, ie, the cancer, patient, and total population registries. The personal identity number, a unique 10-digit identification number assigned to each resident of Sweden, was used to link all of the patients between the registries.

Cancer Registry: The cancer registry was initiated in 1958 and includes the date of diagnosis, tumor site, and histological type of all malignant tumors diagnosed in Sweden. All newly diagnosed tumors in the country must be reported to the cancer registry by a clinician and a pathologist or cytologist. The completeness of the registry approaches 98% to 100%, and 99% of all tumors are morphologically verified.19 The cohorts included all men registered with a first diagnosis of prostate cancer. The years 1958 to 1960 were excluded to avoid inclusion of the prevalence of cancer cases when the registry began. All patients with any diagnosis of other previous cancer were excluded. Any subsequent cancer after prostate cancer was identified throughout the cancer registry, including the outcome of colorectal adenocarcinoma (proximal colon, distal colon, unspecified colon, and rectum).

Patient Registry: The patient registry was initiated in 1964 and covered 2 Swedish counties; starting in 1987, the registry covered 100% of Sweden.20 This registry has achieved accuracy and surgical completeness rates of 95% and 98%, respectively.21 Information on the surgical procedures following the diagnosis of prostate cancer was collected from this registry. The Swedish Classification of Operations and Major Procedures has been included in the patient registry since 1964, and it was used to identify patients undergoing bilateral orchiectomy and prostatectomy.

Total Population Registry: The total population registry provides complete and continuously updated information on dates of emigration, immigration, births, and deaths since 1961. Data of censored cohort members who died or emigrated during follow-up were collected from this registry. However, these patients were censored from the date of first emigration or exact date of death.

Study Cohorts
The methods for treating prostate cancer changed in Sweden during the 1980s, with estrogen therapy being the predominant treatment strategy prior to 1980.22 Bilateral orchiectomy was also an available standard treatment for prostate cancer between the years 1950 and 1980 in many countries, but orchiectomy was not popular in Sweden during these years.23 Other treatments, such as ADT (orchiectomy and GnRH analogues), radical prostatectomy, and radical radiotherapy, increased after the 1980s.24-26 The number of patients who did not receive treatment (active surveillance and watchful waiting) was low.27 Therefore, the cohort was divided into mutually exclusive subcohorts based on the definition of sex hormone treatments following prostate cancer diagnosis (Fig). The cohort diagnosed prior to 1981 included persons diagnosed with prostate cancer before 1981; a second cohort of patients included those diagnosed with prostate cancer between January 1, 1981, and December 31, 2008. The last subcohort was further divided into patients who underwent bilateral orchiectomy, patients who underwent prostatectomy, and patients treated mainly by GnRH therapy, radiotherapy, or both assigned to the “other treatment” group.

Follow-Up
The follow-up of the cohort members started from the date prostate cancer was newly diagnosed or the start of specific treatments in the cohort, and patients were followed-up until any of the following end points: diagnosis of any cancer (except nonmelanoma skin cancer), emigration, age 85 years, death, or end of the study period, whichever came first. The end of the study period for the cohort before the 1980s was set to December 31, 1980, and to December 31, 2008, for all the other cohorts.22 The cutoff date (December 31, 1980) for the end of the first study period or the beginning of the second study period was arbitrarily selected based on the previously reported changes of treatment in Sweden.

Statistical Analyses
Person-years were calculated from the date of prostate cancer diagnosis (or specific treatment, eg, orchiectomy) to the date of the study’s end point.
Standardized incidence ratios (SIRs) were estimated as a measure of relative risk when comparing the data from those diagnosed with prostate cancer and the corresponding general male population. The ratio was calculated based on the observed number divided by the expected number of newly diagnosed cases of CRC. The expected number of cases was calculated by multiplying the observed number of person-years by the age- and calendar year–specific incidence rates with 5-year intervals of the entire Swedish male population. SIRs and 95% confidence intervals (CIs) were calculated with the assumption that the number of cases followed a Poisson distribution. SIRs were separately estimated for cancers of the proximal colon, distal colon, unspecified colon, and rectum in each of the cohorts. We also performed sensitivity analyses with respect to the separate cohorts, which we assumed were exposed to various prostate cancer treatments. For the cohort diagnosed between 1961 and 1980, we analyzed the cohort members who were followed from 1961 to 1975, with the end point being 5 years earlier than the prior assumed cutoff date. For the 3 cohorts diagnosed after 1980, we performed analyses on patients who entered into the cohort from 1986 through 2008, with the start point being 5 years later than the prior assumed cutoff date. In the main analysis, we excluded the first year of follow-up after the diagnosis of prostate cancer because cancers diagnosed in the first year were particularly prone to detection bias and unlikely to be related to the treatment of prostate cancer.

All tests were 2-sided with a significance level of 0.05. Analyses were performed using the SAS statistical package, version 9.0 (SAS Institute, Cary, North Carolina).

Results
A total of 149,743 patients with prostate cancer were included in the final study cohort and information for the specific cohorts is shown in Table 1. The cohort diagnosed between 1961 and 1980 was composed of 33,373 patients with prostate cancer who were followed-up for 111,809 person-years until 1980, and the total cohort diagnosed with prostate cancer between 1981 and 2008 included 116,370 patients with prostate cancer and 489,733 person-years of follow-up since 1981. During follow-up, we identified a total of 1,698 cases of colorectal adenocarcinoma. Among them, 487 cases of adenocarcinoma were located in the proximal colon, 453 cases in the distal colon, 132 cases in an unspecified site of the colon, and 626 cases in the rectum. Age at entry and age at diagnosis of colorectal adenocarcinoma were significantly different among the groups (all \( P \) values < .01). Those in the prostatectomy cohort were younger than patients in the other cohorts.

Estrogen Exposure
Compared with the general population, the cohort diagnosed between 1961 and 1980 was not associated with the overall development of colorectal adenocarcinoma (SIR 0.98; 95% CI: 0.85–1.12) or when analyzed by subsite (Table 2). Results suggested a statistically nonsignificant decreased risk of adenocarcinoma of the proximal colon, but these results were mainly observed among patients with a short follow-up; however, a nonsignificant trend of increased risk with years of follow-up (\( P \) value for trend = .09) in the proximal colon was identified.

Orchiectomy
Between 1981 and 2008, a total of 21,917 individuals underwent bilateral orchiectomy and had an average follow-up period of 3.4 years (Tables 1 and 3). An overall increased risk of colorectal adenocarcinoma was detected in patients with 1 to 9 years of follow-up, but this risk decrease after 10 years of follow-up. A significantly increased risk
was observed for the overall rate of colorectal adenocarcinoma (SIR 1.30; 95% CI: 1.14–1.47) and for each subsite except for the proximal colon.

**Prostatectomy**

The prostatectomy cohort was composed of 16,521 patients who underwent prostatectomy between 1981 and 2008 and had an average follow-up period of 4.6 years (Tables 1 and 4). Similarly increased risks of colorectal adenocarcinoma overall and by specific subsites were observed among patients in the prostatectomy cohort.
Specifically, an increased SIR was found for the distal colon (1.44; 95% CI: 1.06–1.91) and rectum (1.36; 95% CI: 1.06–1.71).

Other Treatments
Among patients diagnosed with prostate cancer after 1980, a total of 77,932 did undergo bilateral orchietomy or prostatectomy during the study period (see Table 1). Patients in the other treatment cohort had an overall increased risk of colorectal adenocarcinoma (SIR 1.37; 95% CI: 1.29–1.45) and for all subsites (Table 5). Specifically, an increased risk of adenocarcinoma in the proximal colon was associated with age ($P$ value for trend < .01); a decreased risk was observed in association with years of follow-up ($P$ value for trend = .02; see Table 5).

Sensitivity Analyses
Analyses of the cohort diagnosed between 1961 and 1975 did not identify an association between estrogen treatment and overall or subsite risk of CRC, a finding consistent with the results from the originally defined cohort (diagnosed between 1961 and 1980). In the orchietomy cohort, which included patients diagnosed between 1986 and 2008, increased SIRs of CRC were found, in line with the results shown in Table 3. In the prostatectomy and other treatment cohorts, similarly increased and stronger SIRs were observed when compared with the general male population.

Discussion
This nationwide Swedish cohort study identified an increased risk of colorectal adenocarcinoma for all anatomical locations among patients exposed to bilateral orchietomy, ADT, radical prostatectomy, and radiotherapy. No clear association was detected among individuals exposed to estrogen.

Treatment for prostate cancer diagnosed after 1980 may be associated with an increased risk of colorectal adenocarcinoma, implying a possible connection to ADT, one of the most common treatments in Sweden used after 1980. The increased risk of colorectal adenocarcinoma found among patients undergoing bilateral orchietomy could be related to an effect of surgical androgen deprivation, whereas the increased risk seen in patients not undergoing orchietomy or prostatectomy could be due to medically induced androgen deprivation (ie, GnRH therapy). Higher SIRs were observed in the sensitivity analyses for the prostatectomy and other treatment cohorts, particularly in those with short-term follow-up. The results also indicated that other treatments such as GnRH therapy may play a role in the risk of CRC, although the probability value for such a trend did not reach statistical significance. Alternatively, a carcinogenic effect of radiotherapy for prostate cancer may be present; however, this represents exposure for which we have no data. Consistent results have also been found in a US study.

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Table 3. — SIRs and 95% CIs of Colorectal Adenocarcinoma in the Prostate Cancer Cohort With Orchiectomy Compared With the General Population (1981–2008)

<table>
<thead>
<tr>
<th></th>
<th>Colorectal Adenocarcinoma</th>
<th>Adenocarcinoma of the Proximal Colon</th>
<th>Adenocarcinoma of the Distal Colon</th>
<th>Adenocarcinoma of the Rectum</th>
<th>Unspecified Colorectal Adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs</td>
<td>Exp</td>
<td>SIR (95% CI)</td>
<td>Obs</td>
<td>Exp</td>
<td>SIR (95% CI)</td>
</tr>
<tr>
<td>247</td>
<td>190</td>
<td>1.30 (1.14–1.47)</td>
<td>58</td>
<td>55</td>
<td>1.06 (0.80–1.36)</td>
</tr>
<tr>
<td>32</td>
<td>17</td>
<td>1.91 (1.31–2.70)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Age at diagnosis of prostate cancer, y**

| 41–64 | 26 | 17 | 1.55 (1.01–2.27) | 2 | 4 | 0.46 (0.06–1.66) | 10 | 4 | 2.48 (1.19–4.57) | 13 | 7 | 1.85 (0.98–3.16) |
| 65–74 | 132 | 97 | 1.36 (1.14–1.61) | 34 | 27 | 1.24 (0.86–1.74) | 32 | 23 | 1.40 (0.96–1.98) | 44 | 38 | 1.14 (0.83–1.53) |
| ≥75 | 89 | 76 | 1.17 (0.94–1.44) | 22 | 23 | 0.95 (0.59–1.43) | 22 | 17 | 1.26 (0.79–1.91) | 36 | 28 | 1.26 (0.89–1.75) |

**Follow-up**, y

| 1–4 | 158 | 127 | 1.24 (1.06–1.45) | 38 | 36 | 1.05 (0.74–1.44) | 37 | 29 | 1.26 (0.89–1.73) | 58 | 50 | 1.16 (0.88–1.50) |
| 5–9 | 75 | 49 | 1.53 (1.20–1.91) | 15 | 14 | 1.05 (0.79–1.27) | 24 | 11 | 2.10 (1.34–3.12) | 30 | 19 | 1.59 (1.07–2.27) |
| ≥10 | 14 | 14 | 1.00 (0.55–1.68) | 5 | 4 | 1.17 (0.38–2.73) | 3 | 3 | 0.88 (0.18–2.57) | 5 | 5 | 0.96 (0.31–2.24) |

*First year of follow-up was excluded.
CI = confidence interval, Exp = expected, Obs = observed, SIRS = standardized incidence ratio.
that found a strong association between orchiectomy and colorectal adenocarcinoma. The elevated risk (increase in CRC incidence of 30%–40% in men exposed to ADT) was noticeable even after adjust-
ing for potential confounders such as diabetes, obesity, and radiotherapy.  Although that study had robust data regarding orchiectomy and GnRH therapy, it included bias from confounding by indication and its participants were older.  Our study, which measured relative risk based on a comparison between the study cohort groups and the general population, further demonstrated the findings of the US study.  

**Estrogen and Androgen**

We did not find any association between estrogen treatment and colorectal adenocarcinoma. Previous reports, which were based on observational data and results from clinical trials, have suggested that women exposed to exogenous estrogen, including hormone replacement therapy or oral contraceptives, have a decreased risk of CRC.  However, the estrogen hypothesis has seldom been evaluated in men. The relationship between estrogen and androgen is intriguing. Estrogens are produced with androgens as precursors. Progesterone is the first important sexual steroid formed in the body. The androgens (dehydroepiandrosterone, androstenedione, and testosterone) arise thereafter, whereas the estrogens (estrone and estradiol) appear only during the final stage. 

Estrogen and androgen may play a similar role in carcinogenesis among women and men, respectively. Estrogen and androgen were postulated to prevent tumor growth by preventing insulin and insulin-like growth factor from binding to their receptors. By contrast, an increased risk of colorectal adenocarcinoma due to androgen deprivation could be possible as the results from animal studies suggest that androgen may have a protective effect on the development of CRC.  Androgen receptors have also been found more frequently in the normal — as opposed to cancerous — mucosa in the colon.  Thus, orchiectomy or GnRH treatment would directly decrease androgen.

**Specific Subsite**

Our results suggest differences in risk may exist between the proximal and distal colon. The decreasing trend of SIRs associated with adenocarcinoma in the proximal colon over follow-up years could indicate a differing association at that subsite. Select genetic or physiological mechanisms might explain this difference in risk patterns of adenocarcinoma in the proximal and distal colon. The proximal colon originates from the midgut, but the distal colon and rectum originate from the hindgut. Research suggests that different genetic pathways to CRC dominate the proximal and the distal segments of the bowel.  These genetic-dependent pathways are influenced by different sex-related factors.  Estrogen receptors are distributed differently in the proximal and distal colon. Furthermore, chromosomal instability and microsatellite instability — 2 forms of genetic instability in CRC — mostly occur in the proximal and distal colon, respectively, warranting the genetic basis.

**Limitations**

Strengths of this study include its nationwide and population-based cohort design identified from national registries, its large prostate cancer cohort sizes, and its long and complete follow-up times; however, information on individual prostate cancer treatment was limited. Data on bilateral orchiectomy, which is a common ADT, was available in the patient registry from 1964 onward, but we had no detailed information on other hormonal treatments such as estrogen or antiandrogen medications. We specified the cohorts based on time periods and specific treatments. The results of the sensitivity analyses showed fair consistency with the reported results based on the selected cutoff dates.

Another concern is the introduction of prostate-specific antigen (PSA), which could change the profiles of patients with prostate cancer.  PSA screening was introduced in Sweden between 1995 and 2000 and steadily increased from 1% to 10%.  Less aggressive prostate cancer might have been diagnosed after the introduction of PSA testing. However, this would have little influence on our results because we stratified the analysis in all 3 subcohorts. Treatments for the first 2 cohorts were defined, whereas influences on the third cohort could have been overlooked. Considering the lower proportion of PSA screening and the large size of this cohort, PSA screening should not engender a substantial influence on the total results.

It is possible that CRC screening might influence the diagnosis of CRC in patients with prostate cancer. In Sweden, CRC screening commenced in the 1980s but patients were limited; the officially organized screening of CRC began in Stockholm in 2008 and in the rest of Sweden in 2014.  so CRC screening would not have substantially affected the results of our study. Furthermore, we did not find studies to indicate that colonoscopy was increased in the prostate cancer survivor group in Sweden. It may be possible that patients receiving radiotherapy for prostate cancer may also have had bowel symptoms. Because SIRs were calculated based on a comparison of the prostate cancer cohort with the general population at the same period, such an influence would be minor.

The adverse events of hormone therapy are concerning and may contribute to an increased risk of CRC, but such information cannot be specified in the current study. Further adjustment of obesity and diabetes did not change the association of hormone therapy and CRC in one study.
be considered to be confounding factors, including familial background and dietary habits. However, it is unlikely that these factors could explain our results, as it is likely they are equally distributed between patients regardless of prostate cancer treatment.

Although the randomized clinical trial is the gold standard for this type of research, its use was not feasible for our study due to ethical issues.

Conclusions
Results from this population-based cohort study suggest that androgen deprivation therapy, including bilateral orchiectomy, may increase the risk of colorectal adenocarcinoma in men, although confounders of radiotherapy or prostate cancer could not be excluded. Further studies are warranted to elucidate this potential association.

References