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ARTICLE

Risk of colorectal cancer in men on long-term androgen deprivation therapy for prostate cancer

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Background Androgen deprivation with gonadotropin-releasing hormone (GnRH) agonists or orchiectomy is a common but controversial treatment for prostate cancer. Uncertainties remain about its use, particularly with increasing recognition of serious side effects. In animal studies, androgens protect against colonic carcinogenesis, suggesting that androgen deprivation may increase the risk of colorectal cancer.

Methods We identified 107 859 men in the linked Surveillance, Epidemiology, and End Results (SEER)–Medicare database who were diagnosed with prostate cancer in 1993 through 2002, with follow-up available through 2004. The primary outcome was development of colorectal cancer, determined from SEER files on second primary cancers. Cox proportional hazards regression was used to assess the influence of androgen deprivation on the outcome, adjusted for patient and prostate cancer characteristics. All statistical tests were two-sided.

Results Men who had orchiectomies had the highest unadjusted incidence rate of colorectal cancer (6.3 per 1000 person-years; 95% confidence interval [CI] = 5.3 to 7.5), followed by men who had GnRH agonist therapy (4.4 per 1000 person-years; 95% CI = 4.0 to 4.9), and men who had no androgen deprivation (3.7 per 1000 person-years; 95% CI = 3.5 to 3.9). After adjustment for patient and prostate cancer characteristics, there was a statistically significant dose–response effect (P_{trend} = .010) with an increasing risk of colorectal cancer associated with increasing duration of androgen deprivation. Compared with the absence of these treatments, there was an increased risk of colorectal cancer associated with use of GnRH agonist therapy for 25 months or longer (hazard ratio [HR] = 1.31, 95% CI = 1.12 to 1.53) or with orchiectomy (HR = 1.37, 95% CI = 1.14 to 1.66).

Conclusion Long-term androgen deprivation therapy for prostate cancer is associated with an increased risk of colorectal cancer.

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Despite its use in more than one half million men in the United States alone, androgen deprivation therapy for prostate cancer remains controversial (1). Whereas it is clearly indicated for palliation of symptomatic metastatic disease, the benefits are unclear when it is given as primary treatment for localized tumors, a scenario for which it is nevertheless commonly prescribed (2–5). Androgen deprivation therapy is also associated with a host of adverse effects, such as osteoporosis and fractures, cardiovascular disease, and diabetes (4,6). Even when androgen deprivation is used as an adjuvant to radiation in men with localized but high-risk, or locally advanced prostate cancer, a setting for which most clinical trials have demonstrated improved overall survival, a post hoc analysis of one trial showed a trend toward worse overall survival in some subgroups of men (7). Ongoing examination of the risks of androgen deprivation therapy is therefore a priority.

We recently described a case of monozygotic twins who were diagnosed with colon cancers after receiving androgen deprivation therapy for prostate cancer (8). We speculated that shared biological mechanisms in the men may have contributed to the development of colon cancer in the setting of androgen deprivation because data from various studies suggest that androgens exert protective effects against colorectal carcinogenesis (9–13). Furthermore, androgen deprivation therapy has been associated with development of hyperinsulinemia, diabetes mellitus, and obesity, all of which are known risk factors for colorectal cancer (14,15). To explore this issue further, we used the Surveillance, Epidemiology, and End Results (SEER) and Medicare-linked database to assess the risk of colorectal cancer associated with androgen deprivation in the form of orchiectomy or treatment with gonadotropin-releasing hormone (GnRH) agonists in a large population-based sample of men with prostate cancer.

Methods

Data Sources

The SEER–Medicare database links two large population-based sources of data that together provide information about older adults

with newly diagnosed cancer in the United States (16). The SEER program is administered by the National Cancer Institute and consists of regional and state-based tumor registries located throughout the country. It represented approximately 14% of the United States population until 2001 and 26% thereafter. Medicare is a federal program that covers health services for 97% of persons aged 65 years and older. It provides data in the form of claims submitted by providers for reimbursement, which include information on diagnoses and the services, testing, or procedures rendered.

Study Subjects

For this study, we selected data for all men aged 67 years or older who were registered in SEER with a new diagnosis of prostate cancer in the years 1993 through 2002. Follow-up information was available through 2004. By setting the minimum age to 67 instead of 65 years, we allowed for the presence of at least 2 years of Medicare claims before prostate cancer diagnosis for assessment of baseline comorbidities. To ensure completeness of the Medicare claims information, patients who were not enrolled in both Medicare part A and part B for the 24 months before and 6 months after their cancer diagnosis (n = 20 734), those who were members of a Health Maintenance Organization (n = 44 698), and those who were diagnosed by autopsy or on a death certificate (n = 2 408) were excluded, leaving a final study sample of 107 859 men.

Study Definitions

Definitions for all study variables are provided in table format (Table 1). Data concerning patient characteristics (age, race, socioeconomic status, marital status, region of residence, comorbidity, and delivery of routine preventive care) and cancer characteristics (grade and stage) were derived from SEER and/or Medicare files as previously described (4,17,18).

We also specifically examined several potential confounding factors. Delivery of routine preventive care may be a confounder because it can influence both the stage and grade of prostate cancer at diagnosis and therefore likelihood of androgen deprivation therapy use, as well as likelihood of developing colorectal cancer. This was assessed by using Medicare claims to examine the number of visits to a primary care physician and whether a lower gastrointestinal endoscopy was performed in the 12–24 months before diagnosis of the prostate cancer. Differential rates of medical work-up in patients who did or did not undergo androgen deprivation could result in possible detection bias; therefore, use of lower gastrointestinal endoscopy after prostate cancer diagnosis was also examined in a time-dependent manner. Obesity may also be an important confounder because it is a risk factor for the development of colorectal cancer, and although data are conflicting, it has been associated with higher grade or advanced stage prostate tumors that are more likely to be treated with androgen deprivation therapy (19–21). Obesity was identified using diagnosis codes on the Medicare claims (defined in Table 1). Although this approach misses a substantial proportion of obese patients, it still provides an estimate of the relative rates of obesity as a function of androgen deprivation exposure. Patients with diabetes before diagnosis of prostate cancer were also identified as a proxy for obesity (22) and because diabetes has also been independently associated with the development of colorectal cancer (15).

We assessed androgen deprivation therapy using previously published and validated methods (4,23). It was categorized either as the receipt of GnRH agonists or as the occurrence of orchiectomy. Because in some patients low testosterone levels can persist for several months beyond discontinuation of GnRH agonist therapy, we performed sensitivity analyses in which we assumed that patients were on androgen deprivation therapy for a total of either 6 months or 12 months following a monthly depot injection (24). In both cases, the results were similar to the main analysis and are not presented.

The primary outcome was the development of colorectal cancer, as determined from SEER files on second primary cancers. Characteristics of the colorectal cancers—stage, grade, and proximal vs distal site (ie, cecum to splenic flexure vs descending colon to rectum)—were also derived from SEER files (Table 1). Because patients with cancer can be missed by use of the tumor registries, we also performed an analysis in which we additionally identified colorectal cancer cases using diagnosis codes on Medicare claims based on previously published algorithms (25,26).

Statistical Analyses

For all analyses, patients had to survive at least 6 months after diagnosis of prostate cancer to be included. Patients who developed colorectal cancer in the first 6 months following diagnosis of prostate cancer (n = 264) were excluded because it was felt that those cancers were unlikely to be related to the androgen deprivation therapy.

CONTEXT AND CAVEATS

Prior knowledge

Androgen deprivation therapy, via orchiectomy or use of gonadotropin-releasing hormone (GnRH) agonists, is commonly used for prostate cancer. The authors examined whether it might be associated with a risk for colorectal cancer.

Study design

Surveillance, Epidemiology, and End Results (SEER) data for 107 859 American men with prostate cancer were examined for presence or absence of androgen deprivation therapy and for incidence of secondary colorectal cancers.

Contribution

Men who had orchiectomies or GnRH agonist therapy had a higher incidence of colorectal cancer than men who did not have androgen deprivation. Risk increased with increasing duration of this therapy.

Implications

Long-term androgen deprivation therapy puts men at increased risk for colorectal cancer.

Limitations

Efforts were made to adjust for age, socioeconomic status, medical visits, and obesity, but other confounding is possible. All data were for Medicare patients with prostate cancer, so conclusions could be different for younger men or those without prostate cancer.

From the Editors

Table 1. Definition of the study variables*

Variable	Data source	Definition
Patient characteristics		
Age	SEER	Age at diagnosis in years
Race	SEER	White, black, white Hispanic, other
Marital status	SEER	Married at time of diagnosis or not
Place of residence	SEER	SEER geographic region: San Francisco, Connecticut, Michigan, Hawaii, Iowa, New Mexico, Seattle, Utah, Georgia, San Jose (CA), Los Angeles
Socioeconomic status: income	2000 US Census	Available only at patient zip code level: median income in zip code of residence
Socioeconomic status: education	2000 US Census	Available only at patient zip code level: percentage of adults in zip code with <12 years of education
Comorbidity index	Medicare	Based on Klabunde modification of the Charlson index using inpatient, outpatient, and physician Medicare claims. The Charlson index is derived from a scoring system based on a count of certain comorbid diagnoses. Klabunde adaptation allows identification of comorbid diagnoses from Medicare inpatient and outpatient claims
No. of primary care physician visits	Medicare and AMA Masterfile	Calculated from number of physician visits on separate days as defined by the presence of an outpatient physician claim (excluding emergency room visits) for a face-to-face evaluation using †CPT codes of the form 99xxx. The UPIN associated with the claim was linked to AMA data to identify physician specialty as primary care (family practice, general internal medicine, general practice, or geriatricians)
Lower gastrointestinal endoscopy	Medicare	Any claim for ICD-9 procedure codes 45.23, 45.24, CPT codes 45330, 45355, 45378, or HCPCS codes G0104, or G0105
Diabetes mellitus	Medicare	One inpatient claim or two outpatient–physician claims in any position with *ICD-9* diagnosis codes 250.xx, 357.2,362.0-362.0x,366.41,790.2
Obesity	Medicare	Any claim for *ICD-9* diagnosis codes 278.00, 278.01, 783.1, 783.6
Cancer characteristics (at diagnosis)		
Stage	SEER	Prostate cancer: using clinical T stage from SEER Extent of Disease coding; categorized as T1, T2, T3, T4, unknown. Colorectal cancer: using SEER historical staging system; categorized as in situ, localized, regional or distant spread, or unknown
Grade	SEER	Prostate or colorectal cancer: SEER grading information; categorized as well differentiated, moderately differentiated, poorly differentiated, undifferentiated, or unknown
Site (colorectal only)	SEER	Based on site code definitions; categorized as cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, large intestine not otherwise specified, rectosigmoid junction and rectum
Androgen deprivation		
Orchiectomy	Medicare	Any claim with CPT codes 54520, 54521, 54522, 54530, or 54535; or *ICD-9* procedure code 62.4
GnRH agonist	Medicare	Any claim with HCPCS codes J9202, J1950, J9217, J9218, or J9219
Months of GnRH agonist therapy	Medicare	Calculated from each instance of a GnRH agonist HCPCS J-code noted on separate days. GnRH agonists are generally administered as depot injections with the dosage given depend ing on the intended duration of the regimen; usually once a month, once every 3-month or once every 4-month regimens. The intended duration for a given injection was determined first from the unit designation (1, 3, or 4) of the "carrier miles/time/units/serv count" field of the physician services claims or if unavailable, from the "revenue center unit count" field of the outpatient claims
Study outcome		
Incident colorectal cancer	SEER or Medicare	From SEER: site codes indicating colorectal cancer diagnosis following diagnosis of prostate cancer. From Medicare claims algorithm: *ICD-9* diagnosis codes 153.x, 154.0, 154.1, 230.3, 230.4 in any position in at least one inpatient claim or at least two (on different days) outpa tient or physician claims with no claims in preceding 2 years

* AMA = American Medical Association; CPT = Current Procedural Terminology; GnRH = gonadotropin-releasing hormone; HCPCS = Healthcare Common Procedure Coding System; ICD-9 = International Classification of Diseases, Ninth revision; SEER = Surveillance, Epidemiology and End Results; UPIN = unique physician identification number.

Incidence rates of colorectal cancer in person-years during treatment with GnRH agonists, after orchiectomy, or during periods of no androgen deprivation were calculated with corresponding 95% confidence intervals (CI) assuming a Poisson distribution, and the results were stratified by patient characteristics. Survival analyses to calculate hazard ratios (HRs) were performed using Cox proportional hazards regression with androgen deprivation as a time-dependent covariate for the main analysis, and with time to occurrence of colorectal cancer as the dependent variable. Patients were censored at death, loss of Medicare part A or B coverage, switch to a Health Maintenance Organization coverage or end of the study period (December 31, 2004). Using androgen deprivation as a time-dependent covariate allowed men to contribute risk information to the androgen deprivation group for the period after initiation of GnRH agonist treatment or after undergoing orchiectomy, and to the no androgen deprivation group, either before the

initiation of androgen deprivation or if they never received androgen deprivation during the study period. Men who stopped GnRH agonist therapy were assumed to continue to contribute information to the GnRH agonist group for the remainder of study follow-up (re-analysis assigning these men back to the no androgen deprivation group did not substantially alter the results). To assess for a dose–response effect, GnRH agonist use was categorized based on the duration of its administration to men who received 1–4, 5–12, 13–24, or 25 months or more of therapy over the study period (orchiectomy was considered separately). For example, a man who received 3 months of GnRH agonist therapy would start to contribute information to the GnRH agonist 1- to 4-month group. If at some point he went on to receive an additional 3 months of therapy (total of 6 months of treatment), he would then start to contribute information to the GnRH agonist 5- to 12-month group. Tests were performed for interaction between age, race, prostate tumor stage, or prostate tumor grade and the androgen deprivation variable on the outcome of colorectal cancer; none of these associations were statistically significant (using age as a continuous variable, and race, grade, and stage as categorical variables with cut points as presented in Table 2). In a separate analysis, additional Cox modeling was performed using androgen deprivation as a fixed rather than time-dependent covariate and examining GnRH agonist or orchiectomy use limited to the first year after diagnosis of prostate cancer. This model yielded similar results to the main model and the findings are therefore not presented. In this model, the proportionality assumption for the effect of androgen deprivation was verified by determining that the logarithm of the baseline cumulative hazard rates and the Schoenfeld residuals were proportional with follow-up time.

Because this study is observational, propensity score methods were used in an additional analysis to improve the balance of measured confounders between the groups with and without androgen deprivation. Briefly, the propensity scores were generated from a logistic regression model that predicted use of androgen deprivation over the study period. The propensity score quintile was then entered as an independent variable in the Cox model described above along with any covariates that remained statistically significantly imbalanced between the groups with and without androgen deprivation within the propensity quintiles.

All analyses were performed using SAS v.9.1 (SAS institute, Cary, NC). All statistical tests were two-sided, with P values less than .05 considered to be statistically significant. The study protocol was approved by the Institutional Review Board at the University of Michigan.

Results

The primary study sample comprised a total of 107 859 men aged 67 years and older with prostate cancer who were diagnosed from January 1, 1993, to December 31, 2002. Of those men, 55 901 (51.8%) received androgen deprivation during the study period: 50 097 (46.4%) received GnRH agonists and 5804 (5.4%) had undergone orchiectomy. Baseline patient and prostate tumor characteristics, with patients stratified into three groups based on whether they received GnRH agonist treatment, orchiectomy, or no androgen deprivation during the study follow-up, show that patients who received androgen deprivation (GnRH agonists or orchiectomy) were older ($P < .001$; t test for comparison of any use of androgen deprivation vs no androgen deprivation) and more likely to have clinical stage T4 tumors ($P < .001$; χ^2 for comparison of any use of androgen deprivation vs no androgen deprivation) or tumors with poorly differentiated or undifferentiated histology ($P < .001$; χ^2 for comparison of any use of androgen deprivation vs no androgen deprivation) (Table 2). The frequency of obesity and diabetes before the diagnosis of prostate cancer was similar in the three groups, although it was most common in the GnRH agonist group and least common in the orchiectomy group.

We calculated the unadjusted incidence rates of colorectal cancer during GnRH agonist therapy, after orchiectomy, or during periods of no androgen deprivation, stratified by various patient and prostate cancer characteristics (Table 3). The incidence of colorectal cancer was highest among men who had orchiectomies, at 6.3 cancers per 1000 person-years (95% CI = 5.3 to 7.5), intermediate among men taking GnRH agonist therapy, at 4.4 cancers per 1000 person-years (95% CI = 4.0 to 4.9), and lowest among men with no androgen deprivation at 3.7 cancers per 1000 person-years (95% CI = 3.5 to 3.9). This pattern was generally consistent within strata of patient and prostate cancer characteristics.

We tabulated the stage, grade, and proximal vs distal colon site of the 2035 colorectal tumors that were diagnosed over the study period as a function of androgen deprivation exposure (Table 4). There was a statistically significant difference across the three groups (no androgen deprivation, GnRH agonist, and orchiectomy) in the proportion of colorectal tumors that were poorly differentiated or undifferentiated ($P = .013$; χ^2 test), with orchiectomy patients having the highest proportion of such tumors. Tumor stage and site were not associated with androgen deprivation exposure.

The risk of developing colorectal cancer associated with androgen deprivation was assessed with a Cox regression model adjusted for patient and prostate cancer variables (Table 5). Subjects were followed for a mean of 59.4 months after diagnosis. The risk of colorectal cancer increased with increasing duration of GnRH agonist therapy over the study period and was highest for men who underwent orchiectomy ($P_{trend} = .01$). Compared with men receiving no androgen deprivation, there was a gradient of increasing risk of colorectal cancer, from men who received 13–24 months of GnRH agonist therapy (adjusted HR = 1.19, 95% CI = 1.00 to 1.41), to men who received 25 months or more of GnRH agonist therapy (adjusted HR = 1.31, 95% CI = 1.12 to 1.53) and, to men who underwent orchiectomy (adjusted HR = 1.37, 95% CI = 1.14 to 1.66). Other factors that were associated with colorectal cancer in the model included older age, black race, residence in a zip code with lower rates of high school graduation, or a diagnosis of diabetes mellitus before diagnosis of prostate cancer. Use of lower gastrointestinal endoscopy after diagnosis of prostate cancer (entered as a time-dependent covariate) was associated with a statistically significantly lower risk of colorectal cancer.

When these men were included, the results from the Cox model remained similar to the main analysis presented in Table 5: compared with men who received no androgen deprivation,

Table 2. Distribution of patient and prostate tumor characteristics in men who received gonadotropin-releasing hormone (GnRH) agonist treatment, orchiectomy, or no androgen deprivation over study follow-up

Characteristic	No.	Exposure to androgen deprivation over study follow-up		
		None, %	GnRH agonist therapy, %	Orchiectomy, %
Total	107859	51958	50097	5804
Age, y*				
67–69	19899	23.3	14.5	9.3
70–74	36413	37.0	31.7	22.8
75–79	28708	23.7	29.4	28.3
≥80	22839	16.0	24.4	39.7
Race				
White	86524	80.9	79.6	80.3
Black	10286	10.0	9.2	8.4
Hispanic	4598	4.0	4.3	5.6
Other or unknown	6451	5.2	6.9	5.8
Married				
No	34428	30.2	33.5	33.8
Yes	73431	69.8	66.5	66.2
Prostate tumor grade†				
Well differentiated	9013	11.6	5.3	5.8
Moderately differentiated	66389	67.5	57.6	41.7
Poorly differentiated or undifferentiated	24268	13.1	30.0	41.6
Unknown	8189	7.7	7.1	10.9
Prostate tumor clinical stage‡				
T1	32925	36.0	26.8	14.4
T2	56458	52.2	54.0	39.6
T3	4126	2.9	4.4	7.6
T4	6248	2.2	7.0	27.6
Unknown	8102	6.7	7.9	10.8
Zip code education, % of adults with <12 y education				
<9.4	25710	25.3	22.9	18.8
8.4 to <14.8	26305	24.2	24.4	26.0
14.8–23.5	25778	23.6	24.0	25.4
≥23.5	25739	22.8	24.8	25.5
Unknown	4327	4.1	3.9	4.2
Zip code median income				
<$36000	27065	24.3	25.3	30.4
$36000 to <$46000	23889	22.1	21.9	24.8
$46000 to <$60000	25897	24.5	23.6	22.5
≥$60000	26681	25.0	25.3	18.0
Unknown	4327	4.1	3.9	4.2
Comorbidity index				
0	79412	81.5	78.9	78.5
1	19388	12.3	14.1	14.3
2	6001	4.0	4.8	2.8
≥3	3058	2.2	2.3	2.6
Diabetes mellitus in the period 24 mo before diagnosis				
No	90412	84.7	82.6	86.5
Yes	17447	15.3	17.4	13.5
Obesity in the period 24 mo before diagnosis				
No	105156	97.7	97.2	98.6
Yes	2703	2.3	2.8	1.4
Number of primary care physician visits in the period 12–24 mo before diagnosis				
0	41231	40.0	35.4	46.9
1	15031	14.3	13.6	13.3
2	12427	11.7	11.5	10.0
≥3	39170	33.9	39.5	29.9
Lower gastrointestinal endoscopy in the period 12–24 mo before diagnosis				
No	101182	93.4	93.9	96.3
Yes	6677	6.6	6.1	3.7

* Patients with androgen deprivation (any form) were older than those without (P <.001, two-sided t test).

† Patients with androgen deprivation (any form) were more likely to have poorly differentiated or undifferentiated tumors (P < .001, two-sided χ^2 test).

‡ Patients with androgen deprivation (any form) were more likely to have stage T4 tumors than those without (P < .001, two-sided χ^2 test).

Table 3. Unadjusted incidence rates of colorectal cancer for men on gonadotropin-releasing hormone (GnRH) agonist therapy, after orchiectomy, or with no androgen deprivation, stratified by patient and prostate cancer characteristics

	Incidence rate of colorectal cancer per 1000 person-years (95% CI)		
Characteristic	**No androgen deprivation**	**GnRH agonist therapy**	**Orchiectomy**
Total	3.7 (3.5 to 3.9)	4.4 (4.0 to 4.9)	6.3 (5.3 to 7.5)
Age, y			
67–69	3.0 (2.6 to 3.4)	3.2 (2.2 to 4.5)	6.3 (3.5 to 10.6)
70–74	3.4 (3.2 to 3.7)	3.9 (3.1 to 4.8)	6.3 (4.4 to 8.9)
75–79	4.1 (3.7 to 4.5)	4.6 (3.8 to 5.5)	5.6 (3.9 to 7.7)
≥80	5.0 (4.4 to 5.6)	5.3 (4.4 to 6.3)	6.9 (5.2 to 9.0)
Race			
White	3.6 (3.4 to 3.8)	4.6 (4.1 to 5.2)	6.4 (5.3 to 7.7)
Black	5.3 (4.6 to 6.1)	5.0 (3.5 to 6.8)	6.5 (3.1 to 12.0)
Hispanic	3.6 (2.7 to 4.7)	4.1 (2.3 to 6.9)	4.4 (1.4 to 10.2)
Other or unknown	2.4 (1.8 to 3.1)	1.8 (0.9 to 3.2)	6.2 (2.7 to 12.1)
Married			
No	3.8 (3.4 to 4.1)	3.8 (3.1 to 4.6)	5.8 (4.2 to 7.9)
Yes	3.7 (3.5 to 3.9)	4.7 (4.2 to 5.4)	6.6 (5.3 to 8.0)
Prostate tumor grade*			
Well differentiated	4.3 (3.7 to 5.0)	4.2 (2.6 to 6.4)	4.0 (1.5 to 8.7)
Moderately differentiated	3.6 (3.3 to 3.8)	4.4 (3.8 to 5.0)	7.4 (5.8 to 9.3)
Poorly differentiated or undifferentiated	3.8 (3.3 to 4.3)	4.4 (3.7 to 5.3)	5.8 (4.3 to 7.7)
Prostate tumor clinical stage†			
T1	3.4 (3.1 to 3.8)	3.9 (3.0 to 4.9)	3.7 (1.9 to 6.4)
T2	3.8 (3.5 to 4.0)	4.4 (3.8 to 5.1)	7.2 (5.6 to 9.2)
T3	4.3 (3.4 to 5.4)	4.6 (2.8 to 7.0)	6.3 (3.3 to 11.0)
T4	4.0 (2.7 to 5.7)	3.6 (2.3 to 5.4)	7.0 (4.9 to 9.9)
Zip code education,‡ % of adults with less than 12 y education			
< 8.4	3.2 (2.8 to 3.5)	4.2 (3.3 to 5.3)	5.6 (3.6 to 8.3)
8.4 to <13.3	3.6 (3.2 to 4.0)	4.2 (3.3 to 5.2)	6.0 (4.2 to 8.3)
13.4 to 20.3	4.2 (3.8 to 4.6)	4.7 (3.8 to 5.7)	6.4 (4.4 to 8.9)
≥20.4	4.3 (3.9 to 4.8)	4.6 (3.8 to 5.7)	7.1 (5.0 to 9.8)
Zip code median income‡			
<$37 500	4.3 (3.9 to 4.8)	4.7 (3.9 to 5.7)	6.4 (4.6 to 8.6)
$37 500 to <$47 500	3.8 (3.4 to 4.2)	4.1 (3.2 to 5.1)	7.0 (5.0 to 9.5)
$47 500 to <$62 000	3.8 (3.4 to 4.2)	4.4 (3.5 to 5.5)	4.7 (3.0 to 7.1)
≥ $62 000	3.3 (3.0 to 3.7)	4.4 (3.6 to 5.5)	7.1 (4.8 to 10.2)
Comorbidity index			
0	3.7 (3.5 to 3.9)	4.0 (3.6 to 4.6)	6.5 (5.4 to 7.9)
1	3.9 (3.4 to 4.4)	5.3 (4.2 to 6.6)	4.9 (2.9 to 7.8)
2	3.7 (2.7 to 4.7)	5.3 (3.5 to 7.7)	6.0 (2.2 to 13.0)
≥3	2.4 (1.4 to 3.8)	5.8 (3.1 to 10.0)	10.3 (3.3 to 24.0)
Diabetes mellitus in the period 24 mo before diagnosis			
No	3.6 (3.4 to 3.8)	4.3 (3.8 to 4.8)	6.4 (5.3 to 7.7)
Yes	4.2 (3.7 to 4.8)	4.9 (3.8 to 6.3)	5.6 (3.1 to 9.2)
Obesity in the period 24 mo before diagnosis			
No	3.7 (1.7 to 3.9)	4.4 (4.0 to 4.9)	6.3 (5.3 to 7.5)
Yes	2.6 (1.7 to 3.9)	4.5 (2.0 to 8.5)	7.2 (0.9 to25.9)
Number of primary care physician visits in the period 12–24 mo before diagnosis			
0	3.8 (3.5 to 4.1)	5.0 (4.3 to 5.9)	6.1 (4.7 to 7.9)
1	3.6 (3.1 to 4.1)	2.9 (1.9 to 4.1)	5.6 (3.3 to 8.9)
2	3.6 (3.1 to 4.2)	4.4 (3.2 to 6.0)	5.8 (3.1 to 9.9)
≥3	3.7 (3.4 to 4.0)	4.3 (3.6 to 5.1)	7.2 (5.2 to 9.6)
Lower gastrointestinal endoscopy in the period 12–24 mo before diagnosis			
No	3.8 (3.6 to 4.0)	4.5 (4.0 to 5.0)	6.4 (5.3 to 7.6)
Yes	2.5 (1.9 to 3.1)	3.3 (1.9 to 5.4)	4.9 (1.3 to 12.5)

* Results for 8189 cases with unknown prostate tumor grade not presented.

† Results for 8102 cases with unknown prostate tumor stage not presented.

‡ Results for 4327 cases with missing zip code information not presented.

there was an increased risk of colorectal cancer in men who received 13–24 months of GnRH agonist therapy (adjusted HR = 1.24, 95% CI = 1.08 to 1.42), in men who received 25 months or more of GnRH agonist therapy (adjusted HR = 1.24, 95% CI = 1.08 to 1.41) and in men who underwent orchiectomy (adjusted HR = 1.34, 95% CI = 1.14 to 1.57).

Table 4. Characteristics of colorectal cancers as a function of receipt of androgen deprivation*

Androgen deprivation	No. colorectal cancer patients	Tumor stage†		Tumor grade‡		Site of tumor§	
		% Localized	*P*‖	% Poorly differentiated or undifferentiated	*P*‖	% Distal	*P*‖
None	1048	48.0	.073	21.4	.013	53.1	.489
GnRH agonist	849	51.8		18.6		55.6	
Orchiectomy	138	41.5		30.6		52.2	

* GnRH = gonadotropin-releasing hormone; SEER = Surveillance, Epidemiology, and End Results.

† Based on SEER historical staging system, categorized as in situ or localized, regional, or distant spread; for the 1701 patients diagnosed from SEER files and having stage information available.

‡ Based on SEER grading system, categorized as well differentiated, moderately differentiated, poorly differentiated or undifferentiated; for the 1676 patients diagnosed from SEER files and having grade information available.

§ Site of tumor categorized as proximal (cecum through splenic flexure) vs distal (descending colon through rectum) based on SEER files.

‖ All *P* values are two-sided and are based on χ^2 tests for differences in the proportion of colorectal tumors with the characteristic of interest across the androgen deprivation exposure groups.

Because radiation therapy for prostate cancer has been associated in some studies with the development of rectal cancer, we performed additional analyses to exclude this as a contributing factor to the observed results. We repeated the Cox model after excluding patients who received radiation therapy at any time following diagnosis of prostate cancer. The results were essentially unchanged (adjusted HR for development of colorectal cancer for patients who received ≥25 months of GnRH agonist therapy = 1.35, 95% CI = 1.12 to 1.63; for patients who underwent orchiectomy, adjusted HR = 1.36, 95% CI = 1.10 to 1.69). Findings were also similar when the original Cox model was performed to examine development of colon cancer only, with rectal cancers excluded: for patients who received 25 months or more of GnRH agonist therapy, adjusted hazard ratio = 1.27 (95% CI = 1.06 to 1.52) and for men who underwent orchiectomy, adjusted hazard ratio = 1.30 (95% CI =1.04 to 1.63). The corresponding adjusted hazard ratios for the development of rectal cancer only (colon cancers excluded) were 1.42 (95% CI = 1.04 to 1.93) in patients who received 25 months or more of GnRH agonist therapy and 1.54 (95% CI = 1.08 to 2.20) in patients who underwent orchiectomy.

Finally, in a propensity score–adjusted Cox model that was designed to improve the balance of measured confounders between the groups with and without androgen deprivation, the results were again similar to the main findings in Table 5. The adjusted hazard ratios were 1.28 (95% CI = 1.09 to 1.49) for men who received 25 months or more of GnRH agonist therapy, and 1.42 (95% CI = 1.18 to 1.72) for men who underwent orchiectomy.

Additional analyses were performed to examine potential issues of mediation and residual confounding. Because diabetes mellitus is a known risk factor for colorectal cancer and androgen deprivation therapy has been associated with the development of diabetes mellitus (6), we explored whether the observed effect of androgen deprivation on colorectal cancer was mediated by the development of diabetes. We limited the cohort of patients to those without diabetes before diagnosis of prostate cancer and performed the Cox model in Table 5 with and without the inclusion of a time-dependent variable denoting an incident diagnosis of diabetes after diagnosis of prostate cancer. The association between androgen deprivation therapy and colorectal cancer was unaffected by the inclusion of the incident diabetes diagnosis variable (data not shown), suggesting that diabetes was not mediating the effect of androgen deprivation on colorectal cancer risk in our model. Because obesity (defined by body mass index of 30 or more) is a strong risk factor for colorectal cancer (19,20), we explored the potential effect of confounding by obesity on our findings. Although we incorporated a Medicare claims–based obesity variable into the model in Table 5, this variable likely grossly underestimates the true prevalence of obesity due to poor capture of this condition by Medicare claims. We therefore performed sensitivity analyses (27) assuming the presence of an obesity variable with a prevalence of 30% in the group without androgen deprivation [based on the known prevalence of obesity among elderly males in the United States (28)]. Our results were robust to assumptions of up to a 50% higher rate of obesity in the androgen deprivation groups and hazard ratios of 1.5 to 2.0 for risk of colorectal cancer associated with obesity (results shown in Supplementary Table 1, available online).

Discussion

This study provides strong evidence to link androgen deprivation therapy in the setting of prostate cancer to an increased risk of colorectal cancer. After adjustment for a number of potentially confounding variables, there was a 30%–40% increase in the rate of colorectal cancer among men with prostate cancer who were treated with androgen deprivation therapy compared with men with prostate cancer who were not.

There was also a statistically significant dose–response effect, with a higher risk of colorectal cancer with an increasing duration of androgen deprivation, providing support that the observed association between androgen deprivation and colorectal cancer in the setting of prostate cancer may be causal. The study findings also have biological plausibility. Indeed, androgen receptors are present in both normal and malignant human colonic tissues (29,30), and in various animal studies, administration of androgens protects against colon carcinogenesis, whereas androgen ablation promotes it (9,10,12,13). The vast majority of colorectal cancers are related to abnormal activation of Wnt/β-catenin/T-cell factor signaling (31), and there is a large body of evidence that indicates that androgen receptor activation can strongly repress this signaling in colon cancer cells (32–35). This effect is related to competition between

Table 5. Risk of colorectal cancer associated with androgen deprivation therapy*

Characteristic	Unadjusted colorectal cancer risk HR,†‡ (95% CI)	Adjusted colorectal cancer risk HR,‡§ (95% CI)	*P*‖
Androgen deprivation therapy			
None	1.00 (referent)	1.00 (referent)	.002
GnRH agonist 1–4 mo	1.01 (0.87 to 1.17)	1.07 (0.92 to 1.24)	
GnRH agonist 5–12 mo	1.11 (0.97 to 1.27)	1.12 (0.97 to 1.30)	
GnRH agonist 13–24 mo	1.29 (1.09 to 1.52)	1.19 (1.00 to 1.41)	
GnRH agonist ≥ 25 mo	1.48 (1.27 to 1.72)	1.31 (1.12 to 1.53)	
Orchiectomy	1.68 (1.41 to 2.01)	1.37 (1.14 to 1.66)	
Age (for every 5 y older)		1.18 (1.13 to 1.23)	<.001
Race			
White		1.00 (referent)	<.001
Black		1.24 (1.06 to 1.46)	
Hispanic		0.90 (0.71 to 1.15)	
Other or unknown		0.52 (0.40 to 0.68)	
Married			
No		1.00 (referent)	.014
Yes		1.13 (1.03 to 1.25)	
Prostate tumor grade			
Well differentiated		1.00 (referent)	.794
Moderately differentiated		0.93 (0.80 to 1.08)	
Poorly differentiated or undifferentiated		0.92 (0.78 to 1.09)	
Unknown		0.92 (0.74 to 1.14)	
Prostate tumor clinical stage			
T1		1.00 (referent)	.374
T2		1.11 (1.00 to 1.23)	
T3		1.16 (0.94 to 1.44)	
T4		1.10 (0.87 to 1.39)	
Unknown		1.10 (0.91 to 1.31)	
Zip code education, % adult less than 12 y education			
<9.4		1.00 (referent)	.003
8.4 to <14.8		1.08 (0.94 to 1.24)	
14.8–23.5		1.24 (1.06 to 1.46)	
≥23.5		1.26 (1.02 to 1.54)	
Zip code median income			
<$36 000		1.00 (referent)	.860
$36 000 to <$46 000		0.95 (0.83 to 1.10)	
$46 000 to <$60 000		1.00 (0.84 to 1.18)	
≥$60 000		1.01 (0.82 to 1.25)	
Comorbidity index			
0		1.00 (referent)	.766
1		1.04 (0.91 to 1.19)	
2		0.97 (0.77 to 1.23)	
≥3		0.85 (0.58 to 1.24)	
Lower gastrointestinal endoscopy performed after diagnosis			
No		1.00 (referent)	< .001
Yes		0.64 (0.56 to 0.72)	
Diabetes mellitus in the period 24 mo before diagnosis			
No		1.00 (referent)	.030
Yes		1.15 (1.01 to 1.30)	
Obesity in the period 24 mo before diagnosis			
No		1.00 (referent)	.269
Yes		0.83 (0.59 to 1.16)	

* CI = confidence interval; GnRH = gonadotropin-releasing hormone; HR = hazard ratio.

† Based on a Cox regression model with time to occurrence of colorectal cancer as the dependent variable and only androgen deprivation entered as a time-dependent covariate with the outcome censored at death, loss or switch away from Medicare coverage or end of the study period.

‡ Excluding patients who developed colorectal cancer or died within 6 months of diagnosis of prostate cancer.

§ Based on a Cox regression model with time to occurrence of colorectal cancer as the dependent variable, androgen deprivation entered as a time-varying covariate, and age at time of prostate cancer diagnosis, race, marital status, prostate tumor grade, prostate tumor stage, year of diagnosis, SEER region of residence, percentage with less than 12 years of education in zip code of residence, median income in zip code of residence, number of primary care physician visits in the period 12–24 months before diagnosis of prostate cancer, whether lower gastrointestinal endoscopy was performed in the period 12–24 months before diagnosis of prostate cancer, presence of diabetes mellitus in the period 24 months before diagnosis, presence of obesity in the period 24 months before diagnosis and performance of lower gastrointestinal endoscopy after diagnosis (as a time-dependent covariate) entered as independent variables. Outcome was censored at death, loss or switch away from Medicare part A or B coverage or at end of study period. Results for SEER region, year of diagnosis, number of primary care physician visits in the period 12–24 months before diagnosis of prostate cancer and whether lower gastrointestinal endoscopy was performed in the period 12–24 months before diagnosis of prostate cancer are not presented.

‖ *P* values are two-sided and are based on the Cox model and test whether any differences exist within categories of the independent variables.

androgen receptors and T-cell factor for binding to β-catenin, and it can be reversed by anti-androgen administration. In support of this line of evidence, androgen receptor expression levels in colorectal tumors have been shown to be lower than those found in samples of normal mucosa (29,30). Our findings are also consistent with the results of a large clinical trial in postmenopausal women that showed that estrogen plus progestin replacement reduces the risk of colorectal cancer. The authors of that study hypothesized that the protective effect may have been related in part to correction of hyperinsulinemia in estrogen-deficient women (36). Hyperinsulinemia and its correlates, type 2 diabetes mellitus, obesity, and metabolic syndrome are strong risk factors for colorectal cancer (15). Postulated mechanisms for this effect include the ability of insulin to stimulate proliferation and delay apoptosis in colon cancer cells (37,38). Although we were unable to demonstrate that new onset diabetes mediates the effect of androgen deprivation on risk of colorectal cancer in our analysis, the hyperinsulinemia and obesity known to develop in men receiving androgen deprivation therapy for prostate cancer may nevertheless be another potential causal mechanism for our study findings (14).

Given the observational nature of this study, confounding factors that may account for the apparent association between androgen deprivation therapy and colorectal cancer must be considered. Older age is associated both with use of androgen deprivation therapy for prostate cancer and with risk of colorectal cancer (39,40). Lack of routine preventive care or lower socioeconomic status may lead to later stage presentation of prostate cancer, which increases the likelihood of treatment with androgen deprivation, and may also be associated with occurrence of colorectal cancer (41,42). However, the association between androgen deprivation and colorectal cancer persisted after adjustment for age and measures of socioeconomic status and preventive care. Increased medical surveillance resulting from frequent healthcare contacts in men receiving GnRH agonist injections may have led to an increase in colorectal cancer diagnoses. However, if this were the case, a higher proportion of early-stage colorectal tumors would have been expected in the androgen deprivation groups, which was not observed (Table 3). In addition, the risk of colorectal cancer associated with androgen deprivation remained after adjustment for ongoing performance of lower gastrointestinal endoscopies following the diagnosis of prostate cancer. Several other factors associated with colorectal cancer, such as family history, use of nonsteroidal anti-inflammatory drugs, or a history of smoking or heavy alcohol use, could not be assessed in the database. However, as these are not plausibly related to use of androgen deprivation therapy for prostate cancer, they would not be confounders in the analysis. Finally, obesity may be an important confounder because it is known to increase the risk of colorectal cancer in men, and although controversial, has in some studies been associated with higher grade or advanced stage prostate tumors, which are more likely to be treated with androgen deprivation therapy (21,43,44). We examined the degree to which there was imbalance in rates of baseline obesity or diabetes (as a proxy for obesity) as a function of androgen deprivation exposure using Medicare claims–based algorithms. Men who went on to receive GnRH agonists were somewhat more likely to be obese or diabetic when compared with men who never received androgen deprivation therapy, but the lowest rates were in men who received orchiectomy (Table 2). Despite the differences in rates of obesity between the GnRH agonist and orchiectomy groups, both were associated with an increased risk of colorectal cancer, making confounding by obesity less likely. However, given the limitations in the ability to assess obesity based on Medicare claims, we also performed sensitivity analyses to examine the potential impact of obesity on our findings. The association between androgen deprivation and colorectal cancer was robust to assumptions of as much as a 50% higher rate of obesity in the androgen deprivation groups. Nevertheless, in future studies on this issue, it will be important to collect detailed information on baseline obesity.

Beyond issues of confounding, there are other important limitations of this study. Because the study used Medicare data, it was limited to an older cohort of patients. The association between androgen deprivation and colorectal cancer may be different in younger men. It is also important to note that this study was performed entirely among men with prostate cancer. It is conceivable that men with prostate cancer may be more susceptible to the development of colorectal cancer. The expected incidence of colorectal cancer in our study cohort (by matching to general population SEER data on age, sex, race, and calendar year) is 3.1 (95% CI = 2.8 to 3.4) per 1000 person-years, which is lower than the rate (3.7 per 1000 person-years) we observed in our "control" group of men with prostate cancer who did not receive androgen deprivation therapy. As such, caution is warranted when extrapolating our findings outside the context of prostate cancer.

The study results have important implications for men with prostate cancer who are receiving or contemplating initiation of androgen deprivation therapy. Despite a moderate relative risk for colorectal cancer, the impact may nevertheless be large, given that hundreds of thousands of men are on androgen deprivation therapy for prostate cancer (1). Androgen deprivation continues to be used as a primary therapy for localized prostate cancers and for treatment of biochemical recurrence after radical prostatectomy or radiation despite lack of convincing evidence of survival benefit (5,45). In both scenarios, the therapy is likely to be of a prolonged duration given the generally slow progression of disease. Even a small risk of developing a possibly lethal second cancer must be weighed carefully when androgen deprivation therapy is considered in scenarios where its benefits are unclear. However, the size of the study sample did not allow us to examine the impact of the diagnosed colorectal cancers in this study on overall mortality. Consequently, the study findings should not preclude use of androgen deprivation in settings where clinical trials have clearly shown improvements in overall survival. The study findings also highlight the importance of routine preventive care, such as screening for other cancers, in prostate cancer survivors receiving androgen deprivation therapy. The diagnosis of prostate cancer may dominate the focus of medical care, to the detriment of other necessary aspects of care. For example, in colon and breast cancer settings, patients followed by both a primary care physician and a medical oncologist received a higher proportion of recommended preventive care as compared with those only followed by an oncologist (46,47). Men on androgen

deprivation therapy may therefore especially benefit from the continued involvement of a primary care physician in their care in addition to their cancer specialist.

A final point is that the study findings may have broader implications, beyond the field of prostate cancer. Androgen deficiency is now recognized as a relatively common occurrence in the male general population, with one estimate placing the prevalence at 2.4 million men in the United States and incidence at nearly half a million a year (48). Whether the androgen deficiency seen in the general population predisposes importantly to colorectal cancer risk will need to be explored further. In addition, clinical trials of testosterone replacement should consider including colorectal cancer as an outcome.

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