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Androgen deprivation therapy for prostate cancer is associated in increased risk for biliary disease

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Abstract

Background—Androgen deprivation therapy (ADT) for prostate cancer produces benefits in several clinical situations but has adverse metabolic effects including obesity, increased abdominal girth, increased triglycerides, and insulin resistance. Each of these is a risk factor for gallstone disease. ADT with a gonadotropin releasing hormone (GnRH) agonist was recently shown in metabolomic analyses to increase plasma levels of some bile acids. We assessed whether ADT is associated with an increased incidence of biliary disease.

Methods—We studied 249,977 men aged >65 living in Surveillance, Epidemiology, and End Results regions who were diagnosed with prostate cancer during 1992–2007 and followed through 2009. We calculated incidence rates for biliary disease during treatment with GnRH agonists, orchiectomy, or no therapy. We used Cox proportional hazard models to assess the association of ADT with biliary disease.

Results—Among 185,106 men with local/regional prostate cancer, 47.8% received GnRH agonist treatment and 2.2% underwent bilateral orchiectomy during follow-up. GnRH agonist treatment was associated with significantly higher incidence of biliary disease compared with no treatment (14.46 vs. 12.44 cases per 1,000 person years; $P < 0.001$). In adjusted analyses GnRH agonist use was associated with risk of biliary disease (adjusted hazard ratio=1.09, 95% confidence interval 1.04–1.14; $P < 0.001$). Orchiectomy was not significantly associated with biliary disease.

Conclusions—GnRH agonist treatment may be associated with an increased risk of incident biliary disease. This potential risk must be weighed against the potential benefits of therapy.

Keywords

prostate cancer; biliary disease; androgen deprivation therapy; GnRH agonist; orchiectomy

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Introduction

Androgen deprivation therapy (ADT) with a gonadotropin releasing hormone (GnRH) agonist is the central systemic therapy for prostate cancer. It improves survival when given for metastatic disease¹, in combination with external beam radiation for intermediate or high risk localized disease²⁻⁸, or after prostatectomy for node-positive disease⁹. Nonetheless, prospective studies have demonstrated that GnRH agonists use causes several adverse metabolic changes. It is associated with loss of lean muscle mass (approximately 3%) and gain of fat mass (approximately 10%)¹⁰⁻¹³, particularly abdominal fat^{10, 14}. It is associated with an increase in triglycerides (approximately 26%) and total cholesterol (approximately 7-10%).^{10, 15, 16} Finally, it is associated with a rise in fasting insulin^{15, 17} and diminished sensitivity to insulin^{14, 18}. Population-based studies have found that GnRH agonists are associated with an increased incidence of diabetes.¹⁹⁻²¹

Gallstone disease is a prevalent problem in the United States as gallstones are present in at least 8% of men over the age of 40.²² Approximately 80% of all gallstones are composed primarily of cholesterol, with the remaining 20% consisting of pigment stones. The presence of gallstones increases the risk for symptomatic biliary disease such as choledocholithiasis and cholecystitis. Cholecystectomy is the most common elective abdominal surgery in the U.S.²³ Risk factors for gallstone disease are numerous and include ethnic background, female sex, increasing age, family history, certain drugs, rapid weight loss, diet, total parenteral nutrition, and sedentary lifestyle.²⁴ Several risk factors for gallstone disease are side effects of ADT., including obesity²⁵⁻²⁸, abdominal girth²⁸, hypertriglyceridemia^{29, 30}, and insulin resistance^{31, 32}.

Hypothesis-driven prospective studies of ADT-induced adverse effects have focused primarily on metabolic problems associated with obesity (e.g. hypertriglyceridemia, impaired insulin sensitivity). Metabolomics is a technique that can be used to screen more broadly for hormones and small-molecule metabolites of potential biologic significance.³³ Unbiased plasma metabolomic analyses were recently carried out on baseline and 12-week plasma samples from hormone-naïve men initiating GnRH agonist therapy for prostate cancer. These studies demonstrated qualitative increases in most measured bile acids during the first 12 weeks of treatment.³⁴ The causative mechanism(s) and the clinical implications of this novel finding are not yet known. Quantitative changes in individual bile acids and are also not yet known.

Given the metabolic changes observed with ADT and the metabolomics analyses described, we hypothesized that ADT would be associated with a higher incidence of biliary disease such as cholecystitis necessitating percutaneous drainage and/or cholecystectomy. We conducted population-based analyses of older men with prostate cancer to examine whether ADT is associated with biliary disease.

Methods

Data

We used Surveillance, Epidemiology, and End Results (SEER)-Medicare data, which combines uniformly reported data from population-based cancer registries covering approximately 28% of the U.S. population with Medicare administrative data.^{35, 36} For each incident cancer, SEER registrars document patient demographics, tumor characteristics, and primary treatments. Additional information about healthcare utilization, including treatments and comorbid illness, can be ascertained from the Medicare claims.

Cohort

We identified men with a first diagnosis of prostate cancer during 1992-2007 who were aged >65 years and continuously enrolled in Parts A and B of fee-for-service Medicare as of 1 year before diagnosis (N=249,977). We excluded men diagnosed at death or autopsy (N=3,372), those without administrative claims in the 6 months around diagnosis (because we were concerned about incomplete data; N=6,411). We then restricted the cohort to 185,106 men with local/regional stage disease at diagnosis.

Biliary disease

We identified biliary disease using diagnosis codes for acute cholecystitis or common bile duct stones, or procedure codes for open or laparoscopic cholecystectomy, biliary drainage, biliary track surgery, injection for cholangiography, biliary endoscopy, biliary stone extraction, cholecystography, cholangiography endoscopic catheterization of the biliary ducts, dilation of the biliary ducts, or other hepatobiliary diagnostic procedures.³⁷⁻³⁹ We classified each patient as having (1) surgery or biliary procedures and (2) biliary disease based on diagnosis code only, which required a primary diagnosis code or diagnosis-related group code on an inpatient admission or at least 2 claims associated with an outpatient office visit or a secondary diagnosis code on an inpatient admission. If a patient's first code was a diagnosis code only, but the patient later had a biliary procedure, he was coded as having biliary disease based on a procedure at the time of the first diagnosis code.

Androgen deprivation therapy

We ascertained receipt of androgen deprivation therapy, including gonadotropin releasing hormone (GnRH) agonists and bilateral orchiectomy (Appendix) based on administrative data. Most doses were for 3- or 4-month equivalent doses. Since hypogonadism may persist for prolonged periods after GnRH agonist discontinuation,^{40, 41} men were considered continuously treated for 6 months after each dose of GnRH agonist.

Control variables

We characterized each man's age at diagnosis, race, Hispanic ethnicity, marital status, year of diagnosis, tumor grade and size, type of primary treatment (surgery, radiation, or neither),^{21, 42} SEER region, urban residence, census-tract level income and education (categorized in quartiles within registries). We characterized comorbid illness during the 12

months before diagnosis using the Klabunde modification⁴³ of the Charlson score.⁴⁴ Variables were categorized as detailed in Table 1.

Analyses

Men were censored on December 31, 2009 (the last date for which data were available) or sooner if they died or disenrolled from Parts A and B of fee-for-service Medicare. We calculated incidence rates for biliary disease (overall and based on diagnosis codes or procedure codes) during treatment with GnRH agonists, orchiectomy, or no therapy. Using time-varying treatment variables, men contributed information to the treatment groups only when on treatment. We used two-sample hypotheses tests to assess whether rates with orchiectomy and GnRH agonist treatment differed from rates without these therapies. We used Cox proportional hazard models to assess the association of ADT with biliary disease. These models included time-varying variables for use of ADT. Men were followed until developing an event of interest or censoring. In sensitivity analyses, we repeated the unadjusted and adjusted analyses defining biliary disease as (1) receipt of a biliary procedure or surgery and (2) based on diagnosis codes only.

All tests of statistical significance were two-sided; analyses were conducted with SAS statistical software, version 9.2 (SAS Institute, Inc., Cary, North Carolina). The study was approved by the Harvard Medical School Human Subjects Committee.

Results

The mean age (standard deviation) of the 185,106 men with local/regional prostate cancer diagnosed in 1992 through 2007 was 74.3 (5.9). Overall, 47.8% of men received GnRH agonists and 2.2% underwent bilateral orchiectomy at some time after their prostate cancer diagnosis. Table 1 shows use of androgen deprivation by patient characteristics. The median duration of treatment for men who received ADT was 450 days (interquartile range 96-804).

Table 2 displays the association of ADT with biliary disease. GnRH agonist use was associated with significantly higher incidence of biliary disease. The unadjusted rate of biliary disease was 14.46 per 1000 person years with GnRH agonist therapy and was 12.44 without ADT ($P < 0.001$). In adjusted analyses using Cox proportional hazards models with time varying treatment variables and adjusted for all variables in Table 1 and year of diagnosis, GnRH agonist use was associated with an adjusted hazard ratio of 1.09 (95% confidence interval 1.04 – 1.14; $P < 0.001$). No significant difference in biliary disease was seen for men who underwent orchiectomy compared with men not currently treated with ADT (adjusted hazard ratio 0.91, 95% CI 0.80-1.04; $P = 0.16$).

In sensitivity analyses, the association of GnRH agonists with biliary disease was also seen when we defined biliary disease based only on receipt of a biliary procedure or based on only diagnosis codes (Table 3). When we defined biliary disease based on receipt of a biliary procedure, orchiectomy was associated with a significantly lower adjusted hazard ratio for biliary disease (adjusted hazard ratio 0.86, 95% CI 0.75-0.99; $P = 0.04$).

Discussion

We examined in the incidence of biliary disease among men aged >65 years who were diagnosed with prostate cancer and continuously enrolled in fee-for service Medicare and observed that GnRH agonist use was associated with modestly but significantly higher incidence of biliary disease. To our knowledge, this has not previously been described. It is particularly notable that biliary surgery and/or biliary procedures were performed more often among men receiving GnRH agonist therapy, an observation that demonstrates the clinical significance of the findings.

There are several notable strengths of this study. First, it included a large number of older men from areas representing more than one fourth of the U.S. population. Second, the analyses were hypothesis-driven. Several known adverse effects of ADT are described risk factors for gallstone disease, including obesity²⁵⁻²⁸, increased abdominal girth²⁸, hypertriglyceridemia and insulin resistance²⁹⁻³². Given these factors and the recent observation that plasma bile acids rise during GnRH agonist therapy³⁴, we hypothesized that incidence of biliary disease would be higher in men receiving this therapy. Third, our findings were robust to various definitions of biliary disease, including a requirement that men underwent a biliary procedure or cholecystectomy.

Although the pathophysiology of cholesterol gallstone formation is complex, two broad circumstances typically exist. First, stone formation is more likely when biliary cholesterol concentration is elevated relative to the concentration of the phospholipids and bile acids that maintain cholesterol solubility. Second, cholesterol gallstone and biliary sludge formation are more likely when conditions support cholesterol nucleation and precipitation, such as with bile stasis due to impaired gallbladder motility. Although the present study does not illuminate the mechanism(s) by which GnRH agonist therapy is associated with increased incidence of biliary disease, several aspects deserve specific discussion.

Cholesterol is water insoluble and can only be maintained in aqueous suspension by the presence of an adequate amount of amphipathic bile acids and phospholipids. Anything that increases the relative quantity of cholesterol in bile can promote precipitation and stone formation. Increased biliary secretion of cholesterol can occur a result of tissue catabolism, in the setting of obesity, as a medication effect, or due to other factors. Obesity is associated with increased activity of 3-hydroxyl-3-methyl-glutaryl co-enzyme A (HMG-CoA) reductase, the rate limiting step in hepatocyte cholesterol synthesis; heightened cholesterol synthesis leads to increased cholesterol secretion into bile.^{26, 45, 46} ADT causes both obesity and hypertriglyceridemia and may contribute to this effect. Muscle loss due to ADT may also contribute as tissue catabolism liberates membrane-associated cholesterol.

In addition, abdominal adiposity is a specific side effect of ADT^{10, 14} and is known to be an independent risk factor for gallbladder disease. In the large prospective Health Professionals Follow-Up Study, waist circumference was strongly associated with symptomatic gallstone disease, even after adjustment for body mass index.²⁸

Recent evidence suggests that ADT causes qualitative increases in a number of bile acids within 12 weeks of treatment.³⁴ Although additional studies are needed to further

understand the consequences of these changes, it is possible that they are associated with the increased incidence of biliary disease that we observed. Changes in the size or composition of the bile acid pool can alter the ratio of cholesterol to the other factors that maintain its solubility, since specific bile acids are differentially more or less able to solubilize fats. Thus, these changes have the potential to affect the incidence of gallstone disease. The significance of GnRH agonist-associated plasma bile acid elevations is not known. Effects of ADT on hepatic conversion of cholesterol to primary bile acids and on individual bile acid levels are not known. Further, enteric bacteria are responsible for substantial effects on bile acid composition as they convert primary bile acids to various secondary and tertiary bile acids. Though plasma bile acids appear to rise, biliary bile acids may rise, fall, or remain unchanged. Further study is clearly needed.

It is also possible that other mechanisms could contribute to gallbladder disease among men treated with ADT. Gallbladder dysmotility can result from hormonal changes and increase risk for stone formation.²² Stone formation can also be powerfully affected by changes in biliary concentrations of individual glycoproteins that either promote or prevent nucleation.²² Numerous membrane transporters in hepatocytes and in bile duct epithelial cells play important roles in biliary function and are each subject to regulatory signals.⁴⁷ The effects of ADT on these factors are not known.

ADT was common in the analyzed population with more than 50% of men at least 75 years old receiving ADT at some point during follow up. This is consistent with previous reports that have detailed a rising prevalence of ADT in the 1990s⁴⁸ and stable/common use in more recent years.⁴⁹ ADT-induced adverse effects on bone⁵⁰ and metabolism⁵¹ are prominent concerns. Given the known and emerging adverse effects of ADT, it is important to the health of prostate cancer survivors that clinicians confine its use to situations in which it has convincingly been shown to produce benefits.

Our study has several limitations. First, we identified disease outcomes based on administrative data, which may be subject to some error. Second, we studied older men living in a number of specific regions of the U.S. We therefore can not be certain that our findings can be generalized to other populations. Nevertheless, most prostate cancers are diagnosed in older men, and the SEER areas represent 28% of the U.S. population. Third, we could not ascertain use of oral antiandrogens because oral medications were not available in SEER-Medicare data before 2007 and only for a portion of patients in 2007 onward. Oral antiandrogen monotherapy is not approved for prostate cancer treatment in the U.S., making it unlikely that this is a significant confounding factor. Biliary effects of combined androgen blockade (i.e. GnRH agonist with concurrent oral antiandrogen) can not be addressed with the present analysis. Fourth, differences in healthcare utilization may lead to differences in ascertainment of disease. Men who receive GnRH agonist treatment are typically seen in clinic and may be more likely to have symptoms noted and diagnoses reported. Nevertheless, our results were robust to definitions of biliary disease that required patients to undergo a surgical procedure, which would only be likely with persistently symptomatic disease. Finally, unobserved confounders or differences in healthcare utilization may contribute to the associations we observed. Our use of time varying treatment variables means that men could serve as their own control before or after treatment with ADT, which

would likely lessen any bias. Still, the finding of fewer biliary procedures among men treated with orchiectomy may reflect the fact that orchiectomy is often performed among men who are older and may not be good candidates for future surgical interventions.

In conclusion, we found that the incidence of biliary disease was significantly higher among men receiving GnRH agonist therapy for prostate cancer than men not on ADT. This finding may result from ADT-associated central adiposity, increases in serum triglycerides and fasting insulin, alterations in plasma bile acids, or other factors. Further research is needed to verify this association, clarify the causative mechanism, and optimize medical management in light of this novel finding.

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Appendix

ICD-9 diagnosis and procedure codes and CPT codes for acute cholecystitis and gallstone related disease

Description	ICD-9 Diagnosis	ICD-9 Procedure	HCPCS/CPT	DRG (inpatient)
<i>Acute cholecystitis</i>				
Calculus of gallbladder with acute cholecystitis ³⁷	574.00, 574.01			
Calculus of gallbladder with other cholecystitis ³⁷	574.10, 574.11			
Acute cholecystitis ³⁷	575.0			
Other cholecystitis (excludes 574.4, 574.8, 574.1) ³⁷	575.1			
Obstruction of gallbladder ¹	575.2			
Hydrops of gallbladder ³⁷	575.3			
Perforation of gallbladder ³⁷	575.4			
<i>Common bile duct stones</i>				
Calculus of bile duct without mention of cholecystitis ³⁷	574.20, 574.21			
Calculus of bile duct with acute cholecystitis ³⁷	574.30, 574.31			

Description	ICD-9 Diagnosis	ICD-9 Procedure	HCCPS/CPT	DRG (inpatient)
Calculus of bile duct with other cholecystitis ³⁷	574.40, 574.41			
Calculus of bile duct without mention of acute cholecystitis ³⁷	574.50, 574.51			
Calculus of gallbladder and bile duct with acute cholecystitis ³⁷	574.60, 574.61			
Calculus of gallbladder and bile duct with other cholecystitis ³⁷	574.70, 574.71			
Calculus of gallbladder and bile duct with acute and chronic cholecystitis ³⁷	574.80, 574.81			
Calculus of gallbladder and bile duct without cholecystitis ³⁷	574.90, 574.91			
Open cholecystectomy ³⁸		51.22		
Laparoscopic cholecystectomy ³⁸		51.23		
Endoscopic biliary drainage ³⁹		51.84, 51.85, 51.86, 51.87		
Percutaneous biliary drainage ³⁹		51.98, 51.99		
Biliary tract surgery with incision			47400, 47420, 47425, 47460, 47480, 47490	
Injection for cholangiography			47500, 47505	
Catheter introduction or change			47510, 47511, 47525, 47530	
Biliary endoscopy			47550, 47552, 47553, 47554, 47555, 47556	
Biliary laparoscopy and/or laparoscopic cholecystectomy			47560, 47561, 47562, 47563, 47564, 47570, 47579	
Cholecystectomy			47600, 47605, 47610, 47612, 47620	
Biliary duct stone extraction			47630	
Cholecystography			74290, 74291	
Cholangiography and/or pancreatography, intraoperative			74300, 74301, 74305	
Cholangiography, percutaneous			74320	
Postoperative biliary duct calculus removal			74327	
Endoscopic catheterization of the biliary ductal system			74328	
Combined endoscopic catheterization of the biliary and pancreatic ductal systems			74330	
Percutaneous transhepatic dilation of biliary duct stricture with or without placement of stent			74363	
Biliary tract procedure				193, 194
Cholecystectomy				195, 196, 197, 198

Description	ICD-9 Diagnosis	ICD-9 Procedure	HCPCS/CPT	DRG (inpatient)
Hepatobiliary diagnostic/other procedure				200, 201
Disorders of the biliary tract				207, 208
Androgen deprivation therapy				
Leuprolide Injection			J9217, J9218, J9219, J1950	
Goserelin Injection			J9202	
Orchiectomy		62.3, 62.4, 62.41, 62.42	54520, 54521, 54522, 54530, 54535, 54690, 49510	

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Table 1
Patient characteristics and receipt of androgen deprivation therapy

	N (%)	% who received GnRH agonist during follow-up	% with orchiectomy during follow-up
Total	185,106	47.8	2.2
Age in years			
66-69	45,844 (25)	36.6	1.2
70-74	58,450 (32)	45.6	1.6
75-79	45,379 (25)	54.6	2.4
80-84	24,036 (13)	60.4	4.0
85	11,397 (6)	60.0	5.3
Race			
White	157,064 (85)	47.9	2.3
Black	16,502 (9)	49.1	2.1
Other	7285 (4)	54.1	2.4
Unknown	4255 (2)	54.2	0.7
Hispanic ethnicity			
No	170,613 (92)	48.2	2.2
Yes	9266 (5)	50.7	3.0
Unknown	5227 (3)	51.6	0.8
Marital status			
Unmarried	37,085 (20)	49.0	2.8
Married	127,939 (69)	47.0	2.2
Unknown	20,082 (11)	56.0	1.5
Residence*			
Major metropolitan area	104,884 (57)	48.4	1.7
Metropolitan county	51,784 (28)	47.7	2.3
Urban	10,878 (6)	50.0	3.6
Less urban	14,420 (8)	49.3	4.2
Rural	3140 (2)	50.6	4.1
SEER region			
San Francisco	8296 (4)	45.2	2.6
Connecticut	14,672 (8)	52.6	2.1
Detroit	21,547 (12)	45.2	1.7
Hawaii	3279 (2)	54.9	3.5
Iowa	14,904 (8)	49.3	4.4
New Mexico	6196 (3)	36.8	5.7
Seattle	14,100 (8)	40.0	2.9
Utah	8338 (5)	40.0	3.4
Atlanta	6759 (4)	36.5	1.6
San Jose	5050 (3)	58.5	3.0
Los Angeles	16,656 (9)	47.6	2.2

	N (%)	% who received GnRH agonist during follow-up	% with orchiectomy during follow-up
Rural Georgia	540 (0)	37.6	3.2
Great California	22,995 (12)	45.7	1.3
Kentucky	9557 (5)	50.7	1.9
Louisiana	10,260 (6)	55.7	1.9
New Jersey	21,957 (12)	60.7	0.7
Median household income in census tract of residence			
Quartile 1 (lowest)	45,872 (25)	51.0	2.8
Quartile 2	45,946 (25)	49.2	2.4
Quartile 3	46,072 (25)	47.5	2.2
Quartile 4 (high)	46,077 (25)	46.0	1.5
Unknown	1139 (1)	41.1	5.3
% high school graduates in census tract of residence			
Quartile 1 (lowest)	46,124 (25)	50.7	2.8
Quartile 2	46,005 (25)	49.0	2.4
Quartile 3	46,002 (25)	48.1	2.0
Quartile 4 (high)	45,836 (25)	46.0	1.7
Unknown	1139 (1)	41.1	5.3
Tumor grade (Gleason)			
Well differentiated (2-4)	8265 (4)	32.7	2.5
Moderately differentiated (5-7)	108,475 (59)	42.3	1.7
Poorly differentiated/undifferentiated (8-10)	62,389 (34)	61.6	3.1
Unknown	5977 (3)	42.8	3.2
DCG comorbidity score			
Quartile 1 (lowest)	131,027 (71)	47.1	2.2
Quartile 2	35,419 (19)	51.0	2.3
Quartile 3	11,530 (6)	52.6	2.2
Quartile 4 (high)	7130 (4)	51.4	2.2
Primary treatment received in the 6 months after diagnosis			
Radical prostatectomy	28,662 (15)	22.9	3.9
Radiation therapy	83,022 (45)	56.7	1.0
Neither	73,422 (40)	48.9	1.7

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

* Four patients missing information about residence.

Table 2
Unadjusted rate of biliary disease and adjusted hazard ratio associated with androgen deprivation therapy

Treatment	Rate of biliary disease per 1000 person years	P value*	Adjusted Hazard Ratio (95% CI)	P value [†]
No treatment	12.44	--	reference	--
GnRH agonist	14.46	<0.001	1.09 (1.04 to 1.14)	<0.001
Orchiectomy	12.39	0.95	0.91 (0.80 to 1.04)	0.16

GnRH=gonadotropin releasing hormone

* P values based on two-sample hypotheses tests evaluating whether the rate for men during GnRH agonist treatment differed from the rate under no treatment and whether the rate for men treated with orchiectomy differed from the rate under no treatment.

[†] Using Cox proportional hazards models adjusting for age, race, Hispanic ethnicity, marital status, residence, SEER region, census tract level measures of income and education, tumor grade, comorbidity score, year of diagnosis, primary surgical therapy.

Table 3

Unadjusted rate of biliary disease and adjusted hazard ratio associated with androgen deprivation therapy, in sensitivity analyses where biliary disease was defined based on receipt of a biliary procedure (top set of rows) or diagnosis codes only (bottom set of rows)

Treatment	Rate of biliary disease per 1000 person years	P value*	Adjusted Hazard Ratio (95% CI)	P value†
Biliary disease defined based on receipt of biliary procedure				
No treatment	12.3	--	reference	--
GnRH agonist	13.9	<.001	1.07 (1.02-1.13)	.005
Orchiectomy	11.8	.53	0.86 (0.75-0.99)	.04
Biliary disease defined based on diagnosis codes only				
No treatment	1.22	--	reference	--
GnRH agonist	1.75	<.001	1.22 (1.06-1.40)	<.001
Orchiectomy	1.78	0.08	1.33 (0.92-1.92)	0.13

GnRH=gonadotropin releasing hormone

* P values based on two-sample hypotheses tests evaluating whether the rate for men during GnRH agonist treatment differed from the rate under no treatment and whether the rate for men treated with orchiectomy differed from the rate under no treatment.

† Using Cox proportional hazards models adjusting for age, race, Hispanic ethnicity, marital status, residence, SEER region, census tract level measures of income and education, tumor grade, comorbidity score, year of diagnosis, primary surgical therapy.