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Prostate Cancer

Androgen-deprivation Therapy and Risk for Biliary Disease in Men with Prostate Cancer

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Abstract

Background: Androgen-deprivation therapy (ADT) by either a gonadotropin-releasing hormone (GnRH) agonist or bilateral orchiectomy improves disease-related outcomes of men with prostate cancer but has a variety of adverse metabolic effects including obesity, increased abdominal girth, increased triglycerides, and insulin resistance. Each is a risk factor for gallstone disease. Additionally, GnRH agonist treatment was recently shown in metabolomic analyses to increase plasma levels of some bile acids.
Objective: To assess the relationship between ADT and the incidence of biliary disease in men with prostate cancer.
Design, setting, and participants: We studied 183 842 men >65 yr of age living in Surveillance, Epidemiology, and End Results regions who were diagnosed with prostate cancer from 1992 to 2007 and followed through 2009.
Outcome measurements and statistical analysis: 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 and limitations: Among 183 842 men with locoregional prostate cancer, 48.4% received GnRH agonist treatment and 2.2% underwent bilateral orchiectomy during follow-up. GnRH agonist treatment was associated with a significantly higher incidence of biliary disease compared with no treatment (15.7 vs 13.4 cases per 1000 person-years; $p < 0.001$). In adjusted analyses, GnRH agonist use was associated with the risk of biliary disease (adjusted hazard ratio: 1.10; 95% confidence interval, 1.05–1.15; $p < 0.001$). Orchiectomy was not significantly associated with biliary disease.
Conclusions: GnRH agonist treatment may be associated with a greater risk of incident biliary disease.

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1. 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 disease, in combination with external-beam radiation therapy for intermediate- or high-risk localized disease, or after prostatectomy for node-positive disease. Nonetheless, prospective studies have demonstrated that GnRH agonist use causes several adverse metabolic changes. It is associated with loss of lean muscle mass (approximately 3%) and gain of fat mass (approximately 10%) [1–3], particularly abdominal fat [1,4]. It is associated with an increase in triglycerides (approximately 26%) and total cholesterol (approximately 7–10%) [1,5,6]. Finally, it is associated with a rise in fasting insulin and diminished

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sensitivity to insulin. Population-based studies have found that GnRH agonists are associated with an increased incidence of diabetes [7].

Gallstone disease is a prevalent problem in the United States. Gallstones are present in at least 8% of men >40 yr of age. 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 United States [8]. 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 [9]. Several risk factors for gallstone disease are side effects of ADT including obesity [10–12], abdominal girth [12], hypertriglyceridemia [13,14], and insulin resistance [15,16].

Hypothesis-driven prospective studies of ADT-induced adverse effects have focused primarily on metabolic problems associated with obesity (eg, 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 [17]. Unbiased plasma metabolomic analyses were recently carried out on baseline and 12-wk plasma samples from hormone-naive men initiating GnRH agonist therapy for prostate cancer. These studies demonstrated qualitative increases in most measured bile acids during the first 12 wk of treatment [18]. The causal mechanisms and the clinical implications of this novel finding are not yet known. Quantitative changes in individual bile acids 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 the relationship between ADT and the incidence of biliary disease.

2. Materials and methods

2.1. Data

We used Surveillance Epidemiology and End Results (SEER)–Medicare data that combines uniformly reported data from population-based cancer registries covering approximately 28% of the US population with Medicare administrative data. For each incident cancer, SEER registrars document patient demographics, tumor characteristics, and primary treatments. Additional information about health care utilization including treatments and comorbid illness can be ascertained from the Medicare claims. This work was done with institutional review board approval (protocol M16508).

2.2. Cohort

We identified men with a first diagnosis of prostate cancer from 1992 to 2007 who were >65 yr of age and continuously enrolled in Parts A and B of fee-for-service Medicare as of 1 yr before diagnosis (n = 249 977). We excluded men diagnosed at death or autopsy (n = 3372) and those without administrative claims in the 6 mo around diagnosis (because we were concerned about incomplete data; n = 6411). We restricted the cohort to 185 106 men with locoregional stage disease at diagnosis. We then excluded 1264 men with evidence of biliary disease in the year before prostate cancer diagnosis, leaving a final cohort of 183 842 men.

2.3. 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 tract 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 (Appendix) [19,20]. We classified each patient as having (1) surgery or biliary procedures and (2) biliary disease based on diagnosis code only that required a primary diagnosis code or diagnosis-related group code on an inpatient admission or at least two 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.

2.4. Androgen-deprivation therapy

We ascertained receipt of ADT including GnRH agonists and bilateral orchiectomy (Appendix) based on administrative data. Most doses were for 3- or 4-mo equivalent doses. Because hypogonadism may persist for prolonged periods after GnRH agonist discontinuation [21], men were considered continuously treated for 6 mo after each dose of GnRH agonist.

2.5. 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) [22], SEER region, urban residence, census-tract level income, and education (categorized in quartiles within registries). We characterized comorbid illness during the 12 mo before diagnosis using the Klabunde modification [23] of the Charlson score [24]. Variables were categorized as detailed in Table 1.

2.6. 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 and at other times contributed information to the control group, thereby functioning as self-controls. Thus current use of ADT is a time-varying treatment indicator variable. 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 current ADT use with biliary disease. 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.

In a second set of Cox proportional hazard models, we replaced the GnRH agonist variable with a set of variables reflecting the cumulative