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Original article

Hormonal therapy for breast cancer and diabetes incidence among postmenopausal women

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ABSTRACT

Purpose: The purpose of this study was to evaluate associations between hormonal therapy for breast cancer and subsequent diabetes incidence.
Methods: The Surveillance, Epidemiology and End Results—Medicare linked data were used. Stage I–III breast cancer patients 65 years or older who filled at least two prescriptions for an aromatase inhibitor (AI) or tamoxifen by the end of 2008, and within 12 months of breast cancer diagnosis, were selected. Women without cancer from a 5% random sample of Medicare beneficiaries were frequency matched to patients by age group, and new onset diabetes was monitored for 24 months postbaseline in both groups of women.
Results: Cox-proportional hazards analysis failed to show an association between AI use and subsequent diabetes onset after adjusting for age, race, and comorbidity (hazard ratio: 0.99; 95% confidence interval: 0.84–1.18). This study also failed to show an association between tamoxifen use and diabetes onset (hazard ratio: 0.79; 95% confidence interval: 0.54–1.17).
Conclusions: Study findings provide evidence that postmenopausal AI and tamoxifen users do not experience an increased risk of diabetes in the 2 years after treatment initiation. Whether these findings will hold with longer duration follow-up deserves a closer look.

Introduction

Breast cancer is the most common invasive cancer in American women. Individuals diagnosed with breast cancer often survive for many years, raising important questions about the effects of cancer treatment on subsequent morbidity and quality of life [1,2]. Adjuvant hormonal therapy continues to be prescribed as standard clinical practice for women with hormone receptor positive breast cancer, the most commonly diagnosed subtype [3]. For postmenopausal women, tamoxifen was the hormonal therapy of choice until the early 2000s when clinical trials showed aromatase inhibitors (AIs; anastrozole, exemestane, letrozole) to be more efficacious for this patient group, whether introduced initially or after several years of tamoxifen treatment [4,5]. AIs may also be seen as favorable from a safety perspective since tamoxifen increases the risk of endometrial cancer and thromboembolic events [4,6].

Initial treatment with an AI is now considered first-line hormonal therapy for most postmenopausal women with hormone receptor positive breast cancer. While AIs have been associated with improvement in disease-free survival relative to tamoxifen, they have not been associated with improvement in overall survival leading to speculation that this class of medications may have other effects that influence mortality [5–7]. Clinical trials have shown that AIs are associated with an increased risk of cardiovascular events, bone fractures, and musculoskeletal symptoms; however, their effect on diabetes remains largely unknown [5,6]. A Canadian case-control study reported tamoxifen to be associated with a 24% increase in the odds of diabetes compared to breast cancer patients without tamoxifen use while a study from Taiwan reported a 19% hazard increase for tamoxifen users relative to noncancer controls [8,9]. The study from Taiwan also reported a protective effect of AIs on diabetes incidence; however, the authors interpreted that finding cautiously and as being outside the scope of their

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investigation. Additional studies on AIs and diabetes incidence have not been identified in the literature and there is no known research from the United States on the effects of either type of hormonal therapy on diabetes incidence.

The purpose of this study was to evaluate associations between hormonal therapy and the incidence of diabetes mellitus among postmenopausal women with breast cancer in the United States.

Materials and methods

Setting

The linked Surveillance, Epidemiology, and End Results (SEER)—Medicare linked data files were used to conduct a retrospective cohort study.

SEER registries data

The SEER registries capture incident cancer for approximately 28% of the United States population [10] serving as a key population-based source for cancer information. The National Cancer Institute oversees the SEER program and ensures high standards for quality control and quality improvement [11].

Medicare data

Approximately 93% of SEER records, for patients older than 65 years, have been linked with Medicare enrollment records [12]. Medicare is a federal health insurance program in the United States and nondisabled adults become eligible at 65 years of age. About 97% of older adults are enrolled in Part A, which includes coverage for hospitalizations. About 96% of older adults with Part A coverage, pay the premium to enroll in Part B, which includes coverage for physician services and other outpatient care [12]. Since July 2006, prescription coverage has also been available through Part D, and in 2008, 53.4% of SEER-Medicare linked patients with breast cancer were enrolled in this prescription program [13].

Study population

The study population included older women without diabetes who were diagnosed with stage I–III breast cancer (AJCC sixth edition) in 2007–2008 and who initiated treatment with AI or tamoxifen. Comparison women without cancer were also included.

Breast cancer patients

Breast cancer patients without a previous cancer history were eligible except when the source of cancer diagnosis was noted as autopsy or death certificate. Patients who filled a prescription for an AI (anastrozole, exemestane, letrozole) or for tamoxifen by the end of 2008, and within 12 months of breast cancer diagnosis, were selected if they filled at least two prescriptions for either type of medication and if they were older than 65 years of age at the time of initial fill. Women who were dispensed both types of medication were excluded. Study enrollment criteria included continuous fee-for-service enrollment in Parts A and B during the 12 months before the earliest hormonal therapy fill date. Inpatient, outpatient, and physician claims were reviewed from this timeframe and any subjects with a history of diabetes were excluded. A history of diabetes was defined as having any claim with a listed ICD-9 diagnosis code of 250.x (diabetes mellitus). Continuous Part D prescription coverage and fee-for-service enrollment in Parts A and B was also required for 2 years after baseline to maximize the likelihood that complete claims were available for the follow-up period. The final study population included 2205 breast cancer patients who used AIs and 473 breast cancer patients who used tamoxifen.

Comparison women

A comparison group of women without cancer was selected from a 5% random sample of Medicare beneficiaries living in areas served by the SEER cancer registries. Women who were alive on December 31, 2006, were randomly assigned a mock hormonal therapy start date from January 1, 2007, to December 31, 2008, and those beneficiaries who were 65 years and older on the assigned date were eligible for inclusion. Comparison women who met all Medicare enrollment criteria and who did not have diabetes were frequency matched to breast cancer patients by age using four times as many comparison women in each stratum.

Outcomes

Subjects were monitored for 24 months after the initiation of hormonal therapy, or after the mock therapy start date for comparison women. Inpatient, outpatient, and physician claims were reviewed for this time period and any subject with a listed ICD-9 diagnosis code of 250.x (diabetes mellitus) was considered to have developed diabetes. To improve certainty of diagnosis, diabetes noted only in outpatient records and not listed on at least two different claims more than 30 days apart was not counted unless a prescription was also filled for a diabetes medication (insulin, bile acid sequestrant, biguanide, sulfonylurea, thiazolidinedione, alpha-glucosidase inhibitor, glucagon-like peptide (GLP)-1 receptor agonist, meglitinide, dipeptidyl peptidase-4 inhibitor, amylin analog) during the follow-up period [14]. For subjects who developed diabetes, the earliest claim date with a diabetes diagnosis code was considered the date of onset. Time to diabetes diagnosis was calculated as the number of days that elapsed between treatment start date and date of diabetes onset. Subjects who did not develop diabetes at the end of the follow-up period and subjects who died were censored.

Exposure

The main exposure variable indicated whether each subject was a breast cancer patient that received hormonal therapy or a comparison woman.

Other variables

Demographic variables included age and race. Date of birth from the Medicare enrollment record was compared to the treatment start date to calculate age, which was further categorized into groups (65–69 years, 70–74 years, 75–79 years, 80–84 years, 85+ years). The race of subjects was based on information in Medicare enrollment records and was categorized as white, black, Hispanic, or other. As an overall measure of baseline comorbidity, the National Cancer Institute (NCI) Index was calculated for each subject [15–19] using claims filed during the year before treatment began. This index was further categorized as zero, level 1 (>0 to <1), level 2 (1 to <2), or level 3 ($2+$), with a higher level indicating a more severe index of comorbidity. Hypertension and lipid disorder were also considered as separate comorbidities because these conditions are not included in construction of the NCI index. Hypertension was classified using ICD-9 diagnosis codes for essential hypertension (401), hypertensive retinopathy (362.11), hypertensive encephalopathy (437.2), hypertensive heart disease (402), hypertensive chronic kidney disease (403), hypertensive heart, and chronic kidney disease (404). Lipid disorder was classified using ICD-9 codes for pure hypercholesterolemia (272.0), pure hyperglyceridemia (272.1), mixed hyperlipidemia (272.2), hyperchylomicronemia (272.3), other, and unspecified hyperlipidemia (272.4).