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# Multiple sclerosis and breast cancer

P.W. O'Malley [a,b,1], Z.D. Mulla [c,d,1], O. Nesic [e,*]

[a] Texas Tech University Health Sciences Center El Paso, Paul L. Foster School of Medicine, United States
[b] University of Texas School of Public Health at Houston, United States
[c] Department of Obstetrics and Gynecology, Texas Tech University Health Sciences Center El Paso, Paul L. Foster School of Medicine, TX, United States
[d] Department of Public Health, Graduate School of Biomedical Sciences, Texas Tech University Health Sciences Center, Lubbock, TX, United States
[e] Department of Medical Education, Texas Tech University Health Sciences Center El Paso: Paul L. Foster School of Medicine, United States

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ABSTRACT

Multiple sclerosis (MS) and breast cancer (BC) share common features; most notably, both are more frequent in women than in men. In addition to the involvement of sex hormones, a number of genetic and pharmacological studies support a possible relationship between these two diseases. However, there are no conclusive epidemiological findings related to MS and BC worldwide, and there are no recent data for the US population.
We conducted a case–control study using a hospital inpatient discharge dataset (21,536 cases and two control series totaling 59,581 controls) from the Texas Health Care Information Collection. We assessed occurrence of MS in BC cases and in two control series: diabetes mellitus type II, and open wounds. After controlling for age, race-ethnicity, and health insurance status, a statistically-significant protective association was detected: BC cases were 45% less likely than diabetic controls to have MS (OR = 0.55, 95% CI = 0.37–0.81), and 63% less likely than open wound controls to have MS (OR = 0.37, 95% CI = 0.21–0.66). Our study presented here is the only current assessment of the association between MS and BC in the USA and suggests a protective effect of MS on BC in the hospitalized population.

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## 1. Introduction

Multiple sclerosis (MS) is a demyelinating disease affecting 400,000 people in the United States [1]. The prevalence of MS is higher in women (3.2:1), suggesting a potential role of sex hormones and/or sex chromosomes in the pathogenesis or progression of the disease [2,3]. Interestingly, both estrogens and androgens appear to have a protective role in multiple sclerosis [4,5].

Although the role of sex hormones in MS remains incompletely understood, it raises questions regarding comorbidities with other diseases involving sex hormones, such as breast cancer (BC), given that higher estrogen levels are implicated in breast cancer for both pre-and post-menopausal women [6,7], and that BC treatments often involve drugs that target estrogen receptors [8] or estrogen synthesis [9].

However, despite compelling endocrinological, pharmacological, and genetic [10] evidences that strongly link MS and BC, we currently lack a conclusive epidemiological answer to whether MS increases or decreases risk for BC. Few population-based studies have been conducted in the U.S. investigating the comorbidity of MS and BC; one in Minnesota (1975 to 1984) reports a prevalence of BC in MS patients of 2.01% [11]. The other studies performed in the US report either decreased prevalence of BC in hospitalized MS patients [25] or reduced comorbidity of BC in self-reports of MS patients evaluated through the NARCOMS registry (NARCOMS: North American Research Committee on Multiple Sclerosis) [12].

However, a systematic review of published findings assessing risks of BC in MS patients evaluated in different countries/continents, found much variation. The dearth of conclusive epidemiological findings related to MS and BC worldwide and the absence of current data for the US population compelled us to investigate the relationship between MS and BC using data collected by the Texas Health Care Information Collection, Center for Health Statistics.

## 2. Materials and methods

### 2.1. Source population and inclusion criteria

A case–control study was conducted using the Texas Public Use Data File, a hospital inpatient discharge dataset from the Texas Health Care Information Collection (THCIC), Texas Department of State Health Services (Austin, Texas). THCIC data are from all state licensed hospitals

* Corresponding author at: Texas Tech University Health Science Center Paul L. Foster School of Medicine, 5001 El Paso Dr. El Paso, TX 79905, United States.
*E-mail address:* Olivera.nesic-taylor@ttuhsc.edu (O. Nesic).
[1] Authors contributed the same.

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except those that are exempt from reporting to the THCIC. Exempt hospitals include those located in a county with a population less than 35,000, or those located in a county with a population more than 35,000 and with fewer than 100 licensed hospital beds and not located in an area that is delineated as an urbanized area by the United States Bureau of the Census (Section 108.0025). Exempt hospitals also include hospitals that do not seek insurance payment or government reimbursement (Section 108.009). According to our university's Institutional Review Board Policies and Procedures Manual 1.4.1.2: "Research using unidentifiable publicly or commercially available databases, human cell lines, or material from human cadavers is not considered to meet the definition of a human subject, and, as such, does not require IRB review or approval."

The dataset that was available in our institution contained clinical and demographic information for patients who were discharged in calendar years 2004 through 2007. Because of the relatively low prevalence of MS we analyzed data collected over four consecutive years. The principal discharge field and 24 secondary discharge diagnosis fields were examined in our study. The discharge variables had been coded using the *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (ICD-9-CM). The records of women who were less than 20 years of age or who had their age classified in one of several broad age categories due to HIV infection and/or drug and/or ethanol use were excluded.

### 2.2. Definition of cases and controls

BC was the outcome of interest. Cases were women whose principal discharge diagnosis field contained an ICD-9-CM code beginning with 174 (malignant neoplasm of the female breast). Although the frequency of BC among different races in our data base (biased towards white non-Hispanics) was different than in the general population, the age distribution (see Table 1) closely matched the bell-shaped age distribution of BC cases in the general population (*National Cancer Institute*: *Breast cancer*).

To strengthen our analyses we used two control series: (1) "controls series 1" were women whose principal discharge diagnosis code began with 250 and ended in 0 or 2 (code 250.XX identifies patients with diabetes mellitus while the fifth digit of 0 or 2 identifies patients with type II diabetes mellitus) and who did not have an ICD-9-CM code beginning with 174 in any of her secondary discharge diagnosis fields, and (2) "controls series 2" was composed of women whose principal discharge diagnosis code began with 870 through 887 or 890 through 897 (open wound) and who did not have an ICD-9-CM code beginning with 174 in any of their secondary discharge diagnosis fields. We have chosen two control conditions that have not been associated with MS. Although the prevalence of Type I diabetes is 3-fold greater in the MS population [14], no association between diabetes type II and MS has been found [15]. For our second control series we have chosen patients hospitalized with the primary diagnosis of open wounds, as there is no evidence that there is any association between MS and open wounds. The use of two control series (a chronic condition, that is, Type II diabetes, and an acute condition, open wounds) with varying hospital admission probabilities most likely reduces the risk that our results were wholly due to Berkson's bias [16].

### 2.3. Definition of MS

MS was the main exposure variable. MS was defined as the presence of an ICD-9-CM code beginning with 340 in any of the secondary discharge diagnosis fields. Patients who did not have a code beginning with 340 in any of their secondary discharge diagnosis fields were considered to be free of MS.

### 2.4. Data analysis

Data were analyzed using SAS 9.3 software (SAS Institute, Inc., Cary, North Carolina). Initial analyses involved the creation of contingency tables with a significance level of 0.05. Unadjusted and adjusted odds ratios (OR), 95% confidence intervals (CI), and *P* values were calculated from unconditional logistic regression models. ORs for the association between MS and BC were adjusted for the patient's age (seven age groups modeled using six indicator variables), the patient's race-ethnicity (four groups), and the patient's health insurance information (3 groups). The original health insurance variable found in our dataset has over 20 possible response values. We collapsed these categories and created a new health insurance variable with the following three groups: (1) self-pay or indigent (combined together, see Anderson, 2007 [17]), (2) Medicaid, and (3) cases that are not in either group (1) or (2).

Parity is another possible confounding factor in any analysis in which the outcome is BC and MS since nulliparous women have a higher risk of developing BC [18] and nulliparity is more frequent among MS patients [19]. We sought to control for parity indirectly by adjusting

**Table 1**
Characteristics of the study sample. Female breast cancer (BC) cases were compared with female type II diabetic controls (DC) and female open wound (OW) controls. Controls did not have a secondary discharge diagnosis of BC. The patients were discharged throughout Texas between 2004 and 2007 and found in the Public Use Data File.

| Variable | BC cases | DC | *P* | OW controls | *P* |
|---|---|---|---|---|---|
| | | | BC cases vs. DC | | BC cases vs. OW Controls |
| | N = 21,536 | N = 54,141 | | N = 5440 | |
| | Number (%) | Number (%) | | Number (%) | |
| Age (years) | | | <0.0001 | | <0.0001 |
| 20–29 | 156 (0.72) | 1443 (2.7) | | 811 (14.9) | |
| 30–39 | 1348 (6.3) | 3729 (6.9) | | 721 (13.3) | |
| 40–49 | 4394 (20.4) | 7959 (14.7) | | 888 (16.3) | |
| 50–59 | 5498 (25.5) | 12,212 (22.6) | | 783 (14.4) | |
| 60–69 | 4509 (20.9) | 11,198 (20.7) | | 540 (9.9) | |
| 70–79 | 3490 (16.2) | 10,369 (19.2) | | 634 (11.7) | |
| ≥80 | 2141 (9.9) | 7231 (13.4) | | 1063 (19.5) | |
| Race-ethnicity | | | <0.0001 | | <0.0001 |
| Black non-Hispanic | 2812 (13.1) | 12,955 (23.9) | | 687 (12.6) | |
| White Hispanic | 1355 (6.3) | 7550 (14.0) | | 511 (9.4) | |
| White non-Hispanic | 14,015 (65.1) | 19,497 (36.0) | | 3285 (60.4) | |
| Other (Asian, Native American, etc.) | 3354 (15.6) | 14,139 (26.1) | | 957 (17.6) | |
| Health insurance | | | <0.0001 | | <0.0001 |
| Self-pay, indigent | 1574 (7.3) | 6799 (12.6) | | 957 (17.6) | |
| Medicaid | 1309 (6.1) | 6582 (12.2) | | 395 (7.3) | |
| Other | 18,653 (86.6) | 40,760 (75.3) | | 4088 (75.2) | |
| Has multiple sclerosis | 37 (0.17) | 103 (0.19) | 0.59 | 17 (0.31) | 0.04 |

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