HHS Public Access

Author manuscript

Int J Cancer. Author manuscript; available in PMC 2019 March 15.

Published in final edited form as:

Int J Cancer. 2018 March 15; 142(6): 1202–1208. doi:10.1002/ijc.31148.

Autoimmune diseases and breast cancer risk by tumor hormone-receptor status among elderly women

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Abstract

The female preponderance of many autoimmune diseases suggests a possible hormonal etiology. Little research exists on systemic and organ-specific autoimmune diseases and risk of breast cancer by tumor estrogen receptor (ER)- and progesterone receptor (PR)- status. Here we evaluate associations between selected systemic and organ-specific autoimmune diseases and breast cancer risk overall and by tumor ER- and PR-status. We used linked Surveillance, Epidemiology and End Results (SEER)-Medicare data, with first female breast cancer cases ages ≥66 years identified by SEER registries (years 1992–2011) (N = 209,929). We selected female controls (N = 200,000) from a stratified 5% random sample of Medicare recipients who were alive and breast cancer-free. We assessed exposures until 12 months before breast cancer diagnosis/selection using Medicare claims data. We estimated odds ratios (OR) and 99.9% confidence intervals (CI) using unconditional and multinomial logistic regression. We found reduced breast cancer risk among those with rheumatoid arthritis (OR=0.84; 99.9% CI 0.79–0.89), systemic lupus erythematosus (OR=0.82; 99.9% CI 0.70–0.97), and pernicious anemia (OR=0.90; 99.9% CI 0.83–0.97), and increased risk among those with psoriasis (OR=1.16; 99.9% CI 1.06–1.27). Statistically significant alterations in risk for rheumatoid arthritis were limited to ER-positive (+) breast cancer, whereas those for the other three conditions were further limited to ER+/PR+ breast cancer. However, only differences for rheumatoid arthritis by ER-status were statistically significant (p-heterogeneity=. 0001). The reasons for these associations need to be investigated in future studies accounting for host characteristics and autoimmune disease treatment.

Keywords

breast cancer; autoimmune disease; estrogen receptor; progesterone receptor

Introduction

Autoimmune diseases are a heterogeneous group of diseases, but all are characterized by the presence of autoantibodies and autoreactive T cells that attack “self” antigens, either systemically or organ-specifically (1, 2). Some evidence suggests that some parts of the immune system may protect against cancer, while other parts may promote cancer

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development (3). A previous analysis of systemic autoimmune rheumatic diseases (SARDs) and breast cancer risk in the female Surveillance, Epidemiology, and End Results (SEER)-Medicare population reported that women diagnosed with rheumatoid arthritis were less likely to be diagnosed with breast cancer; reductions in risk were not statistically significantly different for estrogen receptor (ER)-positive (+) and ER-negative (−) breast cancer (4). Breast cancer risk was not associated with any other SARDs, except for a reduction in risk of ER− breast cancer among those with systemic lupus erythematosus. To our knowledge, associations between organ-specific autoimmune diseases and breast cancer risk have not been previously reported in the SEER-Medicare population, except for a reduction in risk after pernicious anemia (5).

The female preponderance of many autoimmune diseases suggests a possible hormonal etiology (6). Therefore, it is of interest to examine associations with breast cancer by the hormone-receptor status of the tumors. While others have examined the risk of breast cancer associated with both SARDs and organ-specific autoimmune diseases (e.g. reference 1), to our knowledge, no studies other than the earlier one in the SEER-Medicare database (4) have examined associations between autoimmune diseases and the risk of breast cancer by ER-status of the tumor and none have accounted for both ER- and progesterone receptor (PR)-status.

In this manuscript, we expand on the previous analysis of SARDs and breast cancer risk in the SEER-Medicare database (4) by including additional years of breast cancer case ascertainment (through 2011), organ-specific autoimmune diseases, and analyses by tumor ER- and PR-status.

Materials and Methods

We designed a case-control study within the SEER-Medicare linked database (https://healthcaredelivery.cancer.gov/seermedicare/), with cases identified by SEER registries and information on medical exposures obtained from Medicare claims data. Details on the design have been published previously (7).

The study was limited to females, aged 66 years of age or older (persons of age 65 were excluded because they did not have sufficient time to accrue exposure information) with a minimum of 13 months of Part A, Part B non-health maintenance organization Medicare coverage preceding cancer diagnosis, as assessed using Medicare claims data. First invasive breast cancers (ICD-O-3 site codes C50.0-C50.9 where behavior = 3 (malignant)) diagnosed between January 1, 1992 and December 31, 2011 from 13 SEER registries and from January 1, 2000 to December 31, 2011 from the additional 5 registries in SEER 18 were included. A total of 313,159 cases of first invasive breast cancer among women aged 66 years and older were identified. We then excluded cases diagnosed at only autopsy or death (n = 3,431), without a known month of cancer diagnosis (n = 1,636), not living in the included SEER areas at the time of diagnosis (n = 2,408), without a Medicare claim between their entry date and 1 year prior to breast cancer diagnosis (n = 71,166), without 13 months of Medicare Part A, Part B excluding HMO claims (n = 24,574), or whose death date was prior to cancer diagnosis date (n = 15), leaving 209,929 invasive breast cancer cases included in the

analysis. Information on ER- and PR-status of the tumors was available from the SEER registry data for the years of case ascertainment. Fifteen percent of tumors overall had unknown ER-status, with the percentage declining from 26% in 1992 to 5% in 2011. The corresponding percentages for PR-status were 16%, declining from 28% to 5%.

A total of 200,000 female controls were selected from a file created from two subsets of a 5% random sample of Medicare recipients: the Summarized Denominator (SUMDENOM) file, which is made of 5% random sample of Medicare recipients who never developed cancer and the Patient Entitlement and Diagnosis Summary File (PEDSF) 5% file, which is a 5% random sample of all people with cancer. Controls were selected in strata by calendar year and 5-year age group and were frequency-matched to the distribution among breast cancer cases. To be eligible for selection as a control in a particular calendar year, recipients had to be alive and breast cancer-free as of July 1 in that year.

We identified SARDs and organ-specific autoimmune diseases, the exposures of interest, as well as diabetes and dyslipidemia, adjustment factors, using codes shown in Table 1. ICD-9-CM diagnosis codes were considered if there was at least one inpatient or two outpatient/physician claims with a minimum of 30 days between claims. We defined medical conditions as present if they met the claims definition at least 12 months prior to cancer diagnosis or selection. This 12-month window was chosen to minimize the potential effects of breast cancer on the diagnosis of exposures, while still ensuring that all participants had at least one month out of the 13 months of Medicare coverage required for entrance into the study to assess exposure.

We calculated ORs and 99.9% confidence intervals (CIs) (to account for multiple comparisons) using unconditional logistic regression analyses. All statistical tests were two-sided with an α of .0009. We performed statistical analyses using SAS version 9.3 (SAS Institute). Unless otherwise noted, all analyses were adjusted for the matching factors of age (continuous) and year of diagnosis/selection (continuous), and additionally for race/ethnicity (white, black, mixed, Asian, Hispanic, North American Indian, other/unknown), grouped SEER region categorized as western (San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles, greater California), northeastern (Connecticut, New Jersey), north-central (Detroit, Iowa), and southern (Atlanta, rural Georgia, Kentucky, Louisiana, greater Georgia), months between study entry and diagnosis/selection date (continuous), and dyslipidemia and diabetes, which were previously identified risk factors in breast cancer subgroups (7), both coded yes/no. We used multinomial logistic regression with nominal outcomes for analyses by tumor hormone-receptor status compared to controls with the Wald test for assessing statistical significance of effect differences.

Results

Basic information on the study population is shown in Table 2. As expected, cases and controls were similar on study design matching factors. The distributions of mammography screening, dyslipidemia and diabetes were also similar in cases and controls. Cases were slightly more likely to be Caucasian (87% vs. 83%).

Nearly 6% of controls were diagnosed with SARDs; 64% of controls with SARDs had rheumatoid arthritis. There were very few subjects with Goodpasture's syndrome (7 total) or Behcets syndrome (14 total), and none with Chagas disease. Approximately 5% of controls were diagnosed with organ-specific autoimmune diseases, but individual conditions were very rare; fewer than 1% had each disease, except for pernicious anemia (1.9%) and psoriasis (1.2%). Among controls with SARDs, 11.6% also had organ-specific autoimmune diseases; of those with organ-specific autoimmune diseases, 13.6% also had SARDs.

Dyslipidemia and diabetes were more prevalent in controls with SARDs (62.6% and 31.3%, respectively) and organ-specific autoimmune diseases (67.5% and 32.8%) than in controls without SARDs (50.2% and 21.8%) or organ-specific autoimmune diseases (52% and 21.8%).

Unadjusted ORs for breast cancer associated with SARDs and organ-specific autoimmune diseases were 0.86 (99.9% CI 0.82–0.90) and 0.99 (99.9% CI 0.94–1.04), respectively. The corresponding adjusted estimates, including mutual adjustment for each other, were 0.86 (99.9% CI 0.82–0.90) and 0.98 (99.9% CI 0.94–1.03) (Table 3). The reduction in risk with SARDs was primarily attributable to rheumatoid arthritis (OR = 0.84; 99.9% CI 0.79–0.89) and systemic lupus erythematosus (OR = 0.82; 99.9% CI 0.70–0.97). The overall null association with organ-specific autoimmune diseases obscured the reduced risk associated with pernicious anemia (OR =0.90; 99.9% CI 0.83–0.97) and the increased risk associated with psoriasis (OR = 1.16; 99.9% CI 1.06–1.27).

All of the statistically significant associations mentioned above were limited to ER+ breast cancer, although only differences for rheumatoid arthritis by ER-status were significant at $\alpha = .0009$. Of note, the percentage of cases with missing ER-status was similar for those with and without SARDs and for those with and without organ-specific autoimmune diseases.

Reductions in risk of ER+ breast cancer associated with total SARDs and rheumatoid arthritis were statistically significant regardless of tumor PR-status (Table 4). The associations with systemic lupus erythematosus, pernicious anemia and psoriasis were statistically significant only for ER+/PR+ tumors. In general, associations were stronger for ER+/PR+ than ER+/PR− breast cancer, but p-values for heterogeneity were .01 (all SARDs), .02 (rheumatoid arthritis), .06 (systemic lupus erythematosus), .06 (pernicious anemia), and .53 (psoriasis), and did not meet the .0009 criterion for statistical significance. There were no statistically significant associations for any cross-classification of ER/PR status with the other autoimmune conditions.

Discussion

We found reductions in risk of breast cancer among elderly women with rheumatoid arthritis, systemic lupus erythematosus, and pernicious anemia, and increases in risk with psoriasis. Statistically significant alterations in risk for rheumatoid arthritis were limited to ER+ breast cancer, whereas those for the other three conditions were further limited to ER+/PR+ breast cancer. However, only differences for rheumatoid arthritis by ER-status were statistically significant.

To our knowledge, no studies have conducted similar analyses considering both tumor ER- and PR-status. In the only study of which we are aware that considered ER-status, also in the SEER-Medicare database but with many fewer cases and controls, risk reduction associated with rheumatoid arthritis was statistically significant for ER+, but not ER− breast cancer, although this difference was not statistically significant (4). Contrary to the current analysis, risk of ER− but not ER+ breast cancer was reduced in those with systemic lupus erythematosus, but this association was based on only 10 cases (4) and may likely be due to chance.

Risk of breast cancer in those with autoimmune diseases was most comprehensively examined in a Swedish study among 200,000 patients hospitalized with any of 33 different autoimmune diseases (1). Our findings for rheumatoid arthritis, systemic lupus erythematosus, and pernicious anemia are consistent with results from this study. Rheumatoid arthritis has also been associated with reduced breast cancer risk in two meta-analyses (8, 9), systemic lupus erythematosus with reduced risk in a meta-analysis (10) but not in other analyses in the Medicare population (4,11), and pernicious anemia with reduced risk in the SEER-Medicare population (5). Psoriasis has been linked to increased breast cancer risk in a meta-analysis (12), but not in the Swedish study (1) or a more recent study (13). Notably, effect sizes and number of cases for this association are small.

Our findings for systemic sclerosis and sarcoidosis are also consistent with the Swedish study and two meta-analyses (15, 16); those for multiple sclerosis agree with the Swedish study (1), but variable results have been reported elsewhere (17). Sjögren's syndrome, Celiac disease, Crohn's disease, and Hashimoto/hypothyroidism were all associated with statistically significantly reduced risk in the Swedish study (1), but not in our study. Inconsistent results have also been reported elsewhere for Crohn's disease (18). Our results also differ for Grave's disease/hyperthyroidism and inflammatory bowel disease, which were associated with small but statistically significant increases in risk in the Swedish study (1). We note that the Swedish study included those of any age hospitalized for autoimmune disorders, and was likely skewed to more severe disease. This contrasts with our study which included older women with autoimmune diagnoses from inpatient or outpatient records. Moreover, it is likely that the relatively small number of breast cancer cases in the Swedish study (N = 4607), sometimes small effect sizes, and the differing levels of statistical significance account for some of the differences in the results of the two studies.

The associations with ER+ but not ER− breast cancer in the current analysis suggest that hormonal factors might be related to the observed associations. At least seven of the autoimmune diseases we examined have an excess in women (19, 20). Notably, we found reductions in risk of ER+ breast cancer with only two (rheumatoid arthritis, systemic lupus erythematosus) of the seven, increased risk of ER+ breast cancer for one (psoriasis) of five with no known female excess, and reduced risk with another with no known female excess (pernicious anemia) (21). Although it is thought that sex hormones contribute to the female excess in autoimmune diseases, levels of these hormones have not been found to be significantly different in women with and without autoimmune diseases, except possibly for higher levels in patients with systemic lupus erythematosus (19). Thus, our findings of a reduced risk of ER+ breast cancer with systemic lupus erythematosus are puzzling given that

higher estrogen levels may also be associated with increased risk of ER+ breast cancer (22). In spite of the female excess of rheumatoid arthritis, the peak incidence in women occurs at the time of menopause, which is associated with decreased production of estrogens; in many women with rheumatoid arthritis, disease activity diminishes during pregnancy, when levels of female sex hormones are high. Furthermore, there is some evidence that menopausal hormone therapy decreases disease activity in postmenopausal rheumatoid arthritis patients (23, 24). Thus, lower hormone levels might be associated with increased risk of rheumatoid arthritis but decreased risk of hormone sensitive breast cancers. The relationships between pernicious anemia and psoriasis and hormonal factors are unclear (21, 25).

Treatments for autoimmune diseases, particularly if they differentially affect ER+ and ER− breast cancer, also need to be considered in interpreting our findings. Non-steroidal anti-inflammatory drugs (NSAIDs) are among current treatment options (26) that have been associated with a greater reduction in risk of ER+ breast cancer than breast cancer altogether (27). Thus, NSAID use may contribute to the reduced risk we found for ER+ but not ER− breast cancer in those with rheumatoid arthritis. On the other hand, reduced breast cancer risk was not evident for other autoimmune diseases that might be treated by NSAIDs. Glucocorticoids, potent anti-inflammatory drugs, have not been associated with breast cancer risk (28). Some disease-modifying-antirheumatic drugs (DMARDs) used to treat rheumatoid arthritis, appear to increase risk of specific cancer types, such as bladder cancer, but few appear to increase the overall cancer risk (29). There is no evidence that the increased risk of breast cancer associated with psoriasis is due to treatment (30).

Assessing the effects of possible confounding factors is also important in evaluating our results. Low to moderate alcohol consumption has been associated with reduced risk of rheumatoid arthritis (31) and possibly systemic lupus erythematosus (32), and increased risk of ER+ breast cancer (33). Had we been able to adjust for alcohol consumption, our associations with these two conditions and breast cancer risk would most likely be closer to the null (34). Obesity has been associated with increased risk of both rheumatoid arthritis (35), psoriasis (35) and ER+ breast cancer (22); thus, adjustment for body mass index would likely have resulted in estimates associated with rheumatoid arthritis further from the null and estimates for psoriasis closer to the null (34). Estimated prevalence of oral estrogen-progestin use is very low in the age group included in this analysis (36), minimizing concerns about lacking this information.

Strengths of this study include a larger number of breast cancer cases following most autoimmune diseases than available in previously published studies. In addition, we have information on both ER- and PR-status of the tumors. Other strengths include the population-based nature of the study, claim-based data on autoimmune conditions, and information on frequency of medical visits and mammographic screening to address the intensity of medical surveillance. The study design ensured that there was no bias in recall of autoimmune conditions. We have accounted for the potential influence of reverse causality and detection bias around the time of cancer diagnosis by ascertaining exposures only until one year prior to cancer diagnosis or selection of controls.

Limitations include the relatively short period of exposure ascertainment, but given that these are chronic health conditions, their capture in the medical records may be adequate. However, we did not have detailed information on the duration and severity of the conditions. As treatment data were not available, we could not untangle the effects of disease and treatment. As indicated above, we were also unable to adjust for several potential confounding factors, such as alcohol and obesity. Although approximately 15% of tumors had missing hormone-receptor status, the degree of missing data did not vary by exposures.

In summary, this study suggests that tumor hormone receptor status is important to consider when assessing the relationship between autoimmune diseases and breast cancer risk. Future research that accounts for such tumor characteristics as well as treatment for the autoimmune diseases and other patient characteristics will be important in untangling the complex relationship between these diseases and breast cancer risk.

Acknowledgments

We would like to acknowledge the programming support of Winnie Ricker at Information Management Services, Inc.

Abbreviations

ER	estrogen receptor
+	positive
−	negative
PR	progesterone receptor
SARD	systemic autoimmune rheumatic disease
SEER	Surveillance, Epidemiology, and End Results
NSAIDs	non-steroidal anti-inflammatory drugs

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Novelty and Impact

This is the first study to examine associations of systemic and organ-specific autoimmune diseases with breast cancer according to tumor estrogen receptor (ER)- and progesterone receptor (PR)-status. Our findings that statistically significant alterations in risk with rheumatoid arthritis, systemic lupus erythematosus, pernicious anemia, and psoriasis varied according to tumor ER- and PR-status offer important clues to the complex relationship between certain autoimmune diseases and breast cancer risk.

Table 1

Codes used to define autoimmune diseases and other medical conditions that were adjusted for in the analyses

Autoimmune diseases	**Codes**
Systemic autoimmune rheumatic diseases (SARDs)	rheumatoid arthritis (ICD-9 714.0, 714.1, 714.2, 714.3, 714.81, or V82.1), systemic lupus erythematosus (ICD-9 710.0), Sjogren's syndrome (ICD-9 710.2), dermatomyositis (ICD-9 710.3), systemic sclerosis (scleroderma) (ICD-9 710.1), sarcoidosis (ICD-9 135), Goodpasture's syndrome (ICD-9 446.21), and Behcet's syndrome ICD-9 136.1), other (ICD-9 codes 446.5, 710.4, 725.x).
Organ-specific autoimmune diseases	Hashimoto's thyroiditis (ICD-9 code 245.2), pernicious anemia (ICD-9-CM 281.0), vitiligo (ICD-9 code 709.01), multiple sclerosis (ICD-9 340), Grave's disease (ICD-9 codes 242.00, 242.01), glomerulonephritis (ICD-9 code 580.4, 582.x), ankylosing spondylitis (ICD-9 code 720.0), Celiac disease (ICD-9 code 579.0), Chagas disease (ICD-9 code 086.0, 086.2), Crohn's disease (ICD-9 code 555. x),inflammatory bowel disease (ICD-9 codes 555.0, 555.1, 555.2, 555.9, 556.0, 556.1, 556.2, 556.3, 556.4, 556.5, 556.6, 556.8, 556.9,), psoriasis (ICD-9 code 696.x).
Medical conditions adjusted for in the analyses	
Diabetes	Icd-9-CM codes 250, 357.2x, 362.0x, 366.41, 249.xx
Dyslipidemia	ICD-9 272

Table 2

Characteristics of the study population

Characteristic	Cases (N = 209,929)	Controls (N = 200,000)
Age in years (mean)	76	76
Year of diagnosis (mean)	2003	2003
Duration of coverage in months (mean)	66	66
SEER region[a] (%)		
Western	45.2	45.4
Northeastern	19.0	18.2
North-central	17.4	17.5
Southern	18.4	19.0
Race/ethnicity (%)		
White	87.3	83.2
Black	7.5	8.0
Mixed	1.6	2.1
Asian	2.1	3.8
Hispanic	1.2	2.2
North American Indian	0.2	0.4
Other/Unknown	0.2	0.2
Mammogram between 1 and 4 years before diagnosis (%)	35.2	34.5
Dyslipidemia (%)	51.2	50.9
Diabetes (%)	22.2	22.4

[a]Western (San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles, greater California), Northeastern (Connecticut, New Jersey), North-central (Detroit, Iowa), and Southern (Atlanta, rural Georgia, Kentucky, Louisiana, greater Georgia).

Table 3

ORs (99.9% CI) for breast cancer overall and by estrogen (ER)-status (positive (+) or negative (−)) associated with systemic autoimmune rheumatic diseases (SARDs) and organ-specific autoimmune diseases

Autoimmune disease	Controls N=200,000	Total breast cancer N = 209,929		ER+ breast cancer N=149,306		ER− breast cancer N = 28,140		p-value for ER+ vs. ER−
	# exposed	# exposed	OR[a] (99.9% CI) vs. unexposed	# exposed	OR[a] (99.9% CI) vs. unexposed	# exposed	OR[a] (99.9% CI) vs. unexposed	
Total SARDs	11769	10720	**0.86 (0.82–0.90)**	7570	**0.84 (0.80–0.88)**	1543	0.93 (0.85–1.02)	.0004
Rheumatoid arthritis	7477	6474	**0.84 (0.79–0.89)**	4480	**0.80 (0.75–0.86)**	972	0.92 (0.82–1.04)	.0001
Sjogren's syndrome	782	721	0.94 (0.79–1.11)	528	0.93 (0.77–1.13)	95	0.90 (0.62–1.29)	
Systemic sclerosis	262	238	0.90 (0.67–1.21)	183	0.94 (0.68–1.30)	26	0.76 (0.39–1.47)	
Systemic lupus erythematosus	958	777	**0.82 (0.70–0.97)**	552	**0.79 (0.66–0.95)**	128	0.95 (0.69–1.31)	.07
Sarcoidosis	288	287	0.94 (0.71–1.24)	210	0.94 (0.70–1.28)	41	0.89 (0.51–1.55)	
Total organ-specific	10262	10667	0.98 (0.94–1.03)	7739	0.97 (0.92–1.02)	1432	1.01 (0.91–1.11)	277
Crohn's disease	623	582	0.91 (0.70–1.17)	421	0.91 (0.69–1.21)	83	0.90 (0.53–1.51)	
Multiple sclerosis	395	406	0.95 (0.75–1.20)	293	0.92 (0.71–1.19)	64	1.09 (0.70–1.71)	
Pernicious anemia	3841	3608	**0.90 (0.83–0.97)**	2510	**0.87 (0.80–0.95)**	495	0.96 (0.82–1.13)	.04
Psoriasis	2368	2899	**1.16 (1.06–1.27)**	2174	**1.18 (1.07–1.30)**	343	1.04 (0.86–1.26)	.03
Inflammatory bowel disease	1340	1322	0.96 (0.81–1.15)	961	0.93 (0.77–1.13)	189	1.04 (0.74–1.47)	
Vitiligo	95	108	1.17 (0.73–1.86)	80	1.15 (0.69–1.92)	17	1.26 (0.52–3.02)	
Glomerulonephritis	323	272	0.83 (0.63–1.09)	186	0.81 (0.60–1.11)	38	0.81 (0.46–1.43)	
Celiac disease	156	127	0.75 (0.51–1.12)	98	0.76 (0.50–1.18)	16	0.73 (0.31–1.75)	
Ankylosing spondylitis	136	123	0.91 (0.60–1.38)	76	0.78 (0.48–1.26)	23	1.26 (0.60–2.68)	
Grave's disease	756	849	1.07 (0.91–1.27)	643	1.10 (0.92–1.31)	121	1.13 (0.81–1.56)	
Hashimoto thyroiditis	908	975	1.00 (0.85–1.16)	744	1.01 (0.86–1.19)	124	0.96 (0.70–1.32)	

[a]Variables included in the models: age, race/ethnicity, region, year of diagnosis/selection, months between entry and diagnosis/selection, mammogram, diabetes, dyslipidemia, autoimmune conditions included in the table (for analysis of total SARDs and total organ-specific autoimmune diseases, only these conditions were included in the model; for analyses of the individual conditions, the total variables were not included in the models, only the individual conditions). Statistically significant ORs are bolded.

Table 4

ORs (99.9% CIs) for breast cancer cross-classified by estrogen receptor (ER)- and progesterone receptor (PR)-status (both classified as positive (+) or negative (−)) associated with selected autoimmune diseases

	ER+/PR+ breast cancer N=121,349		ER+/PR− breast cancer N = 25,256		ER−/PR+ breast cancer N = 1,946		ER−/PR− breast cancer N = 25,837	
	# exposed cases	OR[a] (99.9% CI)	# exposed cases	OR[a] (99.9% CI)	# exposed cases	OR[a] (99.9% CI)	# exposed cases	OR[a] (99.9% CI)
Systemic autoimmune rheumatic diseases (SARDs)								
Total SARDS	6090	**0.83 (0.72–0.87)**	1356	**0.89 (0.81–0.99)**	124	1.17 (0.86–1.61)	1405	0.91 (0.83–1.01)
Rheumatoid arthritis	3582	**0.79 (0.74–0.85)**	811	**0.87 (0.76–0.98)**	72	1.02 (0.68–1.53)	895	0.92 (0.82–1.04)
Systemic lupus erythematosus	437	**0.77 (0.63–0.93)**	109	0.94 (0.67–1.33)	15	1.62 (0.66–3.95)	113	0.91 (0.65–1.27)
Organ-specific autoimmune diseases								
Total	6270	0.96 (0.91–1.02)	1345	1.02 (0.92–1.12)	103	1.15 (0.81–1.61)	1311	0.99 (0.90–1.10)
Pernicious anemia	2012	**0.86 (0.78–0.94)**	463	0.95 (0.80–1.12)	45	1.36 (0.82–2.26)	447	0.94 (0.79–1.11)
Psoriasis	1789	**1.19 (1.07–1.32)**	352	1.14 (0.95–1.39)	20	0.93 (0.44–1.97)	317	1.04 (0.85–1.27)

[a]Variables included in the models: age, race/ethnicity, region, year of diagnosis/selection, months between entry and diagnosis/selection, mammogram, diabetes, dyslipidemia, autoimmune conditions included in the table (for analysis of total SARDs and total organ-specific autoimmune diseases, only these conditions were included in the mode l; for analyses of the individual conditions, the total variables were not included in the models, only the individual conditions). Statistically significant ORs are bolded.