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Association Between Breast Cancer Recurrence and Immunosuppression in Rheumatoid Arthritis and Inflammatory Bowel Disease

A Cohort Study

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Objective. **Breast cancer recurrence may be promoted by immunosuppression due to decreased immune surveillance. The aim of this study was to examine the rates of breast cancer recurrence in patients with immune-mediated disease and treated breast cancer who received therapy with methotrexate, thiopurines, or anti–tumor necrosis factor (anti-TNF).**

Methods. **Three retrospective cohort studies within Medicare (2000–2012) included women with rheumatoid arthritis (RA) or inflammatory bowel disease (IBD) who underwent surgery for primary breast cancer. Recurrent or second primary breast cancers occurring more than 365 days after the initial surgery were identified. Separate Cox regression models were used to examine the risk of cancer recurrence in patients treated with methotrexate, thiopurines, or anti-TNF agents after surgery, each compared with no use. Analyses were matched for type of breast surgery and receipt and type of adjuvant therapy.**

Results. **Across all medication groups, 107 women experienced breast cancer recurrence during 5,196 person-years. The incidence rates were 20.3 and 19.6 per 1,000 person-years in methotrexate users and nonusers, respectively, 32.3 and 17.6 in thiopurine users and nonusers, respectively, and 22.3 and 19.5 in anti-TNF users and nonusers, respectively. There was no significantly increased risk of breast cancer recurrence with use of methotrexate (adjusted hazard ratio [HR] 1.07, 95% confidence interval [95% CI] 0.67–1.69), anti-TNF therapy (HR 1.13, 95% CI 0.65–1.97), or thiopurines (HR 2.10, 95% CI 0.62–7.14).**

Conclusion. **The risk of breast cancer recurrence in patients who received methotrexate, thiopurine, or anti-TNF therapy was not statistically significantly increased, although we cannot rule out a 2-fold or greater increased risk in those treated with thiopurines. These data provide reassurance to clinicians choosing to start methotrexate or anti-TNF therapy in RA or IBD patients with treated breast cancer.**

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The incidence of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) is increasing worldwide (1,2). These conditions are treated primarily with immunosuppressive drugs (3,4), including thiopurines, methotrexate, anti–tumor necrosis factor (anti-TNF) agents, and other biologic agents. Some (5–9) but not all studies (10–12) have demonstrated an increased incidence of solid malignancies associated with these medications. Among patients with previous cancer, however, the risk of recurrent cancer after exposure to immunosuppressive therapy is even less clearly understood (13,14). Prior studies in RA showed no difference in cancer recurrence between patients treated with the combination of anti-TNF therapy plus methotrexate versus those treated with methotrexate alone (15,16). Similarly, no association was observed between exposure to immunosuppressants and the risk of cancer recurrence in patients with IBD (17,18). However, these studies were small, did not distinguish recurrence of a prior malignancy from occurrence of a second malignancy, and combined many different cancers, thereby risking bias toward the null if the effect of immunosuppression is not universal across all solid cancers.

To address these limitations, we assessed the effect of immunosuppressive therapies on the risk of breast cancer recurrence after primary surgery for breast cancer among women with RA or IBD. Considering the 4 most common solid cancers, there are several advantages to studying breast cancer. In contrast to colon cancer, breast cancer screening results in earlier detection but is not preventative (19); in contrast to prostate cancer, nearly all early-stage tumors receive treatment with intent to cure (20); in contrast to lung cancer, there is a high survival rate overall (21). Additionally, in patients with breast cancer treated with surgery, the presence of tumor-infiltrating lymphocytes (TILs) in breast tumor tissue is associated with a decreased risk of breast cancer recurrence and death (22), which suggests that the immune system may be important in preventing recurrence.

PATIENTS AND METHODS

Study design and population. We used data from Medicare (2000–2012) to conduct retrospective cohort studies in women with RA or IBD and a primary breast cancer treated with surgery. Medicare is a national health insurance program funded by the US government that covers more than 50 million elderly Americans (age 65 years and older) and some individuals younger than age 65 years with disabilities (including RA or IBD). Medicare data were obtained from the Centers for Medicare and Medicaid Services (23).

Patients with primary breast cancer were identified using a validated algorithm with 99% specificity and 82% positive predictive value that combined a first breast cancer diagnosis with a related breast cancer surgery (24). Patients with RA or IBD were identified using previously published methods (25–28). To avoid misclassification of prevalent breast cancers as incident, patients were included if they met the following criteria: 1) had an International Classification of Diseases, Ninth Revision (ICD-9) code for a breast cancer diagnosis with related surgery (lumpectomy or mastectomy), 2) had a diagnosis of RA or IBD with a prescription for a disease-modifying antirheumatic drug (DMARD) before or after the primary breast cancer surgery but prior to the start of follow-up, and 3) were continuously enrolled in Medicare parts A, B, and D for 6 months preceding the first breast cancer diagnosis.

Patients were excluded if they had a recurrent breast cancer event (i.e., recurrent breast cancer or a second primary breast cancer) prior to or within 365 days of the primary breast cancer surgery (when follow-up for the analysis began). Recurrent breast cancer was identified using a combination of diagnostic (secondary malignant neoplasm), surgical (resection of chest wall tumor), or therapy-related (use of selected chemotherapy, bone-modifying drugs, or palliative radiation) ICD-9, National Drug Code (NDC), and Current Procedural Terminology (CPT) codes consistent with metastatic breast cancer, or ICD-9 diagnosis codes consistent with a second primary breast cancer. Additionally, patients in whom cancer other than breast or nonmelanoma skin cancer was diagnosed within the 5 years prior to the breast cancer surgery were excluded. Finally, we excluded individuals with a gap in coverage between the first surgery and the start of follow-up.

Primary outcome measure. The primary outcome measure was a recurrent breast cancer event occurring more than 365 days after the primary breast cancer surgery. A recurrent breast cancer event included distant recurrence of the original breast cancer or a second primary breast cancer, identified using a high-specificity (97%) and high–positive predictive value (83%) claims-based algorithm as proposed by Chubak et al (29).

Observation period. Follow-up started at the later of the following: 1) 365 days after the primary breast cancer surgery or 2) the first diagnosis of immune-mediated disease (RA or IBD) and the first treatment with a DMARD (Figure 1). Follow-up ended at the earliest of one of the following: 1) new initiation of the immunosuppressive drug of interest among nonusers at the start of follow-up, 2) a recurrent breast cancer event, 3) loss of enrollment, 4) death, or 5) December 31, 2012.

Exposure definition. Medication exposures of interest included methotrexate, thiopurines (azathioprine or mercaptopurine), and anti-TNF drugs (infliximab, adalimumab, certolizumab, golimumab, or etanercept). Patients were categorized as users versus nonusers at the start of follow-up. To be categorized as a user of a medication, a patient was required to have received at least 1 prescription prior to or on the date of the start of follow-up, with an expected end date no later than 60 days prior to the start of follow-up. Nonusers included patients who had never used the medication and those who discontinued the medications at least 60 days prior to the start of follow-up.

Matching factors and potential confounders. Users of the medication of interest were matched to nonusers for risk factors for breast cancer recurrence at the start of follow-up, including surgery type (lumpectomy versus mastectomy), and receipt and type of adjuvant therapy (postsurgery radiotherapy and chemotherapy). These variables were measured within 365 days after the first breast cancer surgery. Among patients with RA, those exposed to methotrexate were matched 1:1 to those

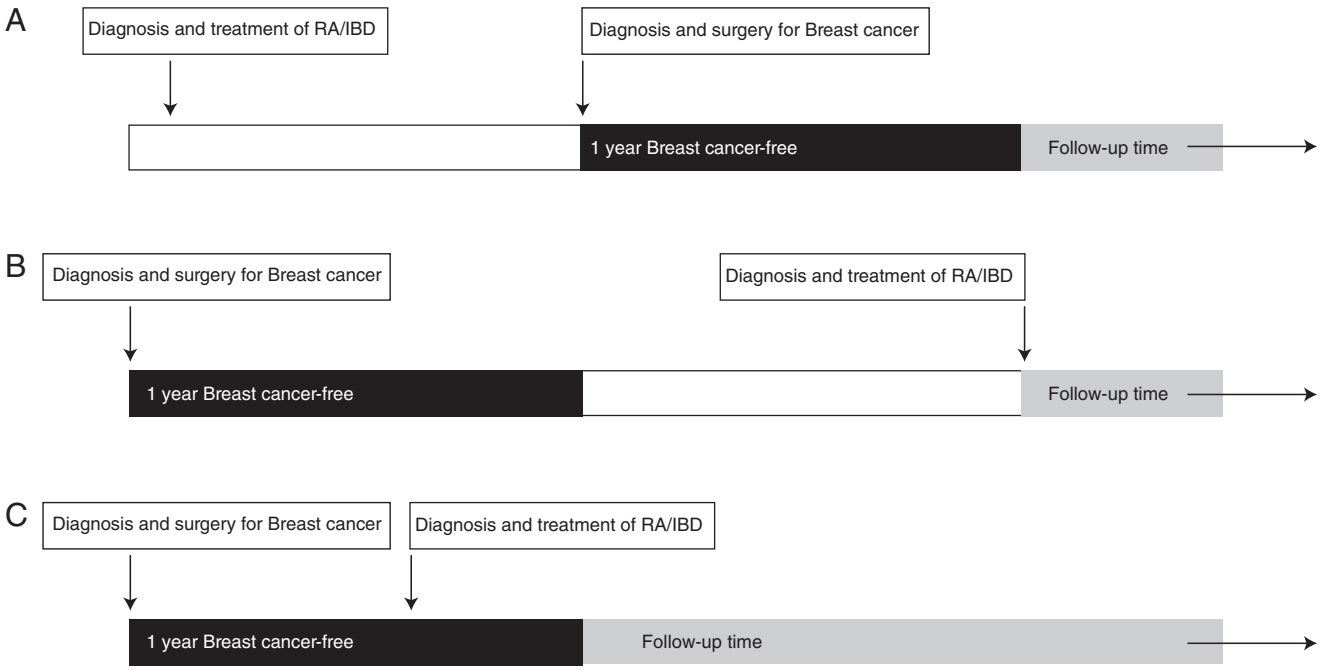

Figure 1. Cohort entry and follow-up. Entry into the cohort required a diagnosis of breast cancer with related surgery and a diagnosis and treatment of rheumatoid arthritis (RA) or inflammatory bowel disease (IBD). Follow-up started at the later of the following: date of the 1-year anniversary of the breast cancer surgery (**A** and **C**) or date of the first recorded diagnosis of RA or IBD and first treatment with a disease-modifying antirheumatic drug (**B**).

who were not exposed. In patients with IBD, those exposed to thiopurines were matched 1:4 to those who were not exposed. In patients with both RA and IBD, those exposed to anti-TNF agents were matched 1:4 to those who were not exposed.

Potential confounders were measured on or before the start of follow-up and included demographics such as age and race; inflammatory disease type (RA or IBD) and prior or concurrent use of immunosuppressive therapy (methotrexate, thiopurines, anti-TNF agents, or other biologic therapy [abatacept, rituximab, tocilizumab]); use of nonsteroidal antiinflammatory drugs in the 90 days prior to the start of follow-up; other comorbidities including history of chronic kidney disease, chronic liver disease, diabetes, coronary artery disease, or congestive heart failure; and breast cancer–specific factors such as time from primary breast cancer surgery to follow-up start and receipt of postsurgery endocrine and human epidermal growth factor receptor 2 HER2 therapy.

Statistical analysis. Descriptive statistics were used to compare the characteristics of the users and nonusers in each medication exposure group. Incidence rates of breast cancer recurrence were computed. In the primary analysis, Cox regression models were used to compute hazard ratios (HRs) for the association between breast cancer recurrence and use versus nonuse of methotrexate (in RA), thiopurines (in IBD), and anti-TNF therapy (in both), adjusted for potential confounders. Matched analyses were iteratively rerun 19 times; the iteration producing the median HR estimate was used as the primary model for confounder selection. This strategy avoids overestimation or underestimation of the HR due to chance related to the selection of unexposed subjects for matching. Confounders were selected into the final multivariable model if inclusion modified the HRs for the primary exposure by ≥10% (30).

Subgroup and secondary analyses. The primary analysis was repeated in the subgroup of patients with immune-mediated disease and documented exposure to immunosuppressive therapy (according to the Medicare files) prior to the start of follow-up, thus comparing those who continued the medication with those who discontinued it prior to the start of follow-up. In secondary analyses, separate HRs were computed for each of the following secondary outcome measures: a second primary breast cancer only, metastatic breast cancer only, and recurrent breast cancer using an alternate definition of recurrence. The latter included a prescription for a chemotherapy agent (identified with Healthcare Common Procedure Coding System, NDC, CPT, or ICD-9 codes) used exclusively in metastatic disease as an additional method to identify patients with breast cancer recurrence.

Analyses were performed using SAS version 9.3. When <11 patients were exposed to a therapy or experienced the outcome, the results were not reported, in adherence to the data use agreement with the Center for Medicare and Medicaid Services. The study protocol was approved by the University of Alabama at Birmingham and University of Pennsylvania institutional review boards.

RESULTS

Among 2,684 women with prior breast cancer and either RA or IBD, 3 matched cohorts were created including 892 users and 892 nonusers of methotrexate, 52 users and 208 nonusers of a thiopurine, and 291 users and 1,164 nonusers of anti-TNF therapy (Table 1). The

Table 1. Baseline characteristics of the patients according to immunosuppressive therapy group and use or nonuse of the therapeutic agent*

Characteristic	Methotrexate		Thiopurine		Anti-TNF	
	User (n = 892)	Nonuser (n = 892)	User (n = 52)	Nonuser (n = 208)	User (n = 291)	Nonuser (n = 1,164)
Age, years						
<65	121 (13.6)	154 (17.3)	<11†	30 (14.4)	55 (18.9)	174 (14.9)
65 to <70	178 (20.0)	137 (15.4)	16 (30.8)	34 (16.3)	71 (24.4)	207 (17.8)
70 to <75	206 (23.1)	229 (25.7)	11 (21.2)	55 (26.4)	71 (24.4)	285 (24.5)
75 to <80	192 (21.5)	176 (19.7)	11 (21.2)	41 (19.7)	60 (20.6)	242 (20.8)
≥80	195 (21.9)	196 (22.0)	<11	48 (23.1)	34 (11.7)	256 (22.0)
Race						
White	767 (86.0)	718 (80.5)	46 (88.5)	189 (90.9)	262 (90.0)	977 (83.9)
Black	89 (10.0)	124 (13.9)	<11	<11	16 (5.5)	132 (11.3)
Other‡	36 (4.0)	50 (5.6)	<11	11 (5.3)	13 (4.5)	55 (4.7)
Rheumatic disease						
RA	892 (100.0)	892 (100.0)	–	–	273 (93.8)	1,092 (93.8)
IBD	–	–	52 (100.0)	208 (100.0)	18 (6.2)	72 (6.2)
Treatment						
MTX						
Never	–	320 (35.9)	50 (96.2)	198 (95.2)	99 (34.0)	322 (27.7)
New use at start of follow-up	128 (14.3)	–	–	–	–	–
Prior§	23 (2.6)	569 (63.8)	<11	<11	64 (22.0)	387 (33.2)
Concurrent¶	741 (83.1)	<11	–	–	128 (44.0)	455 (39.1)
Thiopurine						
Never	883 (99.0)	813 (91.1)	–	193 (92.8)	269 (92.4)	1,104 (94.8)
New use at start of follow-up	–	–	<11	–	–	–
Prior	<11	53 (5.9)	<11	15 (7.2)	15 (5.2)	40 (3.4)
Concurrent	<11	26 (2.9)	48 (92.3)	<11	<11	20 (1.7)
Anti-TNF agent						
Never	664 (74.4)	595 (66.7)	43 (82.7)	189 (90.9)	–	950 (81.6)
New use at start of follow-up	–	–	–	–	<11	–
Prior	111 (12.4)	183 (20.5)	<11	11 (5.3)	<11	214 (18.4)
Concurrent	117 (13.1)	114 (12.8)	<11	<11	280 (96.2)	<11
Other biologic agents#						
Never	840 (94.2)	817 (91.6)	52 (100.0)	208 (100.0)	278 (95.5)	1,078 (92.6)
Prior	32 (3.6)	41 (4.6)	–	–	12 (4.1)	41 (3.5)
Concurrent	20 (2.2)	34 (3.8)	–	–	<11	45 (3.9)
Breast cancer surgery						
Bilateral mastectomy	11 (1.2)	11 (1.2)	<11	<11	<11	20 (1.7)
Mastectomy	371 (41.6)	371 (32.7)	17 (32.7)	68 (32.7)	113 (38.8)	452 (38.8)
Lumpectomy	510 (57.2)	510 (65.4)	34 (65.4)	136 (65.4)	173 (59.5)	692 (59.5)
Radiation therapy**	420 (47.1)	420 (47.1)	31 (59.6)	124 (59.6)	147 (50.5)	588 (50.5)
Adjuvant chemotherapy**	91 (10.2)	91 (10.2)	<11	20 (9.6)	28 (9.6)	112 (9.6)
Hormonal therapy**	518 (58.1)	446 (50.0)	32 (61.5)	136 (65.4)	164 (56.4)	645 (55.4)
Human anti-HER2 therapy**	26 (2.9)	23 (2.6)	<11	<11	<11	34 (2.9)
Prior NSAID treatment¶	295 (33.1)	227 (25.4)	<11	31 (14.9)	90 (30.9)	320 (27.5)
Diabetes mellitus	222 (24.9)	263 (39.5)	<11	49 (23.6)	68 (23.4)	320 (27.5)
Chronic kidney disease	43 (4.8)	72 (8.1)	<11	23 (11.1)	16 (5.5)	75 (6.4)
Chronic liver disease	<11	40 (4.5)	<11	<11	<11	31 (2.7)
Congestive heart failure	98 (11.0)	146 (16.4)	<11	24 (11.5)	35 (12.0)	158 (13.6)
Coronary artery disease	188 (21.1)	278 (31.2)	<11	44 (21.2)	61 (21.0)	305 (26.2)
Carotid artery disease	21 (2.4)	18 (2.0)	<11	<11	<11	29 (2.5)
Time from breast cancer surgery to follow-up start, years						
1	752 (84.3)	834 (93.5)	48 (92.3)	186 (89.4)	283 (97.3)	1,021 (87.7)
1 to 1.5	35 (3.9)	12 (1.3)	<11	<11	<11	38 (3.3)
1.5 to 2	28 (3.1)	18 (2.0)	<11	<11	<11	28 (2.4)
>2	77 (8.6)	28 (3.1)	<11	<11	<11	77 (6.6)
Follow-up, median (IQR) years	2.4 (1.6–3.1)	2.5 (1.5–3.3)	3.4 (1.7–4.8)	3.2 (1.9–3.5)	2.7 (1.7–3.7)	2.5 (1.7–4.4)

* Except where indicated otherwise, values are the number (%). Anti-TNF = anti–tumor necrosis factor; RA = rheumatoid arthritis; IBD = inflammatory bowel disease; MTX = methotrexate; HER2 = human epidermal growth factor receptor 2; NSAID = nonsteroidal antiinflammatory drug; IQR = interquartile range.

† Results were not reported when <11 patients were exposed to a treatment.

‡ Hispanic, Asian/Pacific Islander, North American native, and unknown.

§ More than 90 days prior to the start of follow-up.

¶ Within 90 days prior to the start of follow-up.

Abatacept, rituximab, and tocilizumab.

** Within 365 days after breast surgery.

Table 2. Incidence rate of breast cancer, and HRs for the association between methotrexate, thiopurine, and anti-TNF use and risk of breast cancer recurrence*

	Methotrexate		Thiopurines†		Anti-TNF	
	User	Nonuser	User	Nonuser	User	Nonuser
Recurrent breast cancer, no. of cases	52	28	<11	<11	17	48
Person-years of follow-up	2,557	1,425	–	–	764	2,466
Crude incidence rate (95% CI) of breast cancer recurrence per 1,000 patient-years	20.3 (15.2–26.7)	19.6 (13.1–28.4)	32.3 (8.8–82.6)	17.6 (7.6–34.6)	22.3 (13.0–35.6)	19.5 (14.4–25.8)
Adjusted HR (95% CI) for association between breast cancer recurrence and medication exposure	1.07 (0.67–1.69)‡	Reference	2.10 (0.62–7.14)§	Reference	1.13 (0.65–1.97)‡	Reference

* 95% CI = 95% confidence interval.
† Person-years of follow-up are not shown, to avoid calculation of the absolute number of cases.
‡ None of the covariates assessed modified the hazard ratio (HR) by >10%, including age, race, calendar year, time from breast cancer surgery to start of follow-up, postsurgery hormonal or human epidermal growth factor receptor 2 therapy, use of nonsteroidal antiinflammatory medication in the prior 90 days, prior or concurrent use of immunosuppressive therapy (methotrexate, thiopurines, anti–tumor necrosis factor [anti-TNF]), or other biologic therapy (abatacept, rituximab, tocilizumab), and history of chronic kidney disease, chronic liver disease, diabetes mellitus, coronary artery disease, or congestive heart failure.
§ Adjusted for history of coronary artery disease and congestive heart failure; no other covariates modified the HR by >10%.

cohorts were not mutually exclusive. The median duration of follow-up for each matched pair of exposed and unexposed patients ranged from 2.4 to 3.4 years. Overall, 85% of patients were 65 years of age or older. Within each medication exposure group, baseline demographics and comorbidities were generally similar between users and nonusers. Relative to nonusers, users of methotrexate, thiopurines, and anti-TNF agents were more likely to have been treated with methotrexate (86% versus 64%), thiopurine (92% versus 7%), or anti-TNF therapy (97% versus 18%), respectively, prior to breast cancer surgery.

In total, 107 women were diagnosed as having recurrent breast cancer during 5,196 person-years (Table 2). The crude incidence rates of recurrent breast cancer were 20.3 and 19.6 per 1,000 person-years in methotrexate users and nonusers, 32.3 and 17.6 in thiopurine users and nonusers, and 22.3 and 19.5 in anti-TNF users and nonusers, respectively.

The adjusted HRs for the association between recurrent breast cancer and each of the medication exposures are shown in Table 2. In the methotrexate analysis, there was no statistically significant association between use of methotrexate and the risk of breast cancer recurrence (HR 1.07 [95% CI 0.67–1.69]). Similarly, in the anti-TNF analysis, use of anti-TNF therapy was not associated with breast cancer recurrence (HR 1.13 [95% CI 0.65–1.97]). Repeating the anti-TNF analysis among only patients with RA (>90% of the cohort) yielded nearly identical results (HR 1.11 [95% CI 0.64–1.95]). In the thiopurine analysis, use of thiopurines was associated with an increased but not statistically significant risk of breast cancer recurrence (HR 2.10 [95% CI 0.62–7.14]).

In a subgroup analysis, we repeated the primary analysis in the subset of patients with immune-mediated disease who received immunosuppressive therapy prior to breast cancer surgery (Table 3). Among prior users of methotrexate, there was no increased risk of breast cancer recurrence in those who continued to receive methotrexate (i.e., were prevalent users at the start of follow-up) relative to discontinuers (i.e., were not prevalent users at the start of follow-up) (HR 1.15 [95% CI 0.63–2.08]). Similarly, among prior users of anti-TNF therapy, there was not a statistically significantly increased risk of breast cancer recurrence in those who continued to receive anti-TNF relative to those who discontinued treatment (HR 1.37 [95% CI 0.57–3.30]). There were too few patients who had received prior therapy with thiopurines to produce stable estimates of the HRs in this subgroup.

In secondary analyses, we repeated the primary analysis with the outcome measures of metastatic disease only, a second primary breast cancer only, and an alternate definition of metastatic disease treated with chemotherapy agents used only for metastatic disease (additional information is available upon request from the corresponding author). Treatment with methotrexate, thiopurines, or anti-TNF agents was not statistically significantly associated with any of the secondary outcome measures (additional information is available upon request from the corresponding author). Of note, results from the analysis

Table 3. Breast cancer recurrence in the patients according to immunosuppressive therapy group and continuation or discontinuation of the therapeutic agent prior to the start of follow-up*

	Methotrexate		Thiopurines†		Anti-TNF	
	Continuer	Discontinuer	Continuer	Discontinuer	Continuer	Discontinuer
Recurrent breast cancer, no. of cases	42	15	<11	0	17	<11
Person-years of follow-up	1,858	726	–	–	725	–
Crude incidence rate (95% CI) of breast cancer recurrence per 1,000 patient-years	22.6 (16.3–30.6)	20.7 (11.6–34.1)	34.6 (9.4–88.5)	–	23.5 (13.7–37.6)	14.1 (5.7–29.1)
Adjusted HR (95% CI) for association between breast cancer recurrence and medication exposure	1.15 (0.63–2.08)‡	Reference	–	Reference	1.37 (0.57–3.30)§	Reference

* Continuers were patients who were prevalent users at the start of follow-up. 95% CI = 95% confidence interval.
† Person-years for thiopurine exposure are not shown, to avoid calculation of the absolute number of cases.
‡ None of the covariates assessed modified the hazard ratio (HR) by >10%, including age, race, calendar year, time from breast cancer surgery to start of follow-up, postsurgery hormonal or human epidermal growth factor receptor 2 therapy, use of nonsteroidal antiinflammatory medication in the prior 90 days, prior or concurrent use of immunosuppressive therapy (methotrexate, thiopurines, anti–tumor necrosis factor [anti-TNF]), or other biologic therapy (abatacept, rituximab, tocilizumab), and history of chronic kidney disease, chronic liver disease, diabetes mellitus, coronary artery disease, or congestive heart failure.
§ Adjusted for prior or concurrent use of other biologic agent (none, within 90 days, or >90 days prior to the start of follow-up); no other covariates modified the HR by >10%.

of a second primary breast cancer produced lower HRs that were not statistically significant (ever use of methotrexate, HR 0.82 [95% CI 0.38–1.75]; ever use of thiopurines, HR 0.88 [95% CI 0.10–7.86]; ever use of anti-TNF, HR 0.62 [95% CI 0.21–1.83]). In contrast, the risk of metastatic disease among patients treated with thiopurines was nearly 4-fold higher than that among nonusers, although this difference was not statistically significant (HR 3.87 [95% CI 0.97–15.51]).

DISCUSSION

The risk of cancer recurrence must be considered when selecting a treatment regimen for patients with active symptoms of RA or IBD and a history of cancer. For patients with a solid cancer within the preceding 5 years, the safety of starting or resuming biologic therapy is uncertain (14). This issue is particularly relevant for patients with breast cancer, because it is common (>230,000 new diagnoses in 2015) and has a high 5-year survival rate (31). In the current cohort study of women with immune-mediated disease and prior breast cancer, we observed no statistically significant association between use of methotrexate, thiopurines, or anti-TNF medications and the risk of breast cancer recurrence.

A few prior observational studies have addressed the issue of solid tumor recurrence in DMARD users (15–18). Similar to our study, those studies showed no increased risk of solid cancer recurrence in association with any immunosuppressive treatment (17,18) and showed no difference in the risk of recurrence between anti-TNF agent–treated and biologic agent–naive patients (15,16). However, those studies did not specifically investigate the risk of recurrence of prior breast cancer. Rather, the prior studies combined all types of cancer, an approach that may bias results toward the null if the effect of immunosuppression on the risk of recurrence differs according to tumor type, as has been observed in some studies (32).

We studied breast cancer, because it is common in women and has a high 5-year survival rate but also is associated with a high risk of recurrence after the first year, either as metastatic disease or a second primary cancer, and lymphocyte-mediated tumor surveillance is associated with a decreased risk of metastatic disease. A prior small study by Raaschou et al included 18 women with breast cancer recurrence (33). Similar to our study, no increased risk was observed in those receiving anti-TNF therapy (HR 1.1, 95% CI 0.4–2.8) relative to biologic agent–naive patients.

Our study, with >100 cases of breast cancer recurrence and 5,196 person-years of follow-up, provides important reassurance to rheumatologists and gastroenterologists choosing to start immunosuppressive therapy in patients with RA or IBD and recently treated breast cancer. Our data, which suggest that patients with prior breast cancer who were treated with anti-TNF agents were not at higher risk of recurrence compared with those who did not receive anti-TNF treatment, do not support current clinical practice that generally avoids anti-TNF therapy in this population (14). Furthermore, there was no statistically significantly

increased risk of breast cancer recurrence among the subset of patients who received anti-TNF treatment prior to breast cancer surgery and continued to receive anti-TNF therapy after surgery. Taken together, the results of this study provide some of the strongest evidence to date to support new treatment guidelines recommending that therapy for RA patients with previously treated solid malignancies should not be different from that used for RA patients without this condition (34).

To our knowledge, this study is the first to specifically examine the risk of breast cancer recurrence in patients treated with methotrexate or thiopurines. These drugs have historically been first-line immunosuppressant agents for RA and IBD, respectively. However, both drugs have been linked to an increased risk of cancer. Thiopurines are associated with an increased risk of lymphoma, nonmelanoma skin cancer, and possibly other cancers (35–37). Methotrexate has been associated with an increased risk of recurrent nonmelanoma skin cancer (38). The data from the current study suggest that methotrexate does not increase the risk of a second breast cancer event. Although the association between thiopurines and a second breast cancer event was not statistically significant, the HR was >2.0. Thus, additional studies addressing the risk associated with thiopurines are needed.

The decision to start or resume immunosuppressive therapy in patients with RA or IBD and prior breast cancer should take into consideration the severity of the underlying immune disease, potential alternative therapies, and the biologic factors of the primary breast cancer. For example, some patients with IBD can be managed with nonimmunosuppressive drugs such as mesalamine. Likewise, a major concern for patients with curable breast cancer and treating oncologists is whether treatment with immunosuppression regimens convert occult metastases or dormant cells to clinically apparent metastases or cause a local recurrence. This is particularly relevant for those with triple-negative breast cancer, which is more aggressive and, if it recurs, will do so within 5 years of the initial diagnosis. Additionally, the presence of TILs in the stroma surrounding the primary tumor in patients with triple-negative breast cancer is predictive of an improvement in survival and decreased risk of recurrence (22). Thus, there is theoretical concern that immunosuppressive medications may counteract the benefit of the immune response represented by TILs. Unfortunately, we were not able to perform subgroup analyses to examine patients with triple-negative breast cancer in this study.

The current study has several strengths. A matched cohort design allowed us to control for breast cancer–specific factors known to influence the risk of breast cancer recurrence after surgery. Notably, follow-up time began on the 1-year anniversary of the primary surgery in $>90\%$ of cohort members, and the median follow-up time was similar across exposure groups. A validated claims-based algorithm with high specificity (97%) and positive predictive value (83%) was used to identify breast cancer recurrence (29). In secondary analyses, the study also provided separate estimates for the risk of a second primary and metastatic breast cancer. Furthermore, the Medicare patient population is geographically diverse, and breast cancer incidence rates are highest among women older than age 65 years, most of whom are eligible for Medicare coverage (21). Medicare also covers younger patients for reasons such as disability, for which RA and IBD patients may qualify on the basis of their condition. Notably, 15–20% of the patients in our cohort were younger than age 65 years.

The study also has several potential limitations. As with all observational studies, there is a risk of unmeasured confounding. We were unable to measure RA or IBD disease activity. Higher disease activity almost certainly is associated with receipt of immunosuppressant therapy and perhaps could lead to an increased risk of cancer. As such, failure to adjust for disease activity would be expected to bias the association away from the null. Given that no association was observed with methotrexate or anti-TNF therapy, such bias would not be expected to change the conclusions of this study. Furthermore, an unmeasured confounder would need to be strongly associated with both treatment and the risk of a second breast cancer event to have biased a clinically meaningful association between anti-TNF or methotrexate and the results that we observed. There is also the potential for surveillance bias if clinicians surveyed users of immunosuppressive therapy more frequently than they surveyed nonusers, but this would bias toward an elevated risk of breast cancer recurrence, which we did not observe.

Additionally, there was limited statistical power for the analyses related to thiopurines. For example, in the primary analysis, the HR for breast cancer recurrence with thiopurine ever use was 2.10, but the confidence interval was wide (95% CI 0.62–7.14). Thus, we cannot confidently exclude a meaningful increased risk of breast cancer recurrence among users of this class of medications. Similarly, even in our large cohort, there was limited statistical power for subgroup analyses related to duration of immunosuppressive therapy. Results from the current study cannot be generalized to women with active breast cancer undergoing treatment, because we focused only on those with breast cancer that was presumed to be cured. Finally, the small number of users prevented us from studying rituximab,

which has been recommended by some clinicians for RA patients in this setting.

In summary, among women with immune-mediated disease and treated breast cancer, there was no statistically significant increase in the risk of breast cancer recurrence with use of methotrexate, thiopurine, or anti-TNF therapy, although we cannot rule out a 2-fold or greater increased risk associated with thiopurine. The data from our study may help rheumatologists and gastroenterologists to better assess the risk−benefit relationship when choosing between commonly used immunosuppressant therapies for patients with a history of cancer.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Curtis and Lewis had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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