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Association between breast cancer recurrence with immunosuppression in rheumatoid arthritis and inflammatory bowel disease: A cohort study

Ronac Mamtani, MD MSCE[*,1,2], **Amy S. Clark, MD MSCE**[*,1,2], **Frank I Scott, MD MSCE**[1], **Colleen M Brensinger, MS**[1,3], **Ben Boursi, MD**[1], **Lang Chen, PhD**[4], **Fenglong Xie, MS**[4], **Huifeng Yun, PhD**[5], **Mark T Osterman, MD MSCE**[1], **Jeffrey R Curtis, MD MS MPH**[*,4,5], and **James D Lewis, MD MSCE**[*,1]

[1]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania

[2]Abramson Cancer Center, University of Pennsylvania

[3]Department of Biostatistics and Epidemiology, University of Pennsylvania

[4]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham

[5]Department of Epidemiology, University of Alabama at Birmingham

Abstract

Objective—Breast cancer recurrence may be promoted by immunosuppression due to decreased immune surveillance. Among patients with immune-mediated disease and treated breast cancer, we examined rates of breast cancer recurrence with use of methotrexate, thiopurines, and anti-TNF therapy.

Methods—Three retrospective cohort studies within Medicare (2000-2012) included women with rheumatoid arthritis or inflammatory bowel disease who completed surgery for primary breast cancer. Recurrent or second primary breast cancers beyond 365 days from initial surgery were identified. Separate Cox regression models examined risk of cancer recurrence with use of

Corresponding Author: Ronac Mamtani, MD MSCE, Perelman Center for Advanced Medicine, South Pavilion, Floor 6, 3400 Civic Center Boulevard, Philadelphia, PA, 19104, Phone: 215-360-0699; Fax: 215-614-0456, ronac.mamtani@uphs.upenn.edu.

*Drs. Mamtani and Clark contributed equally to this work. Drs. Lewis and Curtis served as co-senior investigators.

Ms. Brensinger, Drs. Clark, Boursi, Chen, and Xie report no potential conflicts of interest.

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methotrexate, thiopurines, and anti-TNF therapy after surgery, each compared to no use. Analyses were matched on type of breast surgery, and receipt and type of adjuvant therapy.

Results—Across all medication groups, 107 women developed breast cancer recurrence during 5,196 person-years. Incidence rates 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. There was no significantly increased risk of breast cancer recurrence with use of methotrexate (adjusted hazard ratio [HR] 1.07, 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 with methotrexate, thiopurine, or anti-TNF therapy was not statistically significantly increased, although we cannot rule out a 2-fold or greater increased risk 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.

Introduction

The incidence of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) are increasing worldwide[1,2]. Treatment for these conditions is primarily with immunosuppression[3,4] including thiopurines, methotrexate, anti-tumor necrosis factor (TNF) and other biologics. Some[5,6,7-9] but not all studies[10-12] have observed increased incidence of solid malignancies 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 found no difference in cancer recurrence between the combination of anti-TNF therapy with methotrexate versus methotrexate alone[15,16]. Likewise, no association was observed between exposure to immunosuppressants and the risk of cancer recurrence in 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 and IBD. Of the four most common solid cancers, there are several advantages to studying breast cancer. In contrast to colon 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 among 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 and above) and some individuals younger than 65 with disabilities (including RA or IBD). Medicare data were obtained from the Centers for Medicare and Medicaid Services (CMS)[23].

Patients with primary breast cancer were identified using a validated algorithm with 99% specificity and 82% positive predictive value which 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]. Patients were included if they met the following criteria: 1) had a breast cancer diagnosis with related surgery (lumpectomy or mastectomy) code; 2) had a diagnosis of RA or IBD with a prescription for a disease modifying anti-rheumatic drug (DMARD) before or after the primary breast cancer surgery, but prior to the start of follow-up (described below in 'Observation period'); and 3) had 6 months of continuous enrollment in Medicare parts A, B, and D preceding the first breast cancer diagnosis to avoid misclassification of prevalent breast cancers as incident.

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) codes consistent with metastatic breast cancer, or codes consistent with a second primary breast cancer. Additionally, patients diagnosed with cancer other than breast or non-melanoma skin cancer in 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 (described below).

Primary outcome

The primary outcome 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 proposed by Chubak et al[29].

Observation period

Follow-up started with the latest of 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 with the earliest of one of the following: 1) new initiation of the immunosuppressive drug of interest among non users 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 the 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 one 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 on risk factors for breast cancer recurrence at the start of follow-up, including surgery type (lumpectomy vs. mastectomy), and receipt and type of adjuvant therapy – post surgery radiotherapy and chemotherapy. These variables were measured within the 365 days after the first breast cancer surgery. In RA, methotrexate exposed patients were matched 1:1 to unexposed patients; in IBD, thiopurine exposed patients were matched 1:4 to unexposed patients; in RA and IBD, anti-TNF exposed patients were matched 1:4 to unexposed patients.

Potential confounders were measured on or before the start-up of follow up and included demographics such as age and race; inflammatory disease type (RA or IBD) and prior and concurrent use of immunosuppressive therapy (methotrexate, thiopurines, anti-TNF, or other biologic therapy [abatacept, rituximab, tocilizumab)]; use of non-steroid anti-inflammatory medications in the 90 days prior to 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 post surgery endocrine and HER2 therapy.

Statistical analysis

Descriptive statistics compared characteristics between users and nonusers in each medication exposure groups. Incidence rates of breast cancer recurrence were computed. In the primary analysis, Cox regression models computed hazard ratios (HRs) for the association between breast cancer recurrence with 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 over- or under-estimation of the hazard ratio due to chance related to the selection of unexposed subjects for matching. Confounders were selected into the final multivariable model if inclusion modified HRs for the primary exposure by ≥10%[30].

Subgroup and secondary analyses

The primary analysis was repeated among the subset with immune-mediated disease and documented exposure to immunosuppressive therapy in the Medicare files prior to the start of follow-up, thus comparing those who continued the medications versus those who discontinued it prior to the start of follow-up.

In secondary analyses, separate HRs were computed for each of the following secondary outcomes: 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 HCPCS, NDC, CPT, or ICD9 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 (SAS Institute, Cary, NC). Results where <11 patients were exposed to a therapy or experienced the outcome were not reported in adherence to the data use agreement with the Center for Medicare and Medicaid Services. The study protocol was approved by 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, three matched cohorts were created including 892 users and 892 nonusers of methotrexate, 52 users and 208 nonusers of a thiopurine, and 291 users and 1164 nonusers of anti-TNF therapy (Table 1). The cohorts were not mutually exclusive. The median duration of follow-up for each matched pair of exposed and unexposed individuals ranged from 2.4 to 3.4 years. Overall, 85% of patients were aged 65 years or older. Within each medication exposure group, baseline demographics and comorbidities were generally similar between users and nonusers. Relative to nonusers, users of methotrexate, thiopurine, and anti-TNF were more likely to have used methotrexate (86% vs 64%), thiopurine (92% vs 7%), and anti-TNF therapy (97% vs 18%), respectively, prior to breast cancer surgery.

In total, 107 women were diagnosed with recurrent breast cancer during 5,196 person-years (Table 2). The crude incidence rate of recurrent breast cancer was 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.

Adjusted hazard ratios for the association between recurrent breast cancer with each of the medication exposures are presented 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 only among 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 elevated 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 among the subset with immune-mediated disease and immunosuppressive therapy prior to breast cancer surgery (Table 3). Among prior users of methotrexate, there was no increased risk of breast cancer recurrence in methotrexate continuers (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 anti-TNF continuers relative to

discontinuers (HR 1.37, 95% CI 0.57-3.30). There were too few patients who had prior therapy with thiopurines to produce stable estimates of hazard ratios in this subgroup.

In secondary analyses, we repeated the primary analysis with the outcomes of metastatic disease only, a second breast cancer primary only, and an alternate definition of metastatic disease using chemotherapy agents only used for metastatic disease. These results are shown in Supplementary Table 1. Use of methotrexate, thiopurines, or anti-TNF therapy were not statistically significantly associated with any of the secondary outcomes (Supplementary Table 1). Of note, results from the analysis of a second primary breast cancer produced lower hazard ratios 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 among nonusers, although this 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, since it is common (over 230,000 new diagnoses in 2015) and has a high 5-year survival rate[31]. In these cohort studies 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 breast cancer recurrence risk.

A few prior observational studies have addressed the question of solid cancer recurrence in DMARD users[15-18]. Similar to our study, these studies showed no increased risk in solid cancer recurrence with any immunosuppression[17,18] and found no difference in risk of recurrence between anti-TNF treated and biologics-naïve patients[15,16]. However, these studies did not specifically investigate the recurrence risk 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 by tumor type, as has been observed in some studies[32].

We studied breast cancer as this is a common cancer in women, has a high 5-year survival rate, but also has 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 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 using anti-TNF therapy (HR 1.1, 95% CI 0.4-2.8) relative to biologics-naïve individuals.

Our study, with > 100 breast cancer recurrences 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 anti-TNF users with prior breast cancer were not at higher risk of recurrence compared with nonusers, do not support current clinical practice which 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 with anti-TNF use prior to breast cancer surgery who continued anti-TNF therapy after surgery. Taken together, results from this study provide some of the strongest evidence to date to support new treatment guidelines recommending that RA patients with previously treated solid malignancies should not be treated differently than RA patients without this condition [34].

To our knowledge, this is the first study to specifically examine the risk of breast cancer recurrence with methotrexate and thiopurines. These drugs have historically been first line immunosuppressant agents for RA and IBD, respectively. However, both of these have been linked to increased risk of cancer. Thiopurines are associated with an increased risk of lymphoma, non-melanoma skin cancer and possibly other cancers[35-37]. Methotexate has been associated with an increased risk of recurrent non-melanoma 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 hazard ratio was greater than 2.0. Thus additional studies addressing the risk with thiopurines are needed.

The decision to start or resume immunosuppression in patients with RA or IBD and a prior breast cancer should take into consideration both the severity of the underlying immune disease, potential alternative therapies, and biological factors of the primary breast cancer. For example, some patients with IBD can be managed with non-immunosuppressive 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 (TNBC), which is more aggressive and, if it recurs, will do so within 5 years of initial diagnosis. Additionally, TILs in the stroma surrounding TNBC primary tumor predicts for 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 TNBC in this study.

There were several strengths of this study. 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 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 risks of a second primary and metastatic breast cancer. Furthermore, Medicare is a geographically diverse patient population and breast cancer incidence rates are highest among women aged older than 65, most of whom are eligible for Medicare[21]. Medicare also covers younger patients for reasons such as disability, which RA

and IBD patients may qualify for on the basis of their condition. Notably, 15-20% of our cohort were younger than 65.

The study also has several potential limitations. As with all observational studies, there is the 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 to the results that we observed. There is also the potential for surveillance bias if users of immunosuppressive therapy were more frequently surveyed by clinicians than nonusers, but this would bias toward an elevated risks for breast cancer recurrence, which we did not observe.

Additionally, there was limited statistical power for analyses related to the thiopurines. For example, in the primary analysis, the HR for breast cancer recurrence with thiopurine ever use was 2.10, but confidence intervals were 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. Likewise, even in our large cohort there was limited statistical power for subgroup analyses related to duration of immunosuppressive therapy. Results from this study cannot be generalized to women with active breast cancer undergoing treatment as we focused only on subjects with presumed cured breast cancer. Finally, the small number of users prevented us from studying rituximab, which has been recommended by some for patients with RA 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 with thiopurines. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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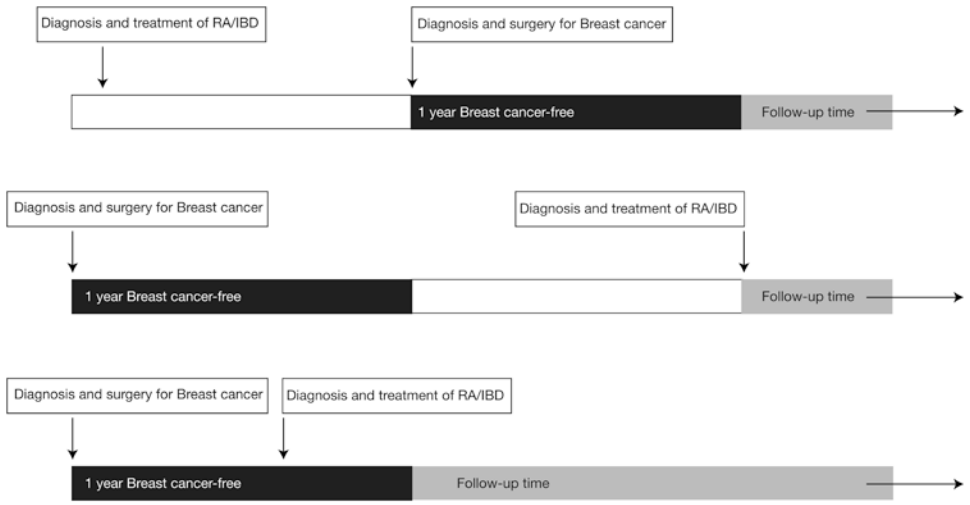

Figure 1.

Examples of cohort entry and follow-up.

Cohort entry required a diagnosis of breast cancer with related surgery and a diagnosis and treatment of RA or IBD. Follow-up started with the latest of the following: date of the 1-year anniversary of the breast cancer surgery (top and bottom panels) or the date of first recorded diagnosis of RA or IBD and first treatment with a DMARD (middle panel).

Table 1

Baseline characteristics of breast cancer and immune-mediated disease cohorts according to immunosuppressive therapy use

		Methotrexate		Thiopurine		Anti-TNF	
Characteristic	**Group**	**User(n=892)**	**Nonuser(n=892)**	**User(n=52)**	**Nonuser(n=208)**	**User(n=291)**	**Nonuser(n=1164)**
Age (y)	<65 y	121 (13.6%)	154 (17.3%)	<11[a]	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[b]	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%)
Rheumatologic disease	RA	892 (100.0%)	892 (100.0%)	--	--	273 (93.8%)	1092 (93.8%)
	IBD	--	--	52 (100.0%)	208 (100.0%)	18 (6.2%)	72 (6.2%)
Methotrexate	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[c]	23 (2.6%)	569 (63.8%)	<11	<11	64 (22.0%)	387 (33.2%)
	Concurrent[d]	741 (83.1%)	<11	--	--	128 (44.0%)	455 (39.1%)
Thiopurines	Never	883 (99.0%)	813 (91.1%)	--	193 (92.8%)	269 (92.4%)	1104 (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	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 biologics[e]	Never	840 (94.2%)	817 (91.6%)	52 (100.0%)	208 (100.0%)	278 (95.5%)	1078 (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%)

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		Methotrexate		Thiopurine		Anti-TNF	
Characteristic	**Group**	**User(n=892)**	**Nonuser(n=892)**	**User(n=52)**	**Nonuser(n=208)**	**User(n=291)**	**Nonuser(n=1164)**
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[f]		420 (47.1%)	420 (47.1%)	31 (59.6%)	124 (59.6%)	147 (50.5%)	588 (50.5%)
Adjuvant chemotherapy[f]		91 (10.2%)	91 (10.2%)	<11	20 (9.6%)	28 (9.6%)	112 (9.6%)
Hormonal therapy[f]		518 (58.1%)	446 (50.0%)	32 (61.5%)	136 (65.4%)	164 (56.4%)	645 (55.4%)
HER2 therapy[f]		26 (2.9%)	23 (2.6%)	<11	<11	<11	34 (2.9%)
Prior NSAIDs[g]		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	1 y	752 (84.3%)	834 (93.5%)	48 (92.3%)	186 (89.4%)	283 (97.3%)	1021 (87.7%)
	1 to 1.5 y	35 (3.9%)	12 (1.3%)	<11	<11	<11	38 (3.3%)
	1.5 to 2 y	28 (3.1%)	18 (2.0%)	<11	<11	<11	28 (2.4%)
	2+ y	77 (8.6%)	28 (3.1%)	<11	<11	<11	77 (6.6%)
Follow-up time	Median (IQR)	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)

Abbreviations: y, years; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; TNF, tumor necrosis factor, HER2, human epidermal growth factor receptor 2; NSAID, non-steroidal anti-inflammatory drug.

[a] Results not reported where <11 subjects were exposed to a therapy

[b] Other race includes Hispanics, Asian/Pacific Islander, Native American, unknown.

[c] Use >90 days prior to the start of follow-up

[d] Use in the 90 days prior to start of follow-up

[e] Biologics assessed included abatacept, rituximab, tocilizumab

[f] Within 365 days after breast surgery

[g] Use in the 90 days prior to start of follow-up

Table 2

Incidence rate and hazard ratios (HRs) for the association between methotrexate, thiopurines, and anti-TNF use and risk of breast cancer recurrence

	Methotrexate		Thiopurines [a]		Anti-TNF	
	User	Nonuser	User	Nonuser	User	Nonuser
Cases of Recurrent breast cancer	52	28	<11	<11	17	48
Person-years of Follow-up	2,557	1,425	--	--	764	2,466
Crude incidence of Breast cancer recurrence (per 1000-py)	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%)	1.07[b] (0.67-1.69)	Reference	2.10[c] (0.62-7.14)	Reference	1.13[b] (0.65-1.97)	Reference

[a] Person-years for thiopurine exposure are not shown to avoid calculation of absolute number of cases.

[b] No covariates modified the HR by > 10%; covariates assessed included: age, race, calendar year, time from breast cancer surgery to start of follow-up, post surgery hormonal or HER2 therapy, use of non-steroid anti-inflammatory medications in the prior 90 days, prior or concurrent use of immunosuppressive therapy (methotrexate, thiopurines, anti-TNF, or other biologic therapy [abatacept, rituximab, tocilizumab], and histories of chronic kidney disease, chronic liver disease, diabetes mellitus, coronary artery disease, and congestive heart failure.

[c] Adjusted for histories of coronary artery disease and congestive heart failure; no other covariates modified the HR by >10%

Table 3

Analysis of breast cancer recurrence in subgroup of methotrexate, thiopurine, or anti-TNF users prior to start of follow-up who continued or discontinued their therapy

	Methotrexate		Thiopurines[a]		Anti-TNF	
	Continuer[b]	Discontinuer	Continuer	Discontinuer	Continuer	Discontinuer
Cases of Recurrent breast cancer	42	15	<11	0	17	<11
Person-years of Follow-up	1,858	726	--	--	725	--
Crude incidence of breast cancer recurrence (per 1000-py)	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%)	1.15[c] (0.63-2.08)	Reference	--	Reference	1.37[d] (0.57-3.30)	Reference

[a] Person-years for thiopurine exposure are not shown to avoid calculation of absolute number of cases

[b] Prevalent users of methotrexate, thiopurines, or an anti-TNF at the start of follow-up

[c] No covariates modified the HR by > 10%; covariates assessed included: age, race, calendar year, time from breast cancer surgery to start of follow-up, post surgery hormonal or HER2 therapy, use of non-steroid anti-inflammatory medications in the prior 90 days, prior or concurrent use of immunosuppressive therapy (methotrexate, thiopurines, anti-TNF, or other biologic therapy [abatacept, rituximab, tocilizumab], and histories of chronic kidney disease, chronic liver disease, diabetes mellitus, coronary artery disease, and congestive heart failure.

[d] Adjusted for prior or concurrent other biologic use (none, within 90 days, > 90 days prior to start of follow-up); no other covariates modified the HR by > 10%.