Increased Malignancy Among Patients Treated With DMARDs and Biologic Therapies in the UPMC Central PA Health System: A Retrospective Multi-Hospital Cohort Study

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Introduction

- Rheumatologic diseases, including rheumatoid arthritis, systemic lupus erythematosus, and psoriatic arthritis, are chronic autoimmune disorders characterized by persistent immune activation, systemic inflammation, and multi-organ involvement.
- Long-term management frequently requires immunomodulatory therapy with conventional DMARDs or biologic agents to prevent disease progression and preserve functional status.
- Chronic immune dysregulation and pharmacologic immunosuppression may impair tumor immune surveillance, potentially increasing the risk of malignancy.
- Previous studies suggest elevated risk for hematologic malignancies, particularly non-Hodgkin lymphoma (NHL) and multiple myeloma, in patients with systemic autoimmune disease.
- Comparative analyses of malignancy prevalence among patients receiving DMARDs or biologics versus untreated controls within large healthcare systems remain limited.

Methods

- Retrospective observational cohort study using EMR data from the Central PA UPMC healthcare system (Jan 31, 2012 – Oct 31, 2025).
- Eligibility: Adults ≥18 years with ≥1 ambulatory or inpatient encounter within the preceding 24 months.
- Exposed cohort:
  - DMARDs (azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, mycophenolate mofetil, sulfasalazine, tacrolimus)
  - Biologics (abatacept, adalimumab, anifrolumab, baricitinib, belimumab, brodalumab, certolizumab, epratuzumab, etanercept, golimumab, infliximab, ixekizumab, rituximab, sarilumab, secukinumab, tofacitinib, tocilizumab, upadacitinib, ustekinumab).
- Control cohort: Patients with no documented DMARD or biologic exposure.
- Malignancies identified via ICD-10 codes:
  - Hematologic: Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, leukemia.
  - Solid tumors: Breast, lung, colorectal, pancreatic, hepatobiliary, renal, bladder, brain.
- Each patient counted once per malignancy category; subgroup analyses performed.
- Statistical analysis: Descriptive statistics, chi-square testing ($p<0.05$); de-identified data with IRB approval and waiver of consent.

Table 1. Hematologic Malignancy Prevalence

Malignancy Type	Exposed (DMARD/Biologic) n (%)	Unexposed n (%)	p-value
Non-Hodgkin lymphoma	290 (0.55%)	3,656 (0.18%)	<0.0001
Multiple myeloma	132 (0.25%)	1,828 (0.09%)	<0.0001
Hodgkin lymphoma	35 (0.07%)	295 (0.01%)	NS
Leukemia	98 (0.19%)	2,010 (0.10%)	NS
Overall hematologic	555 (1.05%)	7,789 (0.38%)	<0.0001

Table 2. Solid Tumor Prevalence

Tumor Type	Exposed (DMARD/Biologic) n (%)	Unexposed n (%)	p-value
Breast	1,480 (2.80%)	18,700 (0.92%)	<0.0001
Colorectal	498 (0.94%)	6,703 (0.33%)	<0.0001
Pancreatic	206 (0.39%)	2,234 (0.11%)	<0.0001
Hepatobiliary	69 (0.13%)	1,828 (0.09%)	0.02
Lung	254 (0.48%)	9,750 (0.48%)	NS
Brain	41 (0.08%)	330 (0.02%)	0.01
Bladder	23 (0.04%)	310 (0.02%)	0.04
Overall solid tumors	2,625 (4.96%)	39,855 (1.96%)	<0.0001

Results

- **Cohort sizes:** Exposed (n=52,902); unexposed controls (n=2,031,290).
- **Overall malignancy prevalence:** Higher in exposed patients (6.03% vs 2.79%, $p<0.0001$).
- **Hematologic malignancies (see table 1):**
  - Non-Hodgkin lymphoma: 0.55% vs 0.18%
  - Multiple myeloma: 0.25% vs 0.09% ($p<0.0001$)
  - Hodgkin lymphoma and leukemia: no significant differences
- **Solid tumors:**
  - Increased prevalence in exposed patients:
    - Breast: 2.80% vs 0.92%
    - Colorectal: 0.94% vs 0.33%
    - Pancreatic: 0.39% vs 0.11%
    - Hepatobiliary: 0.13% vs 0.09%
  - Lung cancer prevalence identical (0.48%); brain and bladder cancers less frequent in exposed cohort.

Conclusion

- Patients treated with DMARDs or biologics exhibit significantly higher malignancy prevalence compared with unexposed controls, driven primarily by hematologic malignancies, especially NHL and multiple myeloma.
- Certain solid tumors, including breast and colorectal cancers, also show increased prevalence.
- Findings emphasize the need for:
  - Increased malignancy awareness in patients receiving long-term immunomodulatory therapy.
  - Careful risk stratification and shared decision-making when initiating or continuing DMARD/biologic therapy.
- Future research should investigate the influence of treatment duration, cumulative drug exposure, and underlying disease severity on malignancy risk.