

ORIGINAL ARTICLE

The prevalence of cancer in patients with multiple sclerosis (MS) who received rituximab: a systematic review and meta-analysis

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KEYWORDS

Neoplasm;
Multiple sclerosis;
Systematic review

Abstract

Objective: To estimate the pooled prevalence of cancer in patients with multiple sclerosis (MS) cases who were under treatment with rituximab.

Methods: We searched PubMed, Scopus, EMBASE, Web of Science, and google scholar along with gray literature up to April 2021.

The search strategy included the MeSH and text words as ((“CD20 Antibody” AND Rituximab) OR “Rituximab CD20 Antibody” OR Mabthera OR “IDEC-C2B8 Antibody” OR “IDEC C2B8 Antibody” OR IDEC-C2B8 OR “IDEC C2B8” OR GP2013 OR Rituxan OR rituximab) AND ((Sclerosis AND multiple) OR (sclerosis AND disseminated) OR disseminated sclerosis OR multiple sclerosis OR acute fulminating).

Results: The literature search revealed 3577 articles, after deleting duplicates 2066 remained. For the meta-analysis, 22 studies were included. Totally, 15599 patients were enrolled while 133 cancers were detected.

The pooled prevalence of cancer in MS patients under treatment with rituximab is 1 in 100,000 (I² = 99.9%, $p < 0.001$).

Conclusion: The results of this systematic review and meta-analysis show that the pooled prevalence of cancer in MS patients who received rituximab is 1 in 100,000 cases.

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PALABRAS CLAVE

Neoplasia;
Esclerosis múltiple;
Revisión sistemática

La prevalencia de cáncer en pacientes con esclerosis múltiple (EM) que recibieron rituximab: una revisión sistemática y meta-análisis

Resumen

Objetivo: estimar la prevalencia combinada de cáncer en pacientes con casos de esclerosis múltiple (EM) que estaban en tratamiento con rituximab.

Métodos: Realizamos búsquedas en PubMed, Scopus, EMBASE, Web of Science y Google Scholar junto con literatura gris hasta abril de 2021.

La estrategia de búsqueda incluyó el MeSH y palabras de texto como ((CD20 Antibody" AND Rituximab) OR "Rituximab CD20 Antibody" OR Mabthera OR "IDEC-C2B8 Antibody" OR "IDEC C2B8 Antibody" OR IDEC-C2B8 OR "IDEC C2B8" OR GP2013 O Rituxan O rituximab) Y ((Esclerosis Y múltiple) O (esclerosis Y diseminada) O esclerosis diseminada O esclerosis múltiple O fulminante aguda).

Resultados: La búsqueda bibliográfica reveló 3577 artículos, después de eliminar los duplicados quedaron 2066. Para el meta-análisis se incluyeron 22 estudios. En total, se inscribieron 15599 pacientes y se detectaron 133 cánceres. La prevalencia combinada de cáncer en pacientes con EM en tratamiento con rituximab es de 1 en 100.000 (I² = 99,9 %, p < 0,001).

Conclusión: Los resultados de esta revisión sistemática y meta-análisis muestran que la prevalencia combinada de cáncer en pacientes con EM que recibieron rituximab es de 1 en 100 000 casos.

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Introduction

Multiple sclerosis (MS) is an autoimmune disease of central nervous system that affects women more than men all over the world.¹ Different medications are administered in subjects with MS while their efficacy and safety vary.

It was assumed that MS is a T-cell mediated disease while, nowadays B-cells along with T-cells are considered in pathogenesis of MS.² So, new disease modifying therapies (DMTs) are considered to have superior effects on disease progression and disability status.

CD20-positive B-cells play an important role in the pathogenesis of MS and therapies targeting these cells such as Rituximab (RTX) (immunoglobulin G1, mouse chimeric) are used widely nowadays.³ Rituximab is a chimeric monoclonal antibody which reduces the number of CD20 presenting B-cells by targeting plasma cell precursors.⁴ It acts peripherally and its level is not high in CSF.⁵ The B-cells depletion will result in antibody production decrease as well as inactivation of T-cells and macrophages.⁶ It is not associated with increased risk of cancer in MS.

Rituximab is approved for patients with rheumatoid arthritis (RA) and lymphatic cancers which is used in MS cases (off-label).⁷ A recent systematic review demonstrated that rituximab has acceptable efficacy and safety in patients with MS.³

Cancers and autoimmune diseases share common etiologies such as smoking, genetics, and vitamin D deficiency and administration of some medications.^{8,9}

Previous published studies show that the prevalence of cancers in MS patients receiving rituximab is diverse. So, we designed this systematic review and meta-analysis to estimate the pooled prevalence of cancer in patients with MS cases who were under treatment with rituximab.

Methods

We searched PubMed, Scopus, EMBASE, Web of Science, and google scholar along with gray literature up to April 2021.

The search strategy included the MeSH and text words as ((CD20 Antibody" AND Rituximab) OR "Rituximab CD20 Antibody" OR Mabthera OR "IDEC-C2B8 Antibody" OR "IDEC C2B8 Antibody" OR IDEC-C2B8 OR "IDEC C2B8" OR GP2013 OR Rituxan OR rituximab) AND ((Sclerosis AND multiple) OR (sclerosis AND disseminated) OR disseminated sclerosis OR multiple sclerosis OR acute fulminating).

Inclusion criteria: Cross sectional studies, cohort studies. Articles published in the English language.

Exclusion criteria: case-reports, RCT studies.

We collected data regarding first author, country of origin, number of enrolled patients, number of possible/confirmed cases, mean age, F/M ratio, mean Expanded Disability Status Scale (EDSS), mean duration of the disease, and number of patients with cancer.

Risk of bias assessment

We evaluated the risk of potential bias by the NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (adapted for cohort studies).¹⁰ The value ≥ 4 was considered acceptable for us.

Statistical analysis

All statistical analyses were performed using STATA (Version 14.0; Stata Corp LP, College Station, TX, USA). We used random effects model.

To determine heterogeneity, inconsistency (I²) was calculated.

We estimated the prevalence in 100 000 cases.

Table 1 Basic characteristics of the included studies.

Author	Year	Country	Design	T. MS F. MS M. MS	MS type	Age	EDSS	Disease duration (mean (sd))	Total Malignancy type	Duration of treatment (mean) (month)	NOS
Joakim Bergman ¹¹	2021	Sweden	Trial	23	SP 15	46 (9)	Median (IQR)	14 (8)	Basalioma 1	12	4 out of 6
				16	PP 8		6.5 (1.0)				
Zrzavy Tobias ¹²	2021	Austria	Cohort	119	RR 87	36.8 (10.2)	3.0 (3.0)	8.7 (6.5)	0	-	7 Out of 9
				89	SP 32						
				30							
Hilde Marie Torgauten ¹³	2021	Norway	Cohort	365	RR 320	42.3 (12.2)	2 (0-8)	5.3 (7)	Malignant disease 2 (colon cancer, melanoma)	19.2	8 Out of 9
				255	SP 23						
				110	PP 22						
Natalia Gonzalez Caldito ¹⁴	2020	USA	Cohort	623	RR 37	43.89 (12.66)	NR	NR	16	-	7 Out of 9
				361	Progressive 35				Breast cancer 11		
				145	NR 551				Malignant melanoma 5		
Peter Alping ⁷	2020	Sweden	Cohort	NR 117							
				4187	PP 168	42.9 (11.3)	2.8 (2.0)	10.3 (8.7)	51	26.4	7 Out of 9
				2968	RR 3215				Basal cell 20		
				1219	PR 71				CIN3 (females) 15		
					SP 732				Breast (females) 6		
									Prostate (males) 2		
									Melanoma 4		
									Non-Melanoma Skin Cancer 3		
									Lymphoma 1		
									0	Between 12 and 36	5 Out of 9
Thomas Mathew ¹⁵	2020	India	Cohort	80	RR 58	NR	NR	NR			
				54	SP 15						
				26	PP 7						
Angelo Bellinva ¹⁶	2020	Italy	Cohort	69	RR 53	30.2 (10.8)	3.0 (2–6)	7.8 (5.7)	pancreatic carcinoma 1	16	5 Out of 9
				51	Progressive 16						
				18							
Alexander Juto ¹⁷	2020	Sweden	Cohort	808	RR 808	38.5 (10.3)	2.0 (0–8)	7.9 (SD 7.2)	Cholangio-carcinoma 2	-	6 Out of 9
						N = 502	N = 502	N = 502	sigmoid cancer 1		
				579		38.6 (10.0)	2.0 (0–6) N = 77	8.0 (SD 7.0) N = 77			
				229		N = 77					
Johan Hellgren ¹⁸	2020	Sweden	Cohort	83	RR 66	44 (17–69)	NR	6.4 (0.0–26.3)	0	23.8	5 Out of 9
				55	SP 13						
				28	PP 4						
Brandi L. Vollmer ¹⁹	2020	USA	Cohort	907	RR 574	43(12.5)	NR	9.1(8.3)	9	40.6	6 Out of 9
				608	SP 215				Breast cancer 4		
				299	PP 118				Papillary thyroid cancer 2		
									Glioblastoma 1		
									Bladder cancer 1		

Table 1 (Continued)

Author	Year	Country	Design	T. MS F. MS M. MS	MS type	Age	EDSS	Disease duration (mean (sd))	Total Malignancy type	Duration of treatment (mean) (month)	NOS
Eleni Leonidou ²⁰	2019	Turkey	Cohort	30	RR 10	mean (SD)	4.5 (2.5–7.5) N = 10	14 (7) N = 10	Metastatic squamous cell carcinoma 1 0	18	5 Out of 9
				14	SP 17	37.9 (7.3) N = 10	6 (3.5–8) N = 17	15 (6.5) N = 17			
				16	PP 3	47.3 (9) N = 17	6 (5–8) N = 3	11 (12.8) N = 3			
Gustavo Luna ²¹	2019	Sweden	Cohort	3260 2358 902	RR 3260	40.4 (10.6)	2.1 (1.5)	8.7 (7.6)	23	36	7 Out of 9
Johan Linden ²²	2019	Sweden	Cohort	272 187 85	RR 207 SP 45 PP 20	40.7 (11.7)	2.0 (0–9)	9.6 (8.0)	4 Cervical cancer 2 Basalioma 2	43	6 Out of 9
A. Langer-Gould ²³	2019	USA	Cohort	3165	NR	NR	NR	NR	Breast cancer 7	24	NA
Chiara Zecca ²⁴	2019	Switzerland	Cohort	*ABS* 3057 108 414	NR	NR	NR	NR	mediastinal neoplasm 1 Cancer 1	22.8	5 Out of 9
Carmen Alcalá ²⁵	2019	Spain	Cohort	27 21 6	RR 27	34.6 (8.3)	3.1 (1.3)	NR		32	5 Out of 9
Pierre Durozard ²⁶	2018	France	Cohort	50 38 12	RR 50	37.5 (19–63)	4.5 (0–7)	NR	Neoplastic 0	13.2	5 Out of 9
S.G. Berntsson ²⁷	2018	Sweden	Cohort	61 39 22	RR 43 SP 13 PP 5	Mean 41.5	NR	Mean years 6.6	7 Neoplasms malignant (rectal squamous cancer) 2 Colorectal carcinoma 5	-	5 Out of 9
Brett Alldredge ²⁸	2018	USA	Cohort	40 28 12	RR 23 PP 17	NR	NR	NR	0	34.8	4 Out of 9
Vollmer, B ²⁹	2018	USA	Cohort	125 90 35	RR 78 SP 30 PP 17	mean 44.1 years	NR	Mean 10.2 years	malignant cancer 2	31.1	NA
Jonatan Salzer ³⁰	2016	Sweden	Cohort	822 545 277	RR 557 SP 198 PP 67	42.6 (11.1)	3 (0–9)	11.3 (8.5)	3 Basalioma 2 Pyoderma gangrenosum 1	21.8	6 Out of 9
Stephen L. Hauser ³¹	2008	USA	Trial	69 52 17	RR 69	39.6 ± 8.7	Median (range)	9.6(6.4) 2.5 (0–5)	malignant thyroid neoplasm 1	12	5 Yes out of 6

EDSS: Expanded Disability Status Scale; F.MS: female MS population; M.MS: male MS population; NOS: NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE; NR: not reported; PP: primary progressive; PR: progressive-relapsing; RR: relapsing-remitting; SP: secondary progressive; T.MS: total MS population.

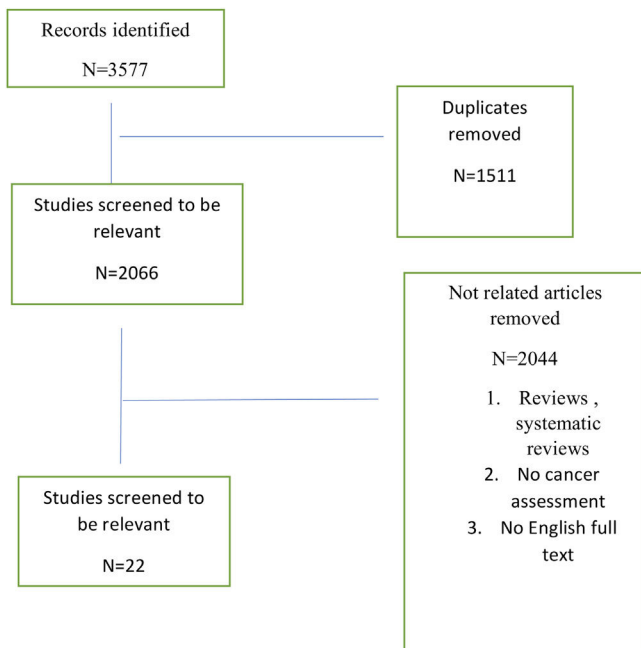


Figure 1 Flow diagram of including studies.

Results

The literature search revealed 3577 articles, after deleting duplicates 2066 remained. For the meta-analysis, 22 studies were included (Fig. 1).

Totally, 15599 patients were enrolled while 133 patients with cancers were detected (Table 1).

All studies did not report the type of the carcinomas, while among reported types, breast cancer and basal cell carcinoma were the most frequent types.

The pooled prevalence of cancer in MS patients under treatment with rituximab is 1 in 100 000 ($I^2 = 99.9\%$, $P < .001$) (Fig. 2).

Discussion

To our knowledge this is the first systematic review and meta-analysis evaluating the pooled prevalence of cancer in MS cases who were under treatment with rituximab. The results show that the pooled prevalence is 1 in 100 000 cases, which is ignorable. A recent systematic review and meta-analysis showed that the relative risk of cancer in MS patients comparing with controls is 0.83 (95% CI: 0.73–0.96),³² showing lower risk of any type of cancers in MS population. A previously done systematic review, showed that the pooled incidence of cancer in MS population was 4.3% (95% CI: 2.6–6.1%), and the pooled prevalence reported as 2.2% (95% CI: 1.1–3.2%). Their results showed that cervical, breast, and digestive cancers had higher incidence than other types of cancer.³³

Literature shows that the incidence of cancer in MS population is lower than general population without considering any specific DMTs.^{34,35}

The relationship between cancer and MS is complex. Persistent inflammation leads to promotion of tumorigenesis. Prolonged administration of immunosuppressive treatments increases the risk of malignancies.³³

Rituximab is administered as an off-label medication for MS for years which was used for cancer therapy then extended to systemic vasculitis and rheumatoid arthritis.³⁶ In 2004, for the first time,

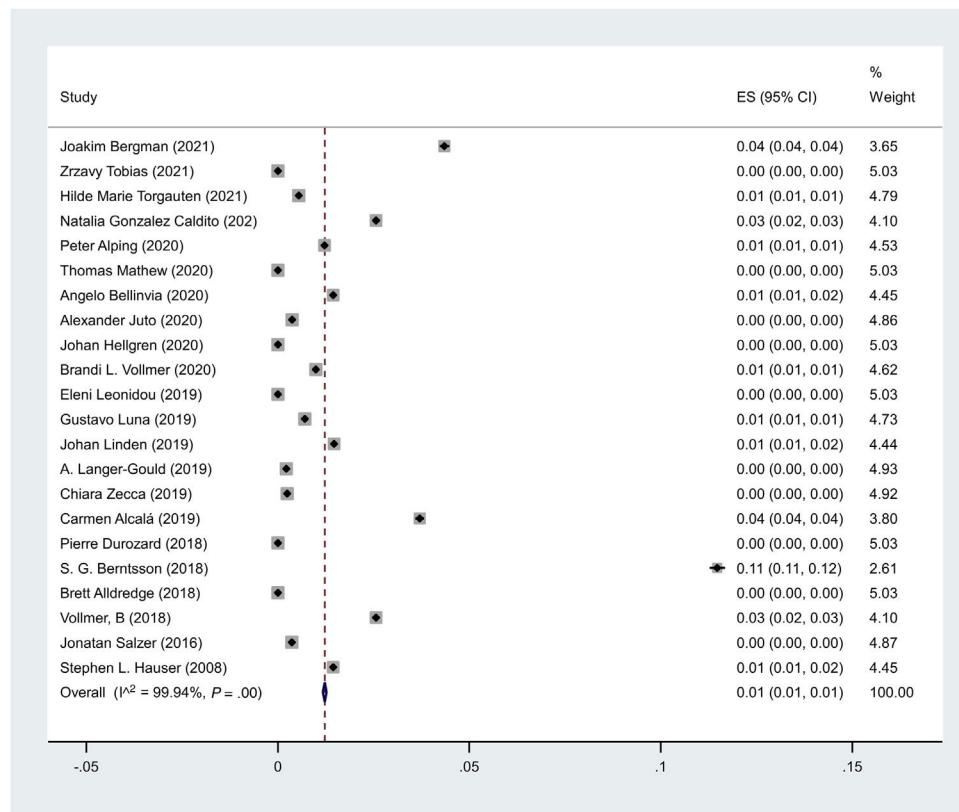


Figure 2 The pooled prevalence of cancer in MS patients who received rituximab.

rituximab was used for relapsing-remitting patients with MS which followed by a multi-centric randomized control trial (RCT).^{37,38}

Alping et al. enrolled 4187 MS patients who were under treatment with rituximab, 1620 under treatment with fingolimod, and 1670 with natalizumab, and found that 33 had cancer in rituximab group. The most frequent carcinoma in MS cases was basal cell carcinoma followed by cervical intraepithelial neoplasia (CIN), which were higher in rituximab group.⁷ Their results demonstrated that prevalence of malignancies in their MS population was 26.6% vs 28.9% in general population (the difference was not significant).

In an Italian study, Zecca et al. enrolled 414 MS patients and reported only one mediastinal cancer among them.³⁹

A study by van Vollenhoven et al. enrolling patients with RA treated with rituximab demonstrated that the risk of cancer in these patients is not higher than general population.⁴⁰

This systematic review and meta-analysis has some strength. First, we included all studies evaluating safety of rituximab in MS patients. Second, we recorded all types of cancers.

The study had some limitations, too. The duration of follow up and treatment was not same in all studies. Also, all studies did not report the type of malignancies in patients who were enrolled in their study.

Conclusion

The results of this systematic review and meta-analysis show that the pooled prevalence of cancer in MS patients who received rituximab is 1 in 100 000 cases.

Conflict of interest

The authors declare no conflict of interest.

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