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REVIEW

ARE MULTIPLE SCLEROSIS PATIENTS PROTECTED AGAINST SOME TYPES OF CANCER?

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Abstract

Introduction. The risk factors for multiple sclerosis (MS) and cancer overlap to a large extent.
The objective of our study was to estimate the prevalence and risk ratios (RR) of cancers in patients with MS and to identify which types of cancer have the lowest frequency.
Materials and methods. We carried out research of the literature in the PubMed, Medline, and Google Academic databases, with the aim of identifying large-scale studies addressing the link between different cancers and MS. From 411 relevant articles, we selected 13 scientific papers for further analysis, comprising 109,276 patients diagnosed with MS from different countries.
Results. Of all MS patients, 5.1% were diagnosed with a certain type of cancer compared to 5.5% in the general population; the cancers with the lowest incidence were respiratory, digestive, and blood cancers.

Résumé

Est-ce que les patients avec de la sclérose en plaques sont-ils protégés contre certains types de cancer ?

Introduction. Les facteurs de risque de la sclérose en plaques (SEP) et du cancer s'entrecroisent dans une large mesure.
L'objectif de notre étude était d'estimer la prévalence et le RR des cancers chez les patients atteints de sclérose en plaques (SEP) et de découvrir lesquels types de cancer ont la plus faible fréquence.
Matériel et méthodes. Nous avons effectué une recherche de la littérature dans les bases de données PubMed, Medline et Google Academic dans le but d'identifier des études d'envergure abordant le lien entre différents cancers et la SEP. À partir de 411 articles pertinents, nous avons sélectionné 13 travaux à analyser plus en détail, comprenant 109276 patients diagnostiqués avec SEP de différents pays.

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Conclusions. The results of our analysis suggested that MS patients are less exposed to respiratory, digestive, and blood cancers, but more research is needed to understand if some disease-modifying therapies play a role in this regard.

Keywords: cancer, multiple sclerosis, tumours, central nervous system, disease-modifying therapies.

Abbreviations list:
MS – multiple sclerosis
IS – immunosuppressive
IM – immunomodulatory
DMTs – disease-modifying therapies
RR – risk ratio
OR – odds ratio
CNS – central nervous system
CI – confidence interval

Résultats. De tous les patients atteints de SEP, 5,1% ont été diagnostiqués avec un certain type de cancer par rapport à 5,5% dans la population générale. Les cancers donc l'incidence est la plus faible sont ceux à localisation respiratoire, digestive et hématologique.
Conclusions. Les résultats de notre analyse suggèrent que les patients atteints de sclérose en plaques sont moins exposés aux cancers respiratoire, digestif et hématologique, mais il faudra davantage de recherches pour comprendre si certaines thérapies modificatrices de la maladie jouent un rôle dans cette perspective.

Mots-clés: cancer, sclérose en plaques, tumeurs, système nerveux central, thérapies modificatrices de la maladie.

Introduction

Multiple sclerosis (MS) represents an inflammatory-degenerative condition of the central nervous system (CNS) which affects million people worldwide, while cancer was responsible for over 9 million deaths in 2018[1]. MS is a neurodegenerative disorder, being the first cause of non-traumatic neurological disability in young adults, with a wide range of signs and symptoms; most often the disease onset is between 20-40 years[2,3]. Although the mechanism of action is not fully known now, it is suggested the important role of autoreactive lymphocytes B and T in the pathophysiology[4]. Even if there is not yet a curative treatment, the long-term prognosis has improved considerably over the past three decades due to the introduction of highly effective, immunosuppressive, or immunomodulatory disease-modifying therapies (DMTs). However, these drugs have attracted the attention of medical experts about the increased risk of cancer, due to immune system modulation or suppression. Many studies were conducted in numerous countries, aiming to determine whether there are interactions between different pathologies and MS, and especially whether DMTs used as MS treatment could be incriminated in cancer development[5-10]. Malignant tumours and MS are known to share similar risk factors[11]. Activation of the immune system in MS will cause additional protection against the proliferation of tumour cells; the use of immunosuppressive treatments and chronic inflammation may decrease this protection, or even turn it into one that favours tumour genesis[11].

The objective of our study was to estimate the prevalence and risk ratios (RR) of cancers in patients with MS and to identify which types of cancer have the lowest frequency. A secondary objective was to review data from the literature regarding the relationship between treatments of MS and the risk of cancer.

Materials and methods

A review of the literature from the PubMed, Medline and Google Academic databases was carried out (studies published since 1990), using the terms „brain cancer", „CNS cancer", „multiple sclerosis", „cancer incidence", „digestive cancer", „urinary cancer", „breast cancer", „skin cancer", „melanoma", „lung cancer", „DMTs"; the terms were combined using „and/or" and the plural was also used. The bibliographic databases of the relevant research were used, and the data were analysed and calculated cumulatively. The data were processed using a spreadsheet (Microsoft Excel), which made it easier to calculate and interpret them.

Inclusion criteria: studies with more than 1000 MS patients, which included at least half of the different types of cancers covered in this study, or which contained statistical data on brain tumours were included.

Exclusion criteria: works published in languages other than English.

Outcome measures

The main outcome was to collectively interpret the data of each study individually, to allow a direct view of the frequency of cancers. The secondary objective was to demonstrate the correlation between a specific DMT and certain types of cancer.

Study selection

In the first phase, an author carried out the search as mentioned above, excluding non-relevant articles by the title. Afterwards, we included articles by assessing the abstracts; when there was doubt about the relevance of an article, it was read the full text.

Studies included

Our first unfiltered research included 31,093 studies. After excluding non-relevant and duplicate articles, 411 were took into consideration for the second phase analysis. Among these, 13 studies were finally retained. The follow-up of the patients included in the studies took place between 1952 and 2016, with an average study period of 24.6 years; one of the studies was performed via correspondence, by answering a questionnaire[12].

The following analyses were included (Table 1): Nielsen et al.[7]; Grytten et al.[8]; Hongell et al.[9]; Bahmanyar et al.[11]; Moisset et al[12]; Lebrun et al.[13,14]; Kingwell et al.[15]; Moller et al.[16]; Midgard et al[17]; Sumelathi et al[18]; Bloomgren et al.[19]; Hemminki et al.[20].

Results

In the effort to identify which cancers have a low RR, we briefly classified the main types of tumours encountered in MS patients. In our analysis, there were enrolled 66,956 women (70.73%) and 27,704 men (29.27%). A total of 5,556 MS patients (5.1%) was diagnosed with a certain type of cancer: RR = 0.93 (95% CI 0.81-1.04). The cancers with the lowest incidence were respiratory, digestive, and blood cancers. The distribution of different types of cancers in these patients was the following (Figure 1):

- 457 (0.42%) patients were diagnosed with lung cancer, which means a RR of 0.72 (95% CI 0.62-0.84).
- 904 (0.82%) patients, meaning a RR of 0.83 (95% CI 0.76-0.88), developed a form of digestive cancer during DMT treatment.
- 305 (0.27%) patients, which means a RR=0.86 (95% CI 0.82-0.94%), were diagnosed with a form of hematological or lymphatic cancer.
- 468 (0.42%) patients were diagnosed with urogenital cancers, RR=0.98 (95% CI 0.93-1.07%).
- 632 (0.58%) patients were diagnosed with skin cancers, including melanoma, RR=1.03 (95% CI 0.94-1.11%).
- 1417 (1.32%) patients were diagnosed with breast cancer, RR=1.42 (95% CI 1.31-1.49).
- 349 (0.32%) patients were diagnosed with a form of brain cancer (including patients studied by Hemminki et al.), RR=1.44 (95% CI 1.36-1.53).

All breast cancer cases were diagnosed in women. MS was the initial diagnosis in all the patients, with the consequent appearance of different malignant tumours. The role of DMTs in the development of cancer is not yet fully understood. In all the studies presented in Table 1, apart from brain tumours, the increased or decreased RR of other cancers can be attributed to MS-associated treatments.

Discussion

In this analysis, we did not find any evidence of a higher risk of cancer in patients with MS; on

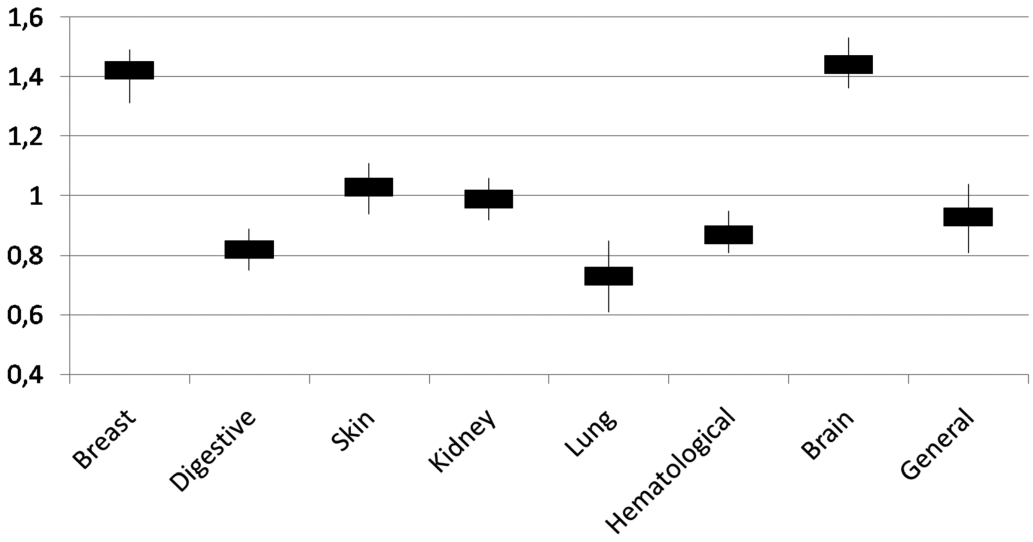

Figure 1. The risk ratio of different types of cancer in DMTs-treated MS patients.

Legend: DMTs= diseases modifying treatments

Table 1. The prevalence of different types of cancer in MS patients.

Category / *Study*	*MS patients*	*Total cancer (%)*	*CNS (%)*	*Digestive (%)*	*Urinary (%)*	*Respiratory (%)*	*Skin (%)*	*Breast (%)*	*Blood (%)*
Bahmanyar et al.	20276	2139 (10.54 %)	131 (6.1%)	352 (16.45%)	155 (7.24%)	119 (5.26%)	81 (3.78%)	454 (21.22%)	82 (3.83%)
Nelsen et al	11817	1037 (8.77%)	30 (2.89%)	180 (17.35%)	96 (9.25%)	95 (9.16 %)	190 (18.32%)	195 (18.80%)	61 (5.88%)
Lebrun et al	7418	131 (1.76%)	4 (3.05%)	12 (9.16%)	7 (5.34%)	5 (3.81%)	14 (10.685)	47 (35.8%)	8 (6.10%)
Grytten et al	6883	774 (11.24%)	74 (9.56%)	113 (14.59%)	54 (6.97%)	65 (8.39%)	74 (9.56%)	160 (20.67%)	48 (6.20%)
Kingwell et al	6667	410 (6.14%)	13 (3.17%)	31 (7.56%)	26 (6.34%)	56 (13.65%)	92 (22.43%)	110 (26.82%)	13 (3.41%)
Moller et al	5359	210 (3.91%)	8 (3.80%)	35 (16.66%)	22 (10.47%)	21 (10%)	38 (18.09%)	31 (14.76%)	9 (4.28%)
Hemminki et al	14616	-	64	-	-	-	-	-	-
Hongell et al	1074	68 (6.33%)	3 (4.41%)	8 (11.76%)	7 (10.29%)	4 (5.88%)	7 (10.29%)	18 (26.4%)	4 (5.88%)
Lebrun et al	20993	253 (1.20%)	11 (4.34%)	12 (4.74%)	10 (3.95%)	5 (1.9%)	19 (17.50 %)	74 (29.24%)	11 (4.34%)
Midgard et al	1271	73 (5.74%)	6 (8.21%)	10 (13.69%)	8 (10.95%)	7 (9.58%)	5 (6.84%)	21 (28.76%)	-
Moisset et al	1111	84 (7.56%)	-	10 (11.90%)	8 (9.52%)	-	15 (17.85%)	28 (33.33%)	4 (4.76%)
Sumelathi et al	1597	85 (5.32%)	5 (5.88%)	-	-	8 (9.41%)	-	17 (20%)	7 (8.23%)
Bloomgren et al	12894	288 (2.3%)	8 (2.77%)	31 (10.76%)	19 (6.59%)	17 (15.90%)	18 (6.25%)	101 (35.06%)	22 (7.63%)
Total	109276	5552 (5.9%) (CI 4.0 – 7.76%)	357 (4.52%) (CI 3.05-5.99%)	794 (12.22%) (CI 9.83-14.6%)	412 (7.9%) (CI 6.53- 9.27%)	402 (6.94%) (CI 4.77 – 9.11%)	553 (12%) (CI 8.37 – 15.6%)	1256 (25.9%) (CI 22 – 29.8%)	270 (5.5%) (CI 4.59 – 6.41%)

Legend: MS= multiple sclerosis; CNS=central nervous system; CI= confidence interval.

the contrary, the reviewed studies highlighted a lower risk of cancer in patients with MS as compared to the general population. The average prevalence of all cancers observed in a large meta-analysis of MS patients was 4.39% (95% CI: 2.67-6.1), and the prevalence of brain tumours was 0.27% (95% CI: 0.10-0.43)[17,21,22].

Our assumption is that these low RRs occur due to a higher concern for living conditions. From our experience, after the diagnosis of MS, the majority of patients approaches a different lifestyle, with a positive impact on their condition: a healthier diet, by reducing the consumption of saturated fats and increasing the intake of fruits and vegetables; reducing or eliminating alcohol consumption and smoking; those without disabilities are increasing the frequency of mild or moderate physical activity; and psychosocial changes, such as protecting mental health; they are taking much more into account pieces of advice that can affect their health in a good way. Most of the patients are more involved in social activities (especially online, on social networks) with other MS patients, learning and helping each other. There are many controversies about the prevalence of cancers in MS patients. Some studies found out the risk of cancers of the urinary tract, CNS, and skin cancers are higher than in the general population (patients treated with Natalizumab, Glatiramer Acetate, or Alemtuzumab administration other results suggested that it is lower, especially for digestive and lung cancers (patients treated with Dimethyl Fumarate and Fingolimod) (Table 2)[7,11,13,15,23-25]. Regarding breast cancer, the results are variable, with some studies suggesting an increased rate, others normal, and some a low one (patients treated with β interferon, Natalizumab, Glatiramer Acetate, Fingolimod or Alemtuzumab)[7,11]. Some researchers suggest that the risk of cancer is not different from that of the general population, but is higher with increasing age and in women[23,26].

In our analysis, the CNS tumours have the highest RR, but there are a lot of studies that did not report a significant difference between the general population and the population with MS in relation to the incidence of brain cancer[20,27,28]. There are over 100 subtypes and 29 histological variants, 70% being represented by gliomas[29]. Glioblastomas (61.5 %) and astrocytomas (18.8%) are the most frequent types of gliomas described in association with MS[30,31]. It is difficult to estimate the incidence of brain tumours general population compared to MS patients, as the latter are constantly monitored by brain imaging[32]. Other less common brain tumours associated with MS are oligodendrogliomas (10.7%), ependymomas (3.6%), and other forms of gliomas (5.4%)[33]. Some tumours such as astrocytomas can be difficult to diagnose only by imaging, the presumptive diagnosis having to be confirmed by biopsy[34]. The most common association is between MS and gliotic astrocytoma, but the association with non-gliotic tumours has been also rarely described[35]. At the same time, MS can present as an acute lesion with cerebral edema associated with inflammation. Some patients with MS diagnosis may require biopsy, so we have some data showing that, at autopsy, on average about 6% of patients diagnosed with MS suffered from a form of brain tumour[36,37].

Sometimes this autoimmune disease appears as multiple small demyelinating plaques, and it can occur in the form of proliferative lesions, difficult to differentiate from a brain tumour According to the McDonald criteria, MS is diagnosed by demonstrating clinical or radiological manifestations of disease dissemination in time and space[38]. Other studies have shown that cranial irradiation is a risk factor for MS reactivation[39,40].

Before the introduction of modern DMTs, the prevalence of cancers in the MS population was equal to or lower than that in the general population[17,41]. There are medium effective DMTs like Interferons, Glatiramer acetate, Dimethyl fumarate, and Teriflunomide and highly effective DMTs such as Natalizumab, Fingolimod, Alemtuzumab, Cladribine or Rituximab (Table 2)[3].

β *interferon* was the first DMT used in MS patients and was introduced in the 1990s (Table 2). In addition to MS treatment, some types of interferons are also used to treat hepatitis B, C, herpes zoster, HIV, and various cancers, such as non-Hodgkin lymphoma, multiple myeloma, Kaposi sarcoma, melanoma, or malignant tumours of the kidneys, bladder, or ovaries. In a recent study, it has been shown that the tumour cells can stop the intrinsic production of interferon by destroying the responsible genes, which can allow malignant cells to metastasize without the involvement of the immune system. Regarding the association of cancers with β interferon treatment, no association has been proven in the literature (OR 1.28, 95% CI 0.87-1.88), although a slight increase in breast cancers was observed after its administration (OR 1.77, 95% CI 0.92-3.42), but without showing consistency with dose[15,19].

Glatiramer acetate was introduced in the mid-1990s, mainly for the recurrent-remissive form of MS. Its administration is not related to the incidence of cancers, but it has been attributed to a slight increase in the number of breast cancers[6]. One article reported a 43-year-old woman who presented with stage IIIb melanoma, with spontaneous remission at the time of treatment discontinuation, in whom glatiramer acetate was associated with skin cancer[42].

Table 2. Diseases modifying treatments, their MoA in cancer and MS and risk of cancer

DMTs	*Date approval for MS*	*MoA in MS*	*MoA in cancer*	*DMT has effects on the following cancer*	*DMT is associated with the following cancer*
Interferonβ-1b	FDA 1993 EMA 1995	Decreases lymphocyte activation and downregulates MHC II expression.	Type I interferons can induce cell death via TRAIL, FLICE and protein kinase B signaling, activation of p38 MAPK pathway	Management of melanoma, bladder and renal cancers, non-Hodgkin's lymphoma, follicular lymphoma, CML, BLL, Kaposi's sarcoma.	No cancers were associated with IFN-β, although a study noted a breast cancer prevalence increase when using this medication.
Interferon β 1a, i.m	FDA 1996 EMA 1997				
Interferon β 1a, s.c.	FDA 2002 EMA 1998 (extended in 2012)				
Interferon β 1a, 2 times a month	FDA 2014 EMA 2014				
Glatiramer acetate	FDA 1996 EMA 2000	It involves activation of Th2 cells, T regulatory cells and M2 monocytes.	-	-	No cancers were reported in previous studies.
Dimethyl fumarate	FDA 2013 EMA 2014	Modulates NF- κB, lowers numbers of CD8+ and Th1 CD4+ T cells and B cells.	Demonstrated as being highly cytotoxic in lung and digestive tract cancers; Targeting cellular pathways like NF-E2, NRF2, DJ-1, NF-κB, ERK1/2, MAPKs, PTEN and miRNA network, inhibits KEAP1, GSH modulation.	Decreases activity of the Nrf2 and Dj-1 antioxidant pathways, contributing to cell death in melanoma, breast, lung, and colon cancers.	No cancers were reported in previous studies; DMF has a beneficial effect in the treatment of brain tumours.
Teriflunomide	FDA 2012 EMA 2013	Blocks de-novo pyrimidine synthesis, inhibiting DHODH.	Blocks de-novo pyrimidine synthesis, thus inhibiting rapidly dividing cells	Contributes to improving basal cell carcinoma outcome.	Associated with cases of cervical carcinoma, possible association with breast and skin cancer.
Natalizumab	FDA 2004 EMA 2006	Interferes with α4β1-integrin receptor molecules, reducing the migration of T-cells through BBB.	Same as in MS.	Effect on melanoma metastasis, but it has not been proven to treat cancers.	Associated with some cases of melanoma, BCL and breast cancer.
Fingolimod	FDA 2010 EMA 2011	Activation of S1PR1 receptor, retaining lymphocytes in lymph nodes.	Potential therapeutic role by inhibiting sphingosine kinase 1.	In vivo and in vitro, it has anti malignant activity, among others, against lung, digestive, liver and breast cancers.	Associated with BCL, different types of lymphomas, basal cell carcinoma etc.
Alemtuzumab	FDA 2014 EMA 2013	Mediates the lysis of CD52+ cells in vitro via toxicity and ADCC.	Same as in MS.	Used for treatment of Hodgkin's lymphoma, T cell lymphomas, and in B cell malignancies.	Associated with thyroid cancer, breast cancer, melanoma etc.
Cladribine	FDA 2019 EMA 2017	It is phosphorylated by CDK which finally produces 2-CdAMP, with an apoptotic effect on lymphocytes.	Has the ability to target B cells, making it effective in HCL and BLL.	Studied for effects on different types of leukemias and lymphomas.	No cancers were reported in previous studies.
Rituximab	FDA off-label EMA off-label	Monoclonal B-cell depleting CD20 antibody.	Destroy malignant B cells with high CD20 levels.	Effect on different types of lymphomas.	Associated with rare cases of melanoma, renal and breast cancer.

Legend: DMTs= diseases modifying treatments; MoA = mechanism of action; MHC = major histocompatibility complex; TRAIL = TNF-related apoptosis-inducing ligand; FLICE = cellular FLIP; MAPK = mitogen-activated protein kinase; CML = chronic myeloid leukemia; BLL = B-cell lymphoblastic leukemia; DHODH = dihydroorotate dehydrogenase; BBB = blood-brain barrier; BCL = B-cell chronic leukemia; ADCC = antibody-dependent cellular cytotoxicity; CDK = cyclin-dependent kinase; HCL = hairy cell lymphoma

Teriflunomide, the oral therapy for MS, has been associated with lymphoma, and it may be possible to correlate with breast cancers. It works by inhibiting the proliferation of lymphocytes and blocking dihydroorotate-dehydrogenase. Since its introduction in 2013, it has been studied alongside leflunomide for antineoplastic effects, this one manifesting due to the low threshold of tumour cells for pyrimidine deprivation.

Dimethyl fumarate was approved for use in MS in the last decade. Originally used to treat psoriasis, it has been associated with an insignificant risk of malignant tumours but has an important action against digestive and lung cancers by inhibiting cell proliferation and contributing to apoptosis; also, it decreased the lymphatic metastases of melanoma in laboratory animals and reduced tumour proliferation in the cell line of breast cancer by blocking the transcription of factor p65[44]. Unfortunately, it has some serious adverse reactions like progressive multifocal leukoencephalopathy and lymphopenia (30%)[45].

From the highly effective DMTs, *Fingolimod*, sphingosine 1-P receptor modulator, was approved in the first half of the 1990s as an oral therapy for MS. It has a highly cytotoxic effect on leukemia lung and digestive cancer cells. It has been shown in animal models that inhibits the cell lines of glioblastoma. A mechanism of action that inhibits the development of the brain, breast, pulmonary and digestive tumours are represented by the degradation of SK1as shown in some papers[12,14]. The main reasons why fingolimod is not administered for its anti-malignant effect are the much higher doses required, compared to those recommended for MS, and the possibility of tumour genesis of another type.

Natalizumab represents a monoclonal antibody, approved for use in MS in the early 2000s. Its effect is selectively blocking α4β1 lymphocyte-integrin (which, for example, is used by malignant cells in melanoma for metastasizing in lymph nodes), being known during its approval as a promising anti-cancer drug due to its ability to block cellular adhesion[3]. In the AFFIRM study, several cancers were detected in combination with the administration of natalizumab, such as breast cancer, melanoma, and lymphoma. The incidence of melanomas is 5/100,000 MS patients per year, and in patients followed by video dermoscopy changes in pigmented lesions have been demonstrated, but without aggressive dysplasia.

Alemtuzumab, an anti-CD52 monoclonal antibody, was approved to be used in MS in 2013. Recently, it was approved as a treatment for different types of tumours such as breast, thyroid, Burkitt lymphoma, or melanoma[3].

Cladribine has received approval for use in MS. There were suspicions about the tumour genesis associated with this therapy, being suspected cases of ovarian or pancreatic cancer, but a phase III trial in 2015 did not find a significant relationship between cladribine and malignant pathologies. Other studies, however, have reported a link between the administration of the drug and the risk of developing cancer.

Rituximab (chimeric anti-CD20 monoclonal antibody) and *ocrelizumab* (humanized anti-CD20 monoclonal antibody), are effective in treating cancers associated with B lymphocytes such as Hodgkin's lymphoma or Burkitt's lymphoma. As a result of OPERA I and II studies, ocrelizumab was FDA-approved for relapsing-remitting multiple sclerosis in 2017, also being the first therapy to slow the progression of primary progressive multiple sclerosis. On the other hand, the use of anti-CD20 therapies is associated with the risk of developing another cancer, such as skin or breast cancer.

Conclusions

We analysed the literature data focusing on the link between MS and cancer. The global risk of MS-patients to develop a form of malignant tumour is nearly the same as in healthy individuals. These patients are partially protected against some forms of cancers, especially lung and digestive tract malignancies. However, they have a statistically significant higher risk of brain cancers (probably because of a high-frequency follow-up), and women are at an increased risk of breast cancer. A large analysis to establish a clear association between different types of DMTs and cancers is also needed.

Author Contributions:

Conceptualization, C.A.S. and T.M.V.; methodology, C.A.S., T.M.V., I.C.; software, T.M.V.; validation, C.A.S., I.C., R.I.D., A.M.M.; formal analysis, C.A.S., F.C.P.; investigation, I.C., T.M.V.; resources, R.I.D.; data curation, I.C.; writing–original draft preparation, R.I.D.; writing–review and editing, R.I.D., T.M.V.; visualization, C.A.S.; supervision C.A.S., C.F.P., A.M.M.; project administration, C.A.S., T.M.V. All authors have read and agreed to the published version of the manuscript.

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