INCIDENCE RATES OF MALIGNANCY AND PRECANCEROUS LESIONS IN NEWFOUNDLAND AND LABRADOR POPULATION WITH IMMUNE MEDIATED INFLAMMATORY DISEASES: PSORIATIC ARTHRITIS and RHEUMATHOID ARTHRITIS

By

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ABSTRACT

Background: Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA) are reported to be associated with an increased risk of malignancy. Newfoundland and Labrador (NL) has one of the highest cancer rates in Canada. There is a paucity of literature on the prevalence of malignancy in NL patients diagnosed with RA and PsA. We hypothesize that the risk of malignancy in these groups of patients is higher compared to the NL general population.

Objective: Evaluate the incidence of malignancy and precancerous lesions in a cohort of PsA and RA patients and compare rates with the general population. Evaluate the impact of therapy and chronic inflammation on these two diseases.

Methods: Data were extracted from the charts of 700 arthritis patients (68% female) seen at a local rheumatology clinic between 2011 and 2014. Statistical analyses were performed using SPSS v. 21.0 (IBM Inc.). Overall cancer incidence rates were calculated per 100,000 person-years. Observed rates were compared with the rates in the NL general population. Multivariate regression analysis was used to assess association between incident cancers and explanatory variables.

Result: The results suggest no significant difference in cancer rates between the cohort and the NL general population ($P<0.3217$). We identified 37(5.3%) different types of cancers. Etanercept and combination therapy (Biologics (bDMARDs) and Methotrexate (MTX)) showed significant risk reduction: (OR=0.1, 95% CI, 0.01-0.89, P=0.039) and (OR=0.3, 95% CI, 0.02-0.44, P=0.003) respectively.

Conclusion: There is no difference in the cancer rate between our study and the NL general population. We also concluded that the analyzed data was reassuring due to OR values less than 1 (OR 0.3, P=0.003) for combined therapy of MTX and Biologics. More epidemiologic studies are required to determine the cancer prevalence in NL population.

Key Words: Malignancies, Psoriatic Arthritis, Rheumatoid Arthritis, Biologic Disease Modifiers (bDMARDs).

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DEDICATION

I would like to dedicate this decertation to my late father Dr. Alhaji Sheku Ba Saccoh who passed away just as I was in the middle of writing my thesis.

Dad, though you left me so soon and at a time when I needed you most, I have never stopped feeling your love and presence. It is impossible to thank you adequately for everything you've done, from loving me unconditionally to raising me to be a good citizen. For instilling in me traditional values, and for teaching your children how to celebrate and embrace life. I could not have asked for a better parent or role model. I will miss hearing your favourite encouraging phrase "To keep going strong even when things get tough for faint hearts never see the end of the battle "Knowing you are now in a better place is such a solace, your memories will remain forever in my heart.

I will always love you Dad.

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ABAT	Abatacept (Orencia)
AB	Alberta
ACR	American College of Rheumatology
ACREU	Arthritis Community Research and Evaluation Unit
ADA	Adalimumab (Humira)
ASIR	Age Standardized Incidence Rate
BC	British Columbia
BCC	Basal Cell Carcinoma
bDMARDs	Biological Disease- Modifying Anti - Rheumatic Drugs
BMI	Body Mass Index
BSRBR	British Society for Rheumatology Biologics Register
CASPAR	Classification Criteria for Psoriatic Arthritis
CANSIM	Canadian Socio-Economic Data Base from Statistics Canada
CC	Cervical Cancer
CDC	Center for Disease Control and Prevention
CEBM	Center for Evidence Based Medicine
CHQ	Hydroxychloroquine
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CRC	Colorectal Cancer
CRP	C-Reactive Protein

DAS28	Disease Activity Scoring System
DIPs	Distal Interphalangeal
DMARDs	Disease Modifying Anti-Rheumatic Drug
FDA	The U.S. Food and Drug Administration
ETN	Etanercept (Enbrel)
ESR	Erythrocyte Sedimentation Rates
FOBT	Fecal Occult Blood Test
GOL	Golimumab (Simponi)
GLOBOCAN	International Agency for Research on Cancer
HAQ	Health Assessment Questionnaire
HLA-B 27	Human Leukocyte Antigen B-27
HREA	Health Research Ethics Authority
HRT	Hormone Replacement Therapy
ICD	International Statistical Classification of Diseases
IRs	Incidence Rates
I.M.I.D. s	Immune Mediated Inflammatory Disorders
IFX	Infliximab (Remicade)
IL	Interleukin
LEF	Leflunomide (Arava)
MB	Manitoba
MCPs	Metacarpophalangeal
MHC	Major Histocompatibility Complex
MTPs	Metatarsophalangeals

MTX	Methotrexate
MUN	Memorial University of Newfoundland
NB	New Brunswick
NCI	National Cancer Institute
NF-Kb	NF-kappa-B
NHL	Non-Hodgkin lymphoma
NIH	National Institute of Health
NL	Newfoundland and Labrador
NLCHI	Newfoundland and Labrador Center for Health Information
NMSC	Non-Melanoma Skin Cancer
NS	Nova Scotia
NT	Northwest Territories
NSAIDs	Non-Steroidal - Anti-Inflammatory Drug
NU	Nunavut
ON	Ontario
OR	Odds Ratio
P	P-value
PASQ	Psoriatic Arthritis Screening Questionnaire
PEI	Prince Edward Island
PHAC	Public Health Agency of Canada
PICO	Population, Intervention, Comparison, Outcome
PSO	Psoriasis
PsA	Psoriatic Arthritis

PYs	Person-time Rate
QC	Quebec
QOL	Quality of Life
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
RTX	Rituxan (Rituximab)
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SIR	Standardized Incidence Ratio
SJC	Swollen Joint Count
SSZ	Sulfasalazine
TAMs	Tumor Associated Macrophages
TCZ	Tocilizumab (Actemra)
TJC	Tender Joint Count
TSJC	Total Swollen Joint Count
TNF	Tumor Necrosis Factor
UK	United Kingdom
US	United States
WHO	World Health Organization
YT	Yukon

LIST OF APPENDICES

CHAPTER 1
INTRODUCTION

1.1 Introduction to the Thesis

Psoriatic Arthritis (PsA) and Rheumatoid Arthritis (RA) both belong to a larger family of diseases known as Immune-Mediated Inflammatory Disorders (IMIDs). IMIDs are defined as a group of chronic and highly disabling diseases involving excessive immune responses caused or accompanied by cytokine dysregulation and acute or chronic inflammation (Williams & Meyers, 2002). Apart from PsA and RA, IMIDs include a wide variety of other illnesses, such as Psoriasis (PsO), Crohn's disease (CD), Ankylosing Spondylitis (AS) and Systemic Lupus Erythematosus (SLE). These disorders are known to be relatively common and are believed to affect an estimated 5% to 7% of the population in Western countries (Beyaert et al., 2013). Although PsA and RA are accounting only for 2% of the of the general population they have a high burden of cost and disability (PHAC, https://www.canada.ca/en/public-health/services).

The most common clinical presentation of PsA and RA is arthritis. The Public health agency of Canada (PHAC, http://www.phac-aspc.gc.ca) and the Center for Disease Control and Prevention (CDC, https://www.cdc.gov) in the United States (US) have reported arthritis as one of the most prevalent chronic health conditions. It was also reported to be the leading cause of disability and use of health care resources. Between 2010-2014, approximately 4.8 million (16.5%) Canadians aged 15 and older (PHAC, http://www.phac-aspc.gc.ca) and 54.4 million US adults (22,7%) (CDC, https://www.cdc.gov) were diagnosed with arthritis. In Canada, these rates have shown a stable trend since 2007 with

around (12%) for males and (19%) for females. Females were more likely than males to have arthritis from 45 years of age and older.

1.2 Arthritis in Canada and Newfoundland and Labrador

In 2007-2008, the crude prevalence of arthritis varied considerably across Canada, (PHAC, http://www.phac-aspc.gc.ca). The highest prevalence of individuals who reported having arthritis was found in Nova Scotia (NS) (23%), followed by Newfoundland and Labrador (NL) (21%), New Brunswick (NB) and Prince Edward Island (PEI) (20% and 19%, respectively). The province of Quebec (QC) (12%) and the Territories (Yukon (YT), Northwest Territories (NT) and Nunavut (NU) (11%) had the lowest percentage of individuals who reported arthritis (PHAC, http://www.phac-aspc.gc.ca).

A more recent 2014 report showed an increase in NL arthritis prevalence rate by 4.4% reaching the highest rate throughout Canada (25.4%) (http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health52b-eng.htm).

Generally, all Atlantic Canadian provinces had comparatively higher prevalence of inflammatory arthritis as compared to other parts of the country (NB and NS-25.0% each, PEI- 21.2%). The province of Manitoba (MB) (19%), Ontario (ON) (18.3%) and Yukon (17.3%) were in second palace. The remaining provinces British Columbia (BC), Alberta (AB), and the North West Territories shared near to similar rates of 16% each. The lowest rate of disease remained in NU (11.7%) and QC (11.0%).

In addition, PHAC has reported arthritis to be the third most common chronic condition in adult Canadian women and men (19.2% vs 12.6%) after back pain (22.2% vs19.8%) and high blood pressure (17.6 vs 16.4%) respectively. Newfoundland and Labrador has also shown to have the highest rates of chronic disease in Canada

(http://www.health.gov.nl.ca). In 2005, the Government of Newfoundland and Labrador released a report on the prevalence of chronic diseases in the province (Government of Newfoundland and Labrador, Department of Health and Community Services, Provincial Healthy Aging Policy Framework, page 37). The report showed higher prevalence rates of many chronic conditions in NL seniors as compared to the rest of Canada: arthritis (51.9% vs 45.9%), high blood pressure (50.0% vs 44.0%), diabetes (19.7 % vs 14.6%), asthma (10.8 %vs 7.4%) and obesity (15.4% vs15.1%). As the NL population ages, the prevalence of chronic diseases is expected to grow. According to the statistical prognostic model, with the aging of the "baby boomers" generation in NL, the number of people with arthritis is expected to increase from 92,000 in 2011 to 127,000 in 2036, with the largest increase occurring among adults aged 65 years and older. This in turn, will increase the utilization of healthcare services as well as resources. Furthermore, statistics published by the Public Health Agency of Canada (PHAC, http://www.phac-aspc.gc.ca) have shown that over 4.8 million Canadians (16.5 %) reported having arthritis, and with the continued growth of the Canadian aging population, this number is expected to increase to approximately 7 million (20%) by 2031. Although arthritis is known to be most prevalent among seniors, it is not necessarily limited to the elderly population and many people are affected in the prime of their younger years. In 2008, 17.2% of males and 24.8% of females ages 45 to 64 (representing more than 1.9 million people) reported a diagnosis of arthritis (http://www.statcan.gc.ca).

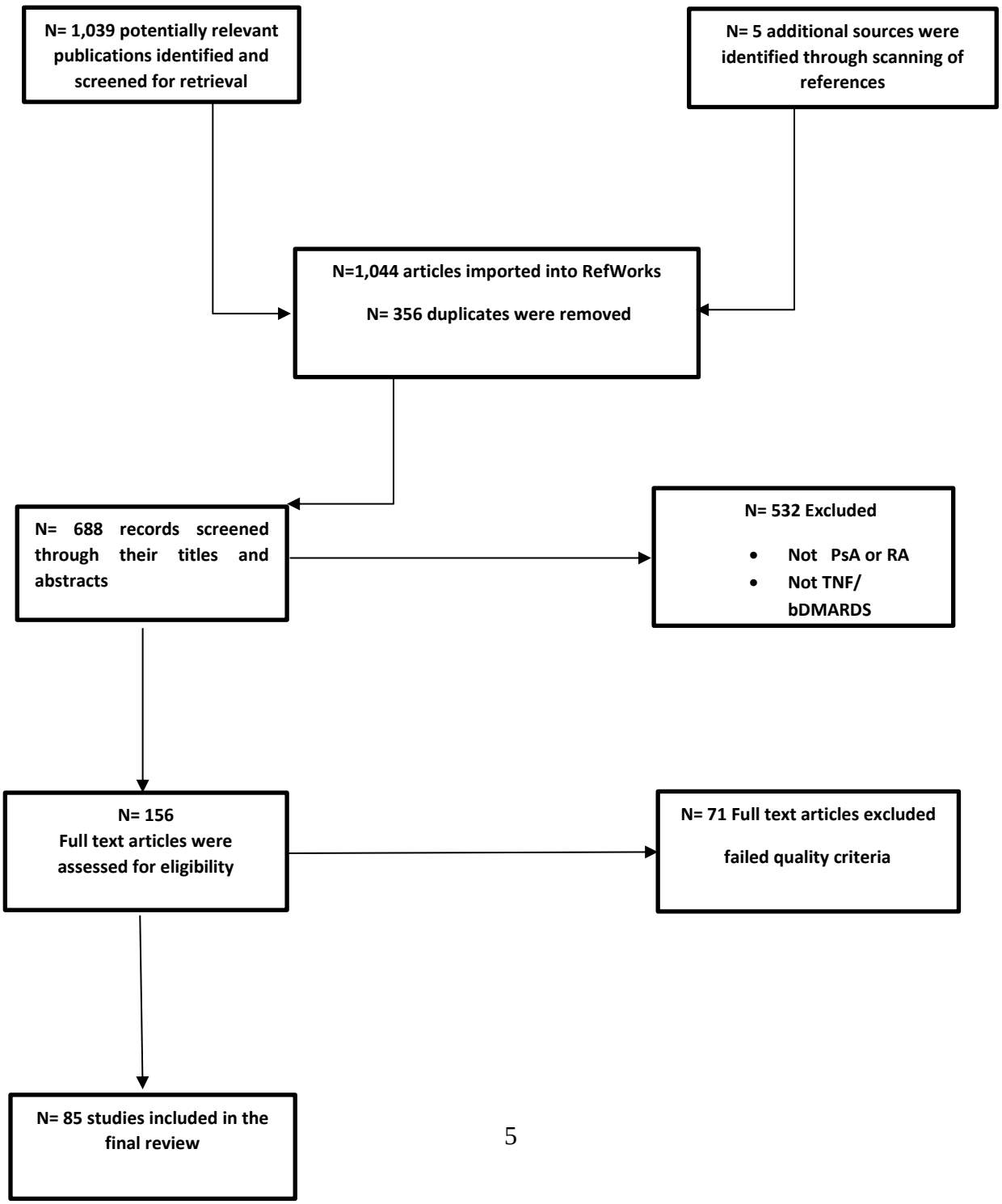
CHAPTER 2
LITERATURE REVIEW

2.1 Details of Search Strategy

In order to gain a better insight and a broader perspective of the issue at hand, a literature search and review was conducted. The aim of the review was to examine different perceptions and knowledge gaps amongst existing literature regarding cancer risk in patients with Inflammatory Arthritis. The following electronic databases were used: PUBMED (MEDLINE), Embase and Cochrane Library using the following key words and MESH terms: (("Neoplasm OR cancer OR malignancy [MESH])) AND "Arthritis Rheumatoid" [MESH] "Arthritis Psoriatic" [MESH])) AND "Tumor Necrosis Factor-alpha/antagonists and inhibitors". The search term "Tumor Necrosis Factor-alpha/antagonists and inhibitors" was used mainly because TNFi's are most commonly prescribed biologics in PsA and RA patients and have been widely used for more than 15 years allowing for cancer incidence in latent cancers to occur. Additional filters were set at: Humans; Adults and English. For environmental scan, Google and Google Scholar were used to help consult with public websites such as Canadian Cancer Statistics, Public Health Agency of Canada (PHAC), World Health Organization (WHO), Newfoundland and Labrador Center for Health Information (NLCHI), Arthritis Community Research and Evaluation Unit (ACREU), as well as Newfoundland and Labrador Government Health websites. Relevant study references were also scanned for possible related citations. The initial combined search yield 1044 citations (Fig 2.1) that were imported into RefWorks. Articles were first selected based on the relevance of their title. Pertinent articles (n=85)

included in the final review (after removal of duplicates and those that did not meet our inclusion criteria) are discussed below.

Fig 2.1 Prisma Flow Chart of Selected Articles



2.2 Reviewed Literature

The literature review showed disagreements amongst studies regarding the risk of malignancy in patients with Inflammatory Arthritis (PsA and RA). Some studies have reported increased malignancy risk, others low risk, whereas a number of studies indicated no risk between their study population and comparison groups. Over the past decades, the question of association of incidence of malignancy with this group of systemic inflammatory diseases has been studied and debated. Even though the existing literature is inconclusive, the available evidence is sufficient to speculate a heightened risk of malignancies in this group of patients.

2.2 a) Studies for Increased Cancer Risk

Evidence from a number of previous studies has shown increased rates of malignancy among people with inflammatory arthritis (Askling et al., 2005; Beyaert et al., 2013; Y. Chen, Chang, Wang, & Wu, 2011; Smitten, Simon, Hochberg, & Suissa, 2008). Chen et al. (2011) investigated the relative risk of cancer in 23,644 Taiwanese RA patients for over a period of eleven years. To do so, they used the Taiwanese National Health Insurance database. The authors in this study observed 935 cancers in patients with RA. Their study results further showed that patients with RA had a significant increased risk of cancer (SIR= 2.74, 95% CI, 2.68–2.81). Among hematologic cancers, the risk of non-Hodgkin's lymphoma was greatest (SIR= 3.54, 95% CI, 3.45–3.63). Although this study had numerous strengths such as large sample size and long duration of follow-up, it was also limited by an inadequate adjustment for important prognostic factors that likely impacted the validity of their results. Several important confounding factors such as

smoking, alcohol use and body mass index were not adjusted for. Smoking for instance, is a known strong risk factor for lung and other cancers (Pesch et al., 2012). In another study, Smitten et al., 2008 conducted a systematic literature review and meta-analysis of 21 articles from 1990-2007. The main objective was to characterize the associated risk of overall malignancy and four site-specific malignancies (lymphoma, lung, colorectal, and breast cancer) in patients with RA. The authors of this study observed that RA patients have approximately a two-fold increase in lymphoma risk (SIR= 2.08, 95% CI,1.80 - 2.39) when compared with the general population. The risk of lung cancer was also significantly increased with a SIR of (1.63, 95% CI, 1.43 - 1.87). The authors of this study concluded that patients with RA are at higher risk of lymphoma and lung cancer, though at a decreased risk for colorectal and breast cancer compared with the general population. In 2005, Askling et al. in a population- based study, described the cancer pattern of RA patients. They conducted the study on three RA cohorts: one prevalent (n=53 067), one incident (n=3703), and one with patients treated with TNF- antagonists (n=4160). These cohorts were linked with Swedish nationwide cancer registers. In the prevalent cohort, the study results showed a minimally increased overall risk of solid cancer (SIR =1.05, 95% CI, 1.01 - 1.08). Lung cancers were significantly more common than expected in both prevalent and incident cohorts (SIR=1.48, 95% CI, 1.33 - 1.65) and (SIR= 2.4, 95% CI, 1.5 - 3.6), respectively. Whereas, the occurrence of non-melanoma skin cancer was significantly increased in TNF -inhibitor treated patients cohorts (SIR=3.6, 95% CI, 1.8 -6.5).

2.2 b) Cancer Association with Chronic Inflammation and Treatment

So far, the risk of developing precancerous lesions and their progression to cancer has been mainly associated with chronic systemic inflammation, disease progression, duration, and with their treatment modalities, particularly biological disease modifying antirheumatic drugs (bDMARDs).

2.2 b.1) Chronic Inflammation and Cancer

The association between chronic systemic inflammation and cancer is complex and controversial. Inflammation is known to have both pro- and anti-tumorigenic effects. Recent literature has expanded the concept that inflammation is an important component of cancer formation (Hiraku et.al., 2014). In addition, cancer-related inflammation is now considered the eighth hallmark of cancer after genome instability and mutation (Hanahan & Weinberg, 2011). The hallmarks of cancer are underlying principles shared by all cancers such as: 1) self-sufficiency in growth signals 2) insensitivity to antigrowth signals 3) evading apoptosis 4) limitless replicative potential 5) sustained angiogenesis 6) tissue invasion and metastasis and 7) genome instability and mutation (Hanahan & Weinberg, 2011).

Pro-Tumorigenic Effect: The pro-tumorigenic effect of chronic inflammation can initiate tumors by directly causing DNA changes or making cells more susceptible to mutagens (Kiraly, Gong, Olipitz, Muthupalani, & Engelward, 2015). In addition, inflammation can act as a tumor promoter. Inflammatory mediators including cytokines (TNF, interleukin IL-1 and IL-6, growth factors and others) produced by tumor-associated lymphocytes and macrophages, can enhance tumor cell growth and metastasis by promoting their survival,

proliferation, and invasion of other tissues. Tumor-associated macrophages (TAMs) are one of the most important players in the inflammation and cancer arena. They are an important source of cytokines that release inflammatory mediators that stimulate tumor-angiogenesis (Mantovani, Allavena, Sica, & Balkwill, 2008). TAMS produce cytokines, including transforming growth factor (TGF) β and IL-10, which can directly suppress immune responses (Hiraku, Kawanishi, & Ohshima, 2014). At the molecular level, the transcription factor NF-kB appears to be a key connecting element between inflammation and cancer (Grivennikov, Greten, & Karin, 2010; Ben-Neriah & Karin, 2011).

Baecklund et al. (2006) performed a case-control study of 378 Swedish RA patients in whom malignant lymphoma occurred between 1964 and 1995 and 378 controls. Their aim was to investigate which patients were at highest cancer risk, and whether antirheumatic treatment was hazardous or protective. The authors noted that the risk of lymphoma is substantially increased in patients with RA with very severe disease. They concluded that high inflammatory activity, rather than its treatment was the major cancer risk determinant. Another group of authors detailed the importance of pro-inflammatory cytokines such as IL-1β, TNF-α and IL -6 in inflammation and cancer development (Hiraku et al. 2014). They pointed out that these cytokines can promote cell growth, supress apoptotic cell death and stimulate production of growth factors.

Anti-Tumorigenic Process: The anti-tumorigenic process involves activation of inflammatory cells (neutrophils, macrophages, monocytes, T and B lymphocytes- and others) by the immune system to destroy a developing tumor (Dunn, Old, & Schreiber, 2004). It is a process that was originally envisioned by Ehrlich in 1909 and in 1957-1959, was formalized by Burnet and Thomas and renamed as “cancer immune-surveillance.” In

this process, M1 macrophages, (activated by IFNγ and microbial products) express high levels of pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-12 or IL-23), major histocompatibility complex (MHC) molecules, inducible nitric oxide synthase and are capable of killing pathogens and priming anti-tumor immune responses (Grivennikov, Greten, & Karin, 2010). MHC- complexes on the surfaces of transformed or malignant cells are recognized and targeted for elimination by the immune system. Recent experiments in mice have demonstrated scenarios in which developing tumors are indeed recognized and destroyed by the intact immune system (Dunn, Bruce, Ikeda, Old, & Schreiber, 2002);(Smyth, Dunn, & Schreiber, 2006). In contrast, "Cancer Research UK" (http://www.cancerresearchuk.org/) demonstrated that even though immune cells can attack fledgling tumors by infiltrating them in an inflammatory response, instead of killing it, the tumor uses the nutrients and oxygen that are part of the inflammatory response to fuel its own growth. Therefore, even though tumor associated inflammatory cells appear to be actively recruited as part of an anti-tumor response, the tumor is not killed but instead this inflammatory response may be apprehended by the tumor to promote tumorigenesis (Beyaert et al., 2013).

2.2 b.2) Inflammatory Arthritis (PsA/RA) Treatment and Cancer

The primary objectives in managing PsA and RA patients were to timely control inflammation, prevent tissue damage, and as much as possible, secure the long-term remission of the disease. In the past, this has been mainly achieved by using corticosteroids, anti-malarias and disease modifying agents (DMARDs) such as sulfasalazine and methotrexate. With the advent of biologic disease modifying agents (bDMARDs), especially tumor necrosis factor (TNF)-alfa antagonists (inhibitors) that suppress

inflammatory pathways, the treatments of these diseases have undergone a revolutionary change (Beyaert et al., 2013). TNF-alpha inhibitors represent important treatment advances for several inflammatory conditions, including Psoriatic Arthritis (PsA) and Rheumatoid Arthritis (RA). Generally, these agents are considered to be safe and well tolerated, but because they possess immunosuppressive properties, which can affect "immunosurveillance" (a process believed to help suppress the development of cancer), there have been concerns that immunotherapies might increase cancer risk in patients receiving this treatment. Lately, there is expressed concern about the risk of infection and malignancy associated with these agents. Tumor necrosis factor (TNF)- alpha is a bioactive cytokine (a chemical produced by the immune system) that causes inflammation in the body and is an important component of the inflammatory and pain pathways (http://www.rheumatology.org). Inhibition of TNF-alpha can decrease the inflammatory response. This cytokine, however, can play a double role: a) defensive, by stimulating natural killer (NK) and cytotoxic T- lymphocytes (CTL) (that can mediate killing of tumor cells), and b) offensive, as a mediator of cancer promoting inflammation (Balkwill, 2009). Consequently, TNF-alpha inhibitors may hypothetically either promote or block cancer growth (Raval et al., 2010).

Over the past years, the role of Inflammatory Arthritis therapies in the development of malignancies has been a subject of a vast debate. A number of studies in the reviewed literature highlighted the impact of therapy on cancer risk in patients with PsA and RA. While some studies have found an increased risk of malignancy with the use of these drugs (Askling et al., 2005; Bongartz et al., 2006; Beyaert et al., 2013; Kavanaugh, et al., 2009; Mariette et al., 2010), others have not found any significant increase in the rate of

malignancy between experimental and control groups (Dommasch et al., 2011; Haynes et al., 2013., Hellgren et al., 2014; Gross et al., 2014; Mercer et al., 2012; Rohekar et al., 2008; Wu et al 2014). Askling et al. (2005), in a Swedish population-based study, observed that patients with Rheumatoid Arthritis who were treated with TNF- alpha antagonist were at a 70% increased risk for non-melanoma skin cancers (NMSC). The occurrence of NMSC was significantly increased in patients treated with TNF-alpha inhibitors (SIR=1.66, 95% CI, 1.50 -1.84). Beyaert et al.'s (2013) review discussed the effect on cancer risk of different drug classes used in IMIDs treatment, including TNF-alpha inhibitors. They reported an overall increased cancer risk for patients with rheumatoid arthritis and psoriasis, with risk profiles differing for different tumor types. Mariette et al. (2010), used national registries to prospectively collect all cases of lymphoma and opportunistic infections occurring in RA patients receiving anti-TNF blockers. They also examined the results from nationwide prospective cohorts to investigate the safety and efficacy of rituximab (RTX), abatacept (ABA) and tocilizumab (TZC) in RA and other autoimmune diseases. Their study results showed that the risk of opportunistic infections, TB and lymphoma were higher with anti-TNF. Patients receiving adalimumab or infliximab had a higher risk of lymphoma than those treated with etanercept: SIR (95% CI) 4.1 (2.3, 7.1) and 3.6 (2.3, 5.6) vs 0.9 (0.4, 1.8). The preliminary reports from nationwide prospective cohorts showed that patients in real life have frequent comorbidities (e.g. history of cancer in 13% of patients receiving RTX and 5% of patients receiving ABA). However, no results for Tocilizumab (TZC) were presented as the study recruitment was still ongoing.

Contrarily to the above, several other studies did not observe any increased risk and have demonstrated similar or decreased cancer rates in patients with PsA and /or RA

and their comparison group (Dommasch et al., 2011; Haynes et al., 2013., Hellgren et al., 2014; Gross et al., 2014; Mercer et al., 2012; Wu et al 2014). Dommasch et al.'s (2011) systematic review of 20 randomized controlled trials of TNF antagonists for psoriasis (PsO) and psoriatic arthritis (PsA) patients did not observe any significant evidence of increased risk in cancer with short-term use of TNF inhibitors (TNFi). This study, however, was limited by inclusion of clinical trials that had a short duration of follow-up (average of 17.8 weeks) to look at a rear event as an outcome. Hellgren et al. (2014) used the Swedish National Patient Register to assess the risk of Lymphoma in AS (n = 8,707) and patients with PsA (n = 19,283) treated with TNFi therapy. The numbers and incidence of lymphoma were not significantly different in TNFi-exposed versus TNFi-naive AS and PsA patients, although the numbers of lymphomas in this study were small. The authors concluded that TNFi does not affect the risk of lymphoma in AS or in PsA patients. Similarly, Haynes and colleagues (2013) used data from national US registries to compare the incidence of cancer amongst patients with IMIDs treated by TNFi versus alternative therapy: (PsA (n=2,498), RA (n=29,555), PsO (n=2,498) and inflammatory bowel disease IBD (n=6,357)). The incidence of solid cancers in this study was not elevated during TNFi therapy compared with alternative therapy. In another study, WU et al. (2014) conducted a 14-year nationwide cohort (4,426 new users of TNF- antagonists and 17,704 users of bDMARDs) using the Taiwan National Health Insurance Research Database. They compared the relative risk of cancer development between RA patients taking TNFi and those taking DMARDs. The risk of cancer was significantly reduced in patients in biologics cohort (HR= 0.63, 95% CI, 0.49 to 0.80, $P < .001$).

Several large-scale clinical trials have also been performed for TNF-alpha inhibitors, in contrast with most non-biologic disease-modifying anti-rheumatic drugs (DMARDs). However, these trials have mostly reported malignancy as an adverse event, were limited by a short time of study duration (to enable them to look at malignancy as an outcome) and generally lacked an adequate post- licensure control group that would allow them to observe for stronger causal inference (Bongartz et al 2006; Kavanaugh, et al., 2009; Rubbert-Roth et al., 2016). For instance, Bongartz et al. (2006) conducted a systematic review and meta-analysis of randomized placebo-controlled trials to assess the extent to which anti-TNF therapy may increase the risk of serious infections and malignancies in patients with RA. They included nine randomized controlled trial (3,493) of patients who received anti-TNF treatment and (1,512) patients who received placebo for 12 or more weeks. The study results showed that there was evidence of a dose-dependent increased risk of malignancies in patients with Rheumatoid Arthritis treated with TNF-alpha inhibitor therapy. The pooled odds ratio for malignancy was (OR=3.3, 95% CI, 1.2-9.1). Malignancies were significantly more common in patients treated with higher doses compared with patients who received lower doses of anti-TNF antibodies. In another study, Rubbert-Roth et al. (2016) in a randomised controlled trial analysed malignancy rates in RA patients treated with tocilizumab ± MTX (n= 2644) and those with placebo+MTX (n=1454). The authors reported that malignancy rates in their study were no greater than those observed in placebo+MTX treated patients (1.35/100 PY (95% CI 0.65 to 2.48) and 0.94/100 PY (95% CI 0.38 to 1.94). The authors concluded that malignancy rates remained stable with long-term tocilizumab treatment. Weinblatt et al. (2013) conducted analysis of safety data from 8 clinical trials of RA patients (n= 4149) treated with IV abatacept, with a

cumulative exposure of 12,132 patient-years. The study objective was to assess the overall safety, including rare events, of intravenous (IV) abatacept treatment in RA patients. The IR of malignancies were similar for IV abatacept- and placebo-treated patients during the short-term period (IR =0.59, 95% CI 0.19-1.37 vs (IR= 0.73, 95% CI 0.42- 1.17). During the cumulative period, the IR of malignancies remained low and relatively consistent over time (IR=0.73, 95% CI, 0.58- 0.89). The authors concluded that long-term safety of Abatacept was consistent with the short-term, with no unexpected events and low incidence rates of serious infections and malignancies.

Another important point worth mentioning is that, patients with Inflammatory Arthritis often receive other medications concomitantly with biologic agents and some studies have reported an associated increased risk of cancer with such practice. As an example, methotrexate (MTX), a traditional DMARD commonly used with TNF-alpha inhibitors in the treatment of RA, is shown to be associated with an elevated risk of Lymphoma in some studies. For instance, in a case study, Girish, Byrd, Roy, & Mehta (2003) reported a patient with RA in whom a rapidly enlarging B-cell lymphoma developed after weekly treatment with methotrexate for five years. After therapy with this drug was discontinued, no clinically detectable recurrence of the lymphoproliferative disorder for two years was observed. This study, however, was limited by its design which was a case -report that lacked a comparison group to support the validity of their findings.

2.2 b.3) Existing Biologic Drugs Approved by Health Canada During the Study Period

At the time of our study period there were nineteen existing biologic drugs approved by Health Canada (http://www.hc-sc.gc.ca/). Table 2.1 shows the most commonly used

biologic drugs at the study facility during the study period. Table 2.1 a) shows biologics that were approved by Health Canada but were beyond the scope of this study

Table 2.1 Existing Biologic Drugs Approved by Health Canada During the Study Period

Tumor Necrosis Factor Inhibitors (Anti-TNF)	*T-cell Costimulatory Inhibitor;*	*B Lymphocyte-Depleting Agent*	*Interleukin 6 (IL-6) Antagonist*	*IL-1 Antagonist*
Etanercept *(ETN)*, Enbrel Infliximab *(IFX)*, Remicade Adalimumab *(ADA)*, Humira Golimumab *(GOL)*, Simponi Cetrolizumab pegol *(CTZ)*, Cimzia	**Abatacept *(ABAT)*, Orencia**	**Rituximab *(RTX)*, Rituxan**	**Tocilizumab (TCZ), Actemra**	**Anakinra, (*Kineret)***

Table 2.1 a) Approved Biologics by Health Canada Beyond the Scope of this Study

Biosimilars	*Interleukin 17 (IL-17) Inhibition*	*Interleukin (IL-12/23) Blockade*	*Interleukin 6 (IL-6) Antagonist*	*IL-1 Antagonist*
Adalimumab-adbm, (Cyltezo) Infliximab-abda, (Renflexis) Trastuzumab-dkst, (Ogivr)	**Secukinumab, (Cosentyx) Ixekizumab, (Taltz)**	**Ustekinumab, (Stelara) Guselkumab, (Tremfya)**	**Sarilumab, (Kevzara)**	**Canakinumab, *(Ilaris)* Rilonacept, (Arcalyst)**

The most frequently prescribed traditional DMARDs are Methotrexate (MTX), Leflunomide (LEF), Sulfasalazine (SSZ), and Hydroxyl -Chloroquine (HCQ).

In our study, we investigated the association of treatment and malignancy in patients with history of exposure to six most-often used biologics at our study site: Etanercept (ETN), Infliximab (IFX), Adalimumab (ADA), Golimumab (GOL), Abatacept (ABAT) and Rituximab (RTX), as well as traditional drugs (DMARDs), mainly Methotrexate (MTX), Sulfasalazine (SSZ), and Hydroxychloroquine. Additionally, we examined the association between Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Corticosteroids (Prednisolone).

2.2b.3) Food and Drug Administration (FDA) Concern Regarding TNFi

Initial concerns regarding a possible association between TNF-alpha inhibitor use and cancer arose from post -marketing reports to the US Food and Drug Administration (FDA). Twenty-six cases of Lymphoma (mostly non-Hodgkin Lymphoma) were reported among Rheumatoid Arthritis (RA) patients treated with Etanercept or Infliximab (Brown et al; 2002). Two patients had regression of their Lymphoma when TNF- inhibitor therapy was discontinued; however, no comparative population was included in this report. Additionally, data presented to an advisory meeting of the US Food and Drug Administration (FDA) in 2003 included 70 cases of Lymphoma among approximately 140,000 patients treated with Etanercept.

Currently, several registries of rheumatic disease patients receiving bDMARDs have been established to provide a real life look at large cohorts. Examples of those are the Danish

(Hetland, 2005), British (Hyrich et al., 2006), Norwegian (Kvien et al., 2005), and Swedish (van Vollenhoven et al., 2005) registries.

2.3 Rheumatoid Arthritis and Psoriatic Arthritis

According to International Classification of Diseases (ICD-10, M05.70) and the National Institute of Health (NIH), Rheumatoid Arthritis (RA) is defined as: an inflammatory, autoimmune disease that causes pain, swelling, stiffness and loss of function in the joints. It occurs when the immune system, which normally defends the body from invading organisms, turns its attack against the membrane lining joints, which means the arthritis results from an immune system attacking the body's own tissues. The etiology of RA is unknown. Family history, genetic inherited factors, environment, hormones, medicine, and lifestyle changes have all been named as possible risk contributors, Public Health Agency of Canada (PHAC, https://www.canada.ca). Despite this uncertainty, it is generally believed that Rheumatoid Arthritis develops as a result of interaction of many factors. Researchers are still trying to understand these factors and how they work together. The course of Rheumatoid Arthritis can range from mild to severe. In most cases, it is chronic, meaning it lasts a long time, often a lifetime. For many people, periods of relatively mild disease activity are punctuated by flares, or instances of heightened disease activity. In others, symptoms are constant. RA often starts between ages 25 and 55 and symmetrically affects small and medium joints of the upper and lower extremities. It can also affect any other body part, including skin, eyes, heart, and lungs as well as renal, nervous and gastrointestinal systems. Estimates given by the World Health Organization (WHO http://www.who.int/en/) indicate that the world prevalence of RA varies between 0.3% and 1% and is more common in women.

Psoriatic Arthritis (PsA) (ICD-10- L 40.50) is a type of arthritis that causes joint pain, swelling, and stiffness in people with psoriasis. Psoriasis (PsO) is a chronic skin condition that causes patches of thick, inflamed red skin that are often covered with silvery scales. Most people who develop Psoriatic Arthritis first have skin symptoms of Psoriasis, followed by arthritis symptoms. However, in about 13-17 % of cases, symptoms of arthritis are noticed before Psoriasis appears. In another 15% of cases, Psoriatic Arthritis is diagnosed at the same time as Psoriasis (Gladman, DD et al; 2017) (http://www.up to date.com/). Nearly 30% of patients with PsO have arthritis and the prevalence is estimated between 0.5-1%. (Mease et al., 2013). According to Dr. Wayne Gulliver, professor of Medicine and Dermatology at Memorial University (MUN), close to 5 % of the NL population are believed to be affected by Psoriasis. Just as with RA, the cause of PsA is unknown. Although both diseases seem to share some similar triggers, Psoriatic Arthritis differs by its asymmetrical pattern of affecting the axial (spinal) and distal (peripheral) interphalangeal joints. It may be characterized by the presence of Human Leukocyte Antigen HLA-B27 (proteins that help the body's immune system tell the difference between its own cells and foreign, harmful substance (https://ghr.nlm.nih.gov/primer/genefamily) and a negative Rheumatoid Factor (RF). The presence or absence of the RF is what defines these diseases to be “seropositive” or “seronegative” arthritis respectively. Unlike RA, which affects more women than men, Psoriatic Arthritis (PsA) affects both men and women equally. Regardless of the many differences in their clinical presentation, PsA and RA do share two very important commonalities: systemic chronic inflammation and the method of treatment, both of which have recently raised several questions and debates about the possibility of been linked to cancer formation.

2.4 Etiology of Cancer

Cancer is a tumor composed of atypical neoplastic, often pleomorphic cells that invades other tissues (ICD-O-3.1). There are many different types of cancers; all are characterized by cells that start growing abnormally and spread to other parts of the body (https://www.cancer.gov). Very few cancers exist that have a single, known cause. Most cancers seem to be the result of a complex mix of many risk factors. These risk factors may play different roles in starting cancer and its progression. Some risk factors include heredity (genetics), lifestyle choices and exposure to cancer-causing substances (carcinogens) in the environment. The more often and the longer the exposure to a risk factor, the greater the probability that cancer will develop.

2.4 Epidemiology of Cancer

2.4 a) Global Cancer Trend

Cancer continues to impose an enormous burden worldwide on both economically developed and less developed countries alike (Torre et al. 2015). This is mainly because of aging populations, an increase in the prevalence of risk factors such as smoking, overweight, physical inactivity, changing reproductive patterns, as well as economic development. Estimates given by an International Agency for Research on Cancer (GLOBOCAN, http://gco.iarc.fr) showed that in 2012, there were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people were living with cancer worldwide. The overall age standardized cancer incidence rate is almost 25% higher in men than in women, with rates of 205 and 165 per 100,000, respectively. Lung cancer was reported to be the leading cause of cancer death among males and has surpassed breast cancer as the leading cause of cancer death among females in more developed countries (GLOBOCAN,

http://gco.iarc.fr). According to this report, Canada compares favourably to other high-income countries on several measures, including survival and mortality rates. Canadian cancer incidence rate was reported as 295.72 per 100,000. Although these rates were higher than United Kingdom rates (UK) 272.90 per 100,000, they were lower compared to those of the United States (US) with 317.97 per 100,000 respectively. In the US, over the past decade, the overall cancer incidence rate (2004-2013) was reported to have been stable in women and declined by approximately 2% annually in men; the cancer death rate (2005-2014) declined by about 1.5% annually in both men and women (Siegel, Miller, & Jemal, 2018). In Canada, between 1988 and 2017, the number of new cancer cases rose steadily, (Canadian Cancer Statistics https://www.cancer.ca). However, age standardized incidence rates (ASIR) as of January 2009, have decreased for males by 0.7% and increased for females by 0.5%. This increase is in part driven by the rise in the incidence of melanoma, thyroid, uterine, as well as liver cancers.

2.4 b) Cancer Trend in Canada

As the Canadian population grows and ages, the number of new cancer cases continues to rise steadily. Based on Canadian Cancer Statistics (https://www.cancer.ca), an estimated 196,900 new cases of cancer and 78,000 deaths from cancer were to occur in Canada in 2015. Males have a 45% lifetime probability (or a 1 in 2.2 chance) of developing cancer. Females had a 42% lifetime probability (or a1 in 2.4 chance) of developing cancer. More than half of all new cases were lung, prostate, breast, and colorectal cancers. Lung cancer continued to be the leading cause of cancer death, causing more cancer deaths among Canadians than the other three major cancer types combined. It has been predicted

that two in five Canadians will develop cancer in their lifetimes and one in four will die of the disease. A more recent Canadian Cancer Statistics (http://www.cancer.ca) report, projected 206,200 new cancer cases to be diagnosed in Canada in 2017, with an equal number among males and females. Half of these included lung, breast, colorectal and prostate cancers.

2.4 c) Cancer Trend in Newfoundland and Labrador

The 2017 Canadian Cancer Statistics report (http://www.cancer.ca) further indicated that ASIR distribution of all new cancers is highest in Newfoundland and Labrador (586.8 per 100,000) when compared to other provinces. This was followed by Quebec (544.9 per 100, 000), with the lowest rates reported in Alberta (480.7 per 100,000) and British Columbia (461.4 per100,000). Newfoundland and Labrador also showed the highest rates for lung cancer in males (98.0 per 100,000), with Alberta showing the lowest lung cancer rates for both sexes (62.2 vs 54.6 per 100,000). Colorectal cancer rates for males and females were equally higher in NL (112.2 vs 76.5 per 100,00) and highest for females in Prince Edward Island. In addition, breast and cervical cancers in NL females [(152.0 per 100,000) vs (10.7 per 100,000)] and prostate in NL males (132.9 per 100,000) were also the highest compared to other provinces. These variations in cancer rates between provinces are presumed to be more likely because of differences in the prevalence of risk factors such as obesity, smoking, unhealthy diet and possibly testing patterns (e.g., PSA or mammogram cancer testing) than differences in population genetic profiles. For instance, in 2011, the prevalence of overweight varied from 31.3% in British Columbia to 41.8% in Newfoundland and Labrador. The rate for obese class I varied from 10.7% in BC to 20.5% in Newfoundland and Labrador (Twells, Gregory, Reddigan, & Midodzi, 2014). In 2013,

there was significant variation in smoking prevalence by province. Smoking rates ranged from a low of 11.4% in British Columbia to a high of nearly 20% in New Brunswick, Newfoundland & Labrador, and Nova Scotia (Reid, Hammond, Rynard, & Burkhalter, 2014). This was a mistake. Corrections made please see below:

Prostate cancer incidence rates have lately seen a decrease both in Canada and the United States, but at a faster pace than in Canada. From 2011 to 2012, the rate in the United States decreased by 19.1% (http://www.cancer.ca) compared with 12.3% in Canada (https://www.statcan.gc.c). In the United States, the decline in the 2012 rate coincides with a significant drop in self-reported PSA screening rates. This is possibly related to revised guidelines released by the United States Preventive Services Task Force (USPSTF) (https://seer.cancer.gov/report). In 2012, the USPSTF issued a grade 'D' recommendation against the use of routine prostate-specific antigen (PSA) based screening for any men. In Canada, although the PSA screening test is widely used, it is not currently recommended as a population-based screening test. For instance, in Ontario the government doesn't pay for the test (http://www.health.gov.on.ca).The peak in prostate cancer incidence rates that occurred in Canada in 1993 and 2000, were likely due to a detection bias as both peaks coincided with two waves of intensified screening activity using the PSA test. It is therefore reasonable to believe that the current decline in prostate cancer rates is been seen because it is not been detected by screening and therefore been under diagnosed.

Colorectal cancer mortality rates are highest in Newfoundland and Labrador for males and in Newfoundland and Labrador and Prince Edward Island for females. This high mortality rates can probably be because of poor patients compliance with screening. Based on 2007 data from the Canadian Community Health Survey Cycle 2.1, the proportion of people who

reported Colorectal Cancer (CRC) screening among the four provinces assessed (Ontario, British Columbia, Saskatchewan, and NL) was lowest in NL at 12.6%. Only 4% of women in NL reported taking a fecal occult blood test (FOBT) in the 2 years before the survey was conducted (Sewitch, Fournier, Ciampi, & Dyachenko, 2008).

With regards to breast cancers, the increases and fluctuations are being partly attributed to increase in mammography screening. Long-term changes in hormonal factors such as early age at menarche, breastfeeding, late age at menopause, and oral contraceptive use are also believed to have played a role. The sharp decrease in incidence that occurred around 2002 may reflect the reduced use of hormone replacement therapy (HRT) among post-menopausal women at that time. De, Neutel, Olivotto, & Morrison, (2010) observed a link between the declines in the use of hormone replacement therapy and breast cancer incidence among Canadian women aged 50-69 years, in the absence of any change in mammography rates.

In Canada, cancer also remains the leading cause of death, responsible for 30% of all deaths, followed by cardiovascular diseases (heart disease and cerebrovascular diseases), accidents and chronic lower respiratory diseases (http://www.cancer.ca). In 2017, The Canadian Cancer Society projected the highest number of deaths 233.3 per 100,000 (1,550 deaths) for Newfoundland and Labrador compared to other provinces. The province also has the highest colorectal cancer mortality rates for males followed by Prince Edward Island for females.

2.5 Psoriatic Arthritis Rheumatoid Arthritis, and Cancer

Both PsA and RA are considered immune-mediated inflammatory diseases in which autoimmunity leads to the activation of certain immune cells (T- helper lymphocytes,

macrophages, synoviocytes -and others) and induces the production of pro-inflammatory cytokines such as TNFα, IL-1, and IL-6. These cytokines play an important role in both inflammation and cancer formation (Hiraku et al., 2014). They trigger the production of degradative enzymes that destroy the joints and further stimulate the T cell response. They also activate various transcription factors, such as nuclear factor NF- kB, signal transducer and activator of transcription (STAT) 3. These factors can promote cell growth, supressing apoptotic cell death and can activate multiple oncogenic pathways (Hiraku Y et al., 2014; Nakachi, Hayashi, Imai, & Kusunoki, 2004). It was observed more than a decade ago that significant amounts of IL-1 and TNFα are found in the joint spaces of RA patients, but not in those of normal controls (Hopkins & Meager, 1988). Furthermore, an early transgenic animal study showed that mice constitutively expressing TNF-alpha developed a chronic arthritis (Keffer et al., 1991) and that this arthritis could be stopped by treatment with anti-TNF-α agents.

Very few studies could be found that examined the risk of malignancy in patients with Psoriatic Arthritis when compared with Rheumatoid Arthritis. (Gross et al; 2014; Hagberg et al., 2016; Hellgren et al., 2014; Rohekar et al., 2008). Although PsA shares some clinical features with both RA and Psoriasis (PsO), the risk of malignancy has been better studied in the latter two. Several large cohort studies have demonstrated an increased risk of malignancy, particularly Lymphoma and hematologic cancers, in patients with RA compared with a control group (Y. Chen et al., 2011; Fantò et al., 2016; Geborek et al., 2005 and Mellemkjaer et al.,1996). For Instance, Fanto et al. (2015) evaluated the risk of malignancy in 399 patients affected by RA, PsA and ankylosing spondylitis (AS) who were treated with TNF-alpha inhibitors and disease modifying drugs (DMARDs) or DMARDs

alone. Their study findings showed no overall increased cancer risk in comparison to the general population. However, the risk of hematologic malignancies was significantly higher in RA patients (SIR= 4.9, 95 CI ,1.35-12.26), particularly in females. In a study done by Gross et al. in 2014, comparing the incidence rates of malignancy among patients with Psoriatic Arthritis (PsA) and patients with Rheumatoid Arthritis (RA), an interesting point was made about a doubt as to whether malignancy risk in PsA patients can be elicited from previous studies done for patients with RA and patients with skin psoriasis. His argument was, since chronic inflammation is a risk factor for certain malignancies in patients with inflammatory arthritis (Baecklund et al., 2006) and disease activity in RA patients is observed to be higher in comparison with PsA patients (Reddy et al., 2010), it would only make sense for one to assume that RA patients stand a greater risk of cancer compared to PsA patients. Contrarily, one might argue that the double impact of inflammation from both skin disease and joint disease may equally put PsA patients at an increased risk of malignancy compared to patients with RA, who have only joint disease. In this study, the authors did not find any difference in the risk of malignancy between patients with PsA and RA and reported non- melanoma skin cancer to be the most common malignancy.

2.6 Summary of The Literature Review

The literature review is inconclusive and had shown inconsistency among authors. Some studies have reported an increased cancer risk (Askling et al., 2005; Bongartz et al.,2006; Beyaert et al., 2013; Y. Chen, Chang, Wang, & Wu, 2011; Smitten, Simon, Hochberg, & Suissa, 2008), others decreased or no risk (Dommasch et al., 2011; Haynes et al., 2013., Hellgren et al., 2014; Gross et al., 2014; Mercer et al., 2012; Wu et al 2014). As an example, randomized control trials were limited by short duration of follow up and

sparse adverse events data which are not powered enough to detect rare adverse events. Two meta-analysis of RCTs in the literature review of patients treated with TNF alpha inhibitors showed different results. Bongartz et al. (2006) reported that malignancies were significantly higher in patients treated with anti- TNF, OR of 3.3 (95% CI 1.2-9.1) where as (Dommasch et al., 2011) did not observe any significant increased cancer risk. Differences between the two study outcomes can be explained by the differences in the placebo- controlled phases duration included in the analysis. Studies chosen by Bongartz et al. (2006) had longer study phases (mean of 32.7, range 12-54 weeks) than those included in Dommasch et al. (2011) study (mean 17.8 range 12-30 weeks). Longer study phases could have led to an increased detection of events (especially if the risk increases over time) whereas, small number of events may affect the precision of risk estimate. Furthermore, number of observational studies (Gross et al., 2014; Hellgren et al., 2014; Mercer et al., 2015; Wu et al., 2014;) have relied on administrative data bases and national cancer registries for their study population. One disadvantage of this is that there may be malignancies that were not reported during the study visits by patients or health providers, leading to underascertainment. Misclassification bias can also occur with the use of administrative databases and can potentially lead to an under estimation of the associations. Follow-up times among observational studies ranged from 5 years to 35 years, whereas the sample size ranged from 399 to as high as 23,644. It is likely that the variability observed in the results may have resulted from these differences. Different patients geographic backgrounds is possibly another contributing factor to differences in study results. For instance, certain types of cancers can be more frequent in some geographic areas than

others. This may be due to difference in distribution of both known and unknown risk factors.

2.7 Study Justification

Our main study objective is to investigate Cancer Incidence in patients with Psoriatic (PsA) and Rheumatoid Arthritis (RA) and to examine the impact of chronic systemic inflammation as well as treatment on cancer formation in these groups of patients. Although PsA and RA are accounting only for 2% of the of the general population (PHAC, https://www.canada.ca/en/public-health/services) they do carry a high burden of cost and disability such as: impaired physical function, reduced quality of life (QOL) and increased mortality Rahman et al. (2017). Despite some of the differences in their clinical presentation, we chose to combine both diseases in our investigation because of their two important shared similarities: systemic chronic inflammation and the methods of treatment. These similarities have recently raised several questions and debates about the possibility of been linked to cancer formation (Kiraly, Gong, Olipitz, Muthupalani, & Engelward, 2015) and (Askling et al., 2005; Bongartz et al., 2006). We also wanted to compare the cancer rates between these two diseases. Bonovas et al. (2016) similarly investigated the risk of malignancies using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Although the reviewed literature is inconclusive, number of studies were found that showed an increased risk of cancer in PsA and RA patients (Askling et al., 2005; Bongartz et al.,2006; Beyaert et al., 2013; Y. Chen, Chang, Wang, & Wu, 2011; Smitten, Simon, Hochberg, & Suissa, 2008). The literature review also indicated that Newfoundland and Labrador has one of the highest cancer incidence rates (586.8 per 100,000) when compared to other provinces (Canadian Cancer Statistics

(http://www.cancer.ca)). It also showed that the province has the highest rates for such cancers such as lung cancer in males (98.0/100,000), colorectal cancer for males and females (112.2/100,000 and 76.5/100,000 respectively), breast and cervical cancers in females (152.0/100,000 and 10.7/ 100,000 respectively), as well as prostate cancer in males (132.9/100,000). These high cancer rates are presumed to be associated with high prevalence of risk factors such as smoking 20% (Reid, Hammond, Rynard, & Burkhalter, 2014), obesity 41.8% (Twells, Gregory, Reddigan, & Midodzi, 2014), unhealthy diet and, possibly, screening programs. For instance, the high colorectal cancer mortality rates in NL are presumed to be because of poor patient's compliance with screening. Based on 2007 data from the Canadian Community Health Survey Cycle 2.1, the proportion of people who reported Colorectal Cancer (CRC) screening among the four provinces (Ontario, British Columbia, Saskatchewan, and NL) was lowest in NL at 12.6%. Only 4% of women in NL reported taking a fecal occult blood test (FOBT) in the 2 years before the survey was conducted Green et. al. (2007). In addition, 2008 provincial screening rates for Newfoundland and British Columbia showed that up to 85.4% and 91.4% of residents had never been screened with FOBT and endoscopy, respectively (Sewitch, Fournier, Ciampi, & Dyachenko, 2008). Information on the prevalence and burden of PsA and RA in NL population is highly limited. The author was unable to find any study that investigated cancer incidence in these two diseases in NL population. However, the evidence found in the literature review was sufficient to make us speculate of a heightened cancer risk in our study population. Based on the aforementioned, we hypothesized that the cancer incidence in our study population is higher compared to the NL general population.

CHAPTER 3
METHODOLOGY

3.1 Study Design

We conducted a retrospective study to examine cancer incidence in Psoriatic Arthritis (PsA) and Rheumatoid (RA) patients. A clinical chart review was conducted on patients who attended a local Dermatology and Rheumatology clinic in St. Johns, NL from 2011-2014. Patients came from various parts of Newfoundland and Labrador. Clinical outcomes of interest were any type of new cancer and precancerous lesion documented in the study cohort from January - 1st 2011 to December 31st, 2014. Data collection began in December 2014 after receiving approval from the Health Research Ethics Authority (HREA). A total of 805 clinical charts of patients who attended the Rheumatology clinic from 2011-2014 were reviewed from a total of 2000 available charts (Fig.2) Of them, 235 were PsA and 570 were RA patients. After exclusion of patients who did not meet inclusion criteria, 700 (200 PsA and 500 RA) patients were included in the final analysis. De-identified data was collected for the study purpose.

3.1a) Eligibility Criteria

Inclusion Criteria:

Adult patients with an established diagnosis of PsA or RA who attended the Rheumatology clinic from 2011-2014

Exclusion Criteria:

Patients ≤19 years of age

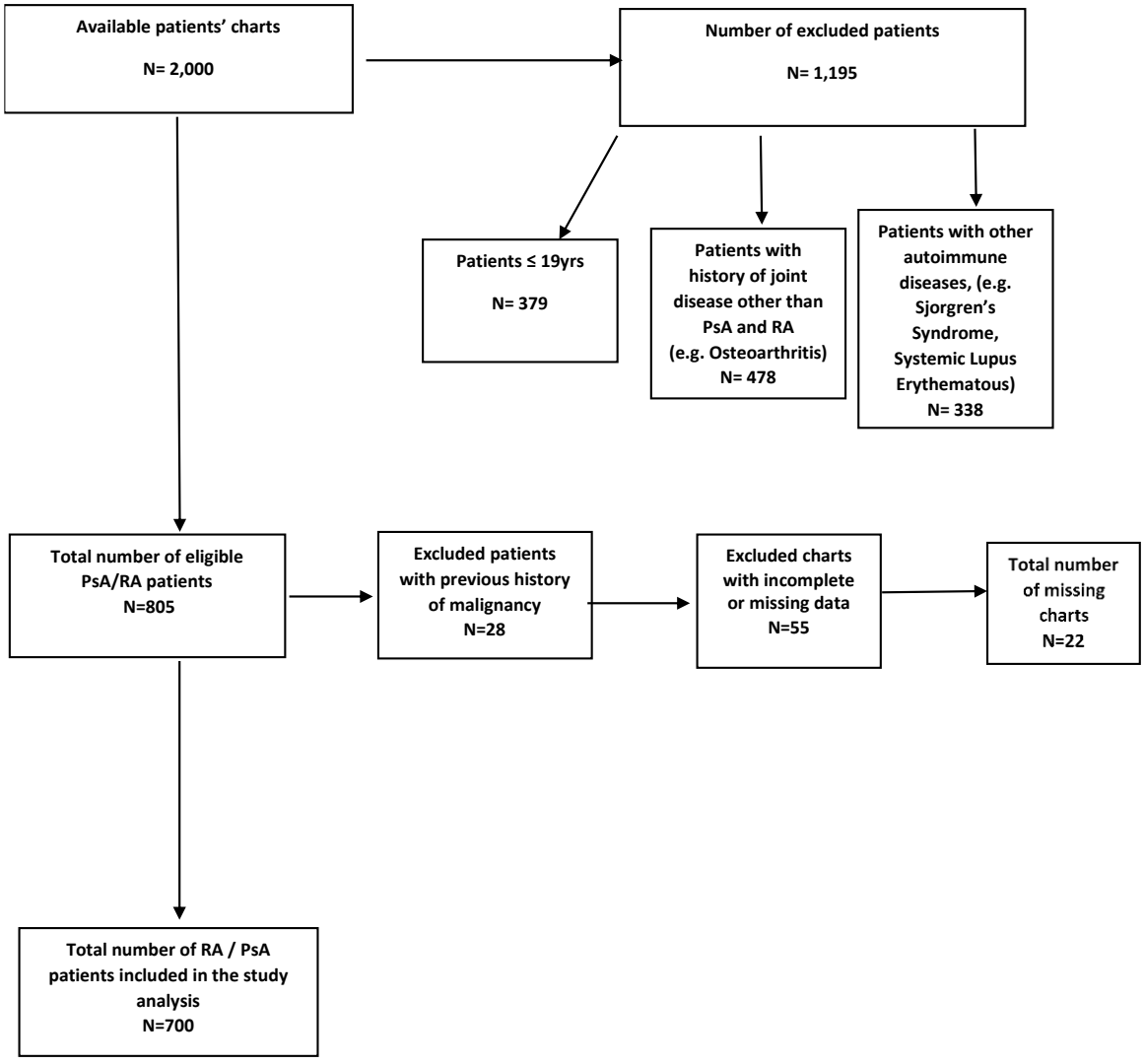
Those with previous history of malignancy

Those with a history of other autoimmune diseases such as Systemic Lupus Erythematous or Sjorgren's syndrome

Patients with skin disease other than Psoriasis

Patients with a history of joint disease other than Psoriatic Arthritis or Rheumatoid Arthritis

Figure 3.1. Flow Chart of Study Subject Selection



3.2 Study Population

Seven hundred adult patients (68.6% females) with established diagnoses of Psoriatic Arthritis (PsA) and Rheumatoid Arthritis (RA) were included in the study. Diagnosis of RA was made using Internationally Accepted Classification Criteria by the American College of Rheumatology (ACR, 2010). Diagnosis of PsA was established by using Classification Criteria for Psoriatic Arthritis (CASPAR) (Taylor et al., 2006).

3.3 Research Questions

Primary Research Question:

Is the incidence of malignancy statistically significantly higher in patients diagnosed with PsA and RA compared to the NL general population?

Secondary Research Questions:

Is there a significant association between confirmed malignancy and disease severity?

Is there a significant association between treatment modalities including Biologic Disease Modifiers (bDMARDs)? Is there a significant difference in cancer rates between these two types of inflammatory arthritis?

3.5 Sample Size Justification

This was a retrospective chart review. The sample size justification was based on total number of clinical charts related to patients with PsA and RA from 2011-2014. The study site archives close to 2,000 active RA and PsA clinical charts and sees approximately 250-300 new patients per year. At the time of data collection, we reviewed 805 clinical charts and found that 700 were eligible according to our inclusion criteria.

We conducted a Post-hoc Power analysis (1- β is computed as a function of α, the population effect size, and N) using G-Power software 3.1 to determine whether our sample size was large enough to provide enough power to detect a meaningful effect**.** http://www.gpower.hhu.de/en.html

A Post -Hoc analysis is performed after a study has been conducted so that the sample size N, is already a matter of fact (Faul, Erdfelder, Buchner, & Lang, 2009). Given our study sample size N-700, α-0.05, and a specified effect size of 0.3 this type of analysis returned the power (95%), or the β error of 5%.

3.6 Study Objectives

The main objective of this study was to investigate the incidence rates of malignancies and precancerous lesions in adult patients with Psoriatic Arthritis and Rheumatoid Arthritis and compare our study findings to that of the general population of Newfoundland and Labrador.

We also investigated the association between the documented malignancy and the disease severity and duration, as well as treatment modalities, including Biologic Disease Modifiers

(bDMARDs). Malignancy rates between these two cohorts of PsA and RA patients were also compared.

3.7 Data Collection

Data collection began in December 2014 until September 2016. All required information was retrieved from patients clinical charts and entered directly into a predefined SPSS database that contained relevant variables. The incidence of malignancy was evaluated in a cohort of 700 patients and compared to the data provided by Statistics Canada. Information was collected on: 1) patients demographics (age, sex, smoking status, duration of disease), 2) past medical history of comorbidities and 3) treatment modalities. We additionally retrieved information on patients disease activity and inflammation severity using disease activity measuring tools, clinical parameters and measurements makers. The above information was normally collected during patient's 1st clinic visit as well as during yearly follow-up visits. Detailed descriptions of questioners are included in the appendix. Patients disease activity was evaluated using predefined questionnaires such as 1) The 28-joint disease activity score (DAS28) [an established and validated tool that is used to determine both disease activity and treatment response in both PsA and RA patients (Salaffi et al., 2014)]. The scores provide ranges that corresponds to high, moderate, and low disease activity. High disease activity relates to DAS28 >5.1, moderate to DAS28 of >3.2 to 5.1, low disease activity is regarded in the range of 2.6 to 3.2. 3, 2) Psoriatic Arthritis Screening Questionnaire (PASQ) is a sensitive and specific self-administered tool used for the diagnosis of Psoriatic Arthritis and to measure the degree of inflammatory symptoms. The PASQ consist of a questionnaire (with a maximum score of 10) and a diagram with a (maximum score of 5) indicating where patients experienced joint swelling or pain

(Khraishi et.al., 2010) and 3) Health Assessment Questionnaire (HAQ) which is an instrument designed to assess patients disability, discomfort, medication side effects, costs, and mortality (Smolen & Aletaha., 2012). Each question is answered on a four-level scale of impairment ranging from 0 to 3: 0 = no difficulty; 1 = some difficulty; 2 = much difficulty; and 3 = inability to do activity of daily living. Severity of inflammation was additionally evaluated using clinical parameters and measurements makers such as: 1) Tender Joint Count (TJC), 2) Swollen Joint Count (SJC 1), 3) C-reactive protein (CRP) [normal range values <10 mg/l], and 2) Erythrocyte Sedimentation Rate (ESR) [normal range values females < 20 mm/hr, males<15mm//hr]. Cancer diagnosis was ascertained from patients medical records using the International Classification of Diseases (ICD-10) codes to define malignancies.

3.8 Statistical Analysis

The main study outcome was any newly diagnosed and documented cancer during the study period. All statistical analyses were performed using SPSS version 21.0 for Windows (IBM Inc.) Descriptive statistics included means (SD) and proportions when appropriate. The difference between groups (PsA vs. RA) was examined using Chi Square test for categorical variables and t-test for continuous variables. Binary logistic regression analysis (Univariate and Multivariate) was carried out to assess potential association between the binary outcomes (cancer 1-yes, 0-no) and explanatory variables (clinical parameters, laboratory markers and set of treatments with biologics). Potential confounding risk factors included in the logistic models were age, sex, obesity, smoking status and disease duration. Amongst confounders, only age was a significant predictor of malignancy. Unadjusted and adjusted binary logistics Odds Ratios (ORs), and 95%

confidence intervals (95% CI) for all cancers were calculated. Cancer Incidence was measured by both Incidence rate (person-time rate) and Incidence proportion rate. Age Standardized Incidence Rates (ASIR) stratified by sex were used to evaluate overall cancer risk and proportion rates for measuring and comparing cancer rates between the two cohorts. Newfoundland and Labrador general population rates were taken from Statistics Canada (http://www5.statcan.gc.ca/cansim). Person-years for each participant were calculated amongst patients with established PsA/RA diagnosis to the date of cancer diagnosis or the end of study period. The minimum level of statistical significance was a priori defined at 5%, all tests were two-tailed. Incidence rates or person-time is a measure of incidence that incorporates time directly into the denominator and describes how quickly disease occurs in a population https://www.cdc.gov. We chose to calculate age incidence rates because person- time can accommodate persons coming and leaving the study such as those who died or were lost to follow up (Tables 4.6 and 4.7). We adjusted our analysis by age and since our cohort was significantly dominated by females (who were more obese than males), we further stratified by sex to help adjust for weight and sex effect. Newfoundland and Labrador general population rates were taken from Statistics Canada (http://www5.statcan.gc.ca/cansim). A person-time rate was calculated from our cohort where our study participants were observed, and occurrence of new cancer cases were documented. Person-years for each participant were calculated amongst patients with established PsA/RA diagnosis to the date of cancer diagnosis, lost to follow up, death or the end of study period. The ASIR was obtained by dividing the number of new of cancer cases during specified period by the total time each person was observed during the study period.

CHAPTER 4

STUDY RESULTS

4.1 Patient's Demographics

Seven hundred patients were included in the analysis. Demographics, clinical and laboratory characteristics for the total population and by PsA and RA cohorts are summarized in Tables 4.1 and 4.2. The study population was normally distributed by age and skewed by sex with more patients being female (68.6 vs 31.4; P= <0.001). The youngest study participant was 21 years of age and the oldest 96. The overall mean (SD) age of participants was 58.4 (12.28) and age at diagnosis of disease was 46.8 (12.88). Three hundred and seventy patients (52.9%) had a history of obesity (BMI>29) and 147 (21.0%) reported having smoked. Females were significantly more obese than males (34.2% vs 18.7%; P=0.018), had higher ESR scores (24.18 vs 19.63; P=0.007), [normal range values females <10mm/hr, males<6mm/hr] and were more likely to be exposed to Hydroxychloroquine (42.7% vs 12.1%; P=<0.001). However, men showed longer treatment duration with DMARDs (MTX) (4.65 vs 3.85; P=0.002).

Table. 4.1 Demographic and Clinical Characteristics for the Cohort (N=700)

Characteristics	*Total*	*Females, N (%)*	*Males, N (%)*	*P* (95%CI)*
Gender (Females)	700 (100)	480 (68.6)	220 (31.4)	<0.001(0.78-.0.94)
Age mean (SD)	58.4 (12.28)	58.42 (12.6)	58.60 (11.46)	0.859 (-1.78-2.14)
Age at diagnosis of disease, mean (SD)	46.83 (12.88)	46.81(13.30)	46.89 (11.93)	0.941 (-1.98-2.1)
Duration (years) disease symptoms, mean (SD)	11.59 (8.38)	11.56 (8.49)	11.66 (8.15)	0.876 (-1.23-1.44)
Smoking	147 (21.0)	102 (14.6)	45 (6.4)	0.842 (0.70-1.55)
Obesity (BMI > 30)	370 (52.9)	239 (34.2)	131(18.7)	0.018 (0.49-0.93)
PASQ score, mean (SD) *(PsA patients only)*	4.52 (2.34)	4.85(3.63)	4.20 (2.16)	0.042 (0.02-1.27)
DAS28, mean (SD)	3.65 (1.23)	3.68 (1.24)	3.61 (1.23)	0.503 (-26-0.13)
C-Reactive Protein (CRP), mean (SD)	10.0 (19.80)	10.28 (21.04)	9.52 (16.76)	0.637 (0.39-2.40)
ESR, mean (SD)	22.75 (20.71)	24.18 (20.35)	19.63 (21.00)	0.007 (-7.84- 1.89)
Total Tender Joint Counts, mean (SD)	8.43(8.1)	8.69 (9.23)	7.85 (8.12)	0.246 (-2.26-0.58)
Total Swollen Joint Counts, mean (SD)	3.20 (3.73)	3.13 (3.35)	3.35 (3.51)	0.458 (-37-0.82)
HAQ score, mean (SD)	0.94 (1.64)	0.95 (0.74)	0.92 (2.71)	0.827 (0.29-0.23)
Exposure to Bios	366 (52.3)	245 (35.0)	121 (17.3)	0.370 (0.61-1.17)
Exposure to MTX	615 (87.9)	421 (60.1)	150 (27.7)	0.907 (0.60-1.51)
Exposure to Bios and MTX,	331(47.3)	227 (32.4)	104 (14.9)	0.996 (0.72-1.37)
Treatment Duration with Bios, mean, (SD)	2.72 (3.64)	2.58 (2.94)	3.01 (3.21)	0.082 (-.055-0.91)
Treatment Duration MTX, mean, (SD)	4.1(3.11)	3.85 (2.8)	4.65 (3.55)	0.002(-1.29- -0.30)
Exposure to Corticosteroids	287 (41.0)	199 (41.5)	88 (40.0)	0.741 (0.76-1.47)
Exposure to Hydroxychloroquine (CHQ)	384 (54.9)	229 (42.7)	85 (12.1)	<0.001(1.89-3.64)
Exposure to NSAIDs	650 (92.9)	444 (63.4)	206 (29.4)	0.717 (0.82-1.83)
Exposure to Sulfasalazine (SSZ)	117 (16.7)	81 (11.6)	36 (5.1)	0.913 (0.67-1.59)

Chi square p for categorical variables and t-test p for continuous variables (Fisher's Exact p when cell count is less than 5)

4.2 Study Population Comparison by PsA and RA Cohort

Among the 700 subjects, 200 (28.6%) were diagnosed with PsA and 500 (71.4%) were diagnosed with RA. Patients' mean age at the time of data collection were (54.7 vs 59.9 vs; P<0.001) respectively. Since we aimed to examine the effect of duration of disease on the risk of cancer, we also collected data regarding arthritis onset. Patients' mean age at the time of PsA and RA diagnosis was not significantly different. The study groups were predominantly female 480 (68.6%). As expected in the RA cohort, the proportion of females 378 (54.0%) was significantly greater than the proportion of males 122 (17.4%), and so was the proportion of females between the two cohorts 378 (54.0%) vs 102 (14.6%); P= <0.001. Whereas, the number of males and females in the PsA cohort were equally distributed 98(14.0%) vs 102 (14.6%). For most part, both cohorts did not differ significantly by their characteristics; however, PsA patients were younger (54.7 vs 59.9; P<0.001) and had shorter disease duration (8.59 vs 12.78; P<0.001) than those with RA. In addition to assessing factors such as age, sex, smoking status etc., disease activity measures for PsA and RA (DAS28, PASQ, CRP, ESR, HAQ, TJC and SJC) were also evaluated. Even though at the time of analysis there were no overall significant differences in the disease activity scores between the two cohorts (P=0.610), patients with RA showed significantly higher disease activity as indicated by a higher mean score for CRP= (11.18 vs 7.19; P=0.016) [normal range values<10mg/l], ESR= (24.7 vs 17.7; P<0.001) [normal range values females < 20 mm/hr, males <15 mm/hr] scores, and number of total swollen joint counts TSJC= (3.41 vs 2.69; P=0.021). The Mean (SD) score for the Psoriasis and Arthritis Severity Questionnaire (PASQ) for patients with Psoriatic Arthritis was 9.75. The PASQ consist of a questionnaire (with a maximum score of 10) and a diagram with a

(maximum score of 5) with a maximum combined score of 15 indicating the severity of the disease.

With respect to treatment exposure, both study groups had similar exposure to most treatment, although RA patients were more likely to be exposed to Methotrexate, 469 (67.0%) vs 146 (20.9%), Corticosteroids 255 (36.4%) vs 32 (4.6%) and Hydroxychloroquine 362 (51.7%) vs 22 (3.1%). Both groups showed similar exposure to combination therapy (Biologics and MTX).

Table 4.2 shows comparison of demographics, clinical and laboratory characteristics between RA and PsA cohorts.

Table 4.2 Comparison of Demographics, Clinical and Laboratory Characteristics Between RA (N=500) and PsA (N=200) Cohorts

Characteristics	Total N (%)	RA Cohort N (%)	PsA Cohort N (%)	P* (95% CI)
Number of patients	700 (100.0)	500 (71.4)	200 (28.6)	----------
Gender (Females)	480 (68.6)	378 (54.0)	102 (14.6)	<0.001
Age in years, mean (SD)	58.5 (12.27)	59.98 (12.47)	54.72 (10.93)	<0.001 (3.28-7.24)
Age at diagnosis of disease, mean (SD)	46.8 (12.8)	47.12 (13.37)	46.13 (11.57)	0.358 (-1.12-3.10)
Duration (years) disease symptoms, mean (SD)	11.58 (8.38)	12.78 (8.24)	8.59 (7.98)	<0.001 (2.84-5.53)
Smoking	147 (21.0)	108 (15.4)	39 (5.6)	0.608 (0.58-1.32)
Obesity (BMI >30)	370 (52.9)	259 (37.1)	111(15.9)	0.403 (0.83-1.60)
PASQ score, mean (SD)		----------	4.52 (2.34)	---------
DAS28, mean (SD)	3.65 (1.23)	3.64 (1.23)	3.69 (1.22)	0.610 (-0.25-0.15)
C-Reactive Protein (CRP), mean (SD)	10.0 (19.78)	11.18 (22.58)	7.19 (9.20)	0.016 (0.75-7.22)
ESR, mean (SD)	22.75 (20.71)	24.76 (20.58)	17.72(20.22)	<0.001 (3.67-10.40)
Total Tender Joint Counts, mean (SD)	8.43 (8.90)	8.62 (9.13)	7.96 (8.28)	0.375 (-80-2.12)
Total Swollen Joint Counts, mean (SD)	3.20 (3.73)	3.41(3.82)	2.69 (3.45)	0.021 (0.11-1.13)
HAQ score, mean (SD)	0.94 (1.64)	1.01(1.89)	0.77(0.63)	0.076 (-0.25-0.51)
Exposure to Bios	366 (52.3)	225 (36.4)	111 (15.9)	0.315 (0.86-1.66)
Exposure to MTX	615 (87.9)	469 (67.0)	146 (20.9)	<0.001(0.08-0.20)
Exposure to Bios and MTX	331 (47.3)	224 (34.9)	87 (12.4)	0.210 (0.58-1.12)
Treatment Duration with Bios, mean, (SD)	2.72 (3.03)	2.68(3.01)	2.82 (3.09)	0.577 (-0.64-0.35)
Treatment Duration MTX, mean, (SD)	4.10 (3.11)	4.08(2.79)	4.17(3.81)	0.725 (-0.60-0.42)
Treatment Duration Bios and MTX	2.72 (3.03)	2.68 (3.01)	2.82 (3.09)	0.577 (-0.64-0.35)
Exposure to Glucocorticoids	287 (41.0)	225 (36.4)	32 (4.6)	<0.001(0.12-0.27)
Exposure to Sulfasalazine (SSZ)	117(16.7)	61(8.7)	56 (8.0)	< 0.001 (1.86-4.21)
Hydroxychloroquine (CHQ)	384 (54.9)	362 (51.7)	22(3.1)	< 0.001(0.29-0.07)

Chi square p for categorical variables and t-test p for continuous variables (Fisher's Exact p when cell count is less than 5)

4.3 Cancer Occurrence

A total of 37 (5.3%) different types of cancers were diagnosed during the study period. Among those affected, 13 (31.4%) were in males and 24 (64.9 %) were in females. Cancer patients were significantly older (65.38 vs 58.10) P= <0.001 and had a higher ESR score (30.21 vs 22.33) P= 0.024. One male patient had multiple cancers at different time periods (Skin cancer in 2011 and Lung cancer in 2013). There were nine (24.3 %) in the PsA group and 28 (75.7%) cases diagnosed in the RA group (Table 4.3). Ten (27 %) patients diagnosed with cancer were smokers. Eight (21.6%) cancers were diagnosed in the first year, nine (24.3%) in the second year, four (10.8%) in the third, and sixteen (43.2%) in the fourth year of the study. Two patients were lost to follow up (one died by the first year and another after three years). Both patients deaths were due to cancer related causes.

Table 4.2 b) Comparison of Demographics, Clinical and Laboratory Characteristics Between Cancer N= 37 and Non-Cancer Patients N= 663

Characteristics	Total N (%)	Patients with Cancer N (%)	Patients without Cancer N (%)	P* (95% CI)
Number of patients	700 (100.0)	37 (5.3)	663 (94.7)	----------
Gender (Females)	480 (68.6)	24 (64.9)	456 (68.8)	0.591(0.58-1.33)
Age in years, mean (SD)	58.5 (12.27)	65.38 (10.66)	58.10 (12.25)	<0.001 (3.24-10.95)
Age at diagnosis of disease, mean (SD)	46.8 (12.8)	51.54 (12.59)	46.57 (12.85)	0.022 (1.21-2.32)
Duration (years) disease symptoms, mean (SD)	11.58 (8.38)	13.78 (9.82)	11.46 (8.28)	0.102 (-0.45-5.09)
Smoking	147 (21.0)	10 (27.0)	137 (20.7)	0.405 (0.64-1.84)
Obesity (BMI >30)	370 (52.9)	16 (43.2)	354 (53.5)	0.240 (0.76-7.22)
DAS28, mean (SD)	3.65 (1.23)	3.76 (1.22)	3.65 (1.23)	0.576 (-0.30-0.53)
C-Reactive Protein (CRP), mean (SD)	10.0 (19.78)	8.34 (10.79)	10.13 (20.17)	0.592 (-8.36-4.77)
ESR, mean (SD)	22.75 (20.71)	30.21 (23.40)	22.33 (20.49)	0.024 (1.03-14.7)
Total Tender Joint Counts, mean (SD)	8.43 (8.90)	7.65 (8.56)	8.46 (8.92)	0.585 (-3.77-2.13)
Total Swollen Joint Counts, mean (SD)	3.20 (3.73)	2.70 (2.48)	3.23 (3.78)	0.405 (-1.76-0.712)
HAQ score, mean (SD)	0.94 (1.64)	1.01(0.83)	0.94 (1.67)	0.638 (-0.23-0.37)
Exposure to Bios	366 (52.3)	16 (43.2)	350 (52.8)	0.311 (-1.12-3.14)
Exposure to MTX	615 (87.9)	35 (94.6)	580 (94.3)	0.299 (0.76-1.55)
Exposure to Bios and MTX	331 (47.3)	12 (32.4)	319 (48.1)	0.089 (0.55-1.33)
Treatment Duration with Bios, mean, (SD)	2.72 (3.03)	2.43 (3.22)	2.73 (3.028)	0.702 (-0.98-1.45)
Treatment Duration MTX, mean, (SD)	4.10 (3.11)	4.32 (3.59)	4.09 (3.09)	0.659 (-0.80-1.26)
Exposure to Glucocorticoids	287 (41.0)	18 (48.6)	269 (40.6)	0.391 (0.54-3.21)
Exposure to Sulfasalazine (SSZ)	117(16.7)	6 (16.2)	111 (16.7)	0.098 (-0.62-1.39)
Hydroxychloroquine (CHQ)	384 (54.9)	18 (48.6)	366 (55.2)	0.498 (0.66-1.54)

Chi square p for categorical variables and t-test p for continuous variables (Fisher's Exact p when cell count is less than 5)

Chart 4.1

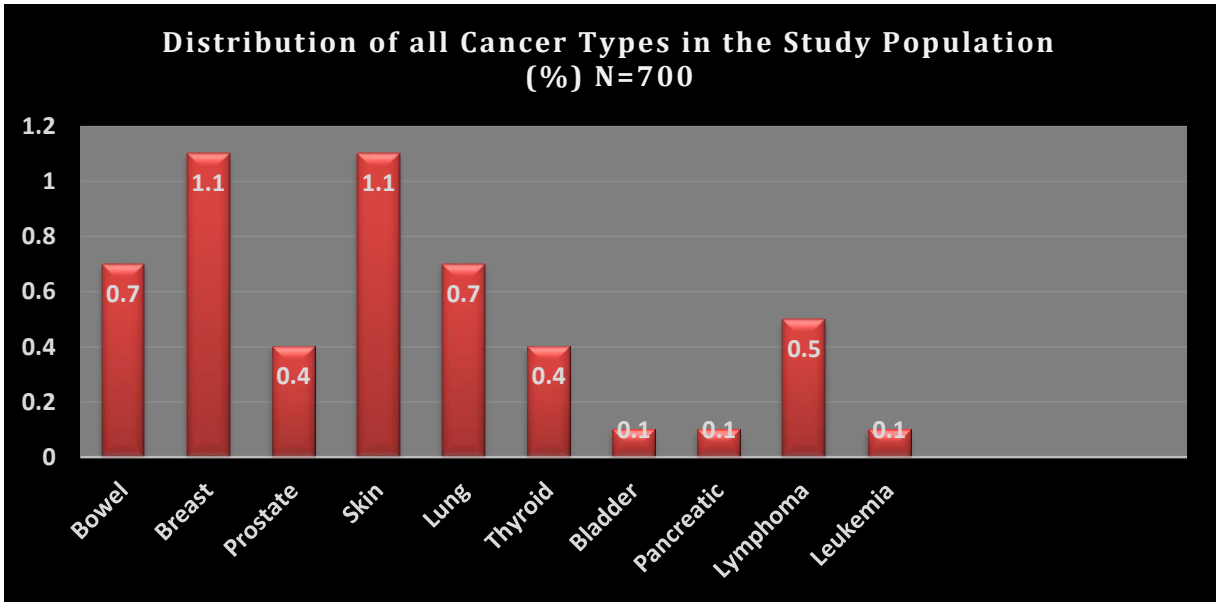

Distribution of all Cancer Types in the Study Population (%) N=700
1.2
1
0.8
0.6
0.4
0.2
0
0.7
1.1
0.4
1.1
0.7
0.4
0.1
0.1
0.5
0.1
Bowel
Breast
Prostate
Skin
Lung
Thyroid
Bladder
Pancreatic
Lymphoma
Leukemia

Chart 4.2

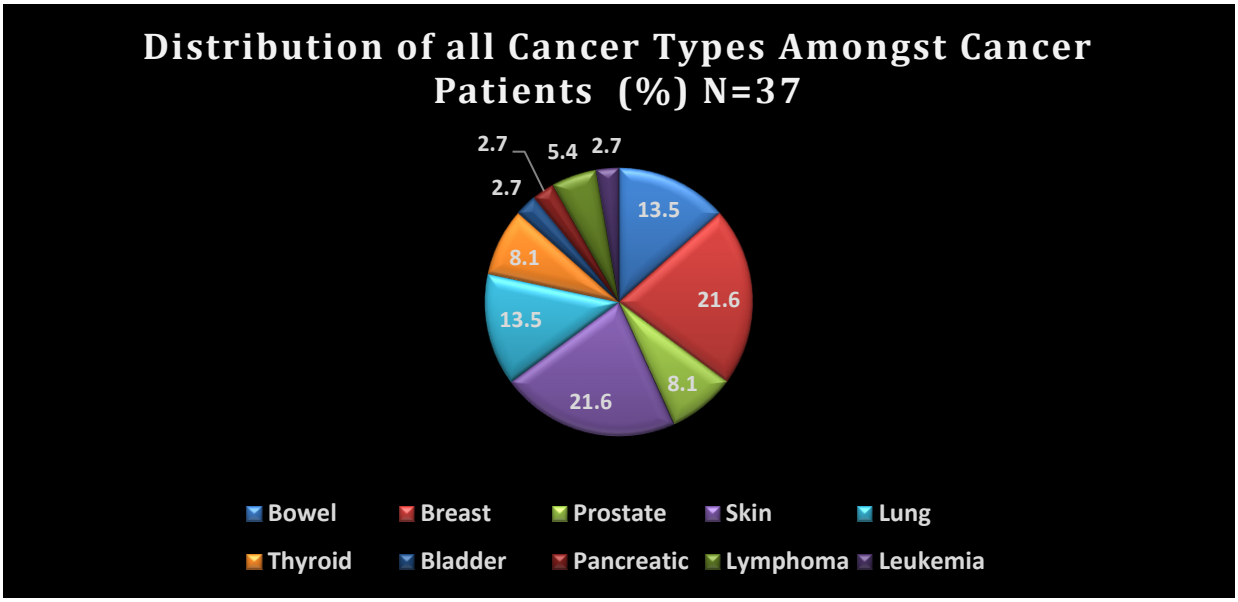
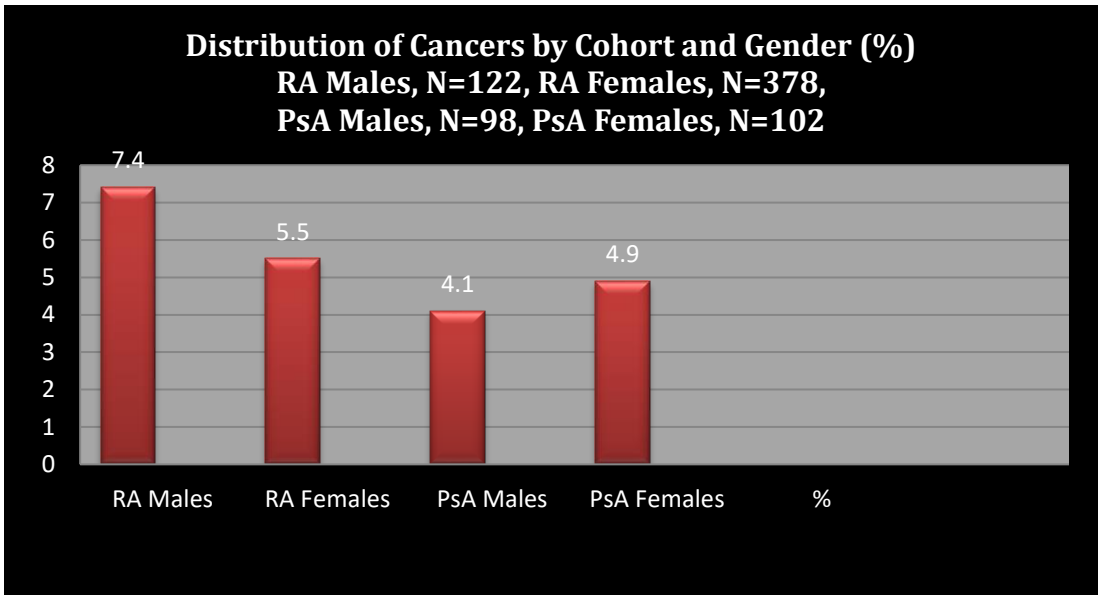

Distribution of all Cancer Types Amongst Cancer Patients (%) N=37
2.7
5.4
2.7
2.7
13.5
8.1
21.6
13.5
8.1
21.6
Bowel
Breast
Prostate
Skin
Lung
Thyroid
Bladder
Pancreatic
Lymphoma
Leukemia

Chart 4.3



RA males showed a higher proportion of cancers (7.4 %) compared to the rest of the cohort. There was no difference in the percentage distribution of cancers between male and female patients in the PsA cohort (4.1% vs 4.9 %). The proportion distribution of cancers between the two cohorts was not significantly different (P=0.709). One Psoriatic Arthritis male patient had multiple cancers at different time periods (Skin cancer in 2011 and Lung cancer in 2013). There were 34 (91.9 %) solid and 3 (8.1 %) hematologic cancers (Table 4.3). All cases were histologically confirmed. The most common solid tumors were Breast and Skin cancers (eight (21.6% each), followed by five Bowel and Lung cancers in equal proportion (13.5%). Of those eight Skin cancers, five were Melanomas (two basal cell carcinomas (BCC), three squamous cell carcinomas (SCC)) and three Non-Melanomas. There were three Prostate and three Thyroid cancers (8.1% each). Hematologic

malignancies were represented by one Myeloblastic leukemia (2.7%) and two Non-Hodgkin lymphomas (NHL) (5.4%).

Table 4.3 Most Common Types of Cancers and Precancerous Lesions by RA and PsA Cohort (%) N=37

Characteristics **Malignancies (ICD-10 code)**	**Total, N (%)**	**RA, N (%)**	**PsA, N (%)**
Most Common Solid Cancers:	***32 (86.5)***	***25(67.6)***	***7 (18.9)***
Bowel Cancer (C7A.02)	5 (13.5)	5 (13.5)	0 (0.0)
Breast Cancer (C50.0)	8 (21.6)	6 (16.2)	2 (5.4)
Prostate Cancer (C61.0)	3 (8.1)	2 (5.4)	1 (2.7)
Skin Cancer (C43-C44)	8 (21.6)	7 (18.9)	1 (2.7)
Lung Cancer (C34.0)	5 (13.5)	2 (5.4)	3 (8.1)
Thyroid Cancer (C73.0)	3 (8.1)	3 (8.1)	0 (0.0)
Other Solid Cancers:	**2 (5.4)**	**1 (2.7)**	**1(2.7)**
Renal, Bladder (C67.9-C68.9)	1 (2.7)	1 (2.7)	0 (0.0)
Pancreatic Cancer (C 25.9)	1 (2.7)	0 (0.0)	1 (2.7)
Hematologic Cancers (C85.9-C 92.0)	**3 (8.1)**	**2 (5.4)**	**1 (2.7)**
Non-Hodgkin's (NHL)	2 (5.4)	2 (5.4)	0 (0.0)
Lymphoma and Myeloblastic Leukemia	1(2.7)	0 (0.0)	1(2.7)
Total # of Incident Cancers	**37 (5.3)**	**28 (75.7)**	**9 (24.3)**
Pre-Cancerous Lesions	**5 (0.7)**	**4 (80.0)**	**1(20.0)**
Oral (K00-14) &Skin(L57.0)	1(20.0)	1 (20.0)	0(0.0)
Buccal Mucosa	1(20.0)	0 (0.0)	1(20.0)
Actinic Keratosis	3 (60.0)	3 (60.0)	0(0.0)
Cervical (N87.9)			

Chart 4.4

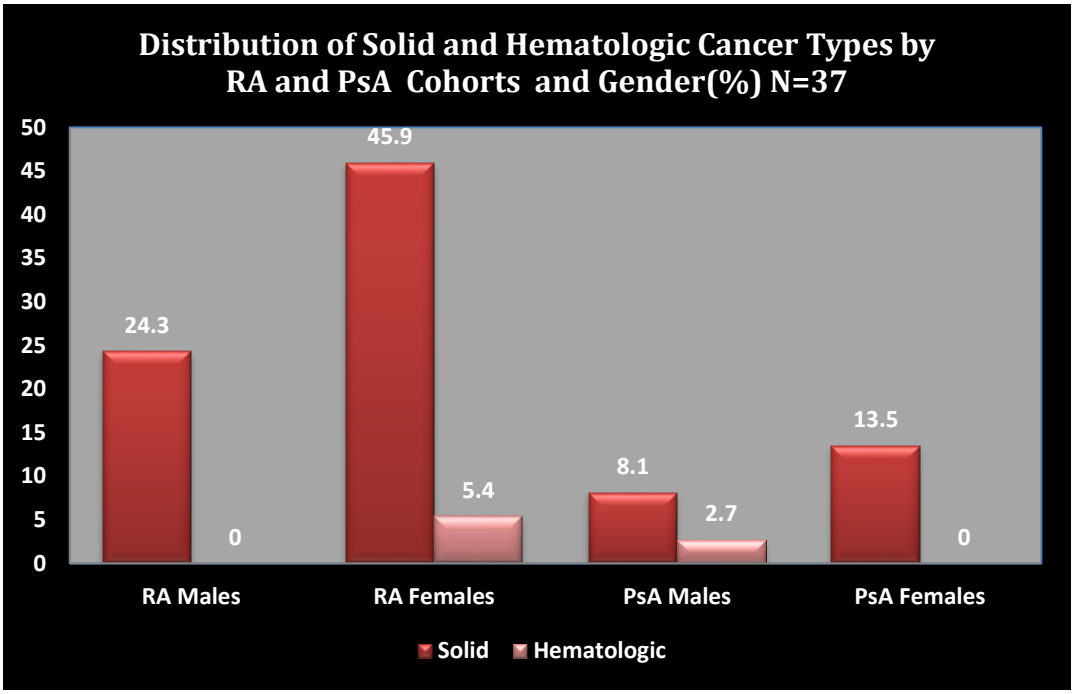
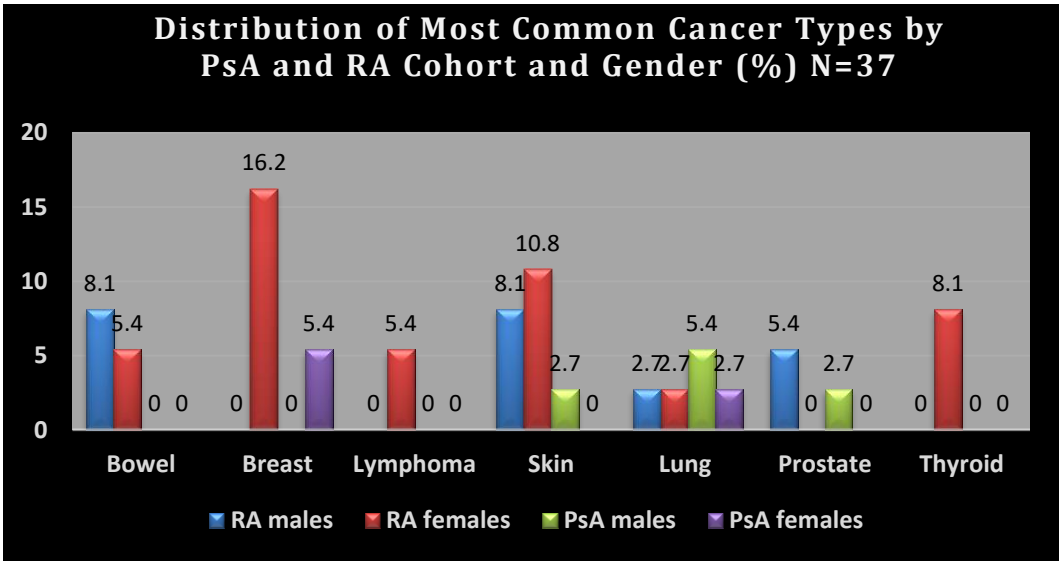

Distribution of Solid and Hematologic Cancer Types by RA and PsA Cohorts and Gender(%) N=37
50
45
40
35
30
25
20
15
10
5
0
24.3
0
45.9
5.4
8.1
2.7
13.5
0
RA Males
RA Females
PsA Males
PsA Females
Solid
Hematologic

Chart 4.5



Rheumatoid Arthritis (RA) female patients showed the highest proportions for Breast (16.2%), Skin (10.8%) and Thyroid (8.1%) cancers. All two Lymphomas, as well as three Thyroid cancers, were also diagnosed only in the RA female population. Both genders in the RA cohort demonstrated higher proportions for Bowel cancer compared to the PsA cohort. RA male patients showed significantly higher promotion for prostate cancer compared to PsA males (5.4 vs 2.7%) P=0.031. A total of 5 (0.7%) precancerous lesions were identified in our study population, with 2 (40%) in men (one of the buccal mucosae

and one skin) and 3 (60%) in females (3 cervical dysplasias). Distribution of pre-cancerous lesions between the two cohorts were not significantly different (P=0.670).

4.4 Treatment Characteristics and Comparison of Cancer Risk

With respect to treatment, more than half of our study population 52.3% had a history of exposure to Biologics. Eighty seven percent of the population had a history of being treated with synthetic DMARDs (mainly MTX) and 47.3% percent had combination therapy with both types of drugs (Biologics and DMARDs (MTX)) (Table 4.1). Table 4.4 compares the overall cancer risk with exposure to various treatment modalities and by PsA and RA cohorts. The overall cancer risk was significantly reduced in patients who were exposed to combination therapy for both Biologics and Methotrexate (OR= 0.3, 95% CI, 0.02-0.44, P = 0.003). Etanercept similarly showed lower risk of cancer in RA patients as compared to other biologics (OR= 0.1, 95% CI 0.01-0.89 P=0.039). Adalimumab showed a non-significant overall cancer risk (P=0.053), whereas Rituximab showed overall non-significant increased risk (P=0.203) in the RA cohort. Many traditional DMARDs (Mtx, SSZ, and HCQ) were numerically protective in RA and increased cancer risk in PsA patients. However, none of this were statistically significant and had wide CI's. This can be explained by the rarity of events in our study (smaller number of patients and smaller number of incident cancers in PsA N= 200, cancers N= 9, vs RA N=500, cancers N=28) and short duration of follow-up. This numerical differences in risk shows how small numbers of can change results. Similarly, Sulfasalazine, P= 0.894, CHQ, P=0.257 and NSAIDs, P=0.070 showed protective effect against cancer but did not reach statistical significance.

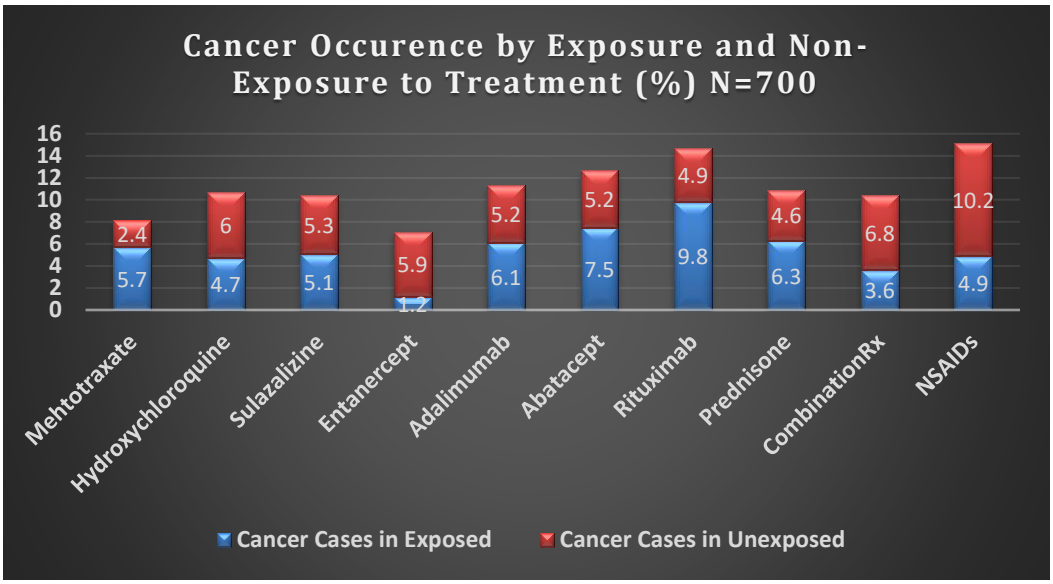
Table 4.4 Comparison of Overall Cancer Risk and Exposure to Treatment Modalities: RA vs. PsA

Exposure to Treatment	**Overall**		**RA**		**PsA**	
Biologics	**OR (95%CI)**	***P Value****	**OR (95%CI)**	***P value****	**OR (95%CI)**	***P value****
Adalimumab	2.9 (0.98 - 8.60)	0.053	3.5 (0.48-24.95)	0.214	4.4 (0.56-39.50)	0.153
Abatacept	1.4 (0.41-4.95)	0.570	1.4 (0.41-4.95)	0.570	----------	
Etanercept	0.2 (0.33-1.95)	0.187	0.1 (0.01-0.89)	0.039*	0.6 (0.07-6.16)	0.728
Rituximab	1.9 (0.70-5.24)	0.203	1.9 (0.70-5.24)	0.203	----------	-------
DMARDs:						
Methotrexate	1.1(0.34-2.98)	0.980	0.5 (0.12-2.65)	0.477	1.6 (0.31-8.51)	0.559
Sulfasalazine	0.8 (0.33-2.39)	0.894	0.5 (0.11-2.49)	0.425	1.7 (0.37-8.09)	0.310
Hydroxychloroquine	0.6 (0.32-1.35)	0.257	0.6 (0.28-1.47)	0.301	2.8 (0.41-19.43)	0.162
MTX + Biologics	0.3 (0.02-0.44)	0.003*	0.2 (0.03-0.35)	0.002*	0.5 (0.78-4.12)	0.842
Other Treatment:						
NSAIDs	0.3 (0.13-1.08)	0.070	0.7 (0.07-8.09)	0.843	0.7 (0.77-8.09)	0.843
Prednisone	1.3 (0.16-2.17)	0.388	1.6 (0.70-3.66)	0.261	0.8 (0.07-9.41)	0.885

OR=ODDs Ratio; 95% CI=95% confidence interval

****P= P Value= significant***

Chart 4.6



Next, we examined the distribution of incident cancers by patients exposure to biologic type. The diagram below demonstrates that all Lymphomas and Breast cancers were diagnosed among patients who had a history of treatment with Rituximab. Patients diagnosed with Skin and Breast cancers had multiple exposures, at various times to different types of biologics (Rituximab and Abatacept). Prostate, Thyroid, Lung and Bowel cancers occurred only in patients exposed to Adalimumab. The only patient with Myeloblastic Leukemia was exposed to Etanercept. None of the cancer patients were exposed to Golimumab or Infliximab.

In this study, we did not observe any statistically significant association between the studied inflammatory factors and cancer including DAS 28 and duration of disease. Table 4.5.

Chart 4.7

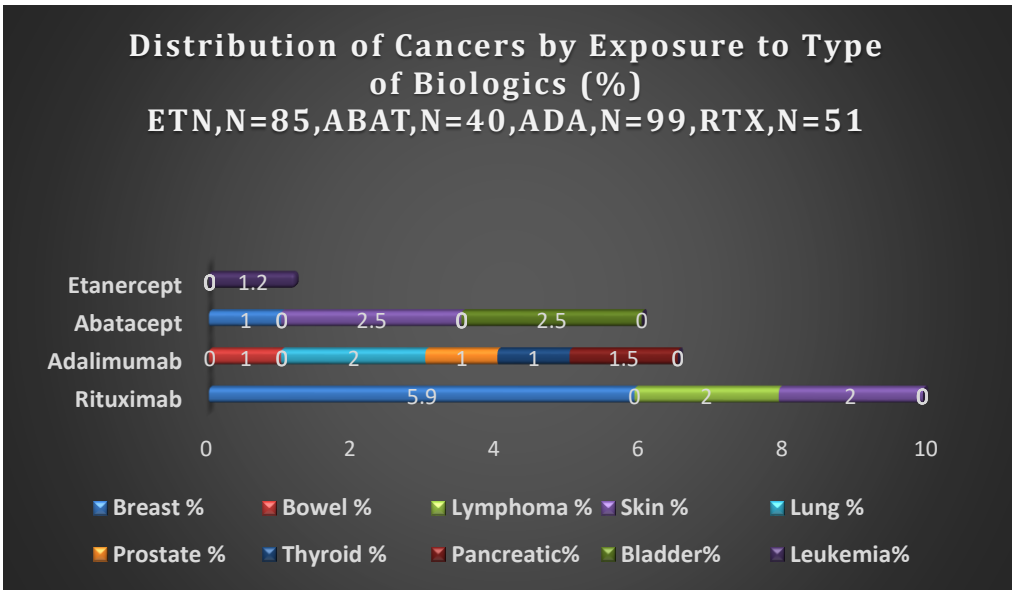

Distribution of Cancers by Exposure to Type of Biologics (%)
ETN,N=85,ABAT,N=40,ADA,N=99,RTX,N=51
Etanercept
Abatacept
Adalimumab
Rituximab
0 1.2
1 0 2.5 0 2.5 0
0 1 0 2 1 1 1.5 0
5.9 0 2 2 0
0 2 4 6 8 10
Breast %
Bowel %
Lymphoma %
Skin %
Lung %
Prostate %
Thyroid %
Pancreatic%
Bladder%
Leukemia%

Table 4.5 Comparison of Cancer Risk between Disease Activity Parameters and Cancer

	Overall		RA		PsA	
Disease Activity Parameters	**OR (95%CI)**	***P Value****	**OR (95%CI)**	***P value****	**OR (95%CI)**	***P value****
TSJC	0.8 (0.79-0.99)	0.048	0.8 (0.75-1.02)	0.093	0.4 (0.18-1.11)	0.086
CRP	0.9 (0.94-1.01)	0.256	0.9 (0.84-0.99)	0.027	1.1 (0.94-1.41)	0.167
ESR	1.0 (0.99-1.03)	0.169	1.0 (0.99-1.05)	0.111	1.0 (0.90-1.12)	0.895
DAS28	1.2 (0.85-1.89)	0.233	1.2 (0.77-1.91)	0.384	2.4 (0.54-10.57)	0.246
HAQ	0.9 (0.77-1.22)	0.842	0.9 (0.77-1.17)	0.646	1.4 (0.99-21.93)	0.780
RF	1.0 (0.81-1.24)	0.943	1.0 (0.82-1.24)	0.898	0.9 (0.34-2.34)	0.834
Disease Duration	1.0 (0.97-1.05)	0.509	1.0 (0.98-1.07)	0.221	0.9 (0.84-1.05)	0.272

OR=ODDs Ratio; 95% CI=95% confidence interval

P= P Value= significant

4.5 Calculations of Cancer Incidence Rate (IRs) / Person-time Rate (PYs)

Incidence rates or person-time is a measure of incidence that incorporates time directly into the denominator and describes how quickly disease occurs in a population https://www.cdc.gov . We chose to calculate age incidence rates because person-time can accommodate persons coming and leaving the study such as those who died or were lost to follow up (Tables 4.6 and 4.7). We adjusted our analysis by age and since our cohort was significantly dominated by females (who were more obese than males), we further stratified by sex to help adjust for weight and sex effect. Newfoundland and Labrador general

population rates were taken from Statistics Canada (http://www5.statcan.gc.ca/cansim). A person-time rate was calculated from our cohort where our study participants were observed, and occurrence of new cancer cases were documented. Person-years for each participant were calculated amongst patients with established PsA/RA diagnosis to the date of cancer diagnosis, lost to follow up, death or the end of study period.

Table 4.6 Age Standardized Cancer Incidence Rate (ASIR) / Person-Time Rate (PYs)/100,000 (Females)

Age Groups	Cancer Cases, Study Population	Person -time Rate (PYs)	Study Population	Standard Population	Cancer Cases Standard Population
20-29	0	48	12	30,659	20
30-39	0	92	23	32,981	55
40-49	0	304	76	39,490	135
50-59	8	529	134	43,078	300
60-69	10	561	144	38,070	525
70-79	13	261	70	20,425	395
80+	2	64.5	21	11,616	230
Total	24	1,859	480	216,319	1,660

Table 4.7 Age Standardized Cancer Incidence Rate (ASIR) / Person-Time Rate (PYs)/100,000 (Males)

Age Groups	Cancer Cases, Study Population	Person -time Rate (PYs)	Study Population	Standard Population	Cancer Cases Standard Population
20-29	0	8	2	31,547	10
30-39	0	40	10	31,525	25
40-49	2	142	36	37,926	65
50-59	3	266	68	42,687	305
60-69	5	280	72	37,257	660
70-79	3	98	26	18,684	535
80+	0	24	6	7,529	230
Total	13	858	220	207,155	1,830

Study Rate: ASIR/(PYs) 1 = 10.07 (6.46,13.68)/ 100,000

General Population (NL) Rate: ASIR/(PYs) 2 = 8.24 (7.97-,8.51)/100,000

ASIR1-ASIR 2= 1.83 (-1.79, 5.44)/100,000, P=0.3217

There is no difference in the cancer rate between our study and the NL general population.

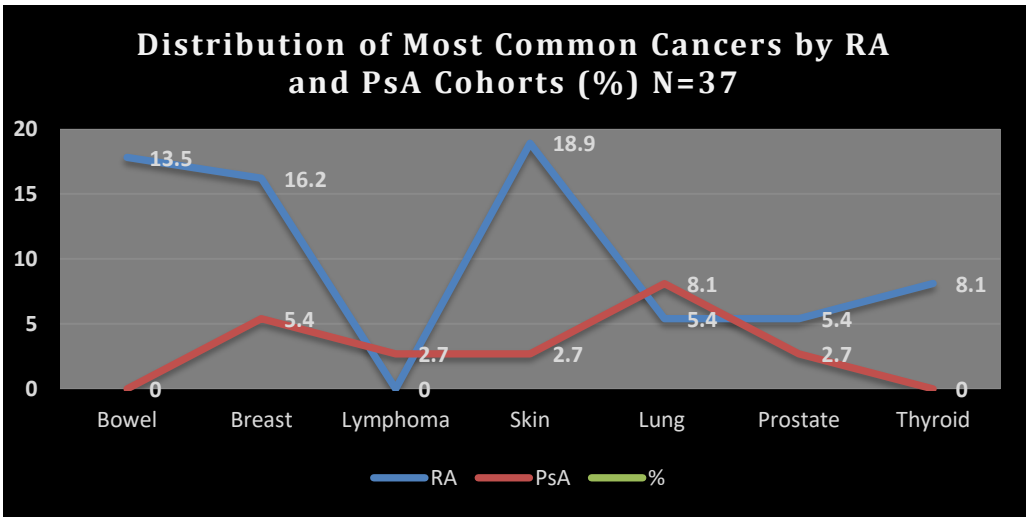
CHAPTER 5
DISCUSSION

5.1 Discussion of the Study Results

In this retrospective study, we investigated the incidence of malignancy among 700 patients diagnosed with Psoriatic and Rheumatoid Arthritis and compared our incidence rate to the incidence rate of cancer in the NL general population.

Inflammatory Arthritis is reported to be the third most common chronic condition in adults in NL (25.4%) (http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health52b). The province also continues to have the highest cancer incidence rates per capita in the country (586.8/100,000) with 3,900 new cases annually); http://www.cancer.ca/en/cancer. Despite these facts, there is a paucity of published information on the incidence of malignancy in this population in Newfoundland and Labrador. We were not able to find studies that compared the risk of malignancy between these two Immune Mediated Diseases: Psoriatic Arthritis and Rheumatoid Arthritis and the Newfoundland and Labrador general population. To our knowledge this is the first epidemiological study of this kind in NL.

Graph 5.1



During this four-year study period of 200 PsA (28.6%) and 500 RA (71.4%) patients, several key observations were made. We did not find any significant difference in the cancer rate between our study and the NL general population (P= 0.3217). Our findings are consistent with prior published studies. In 2014, Fagerli and colleagues used the British Society for Rheumatology Biologics Register (BSRBR) to investigate the risk of cancer in 709 Psoriatic Arthritis patients treated with TNFi. Their study findings suggested that there was no overall increased risk of malignancy compared with the general population. Although, a significant increased incidence for non-melanoma skin cancer (NMSC) was reported in their study. Similarly, in 2008, Lydia Abasolo and colleagues used the EMECAR cohort to investigate the incidence of cancer in 789 RA patients from Spain. The study reported that the overall incidence of cancer was not greater than the expected rate in the general population; even though, - there was a significant increased risk of

hematopoietic (SIR=5.4, CI,1.1-15.7) and lung cancers (SIR =3.5, CI,1.4-7.1). In 2016, in a longitudinal cohort study of 8,439 PsA patients, Hagberg et al. used the Clinical Practice UK Research Datalink to assess the incidence of solid and hematologic cancers. The study findings showed similar cancer rates of solid and nonmelanoma skin cancers in patients with PsA compared with non PsA patients. However, the rates of hematologic cancer in their study were significantly higher in the PsA cohort (P=0.011). In Canada, Cibere, Sibley, & Haga (1997) conducted a 35-year prospective study of RA patients (n=862) to determine the relative risk of malignancy. The authors reported the incidence rates for non-Hodgkin's lymphoma and all other site-specific malignancies not to be significantly different from the general population.

A total of 37 malignancies were documented in our study. Of these, 34 (91.9%) were solid cancers and 3 (8.1%) were hematologic cancers. The most commonly observed cancers were Skin and Breast cancers (21.6% each), followed by Bowel and Lung cancers (13.5% each). Two Lymphomas and three Thyroid cancer cases were documented in our RA female population. One case of Myeloblastic Leukemia was reported among males in the PsA cohort. These findings reflect the data from the Canadian Cancer Statistics (2015), reporting Breast cancer being the leading cancer in women in NL (http://www.cancer.ca). Rohekar et al. (2008), in a 26-year prospective cohort to determine the prevalence of malignancy in PsA patients, reported that the incidence of malignancy in their study did not differ from that in the general population. The most frequent types of cancer in this study were breast, lung, and prostate cancers. In a 5-year retrospective single center study of 399 patients, Fanto et al. (2015) evaluated the risk of malignancy in 399 patients with Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis. The overall cancer

risk in this study was not significantly increased compared to the general population. However, RA females undergoing immunosuppressive therapy had a significantly heightened risk of hematologic malignancies than expected (SIR = 6.9, 95% CI, 1.88-17.66). Our study findings do differ from other studies that have reported an increased cancer risk in their study population. For instance, in the reviewed literature Chen et al. (2011) observed 935 cancers in patients with RA. Their study results showed that patients with RA had a significant increased risk of cancer (SIR= 2.74, 95% CI, 2.68–2.81). Among hematologic cancers, the risk of non-Hodgkin's lymphoma was greatest (SIR= 3.54, 95% CI, 3.45–3.63). Such differences in results between their study and ours could be explained by several factors. The Chen et.al. (2011) study had a longer duration of follow up compared to ours (11years vs 4 years) allowing more time for a rare event such as cancer to occur. The larger sample size of 23,644 vs 700 patients in our study gave their study more power to detect differences between groups. However, their study was also limited by an inadequate adjustment for important prognostic factors that might have likely impacted the validity of their results. Several important confounding factors such as smoking, alcohol use and body mass index were not adjusted for. The authors of this study also relied on the nation database for patients recruitments, which could have allowed for misclassification bias to occur.

There was no significant difference in the proportion of incident cancers between our PsA and RA patients (P=0.709). In 2014, Gross et al. reported similar findings. In their observational study of 2,970 patients with PsA and 19,260 patients with RA, authors reported similar cancer rates between their cohorts (P= 0.864). Just like in our study, Skin cancer was also reported to be the most common cancer in their cohort. Whilst there was

an equal distribution of Lymphoma between the two cohorts in this study (P=0.668), we reported Lymphoma only among RA female patients. Differences in our findings can possibly be explained by the larger and diverse sample of their population, as well as the longer duration of their study (seven years).

The overall risk of developing cancer was significantly lower in patients treated by combination of biologics TNFi and bDMARDs (OR=0.3, 95% CI, 0.02-0.44, P=0.003). Mercer et al. (2015) in a five-year prospective study investigated RA patients enrolled in the British Society for Rheumatology Biologics Register. They compared the risk of solid cancer in RA patients treated with TNFi (n= 11,767) to that in patients treated with DMARDs (n=3,249). The authors did not find any difference in risk of solid cancer for TNFi compared to DMARD treated patients: They concluded that the addition of TNFi to DMARDs does not alter the risk of cancer in RA patients. Monotherapy with Etanercept showed significant lower risk of cancer in RA patients as compared to other biologic drugs (OR =0.10, 95% CI ,0.01-0.89, P=0.039). In 2017, Lan et al. conducted a retrospective population-based study of RA patients treated with TNFi. The main objective of their study was to explore the safety profile of TNFi and identify the potential benefit of Etanercept on the incidence of cancer. Their findings are reflective of our study findings, showing a reduced cancer risk in RA patients treated with Etanercept (HR =0.59, 95% CI, 0.36–0.98, P= 0.04). Similarly, in 2014, Morgan and colleagues in a prospective cohort of RA patients in the UK, examined the long-term safety of Etanercept in comparison with conventional DMARDs. Their study suggested that treatment with ETN was associated with improved survival, reduced risk of lymphoproliferative malignancy and a lower rate of cardiovascular events. Monotherapy with Rituximab in our study showed marginally non-significant

increased cancer risk. However, since all Lymphomas and Breast cancers were diagnosed among patients who had exposure to this drug, the drug is still highlighted below. The author of this thesis believes there could be some degree of clinical relevance to this finding. Generally, Rituximab has been reported by most studies as a safe and effective drug that had shown no association with an increased risk of cancer (D. R. Chen & Cohen, 2012); (van Vollenhoven et al., 2010). However, two studies were found whose findings mirror those of ours. A study done by Tarella et al. (2010) examined the long-term outcome of a large series of patients with Lymphoma who received an intensive chemotherapy schedule (with or without addition of four to six doses of Rituximab). In their study, Rituximab addition was associated with a significant increased risk of solid tumor occurrence (SIR = 3.19, 95% CI, 2.50 - 4.06, P= <0.001). Conversely, Rituximab in their study also had a significant protective role on the risk of death. Aaltonen et al. (2015) conducted a study to assess the incidence of serious infections and malignancies among patients with rheumatoid arthritis (RA) receiving either TNF inhibitor or rituximab (RTX) therapy. They reported the crude rates of malignancies to be highest among the patients treated with RTX (IR 9.5, 95% CI 3.8–20). In addition, all biologicals but RTX were associated with decreased risk for malignancy. However, after adding age and sex into the statistical model, the effect disappeared.

5.2 Pharmacokinetics of Rituximab

Rituximab is a B - lymphocyte-depleting agent. It was funded and developed by the National Cancer Institute (NCI) in 1997 to treat hematologic cancers mainly non-Hodgkin Lymphoma (NHL) and chronic Lymphocytic Leukemia (CLL) https://www.cancer.gov/ and since been approved by the US Food and Drug Administration

and the European Medicines Agency in Europe for the treatment of RA in patients with poor response or intolerance to Tumor Necrosis Inhibitors (TNFi). Rituxan works by primarily targeting a protein called CD20, which is found on the surface of white blood cells called B-lymphocytes (B-cells) (D. R. Chen & Cohen, 2012). Locking of Rituximab on to CD20, triggers the body's immune system to attack the cells and destroy them. Unfortunately, such process destroys not only the abnormal (malignant) B-cells (that occur in many types of NHL and CLL) but also the normal B-cells - a process known as B-cell depletion (Looney, Srinivasan, & Calabrese, 2008). However, once treatment is complete the body supposedly can replace the normal B-cells over a certain time frame, a process that can usually take up to twelve months (Looney et.al., 2008). This can lead to a question as to how vulnerable patients' immune systems are during this window. Under normal circumstances antibodies such as B-cells are produced by the immune system to help fight infections and cancer formation. It is possible that more time is needed to see if repeated B-cell depletion is a safe and effective long-term treatment plan for Rheumatoid Arthritis and whether artificial interference with the immune system will increase susceptibility to malignancies (D. R. Chen & Cohen, 2012).

Lastly, although the pro-cancer effect of chronic inflammation to initiate tumors has been well documented (Grivennikov et al., 2010), our study outcomes were unable to show any significant association between the developed malignancies and various inflammatory makers (CRP, ESR, DAS, HAQ and TSJC).

Based on evidence from the existing literature, both chronic systemic inflammation (Ben-Neriah et al., 2011), therapy with Biologics (Bongartz et al., 2006) and/or MTX (Girish, Byrd, Roy, & Mehta 2003) can play a role in cancer formation. The general

perception is that PsA and RA patients who had severe inflammation where more likely to be treated with combination therapy (Biologics and MTX) and thus, were more likely to develop malignancy. In contrast, this study suggests that the risk of developing cancer was significantly reduced in patients treated with combination therapy and was not associated with disease severity. Clinically this can be explained by the effectiveness of combination therapy on the treatment of severe inflammation. According to literature severe inflammation is a known cancer risk factor (Ben-Neriah et al., 2011). By effectively treating severe inflammation and diminishing disease severity, a cancer risk factor is also eliminated. Statistically, the small number of events and short duration of follow up in our study could have affected our study results. Therefore, we cannot completely rule out potential associations that can be clinically significant.

5.3 Study Strengths Obstacles and Limitations

5.3 a) Study Strengths

The main strength of our study is that patients were seen in a real-world setting by a Canadian rheumatologist during routine clinical practice, which enhances the generalizability of the results to the target population. The patients came from across the province and were regularly treated and followed up in the Rheumatology clinic. To our knowledge, this is the first epidemiologic study in Newfoundland and Labrador to examine the incidence rates of malignancy in and between two-immune mediated inflammatory diseases (PsA and RA). In addition, our study had:

A relatively large sample size (N=700).

A geographic diversity with patients from various parts of the province.

A wide age range of the participants ranging from 21 to 96 years of age.

We used internationally standardized tools such as PASQ, HAQ, and DAS 28 to measure disease severity.

5.3 b) Obstacles

One of the challenges of clinical charts reviews is reliance on extracted data that was originally collected for reasons other than research. Obstacles included: incomplete documentation, missing charts, information that was unrecoverable or unrecorded, difficulty interpreting information found in the documents (e.g. acronyms, photocopies), etc. Out of a total of 805 eligible PsA and RA charts 2.7 % were missing and 6.5% were excluded from the study due to incomplete or difficulty in interpreting information that was relevant to the study (Fig.3.1). It is possible that some cancer patients could have been

missed with the exclusion of this charts. Such exclusion might have negatively affected the numbers of cancers in our study.

5.3 c) Limitations

Our study has several limitations that would be important to note. There is a potential bias given the observational nature of the study, a bias that is avoided when using data from clinical trials. Without a random assignment to treatment it is difficult to infer causation between a drug of interest and risk of cancer occurrence. Confounding by indication may exist and may be responsible for differences between groups. Although our sample size of 700 people with PsA and RA is a representative sample of total NL population affected by arthritis; we cannot entirely exclude sampling bias. There is a possibility that patients seen at our specialty rheumatology clinic were more likely to have been healthier and were able to travel to the facility than the general population who might have consisted of sicker people been hospitalized for other comorbidities.

Even though, all efforts were made to meticulously go through all 700 patients' charts, author cannot completely be certain that all patients with previous cancer were excluded. A prevalent sample of patients with PsA and RA was used to investigate cancer risk only for a period of 2011-2014. Some patients might have had the disease long before the study period. The variability of disease duration in these patients was between 9-13yrs. For example, patients with longer diseases duration could have more than one clinical chart which could have been archived and was beyond the authors reach.

We cannot entirely rule out that some malignancies may have not been captured. Approximately 9.0 % of our eligible study population charts were excluded due to incomplete information or missing charts. Such might have led to a possible selection bias. Furthermore, the main objective of our study was to investigate newly developed cancers during our study period (2011-2014). Because of this we excluded patients with previous history of cancer from the study analysis. Patients with previous history of cancer are at high risk of developing a second cancer, by excluding this patient we could have lowered the cancer rates in our study population compared to controls who would have more cancers due to long life observation. However, this did not affect our study result as we did not find any difference in cancer rates between our study population and the general population.

In this study, we did not have information on when patients started taking medication, switched over to new medication or stopped their treatment. Therefore, we only investigated the association between patients with history of exposure to treatment and cancers. The lack of detailed medication information limited us in our study analysis. For example, we were unable to do a time to event analysis and measure the effect of treatment overtime on cancers which would have provided us with more robust study results. It is also likely that patients might have been exposed to more than one medication at a time as most PsA and RA patients are known to be taking concomitant medication, therefore cross over medication effect cannot be completely ruled out.

We did not have personal information on patient's family history of cancer or their socio-economic status at the time of the study. Neither history of alcohol

consumption or other chronic diseases such as diabetes that can contribute to cancer formation. Patients with past family history of cancer have a greater risk of developing a second cancer. However, we would like to rule out prescription bias as we relied on the knowledge and judgement of the physicians that high risk cancer patients were not treated with TNFi or any other immunosuppressants and were not included in this study.

Not been able to adjust for confounders such alcohol use and diabetes in the study was a big limitation. According to the National Institute of Health (NIH) https://www.cancer.gov/ there is a strong scientific consensus of an association between alcohol drinking and several types of cancer such as (Breast, Colorectal, Esophageal etc.). Comorbidities such as Diabetes (especially type 2) has also been associated with an increased risk for some cancers such as liver, colon, breast and bladder cancers (Shikata, Ninomiya & Kiyohara, 2013).

The four- year duration of our study, although sufficient, was not long enough to look at incidence cancers as an outcome.

We chose to combine multiple cancers together in our outcome. One advantage of this is that the larger number of events increases statistical precision. However, the disadvantage is that the effect of specific cancer rates is obscured in analysis of the composite measure.

5.3 d) Knowledge Translation

The knowledge gained from this study was translated at local and international levels. Locally, the study protocol was disseminated by presenting to co-peers and faculty

during Clinical Epidemiology Seminar Series. The study findings were also presented via poster presentation at the 2018 "Annual Aldrich Interdisciplinary Graduate Research Conference" (Memorial University of Newfoundland). Internationally, the study abstract was accepted for publication by the Annual European Congress of Rheumatology (EULAR 2018, Amsterdam, Netherlands). In the future we plan to further share our research findings with health care providers involved in the circle of RA and PsA patients care (rheumatologists, public health nurses, medical students/residents). Since this is the 1st study of this kind in the province, our findings (especially on treatment and risk of cancer) might be both interesting and useful to health care providers. This knowledge translation could help generate useful debates and discussions contents of which might be used for future cancer risk research in the NL population. It can also help raise awareness of this issue as well have a direct impact on patients quality of care.

5.4 Suggestions for Future Studies

A prospective longitudinal study, with information from various settings in the province, will be a better study design to look at the complete assessment of the relationship between cancer and patients with Psoriatic and Rheumatoid Arthritis.

During our research, we discovered an information gap on the prevalence of cancer rates in the Newfoundland and Labrador general population. Knowing cancer prevalence for a province that has one of the highest cancer rates in Canada will help with better planning for health care needs for the prevalent population with cancer and cancer survivors.

Though a lot of work has been done by researchers to understand factors causing Rheumatoid Arthritis, the etiology of this chronic condition that lasts a lifetime is still unknown. Conducting a study that would try to better understand these factors in the NL population can help prevent future occurrence and burden of this disease in the province.

5.5 Conclusion

This study suggests there is no significant difference in the cancer rate between our study and the NL general population. We also concluded that the analyzed data was reassuring due to OR values less than 1 (OR 0.3, P=0.003) for combined therapy of MTX and Biologics. Our study suggests further research on Rituximab is warranted. Even studies that have considered this drug to be safe and well tolerated, have advised of continuous and long-term monitoring and that only continued use and regular surveillance will show if repeated B-cell depletion is as safe as it now appears (D. R. Chen & Cohen, 2012). The Canadian Cancer Society 2016 report showed the age standardized Incidence cancer rates (ASIR) for males and females to be highest in Newfoundland and Labrador (610.7 per 100,000) http://www.cancer.ca/en/cancer. Inflammatory Arthritis is already a major public health burden, an addition of a cancer diagnosis will likely increase disease burden. Our findings add to the existing body of knowledge about Inflammatory Arthritis and incidence rates of cancer in the targeted population. More epidemiologic studies are required to determine the cancer prevalence in NL population.

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APPENDICES

APPENDIX A:
Description of Disease Activity Measuring Tools

DAS 28- Joint Disease Activity Score (DAS28): is a well-established and validated tool that has been largely used to determine both disease activity and treatment response in both PsA and RA patients (Salaffi et al., 2014). This tool provides a global summative and continuous score for disease activity assessment and has been widely used in clinical trials as well as in practice (Heijde et al., 1993).

The DAS28 scores provides ranges that corresponds to high, moderate, and low disease activity (table 1 and figure 1). High disease activity relates to DAS28 >5.1, moderate to DAS28 of >3.2 to 5.1, low disease activity is regarded in the range of 2.6 to 3.2. A cut-off points for "remission" has also been proposed (DAS28 <2.6). (www.uptodate.com)

DAS-28 Interpretation

DAS-28 <2.6:	Remission
DAS-28 >=2.6 and <=3.2:	Low Disease Activity
DAS-28 >3.2 and <=5.1:	Moderate Disease Activity
DAS-28 >5.1:	High Disease Activity

The CASPAR Criteria: Is a diagnostic criterion based on 7 points that can be used to classify a patient as having psoriatic arthritis (PsA) (Taylor et al., 2006)

A patient with inflammatory musculoskeletal disease such as peripheral arthritis, spondylitis, or enthesitis can be classified as having PsA, if a total of at least three points is accumulated from the presence of the following list of features each of which is assigned a certain number of points:

1) Skin psoriasis that is: - Present – 2 points, OR
2) Previously present by history – 1 point, OR
3) A family history of psoriasis, if the patient is not affected – 1 point
4) Nail lesions (onychosis, pitting) – 1 point
5) Ductility's (present or past, documented by a rheumatologist) – 1point
6) Negative rheumatoid factor (RF) – 1 point
7) Juxta-articular bone formation on radiographs (distinct from osteophytes) – 1 point

Health Assessment Questionnaire (HAQ): is a comprehensive instrument designed to assess patient' disability, discomfort, medication side effects, costs, and mortality (Smolen & Aletaha., 2012) www.uptodate.com

It is used frequently used in clinical trials and clinical practice to evaluate patients' ability to perform activities of daily living through their answers to 20 questions designed to assess upper or lower extremity use. These questions are organized into eight categories: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Each question is answered on a four-level scale of impairment ranging from 0 to 3: 0 = no difficulty; 1 = some difficulty; 2 = much difficulty; and 3 = inability to do activities of daily living (Smolen &Aletaha., 2012) www.uptodate.com

The final HAQ index, which ranges from 0 to 3, is the mean of scores from all eight categories. HAQ scores <0.3 are considered normal, however, the mean HAQ of the population rises with age. A higher HAQ scores indicate increasing disability.

Psoriasis and Arthritis Screening Questionnaire (PASQ): is a sensitive and specific self-administered tool used for the Diagnosis of Early and Established Psoriatic Arthritis and to measure the degree of inflammatory symptoms. The PASQ questionnaire and diagram (Khraishi et.al., 2010) consists of 10 questions for which a positive and negative response are assigned a score of 1 and 0, respectively, with a maximum score of 10. Patients are also asked to indicate on the diagram where they experienced joint swelling or pain either at screening or in the past the diagram is scored 0, 1, 3, or 5, depending on the distribution of the patients' markings. Separate scores for the questionnaire (maximum of 10) and the diagram (maximum of 5), are recorded as a composite score for each subject.

APPENDIX B: Ethics Approval and Renewal Letters

NEWFOUNDLAND AND LABRADOR
HREB
HEALTH RESEARCH ETHICS BOARD

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

September 22, 2014

Dr Alyona Lewis
300 Prince Philip Drive
Memorial University of Newfoundland

Dear Dr. Lewis

Reference #14.188

Re: The Prevalence Rates of Precancerous Lesions and Malignancy in Patients with Psoriasis and Inflammatory Arthritides Compare to the General Population

Your application received an expedited review by a Sub-Committee of the Health Research Ethics Board and **full approval** was granted effective **September 19, 2014.**

This approval will lapse on September 19, 2015. **It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HREB office prior to the renewal date; you may not receive a reminder, therefore the ultimate responsibility is with you as the Principle Investigator.** *The information provided in this form must be **current to the time of submission** and submitted to the HREB **not less than 30 nor more than 45 days** of the anniversary of your approval date.* The Ethics Renewal form can be downloaded from the HREB website http://www.hrea.ca.

This is to confirm that the following documents have been reviewed and approved or acknowledged (as indicated):

- Application approved

The Health Research Ethics Board advises THAT IF YOU DO NOT return the completed Ethics Renewal form prior to date of renewal:

- *Your ethics approval will lapse*
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*

email: info@hrea.ca Phone: 777-6974 FAX: 777-8776

Lapse in ethics approval may result in interruption or termination of funding

It is **your responsibility to seek the necessary approval from the Regional Health Authority or other organization as appropriate. You are also solely responsible for providing a copy of this letter, along with your application form, to the Office of Research Services should your research depend on funding administered through that office.**

Modifications of the protocol/consent are not permitted without prior approval from the Health Research Ethics Board. Implementing changes in the protocol/consent without HREB approval may result in the approval of your research study being revoked, necessitating cessation of all related research activity. Request for modification to the protocol/consent must be outlined on an amendment form (available on the HREB website) and submitted to the HREB for review. This research ethics board (the HREB) has reviewed and approved the research protocol and documentation as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Health Research Ethics Board currently operates according to *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*; *ICH Guidance E6: Good Clinical Practice* and applicable laws and regulations. The membership of this research ethics board is constituted in compliance with the membership requirements for research ethics boards as defined by *Health Canada Food and Drug Regulations Division 5; Part C*
Notwithstanding the approval of the HREB, the primary responsibility for the ethical conduct of the investigation remains with you.

We wish you every success with your study.

Sincerely,

Dr Fern Brunger, PhD (Chair Non-Clinical Trials)
Ms. Patricia Grainger, (Vice-Chair Non-Clinical Trials)
Health Research Ethics Board

email: info@hrea.ca Phone: 777-6974 FAX: 777-8776

RECEIVED AUG 2 0 2015 *May 2015*

Health Research Ethics Authority

Request For Ethics Renewal / Study Closure

- **The Tri-Council Policy Statement- Ethical Conduct for Research Involving Humans (TCPS2; 2010) (article 6.14) requires ongoing review by the approving REB at least on an annual basis. The information provided in this form must be current to the time of submission and submitted to the HREA not less than 30 days nor more than 45 days before the anniversary of your approval date.**
- **Ethics approval is required if there is ongoing subject contact or data collection/transfer is active.**
- **Ethics approval is not required and the file may be closed if the project is in analysis or the writing stage.**
- **Please forward a summary of findings or published abstract to the HREA Office once the study is complete.**
- **Incomplete forms will not be accepted and may result in delay in the review and approval process**

HREB Ref Number:14.188	**Expiry Date of Current Approval**
Principal Investigator: Alyona Lewis	
Title of study (with Protocol Number if applicable): The Prevalence Rate of Precancerous Lesions and Malignancy in Patients with Psoriasis and Inflammatory Arthritides compare to the General Population.	
Email of PI : alyonalewis@rocketmail.com **or** afl876@mun.ca	**Email of Key Contact:**

Please chose one:		
OR	*I am requesting renewal of ethics approval for this file.*	X
	I am requesting to close this file.	

Alyona Lewis — Name typed or printed

Signature of PI

08/19/2015 — Date (MM/DD/YYY)

For HREB Office Use Only:

This project was reviewed on August 20, 2015 *Date* *By Full Board Review* [ ] *By Expedited Review* [✓]

Ethics approval for this project has been granted for a period of 12 months effective *From* Sept 19, 2015 **to** Sept 19, 2016

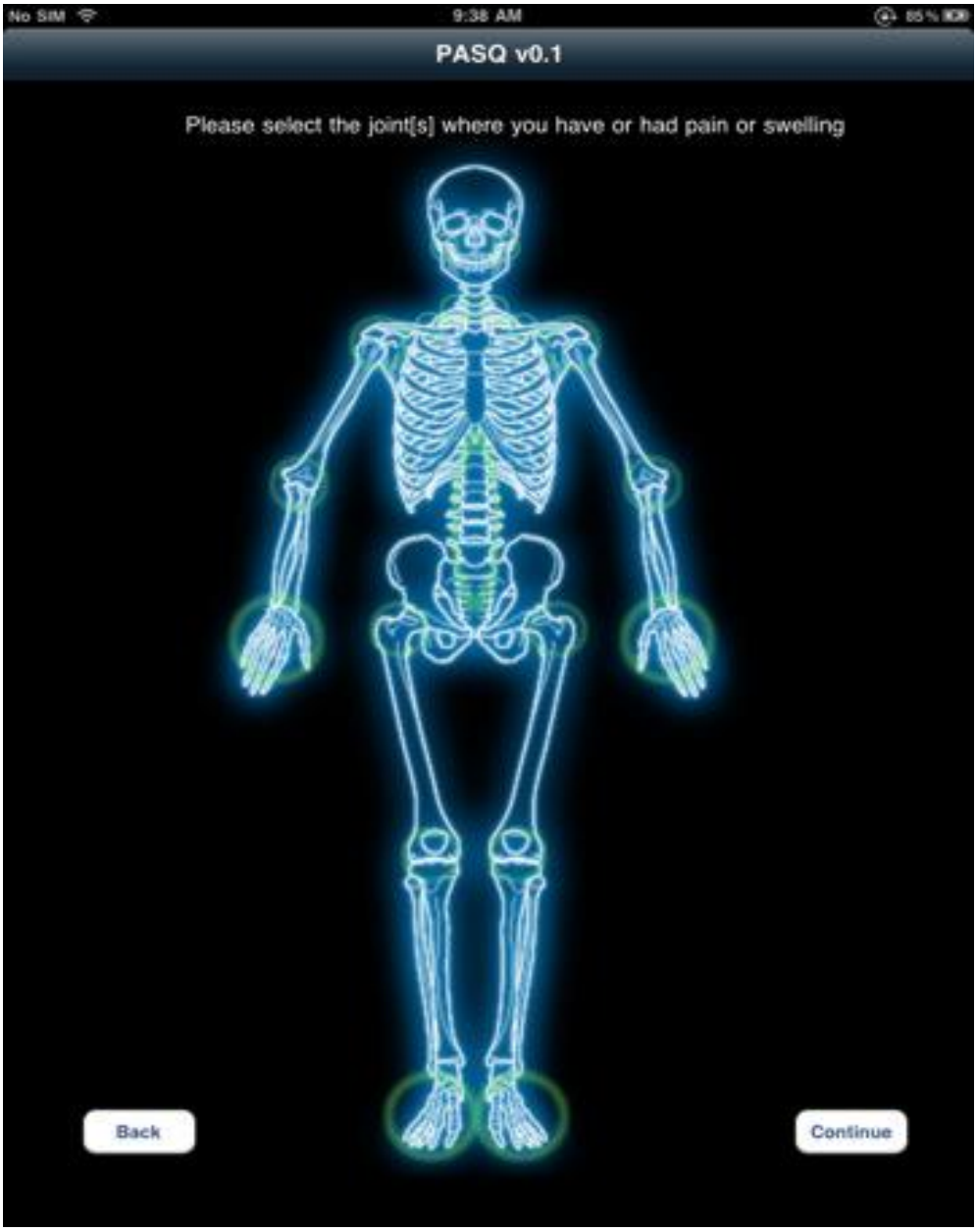
This research ethics board (the HREB) has reviewed and approved the study which is to be conducted by you as the qualified investigator/principal investigator named above. This approval and the views of this Research Ethics Board have been documented in writing. The Health Research Ethics Board operates according to *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, ICH Guidance E6: Good Clinical Practice: Consolidated guideline* and applicable laws and regulations. The membership of this research ethics board is constituted in compliance with the membership requirements for research ethics boards as defined by Health Canada Food and Drug Regulations Division 5; Part C.

This file has been closed as requested [ ]

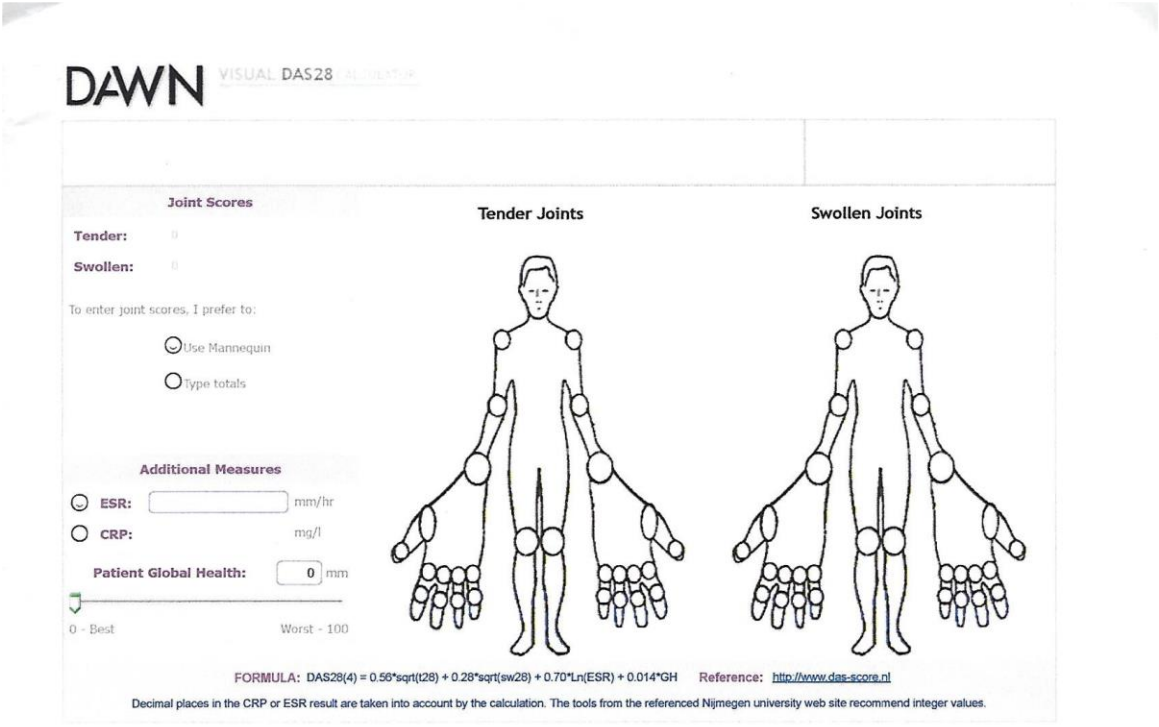
Patricia Granger — *Signature Chair*

APPROVED AUG 2 0 2015 — *Date*

APPENDIX C: Screenshot for PASQ



APPENDIX D: DAS 28 Visual Calculator



http://www.4s-dawn.com/DAS28/DAS28.html

2016-07-28, 12:43
Page 1 of 1

APPENDIX E: Psoriasis and Arthritis Screening Questionnaire

Psoriasis and Arthritis Screening Questionnaire (PASQ) Questions

Question Response

Score for Positive

Response

1. Have you ever thought you might have arthritis? Yes, No 1

2. Have you ever had a swollen joint? Yes, No 2

3. Has a doctor ever told you that you have arthritis? Yes, No 2

4. Are your joints stiff when you wake up in the morning? Yes, No 1

4a. If yes to #4, how long does the stiffness last? ___ min ___ hr 1 if more than 30 min

5. Have you ever had back troubles? Yes, No 0

6. Has your back ever been stiff in the morning? Yes, No 0

7. Do your fingernails or toenails have holes or ‘‘pits’’? Yes, No 1

8. Do your fingernails come loose from the nail bed? Yes, No 1 for any 2 positives

9. Are your nails abnormally thick? Yes, No responses to 7, 8, or 9

10. Does anyone in your family have arthritis? Yes, No 0

10a. If yes to #10, who? 0

APPENDIX F: Health Assessment Questionnaire (HAQ-DI)

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

Name: _____ Date: _____

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
DRESSING & GROOMING				
Are you able to:				
Dress yourself, including shoelaces and buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
Stand up from a straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
Cut your own meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Devices used for Dressing (button hook, zipper pull, etc.)
☐ Built up or special utensils
☐ Crutches
☐ Cane
☐ Wheelchair
☐ Special or built up chair
☐ Walker

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming ☐ Arising ☐ Eating ☐ Walking

- 1 -

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
HYGIENE				
Are you able to:				
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open previously opened jars?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat ☐ Bathtub bar ☐ Long-handled appliances for reach

☐ Bathtub seat ☐ Long-handled appliances in bathroom ☐ Jar opener (for jars previously opened)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene ☐ Reach ☐ Gripping and opening things ☐ Errands and chores

Your ACTIVITIES: To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

COMPLETELY	MOSTLY	MODERATELY	A LITTLE	NOT AT ALL
☐	☐	☐	☐	☐

Your PAIN: How much pain have you had IN THE PAST WEEK?
On a scale of 0 to 100 (where zero represents "no pain" and 100 represents "severe pain"), please record the number below.

☐☐☐

Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (0 represents "very well" and 100 represents "very poor" health), please record the number below.

☐☐☐