HHS Public Access

Author manuscript

Cancer Causes Control. Author manuscript; available in PMC 2015 March 10.

Published in final edited form as:

Cancer Causes Control. 2009 August ; 20(6): 1001–1010. doi:10.1007/s10552-009-9298-y.

Risk of cancer among rheumatoid arthritis patients in California

A. Parikh-Patel,
California Cancer Registry, Public Health Institute, 1825 Bell Street, Suite 102, Sacramento, CA 95825

M. Allen,
California Cancer Registry, Public Health Institute, 1825 Bell Street, Suite 102, Sacramento, CA 95825

R. Cress, and
California Cancer Registry, Public Health Institute, 1825 Bell Street, Suite 102, Sacramento, CA 95825

Department of Public Health Sciences, University of California, Davis, CA, USA

R. H. White
Department of Internal Medicine, University of California, Davis, CA, USA

Abstract

Objective—The objective of this retrospective cohort study was to evaluate cancer risk among rheumatoid arthritis (RA) patients in California.

Methods—The study cohort derived from statewide patient discharge records was followed via linkage with cancer registry data over the period 1991–2002. Age and sex adjusted standardized incidence ratios (SIRs) and 95% confidence intervals were calculated to compare observed to expected numbers of cancers based on age, race, and sex specific incidence rates in the California population.

Results—Among the 84,475 RA patients, who were observed for 405,540 person-years, 5,533 incident cancers were diagnosed during the observation interval. The risk of developing lymphohematopoietic cancer was significantly higher in the cohort for both sexes. Males had significantly higher risks of lung, liver, and esophageal cancer, but a lower risk of prostate cancer. Females were at significantly decreased risk for several cancers including breast, ovary, uterus, cervix, and melanoma, with the risk reduction ranging from 15 to 57% lower than the general population. Hispanics had increased risks of leukemia, vagina/vulva, lung, and liver cancers.

Conclusion—Studies investigating the mechanisms that underlie the reported associations between RA and specific cancer types are needed.

Introduction

Rheumatoid arthritis (RA) is the most common systemic autoimmune disease, affecting an estimated 1% of the population over 18 years of age [1]. The disease is characterized by inflammation of the synovial membrane of multiple joints, often leading to joint destruction, deformity, and loss of function [2]. Epidemiologic studies have estimated the frequency of various cancers in patients with RA to range from 2 to 15% [3]. Overall, the incidence of cancer does not appear to be significantly elevated among RA patients, and over the past 30 years, cancer risk estimates reported by large cohort studies of RA patients have ranged from 0.96 to 1.7% [4–7]. However, there is a growing body of evidence which suggests that risk for specific types of cancers may be elevated in the RA population [4–7].

Individuals with RA appear to have higher risks for developing lymphohematopoietic malignancies, with some studies reporting two to eightfold increases in risk of non-Hodgkin's lymphoma (NHL) [8], leukemia [9, 10], and multiple myeloma [11]. With respect to solid tumors, increased risks of lung cancer [12] and melanoma [13] have been reported. Several studies have observed lower risks of colon and stomach cancers among people with RA [4, 5, 14, 15], supporting the hypothesis that the use of aspirin or other nonsteroidal anti-anflammatory drugs may protect against colorectal cancer occurrence [16].

Whether the development of malignancies in RA patients is the result of the immunologic imbalances, the inflammatory process, or the use of cytotoxic agents that are frequently used in the treatment of the disease remains controversial. Several small studies which have examined the effects of various treatments such as cyclophosphamide, azathioprine, cyclosporine, and methotrexate on the development of lymphomas in RA patients have reported differing results [17–22].

The objective of this retrospective cohort study was to evaluate both overall cancer risk and risk for specific cancer types in a large population of RA patients in California. This study builds on previous work in this area in part because of its unique ability to examine differences in cancer risk by race/ethnicity. To our knowledge, the present study is the largest such study to date that has examined this question.

Materials and methods

Definition of study cohort and outcomes

The study cohort was derived from the statewide patient discharge data set produced annually by California's Office of Statewide Planning and Health Development (OSHPD). This dataset includes a record for each inpatient discharged from all licensed acute care hospitals and includes information on patient demographics, diagnoses, and procedures. The International Classification of Diseases (ICD-9) coding system is used to record diagnostic and procedural information in the patient discharge data set [23]. Individuals hospitalized during the period 1991–2002 with ICD-9 codes 714.0–714.2 designated in any of the 25 diagnostic fields (principal diagnosis and up to 24 other diagnoses) were included in the analysis. When an individual had multiple hospitalizations, only the first hospitalization for an individual with an RA diagnosis was included in the analysis.

Individuals with RA were followed forward in time to assess patterns of cancer development. Information on subsequent cancer outcomes was obtained through electronic linkage of the patient discharge data set to the California Cancer Registry (CCR) data set for the period 1991–2002. The CCR is a high quality data source, with standardized reporting procedures that have been described in several previous publications [24–29]. The CCR data-base contains information on basic demographic factors, tumor characteristics, and cancer directed surgeries and treatment. Follow up for vital status on patients in the database is conducted through routine linkages with several administrative databases, the primary one being the California statewide mortality file. Based on our current definition of loss to follow-up (no identification of patient through passive follow-up methods for 22 months from date of dataset creation), we estimate that ~ 3–5% of our cases are lost to follow up.

The two data sets were electronically linked using Integrity software [30] and a combination of deterministic and probabilistic linkage strategies. The primary variables used to link the two data sets were social security number, date of birth, sex, and residential zip code. Based on prior linkages of these data sets, we estimate that our algorithm identified 95–99% of the cancer cases among RA patients [31].

Statistical analysis

Descriptive statistics were generated for both the entire cohort and those that were diagnosed with cancer during the study period. Person-years at risk were calculated for each individual. Time from the first hospitalization with a diagnosis of RA to one of the following three events (whichever occurred first) was calculated: date of cancer diagnosis, date of death, or the end of the calendar year 2002. Cases lost to follow-up were also censored 22 months after diagnosis if they had no updated identification data. The expected number of cancers was calculated by sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and non-Hispanic Asian/Pacific Islander) and 5-year age group using rates from the general California population for the same time period. Standardized incidence ratios (SIRs), or the ratio of observed to expected cancers, and their 95% confidence intervals were calculated for all major cancer types. Estimates were generated assuming that the numbers of observed cancers follows a Poisson distribution [32]. All estimates were adjusted by sex, age, and race/ethnicity. SIRs for each cancer type were calculated separately for males and females as there were some differences in risk estimates between the groups. Additionally race and age-group specific SIRs were calculated for selected cancer types.

Cancers which occurred within six months of the date of hospitalization were excluded from the analysis in an attempt to establish a temporal sequence between the RA diagnosis and subsequent cancer development. When this period was expanded to one year, we observed minimal differences in the results and, therefore, we chose to exclude only the first six months of follow up to increase statistical power.

In order to assess the internal consistency of our RA diagnoses across multiple hospitalizations, we examined the number of hospitalizations for each individual that recorded a diagnosis of RA after the initial hospitalization for RA, relative to the total number of times an individual was hospitalized.

Results

The cohort consisted of 84,475 individuals with RA who were observed for a total of 405,540 person-years. The average length of follow-up was 4.8 years. Over 98% of individuals in our cohort, who were hospitalized more than once, had an RA diagnosis recorded for every hospitalization (data not shown). Approximately 60% of individuals had RA listed as the primary or secondary diagnosis for their hospitalization. A total of 5,533 patients were diagnosed with cancer during the study period. As shown in Table 1, 77% of the cohort was female and the majority of individuals were 60 years of age or older and non-Hispanic white. The largest minority group was Hispanic, comprising approximately 14% of the study population.

A larger proportion of males (9.4%) were diagnosed with cancer compared to females (5.7%), but the overall cancer risk in the men was not significantly different from that observed in the general population (Table 2). The overall age-adjusted incidence of cancer among females in the cohort was 15% lower than that in the general California population. Both men and women had significantly greater risks of being diagnosed with NHL, and leukemia, with the risk estimates for males being substantially greater compared to females. Only males had a statistically significant increased risk of Hodgkin's disease. Males had a two and threefold greater risk of NHL and Hodgkin's disease, respectively, compared to men in the general population. We did examine NHL by two subtypes: large B-cell and follicular. We found no significant differences by subtype for either males or females. With respect to solid tumors, males had significantly increased risk of lung (SIR = 1.65, 95% CI: 1.49, 1.81), liver (SIR = 1.85, 95% CI: 1.26, 2.61), and esophageal cancer (SIR = 1.78, 95% CI = 1.24, 2.46), but lower risk of prostate cancer (SIR = 0.67, 95% CI: 0.60, 0.74). Females also had increased risk for lung cancer (SIR = 1.28, 95% CI = 1.19, 1.38), but significantly decreased risk for several cancers including breast, ovary, uterus, cervix, and melanoma, with the risk reduction ranging from 15 to 57% lower than the general population. Both males and females had a lower incidence of colon cancer relative to the general California population.

Risks for selected cancer types by race/ethnicity are summarized in Table 3. Both Hispanic women and non-Hispanic white women had significantly decreased risks of breast cancer, with risk reduction ranging from 24 to 38%. However, Hispanic women had an almost threefold higher risk of vagina/vulva cancer compared to the general population (SIR = 2.71, 95% CI: 1.48, 4.55). Lung cancer risk was significantly elevated for all non-Hispanic white and Hispanic patients, as well as for Asian males. The risk of esophageal cancer was significantly increased only among non-Hispanic white males (SIR = 1.79, 95% CI: 1.20, 2.57). Both Hispanic males and Hispanic females had over double the risk of liver cancer relative to their counterparts in the general population. Although Hispanic and non-Hispanic white women had increased risks of NHL, the magnitudes of the SIRs for NHL among males of all race/ethnicities were higher, ranging from 2.01, for non-His-panic whites, to 3.08, among non-Hispanic blacks. With respect to Hodgkin' disease, only non-Hispanic white males were at significantly increased risk. All Hispanic patients, non-Hispanic white males, and Asian females had elevated risks of leukemia.

Table 4 presents risks of selected cancers stratified by age group and sex. Analysis of breast cancer risk by sex revealed disparate results. Women under 40 years of age had significantly increased of breast cancer (SIR = 2.19, 95% CI: 1.39, 3.28), while those in the older age groups had significantly decreased risks relative to the general population, with risk reduction ranging from 23 to 64%. Women under 40 years of age also had significantly decreased risks of vagina/vulva cancer (SIR = 4.94, 95% CI: 2.00, 10.18). Individuals in the 40–59 and 60–79 age groups had significantly increased risks of lung cancer, esophageal cancer, NHL, and leukemia. Individuals in the 40–59 age groups exhibited three to fourfold increased risk of liver cancer.

Discussion

Consistent with several prior cohort studies [3, 5, 6, 14, 33–35], the risk of developing a lymphohematopoietic cancer including NHL, Hodgkin's disease, and leukemia was significantly higher in our cohort relative to the general population, with a higher relative risk observed among males than females. The higher risk among male RA patients compared to female RA patients has been previously reported [4, 5, 13, 33, 34]. Gridley et al. reported an SIR of 2.6 for lymphohematopoietic cancers among males with RA and no increased risk for females [5]. Isomaki et.al had similar findings with a 2.5-fold increase in leukemia among male RA patients and no significant increase for females [4].

It has been hypothesized that the risk of lymphohematopoietic disorders in RA is associated with increased disease activity [36, 37]. A nested case-control study conducted in a Swedish population identified RA patients with high inflammatory activity and reported an odds ratio of 25.8 for lymphoma compared to individuals with lower disease activity [36]. A study of RA patients with Felty's syndrome (a complication of seropositive RA) found a 12-fold increase in NHL among men [13].

The role of RA therapies in the development of lymphoma, leukemia, and other cancer types has been a subject of much debate and study [21, 38–41]. Although some studies have associated the use of these immunosuppressive drugs with an increased risk of malignancies [21, 38, 42], others have not found any significant differences between RA patients treated with these agents and the control groups [18, 19, 43, 44]. Many of these studies had serious methodologic deficiencies, including lack of an appropriate control group and insufficient statistical power to draw conclusions. The issue is further confounded by the fact that RA patients with the most severe disease are the patients who are most likely to be treated with a cytotoxic agent, which makes it difficult to distinguish the increased risk of cancer due to the natural history of the disease from the risk conferred by the use of medications. Because we had no treatment information available for our cohort, we were not able to evaluate the potential effect of treatment on cancer risk.

The increased risk of lung cancer observed among both males and females in our cohort were similar to the results of several other large studies [4, 5, 13, 33]. Case reports have postulated that RA patients with interstitial lung disease may be at increased risk of lung cancer [45]. The observed increase in lung cancer among RA patients may be due to the shared risk factors. Recent studies have suggested that smokers are at greater risk for

developing RA [46–48]. We had no information on smoking history or current smoking status for our study population and therefore were not able to compare smoking rates in our cohort with statewide rates. The increased risks of esophageal and liver cancer that were observed in male patients with RA have not been previously reported. It is possible that the observed increase in esophageal cancer may be due to higher smoking rates in our cohort, although we had no information about this. The observed increased risk of liver cancer may be associated with hepatitis B or C virus infection. The lower risk of developing colon cancer that we observed in our cohort is consistent with many other studies in terms of magnitude and direction [4, 5, 33], and has been attributed to the use of non-steroidal anti-inflammatory drugs [49, 50].

Rheumatoid arthritis patients in our cohort had decreased risks of several hormone driven cancers relative to the general California population. Among men, the risk of prostate cancer was reduced. Women had a lower risk of all gynecologic cancers as well as melanoma. Recent studies suggest that RA patients treated with immunosuppressive agents such as methotrexate are actually at increased risk of melanoma [51], which is counter to our finding if we assume that many of our hospitalized patients have severe RA and are being treated with these agents. Although only one previous large cohort study reported a significantly decreased breast cancer risk among RA patients similar to ours [33], other studies have reported results that are suggestive of such an association [5, 7, 35, 52]. The reasons for these decreased risks are unclear. One possible explanation is that the cohort members had fewer of the known risk factors for these cancers than the referent group. Unfortunately, we had no information on risk factors such as smoking, diet, obesity, or reproductive history in order to evaluate this finding. A growing body of evidence suggests that the widespread use of non-steroidal anti-inflammatory agents may have a protective effect on cancers of the breast, prostate, and uterus [53–58], which is another possible explanation for our results. The lower risks of hormone-related cancers could also be related to endogenous hormone levels, which have also been implicated in RA risk and disease severity [59–62]. The risk of several cancer types were elevated among Hispanics in our study, compared to the statewide Hispanic population in California. Since no previous research has stratified cancer risk among RA patients by race/ethnicity, further analysis of factors that influence differences in cancer risk across race/ethnic groups is needed.

As individuals in our study aged, their risk of developing several types of cancer decreased relative to their counter-parts in the general population, with individuals 80 years of age or older having a lower risk of cancer in many cases than people of the same age in the statewide population. This finding can probably be attributed to the healthy cohort effect. Given that these RA patients survived past age 80 years, their overall health may be better than the general population. Conversely, the high risks seen in younger patients with respect to cancers of the breast, vagina/vulva, and liver may be due to the fact that they represent a sicker population of individuals than the general statewide population, or that they have more of the risk factors for these particular cancer types. An alternative explanation is that younger RA patients may be treated more aggressively and thus exhibit greater immunosuppression.

Our study has several strengths, including the use of a large and diverse population to study cancer risk among RA patients. We were able to confirm the risks of various cancers types with more precise estimates than previous studies which did not have the ability to detect risk differences for rarer cancers. In addition, ours is the first study with the statistical power and diverse population to be able to stratify cancer risk in RA patients by cancer type, sex, race/ethnicity, and age group.

The present study does have some important limitations. Only individuals who required a medical hospitalization were included in this RA cohort, which may limit the generalizability of our results. However, the fact that the observed SIRs of several cancers, with lymphohematopoietic malignancies in particular, are comparable to other studies that analyzed non-hospitalized RA patients supports the assumption that the cohort we analyzed is representative of RA patients in general. Also, despite the large size of this study, it should be acknowledged that the sample size was small for examining associations with certain cancers. This limited power may also account for statistically significant findings in some race/ethnic subgroups, but not others. It is also possible that multiple comparisons or chance may account for some of the findings.

Although we were not able to verify the RA diagnoses in the hospital discharge data, the diagnosis codes had very high levels of internal consistency among repeat hospitalizations for the same individuals. One validation study using Medicare physician claims data reported 90% sensitivity for RA claims using the medical record as the gold standard [63]. In addition, the use of hospitalization data raises the issue of surveillance bias; this does not appear to be an issue in the present study, however, as the risk estimates for screenable cancers such as prostate, breast, and cervix were actually lower than the risk for the general population. There is also the potential for selection bias if prevalent or undiagnosed RA cases were hospitalized for symptoms caused by an unrecognized neoplastic disease [64, 65]. We attempted to address this by excluding cancers that occurred within six months of the follow up period. We were also limited to examining differences by age at hospitalization, rather than age at initial RA diagnosis; it is possible that some patients in the cohort may have been diagnosed with RA prior to 1991, which would affect person-time estimates. Finally, we did not have detailed information about risk factors or RA disease and treatment characteristics.

This study confirmed previous findings that patients with RA have an increased risk of developing lymphoma, leukemia, and lung cancer, and that the risk of being diagnosed with one of these cancers was strongly associated with younger age. Males with RA were at greater risk for several cancer types compared to females in our study. A new and important finding was that women with RA had a lower risk of developing cancer than women in the general population, and this was particularly true for breast, ovary, uterine, and cervical cancer. For several cancer types, the risk of developing cancer decreased with increasing age. Large longitudinal studies, which collect detailed risk factor and treatment information, are needed to investigate the mechanisms that underlie the associations between RA and specific cancer types.

Acknowledgment

This work was funded by grant 1R21CA100759-01A2 from the National Cancer Institute. The collection of cancer incidence data used in this study was supported by the California Department of Health Services as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract N01-PC-35136 awarded to the Northern California Cancer Center, contract N01-PC-35139 awarded to the University of Southern California, and contract N02-PC-15105 awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U55/CCR921930-02 awarded to the Public Health Institute.

References

1. Hochberg MC, Spector TD. Epidemiology of rheumatoid arthritis: update. Epidemiol Rev. 1990; 12:247–252. [PubMed: 2286222]
2. Harris, ED. Clinical features of rheumatoid arthritis. In: Kelly, WN.; Harris, ED.; Ruddy, S.; Sledge, CB., editors. Textbook of rheumatology, 5th edn. Philadelphia: WB Saunders; 1997. p. 895-922.
3. Abu-Shakra, M.; Buskila, D.; Shoenfeld, Y. Rheumatoid arthritis and cancer. In: Gershwin, ME.; Shoenfeld, Y., editors. Cancer and autoimmunity. Amsterdam: Elsevier; 2000. p. 19-30.
4. lsomaki HA, Hakulinene T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. J Chronic Dis. 1978; 31:691–696. [PubMed: 730824]
5. Gridley G, McLaughlin JK, Ekbom A, Klareskog L, Adami H, Hacker DG, et al. Incidence of cancer among patients with rheumatoid arthritis. J Natl Cancer Inst. 1993; 85:307–311. [PubMed: 8426374]
6. Katusic S, Beard CM, Kurland LT, Weis JW, Bergstralh. Occurrence of malignant neoplasms in the Rochester, Minnesota, rheumatoid arthritis cohort. Am J Med. 1985; 78(Suppl 1A):S0–55.
7. Hakulinen T, Isomaki H, Knekt P. Rheumatoid arthritis and cancer studies based on linking nationwide registries in Finland. Am J Med. 1985; 78(suppl IA):29–32. [PubMed: 3970037]
8. Symmons DP, Ahem M, Bacon PA, Hawk.ins CF, Amiot PL, Jones EL, et al. Lymphoproliferative malignancy in rheumatoid arthritis: a study of 20 cases. Ann Rheum Dis. 1984; 43:132–135. [PubMed: 6712288]
9. Seidenfeld AM, Smythe HA, Ogryzlo MA, Urowitz MB, Dollen DA. Acute leukemia in rheumatoid arthritis treated with cytotoxic agents. J Rheumatol. 1984; 11:586–587. [PubMed: 6512790]
10. Taylor HG, Nixon N, Sheeran TP, Dawes PT. Rheumatoid arthritis and chronic lymphocytic leukemia. Clin Exp Rheumatol. 1989; 7:529–532. [PubMed: 2591128]
11. Fam AG, Lewis AJ, Cowan DH. Multiple myeloma and amyloid bone lesions complicating rheumatoid arthritis. J Rheumatol. 1981; 8:845–850. [PubMed: 7310780]
12. Shenberger KN, Schned AR, Taylor TH. Rheumatoid disease and bronchogenic carcinoma-case report and review of the literature. J Rheumatol. 1984; 13:909–911.
13. Gridley G, Klippel JH, Hoover RN, Fraumeni JF Jr. Incidence of cancer among men with the Felty syndrome. Ann Intern Med. 1994; 120(1):35–39. [PubMed: 8250454]
14. Cibere J, Sibley J, Haga M. Systemic lupus erythematosus and the risk of malignancy. Lupus. 2001; 10(6):394–400. [PubMed: 11434573]
15. Kauppi M, Isomaki H. Elevated incidence of hematologic malignancies in patients with Sjogren's syndrome compared with patients with rheumatoid arthritis. Cancer Causes Control. 1997; 1997:201–204. [PubMed: 9134244]
16. Thun MJ, Nambodiri MM, Heathn CW Jr. Aspirin use and reduced risk of fatal colon cancer. N Engl J Med. 1991; 325:1593–1596. [PubMed: 1669840]
17. Askling J, Baecklund E, Granath F, Geborek P, Fored M, Backlin C, et al. Anti-TNF therapy in RA and risk of malignant lymphomas relative risks and time-trends in the Swedish Biologics Register. Ann Rheum Dis. 2008
18. Baecklund E, Askling J, Rosenquist R, Ekbom A, Klareskog L. Rheumatoid arthritis and malignant lymphomas. Curr Opin Rheumatol. 2004; 16(3):254–261. [PubMed: 15103253]

19. Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006; 54(3):692–670 I. [PubMed: 16508929]
20. Kinlen U, et al. Malignancy in autoimmune diseases. J Autoimmun. l992; 5(Suppl A):363–371. [PubMed: 1503633]
21. Silman AJ, Petrie J, Hazleman B, Evans SJ. Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow up study. Ann Rheum Dis. 1988; 47:988–992. [PubMed: 3207388]
22. Tennis P, Andrews E, Bombardier C, Wang Y, Strand L, West R, et al. Record linkage to conduct an epidemiologic study on the association of rheumatoid arthritis and lymphoma in the province of Saskatchewan, Canada. J Clin Epidemiol. 1993; 46(7):685–695. [PubMed: 8326357]
23. Services USDoHaH. , editor. ICD-9-CM: international classification of diseases, 9th revision, clinical modification. 6th edn.. Washington, DC: 2000.
24. Cancer Reporting in California: Standards for Automated Reporting. Cancer Sur-veillance Section. Sacramento, CA: 1997. California cancer reporting system standards, vol II. California Department of Health Services.
25. Cancer Reporting in California: Data Standards for Regional Registries and California Cancer Registry. Cancer Surveillance Section. Sacramento, CA: 1997. California cancer reporting system standards, vol III. California Department of Health Services.
26. Cancer Reporting in California: Reporting Procedures for Physicians. Cancer Surveillance Section. Sacramento, CA: 1998. California cancer reporting system standards, vol IV. California Department of Health Services.
27. Cancer Reporting in California: Abstracting and Coding Procedures for Hospitals. Cancer Surveillance Section. Sacramento, CA: 1997. California cancer reporting system standards, vol I. California Department of Health Services.
28. Chen, VW.; Howe, HL.; Wu, XC. North American Association of Central Cancer Registries. Springfield, IL: 2000. Cancer in North America, 1993–1997 vol I. Incidence.
29. Seiffert JE, Price WT, Gordon B. The California tumor registry: a state-of-the-art model for a regionalized, automated, population-based registry. Top Health Rec Manage. 1990; 11:59–73. [PubMed: 10108499]
30. Vality Technology Inc. Integrity program: data reengineering environment software, ver 3.3. Boston, MA: Vality Technology Inc.; 1999.
31. Allen, M. Validation of OSHPD and CCR insurance status; California association of central cancer registries technical conference; Riverside, CA. 25 September, 2001; 2001.
32. Breslow, NE.; Day, NE. International Agency for Research on Cancer. Lyon: 1987. Statistical methods in cancer research. Vol II. The design and analysis of cohort studies.
33. Mellemkjaer L, Linet MS, Gridley G, Frisch M, Moller H, Olsen JH. Rheumatoid arthritis and cancer risk. Eur J Cancer. 1996; 32A(10):1753–1757. [PubMed: 8983286]
34. Prior P. Cancer and rheumatoid arthritis: epidemiologic considerations. Am J Med. 1985; 78(Suppl 1A):l5–21.
35. Thomas E, Brewster DH, Black RJ, Macfarlane GJ. Risk of malignancy among patients with rheumatic conditions. Int J Cancer. 2000; 88(3):497–502. [PubMed: 11054684]
36. Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. Br Med J. 1998; 3(7(7152)):180–181. [PubMed: 9665898]
37. Wolfe F. Inflammatory activity but not prednisone or methotrexate use predicts non-Hodgkin's lymphoma in rheumatoid arthritis: a 25-year study of 1,767 RA patients [abstract 931). Arthritis Rheum S. 1998; 188
38. Baker GL, Kahl LE, Zee BC, Stolzer BL, Agarwal AK, Medsger TA Jr. Malignancy following treatment of rheumatoid arthritis with cyclophosphamide. Long-term case-control followup study. Am J Med. 1987; 83(1):1–9. [PubMed: 3605161]
39. Kinlen LJ. Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatments. Arn J Med. 1985; 78(supp1 IA):44–49.

40. Matteson EL, Hickey AR, Maguire L, Tilson HH, Urowitz MB. Occurrence of neoplasia in patients with rheumatoid arthritis enrolled in a DMARD registry. Rheumatoid arthritis azathioprine registry steering committee. J Rheumatol. 1991; 8(6):809–814. [PubMed: 1895261]
41. Radis CD, Kahl LE, Baker GL, Wasko MC, Cash JM, Gallatin A, et al. Effects of cyclophospharnide on the development of malignancy and on long-term survival of patients with rheumatoid arthritis. A 20-year followup study. Arthritis Rheum. 1995; 38(8):1120–1127. [PubMed: 7639809]
42. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006; 295(19):2275–2285. [PubMed: 16705109]
43. Beauparlant P, Papp K, Haraoui B. The incidence of cancer associated with the treatment of rheumatoid arthritis. Semin Arthritis Rheum. 1999; 29:148–158. [PubMed: 10622679]
44. Starkebaum G. Rheumatoid arthritis, methotrexate, and lymphoma: risk substitution, or cat and mouse with Epstein-Barr virus? J Rheumatol. 200l; 28(12):2573–2575. [PubMed: 11764198]
45. Helmers R, Galvin J, Hunninghake GW. Pulmonary manifestations associated with rheumatoid arthritis. Chest. 1991; 100(1):235–238. [PubMed: 2060351]
46. Hernandez Avila M, Liang MH, Willett WC, Stampfer MJ, Colditz GA, Rosner B, et al. Reproductive factors, smoking, and the risk for rheumatoid arthritis. Epidemiology. 1990; 1(4): 285–291. [PubMed: 2083305]
47. Silman AJ, Newman J, MacGregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. Arthritis Rheum. 1996; 39(5):732–735. [PubMed: 8639169]
48. Voigt LF, Koepsell TD, Nelson JL, Dugowson CE, Daling JR. Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis. Epidemiology. 1994; 5(5):525–532. [PubMed: 7986867]
49. Baron JA. Epidemiology of non-steroidal anti-inflammatory drugs and cancer. Prog Exp Tumor Res. 2003; 37:1–24. [PubMed: 12795046]
50. Chakravarty EF, Genovese MC. Associations between rheumatoid arthritis and malignancy. Rheum Dis Clin North Am. 2004; 30(2):271–284. Vi. [PubMed: 15172040]
51. Buchbinder R, Barber M, Heuzenroeder L, Wluka AE, Giles G, Hall S, et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum. 2008; 59(6):794–799. [PubMed: 18512713]
52. Abasolo L, Judez E, Descalzo MA, Gonzalez-Alvaro I, Jover JA, Carmona L. Cancer in rheumatoid arthritis: occurrence, mortality. and associated factors in a South European population. Semin Arthritis Rheum. 2008; 37(6):388–397. [PubMed: 17977580]
53. Gao J, Niwa K, Sun W, Takemura M, Lian Z, Onogi K, et al. Non-steroidal anti-inflammatory drugs inhibit cellular proliferation and upregulate yclooxygenase-2 protein expression in endometrial cancer cells. Cancer Sci. 2004; 95(11):901–907. [PubMed: 15546508]
54. Gonzalez-Perez A, Garcia Rodriguez LA, Lopez-Ridaura R. Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis. BMC Cancer. 2003; 3:28. [PubMed: 14588079]
55. Mahmud SM, Tanguay S, Begin LR, Franco EL, Aprikian AG. Non-steroidal anti-inflammatory drug use and prostate cancer in a high-risk population. Eur J Cancer Prev. 2006; 15(2):158–164. [PubMed: 16523013]
56. Moorman PG, Grubber JM, Millikan RC, Newman B. Association between non-steroidal anti-inflammatory drugs (NSAIDs) and invasive breast cancer and carcinoma in situ of the breast. Cancer Causes Control. 2003; 14(10):915–922. [PubMed: 14750530]
57. Pereg D, Lishner M. Non-steroidal anti-inflammatory drugs for the prevention and treatment of cancer. J Intern Med. 2005; 258(2):115–123. [PubMed: 16018788]
58. Stock DC, Groome PA, Siemens DR, Rohland SL, Song Z. Effects of non-selective non-steroidal anti-inflammatory drugs on the aggressiveness of prostate cancer. Prostate. 2008

59. Cevik R, Em S, Our A, Nas K, Sarac AJ, Colpan L. Sex and thyroid hormone status in women with rheumatoid arthritis: are there any effects of menopausal state and disease activity on these hormones? Int J Clin Pract. 2004; 58(4):327–332. [PubMed: 15161114]

60. Cutolo M, Villaggio B, Craviotto C, Pizzomi C, Seriolo B, Sulli A. Sex hormones and rheumatoid arthritis. Autoimmun Rev. 2002; 1(5):284–289. [PubMed: 12848982]

61. Kuiper S, van Gestel AM, Swinkels HL, de Boo TM, da Silva JA, van Riel PL. Influence of sex, age, and menopausal state on the course of early rheumatoid arthritis. J Rheumatol. 2001; 28(8): 1809–1816. [PubMed: 11508583]

62. Masi AT. Sex hormones and rheumatoid arthritis: cause or effect relationships in a complex pathophysiology? Clin Exp Rheumatol. 1995; 13(2):227–240. [PubMed: 7656469]

63. Katz JN, Barrett J, Liang MH, Bacon AM, Kaplan H, Kieval Rl, et al. Sensitivity and positive predictive value of medicare part B physician claims for rheumatologic diagnoses and procedures. Anhritis Rheum. 1997; 40(9):1594–1600.

64. Brooks PM. Rheumatic manifestations of neoplasia. Curr Opin Rheumatol. 1992; 4(1):90–93. [PubMed: 1543670]

65. Butler RC, Thompson JM, Keat AC. Paraneoplastic rheumatic disorders: a review. J R Soc Med. 1987; 80(3):168–172. [PubMed: 3553593]

Table 1

Demographic characteristics of a cohort of patients with rheumatoid arthritis (RA), California, 1991–2002

Variable	Whole cohort (*n* = 84,475) *n* (%)	RA patients diagnosed with cancer (*n* = 5,533) *n* (%)
Sex		
Female	65,236 (77.2)	3,717 (67.2)
Male	19,239 (22.8)	1,816 (32.8)
Age -at hospitalization		
<40	5,616 (6.7)	75 (1.4)
40–59	20,970 (24.8)	931 (16.8)
60–79	43,316 (51.3)	3,741 (67.6)
80+	14,573 (17.2)	786 (14.2)
Race		
Non-Hispanic White	60,883 (72.1)	4,306 (77.8)
Non -Hispanic Black	6,517 (7.7)	392 (7.1)
Hispanic	11,651 (13.8)	596 (10.8)
Non-Hispanic Asian/Pacific Islander	3,693 (4.4)	194 (3.5)
Other/Unknown	1,731 (2.0)	45 (0.8)
Period of hospitalization		
1991–1994	33,354 (39.5)	3000 (54.2)
1995–1998	28,266 (33.5)	1,894 (34.2)
1999–2001	22,855 (27.0)	639 (11.6)
Period diagnosed with cancer		
1991–1994		808 (14.6)
1995–1998		1,919 (34.7)
1999–2002		2,806 (50.7)

Table 2

Sex, age, and race adjusted standardized incidence ratios (SIRs) for selected cancers among a cohort of female and male patients with rheumatoid arthritis, California, 1991–2002 (*n* = 84,475)

Cancer type	Females (*n* = 65,236)				Males (*n* = 19,239)			
	Observed	Expected	SIR	95% C	Observed	Expected	SIR	95% CI
Breast	842	1343.5	0.63	0.59–0.67				
Ovary	89	142.3	0.63	0.50–0.77				
Uterus	126	237.3	0.53	0.44–0.63				
Vagina/vulva	56	56.6	0.99	0.75–1.29				
Cervix	47	1100	0.43	0.31–0.57				
Prostate					407	609.6	0.67	0.60–0.74
Lung	762	593.7	1.28	1.19–1.38	416	252.3	1.65	1.49–1.81
Esophagus	27	25.3	1.07	0.70–1.55	36	20.3	1.78	1.24–2.46
Stomach	72	67.1	1.07	0.84–1.35	41	36.0	1.14	0.82–1.54
Colon/rectum	415	545.5	0.76	0.69–0.84	137	196.7	0.70	0.58–0.82
Liver	36	25.5	1.41	0.99–1.96	32	17.3	1.85	1.26–2.6 1
Pancreas	115	117.0	0.98	0.67–1.03	35	35.9	0.97	0.68–1.36
Bladder	90	107.3	0.84	0.74–1.14	108	112.7	0.96	0.79–1.16
Kidney	82	69.6	1.18	0.94–1.46	43	38.7	1.11	0.80–1.50
Thyroid	26	37.1	0.70	0.46–1.03	3	5.8	0.52	0.11–1.52
Brain/CNS	29	39.3	0.74	0.49–1.06	10	15.8	0.63	0.30–1.16
Non-Hodgkin 's lymphoma	208	151.9	1.37	1.19–1.57	117	56.6	2.07	1.71–2.48
Hodgkins disease	15	9.2	1.62	0.91–2.68	10	3.6	2.76	1.32–5.08
Leukemia	110	86.9 951.6	1.27	1.03–1.51	68	41.1	1.65	1.29–2.07
Myeloma	41	51.6	0.79	0.57–1.08	23	19.3	1.19	0.75–1.78
Melanoma	107	170.5	0.63	0.51–0.76	77	96.3	0.80	0.63–1.00

Table 3

Race-specific standardized incidence ratios for selected cancers among a cohort of female and male patients with rheumatoid arthritis, California, 1991–2002 (*n* = 84,475)

Cancer type	Females (*n* = 65,236)				Males (*n* = 19,239)			
	Observed	Expected	SIR	95% CI	Observed	Expected	SIR	95% CI
Breast								
Non-Hispanic white	662	1076.4	0.62	0.57–0.66				
Non-Hispanic black	67	82.9	0.81	0.63–1.03				
Hispanic	79	104.3	0.76	0.60–0.94				
Asian/PI	27	30.2	0.89	0.59–1.30				
Vagina/Vulva								
Non-Hispanic white	33	39.4	0.84	0.58–1.17				
Non-Hispanic black	5	3.4	1.47	0.48–3.42				
Hispanic	14	5.2	2.71	1.48–4.55				
Asian/PI	2	0.9	2.19	0.26–7.9				
Lung								
Non-Hispanic white	632	501.4	1.26	1.16–1.36	350	209.5	1.67	1.50–1.86
Non-Hispanic black	51	40.4	1.26	0.94–1.66	23	17.0	1.35	0.86–2.03
Hispanic	63	32.7	1.93	1.48–2.47	24	13.8	1.75	1.12–2.60
Asian/PI	160	12.4	1.29	0.74–2.10	18	9.1	1.98	1.17–3.12
Esophagus								
Non-Hispanic white	20	20.1	0.99	0.61–1.54	29	16.2	1.79	1.20–2.57
Non-Hispanic black	4	2.74	1.46	0.40–3.74	2	1.5	1.34	0.16–4.85
Hispanic	3	1.63	1.84	0.38–5.39	4	1.6	2.54	0.69–6.51
Asian/PI	0	0.55				0.6	1.54	0.04–8.59
Liver								
Non-Hispanic white	12	14.2	0.84	0.44–1.47	17	10.2	1.67	0.97–2.68
Non-Hispanic black	7	2.2	3.19	1.28–6.58	4	1.3	3.19	0.87–8.18
Hispanic	13	5.1	2.56	1.36–4.38	8	3.0	2.70	1.17–5.33
Asian/Pl	4	3.5	1.14	0.31–2.92	3	2.7	1.13	0.23–3.30
NHL								

Cancer type	Females (*n* = 65,236)				Males (*n* = 19,239)			
	Observed	**Expected**	**SIR**	**95% CI**	**Observed**	**Expected**	**SIR**	**95% CI**
Non -Hispanic white	165	116.8	1.41	1.21–1.65	92	45.7	2.01	1.62–2.47
Non-Hispanic black	12	6.8	1.75	0.91–3.06	6	2.0	3.08	1.13–6.69
Hispanic	26	15.4	1.69	1.10–2.48	11	4.5	2.45	1.22–4.38
Asian/Pl	4	4.4	0.92	0.25–2.35	6	2.0	2.96	1 .09–6.44
Hodgkin's disease								
Non-Hispanic white	11	6.8	1.62	0.81–2.90	8	2.8	2.86	1.22–5.58
Non-Hispanic black	1	0.6	1.67	0.04–8.98	0	0.2		
Hispanic	3	1.3	2.31	0.48–6.87		0.5	2.00	0.06–12.30
Asian/PI	0	0.2				0.1	10.00	0.31–68.45
Leukemia								
Non-Hispanic white	80	69.6	1.15	0.92–1.42	56	34.2	1.64	1.25–2.11
Non-Hispanic black	9	5.1	1.76	0.86–3.23	4	1.6	2.50	0.79–6.03
Hispanic	13	7.0	1.85	1.03–3.10	6	2.4	2.50	1.01–5.20
Asian/PI	7	1.9	3.68	1.61–7.29	2	2.2	0.90	0.15–3.00

Cancer Causes Control. Author manuscript; available in PMC 2015 March 10.

Table 4

Age-specific standardized incidence ratios (SIRs) for selected cancers among a cohort of female and male patients with rheumatoid arthritis, California, 1991–2002 (*n = 84,475*)

Cancer type	Females (*n* = 65,236)				Males (*n* = 19,239)			
	Observed	Expected	SIR	95% CI	Observed	Expected	SIR	95% CI
Breast								
<40	23	10.5	2.19	1.39–3.28				
40–59	87	242.8	0.77	0.66–0.89				
60–79	550	860.9	0.64	0.59–0.70				
80+	82	229.2	0.36	0.28–0.45				
Vagina/Vulva								
<40	7	1.4	4.94	2.00–10.18				
40–59	14	1 1.5	1.22	0.67–2.05				
60–79	27	32.2	0.84	0.55–1.22				
80+	8	11.5	0.70	0.30–1.37				
Lung								
<40	0	0.6	-	-	1	0.2	6.38	0. 16–35.5
40–59	122	46.6	2.62	2.17–3.12	50	21. 1	2.37	1.76–3.12
60–79	553	429.6	1.29	1.18–1.40	329	185.6	1.77	1.59–1.97
80+	87	116.8	0.75	0.60–0.92	36	45.5	0.79	0.55–1.10
Esophagus								
<40	0	0	-	-	1	0	-	-
40–59	6	1.7	3.47	1.27–7.55	6	2.2	2.62	0.96–5.71
60–79	19	17.0	1.12	0.67–1.75	24	14.4	1.67	1.07–2.48
80+	2	6.6	0.30	0.03–1.10	5	3.6	1.40	0.45–3.27
Liver								
<40	0	0.1	-	-	1	0.0	-	-
40–59	6	2.0	3.00	1.08–6.40	11	2.6	4.29	2.14–7.68
60–79	20	17.3	1.16	0.71–1.78	18	12.0	1.50	0.89–2.37
80+	10	6.1	1.65	0.79–3.03	2	2.7	0.73	0.09–2.65
NHL								

Cancer type	Females (*n* = 65,236)				Males (*n* = 19,239)			
	Observed	**Expected**	**SIR**	**95% CI**	**Observed**	**Expected**	**SIR**	**95% CI**
<40	4	1.1	3.61	0.98–9.25	2	0.7	3.06	0.37–11.04
40–59	39	15.I	2.58	1.83 –3.52	20	8.2	2.44	1.49–3.76
60–79	141	96.2	1.47	1.23–1.73	92	36.5	2.52	2.03–3.09
80+	24	39.4	0.61	0.39–0.91	3	11.2	0.27	0.06–0.78
Hodgkin's Disease								
<40	0	0.9	-	-	0	0.2	-	-
40–59	6	1.6	3.71	1.36–8.09	2	0.9	2. 17	0.26–7.87
60–79	9	5.3	1.7 1	0.78–3.24	7	2.0	3.49	1.40–7.19
80+	0	1.5	-	-	1	0.5	2.09	0.05–11.62
Leukemia								
<40	0	0.6	-	-	0	-	-	-
40–59	19	7.5	2.53	1.57–3.88	6	3.9	1.54	0.62–3.20
60–79	67	51.1	1.31	1.01–1.67	51	26.9	1.90	1.43–2.47
80+	24	27.6	0.87	0.57–1.27	11	10.2	1.08	0.57– 1.87