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CONTRIBUTION FROM THE FIELD

Race/Ethnicity and Cancer Occurrence in Systemic Lupus Erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a chronic rheumatic disease whose long-term sequelae may include many types of comorbidity, including neoplasia (1–7). There is abundant evidence that race and ethnicity are important to consider when studying outcomes in chronic disease; in particular, it is known that race and ethnicity affect SLE incidence, disease activity, damage, and mortality. However, to date the influence of race and ethnicity on cancer incidence in SLE has not been evaluated. To do so requires a very large number of subjects. The purpose of this study, therefore, was to evaluate the occurrence of cancer in individuals with SLE, according to race and ethnicity, using a large, multicenter, international SLE cohort.

Subjects and Methods

An international cohort of subjects with SLE from North America, the United Kingdom, Europe, and Asia was constructed as previously described (1). The study was approved by the ethics review boards of all participating institutions and was conducted in accordance with the Declaration of Helsinki ethical principles.

All subjects with definite SLE according to American

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College of Rheumatology criteria (8) or clinical criteria (i.e., consistent multisystem disease and serology) were eligible for inclusion. Subjects were linked with regional cancer registries to ascertain cancer occurrence. The number of person-years for each subject was determined by subtracting the later of 2 entry dates (the beginning of the cancer registry observation interval or the first visit to the respective lupus clinic) from the earliest of 2 exit dates (the end date of cancer registry data or death).

Data on race/ethnicity and demographic variables were available from 20 centers across the 4 continents (N = 7,312). Complete information on covariates (race, age, sex, duration of SLE) was available for 7,171 (98%) subjects. Information on race and ethnicity was self designated and was classified according to the National Institutes of Health guidelines for reporting race and ethnicity data (9). According to these guidelines, the racial categories include the following groups: white, black/African American (AA), Asian, and American Indian. The Asian group includes the Far East, Southeast Asia, and the Indian subcontinent. Furthermore, the guidelines indicate that ethnicity is represented by the title "Hispanic (or Latino)," which categorically indicates whether an individual is of this origin (including Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin), regardless of race.

The influence of race and ethnicity on cancer occurrence was examined using Cox proportional hazard regression models adjusted for demographic variables and SLE duration. For these analyses, Epicure software version 2.10 was used (10). In the primary analyses, we generated adjusted hazard ratios (HRs) for race by forming dummy variables (where black/AA race formed the reference group) for the following groups: white, Asian, Hispanic, and native American Indian. The black/AA group was chosen as the reference because findings from a previous study suggest that white patients with SLE may be at higher risk of some forms of cancer, compared with black/AA patients (6). However, because interpretation of dummy variable parameter estimates will differ depending on what reference group is chosen (11), we also ran a regression model where the Asian racial group formed the reference group, and another model where white race was considered the reference group. We also ran simple models where white subjects were compared with all nonwhites.

Standardized incidence ratios (SIRs, the quotient of observed to expected cancers) were also calculated, and were stratified by race. To calculate the expected number of malignancies for the stratified estimates, race-specific population data from the US Surveillance, Epidemiology, and End Results (SEER) Program were used (12). All SIRs were adjusted for sex and age.

Results

Of the 7,312 subjects, 6,657 (91%) were women. Information on race/ethnicity was complete for 7,171 (98%) of the 7,312 subjects. Of these 7,171 subjects, 4,354 (60.7%) were white, 1,732 (24.2%) were black/AA, 701 (9.8%) were Asian, and the remainder were Hispanic (N = 318) or of native North American Indian origin (N = 66).

Table 1. Hazard ratios for cancer occurrence (all types) for SLE cohort subjects, by racial/ethnicity group*

	Hazard ratio	95% CI
Black/AA as comparator group		
White	1.49	1.08–2.05
Asian†	0.42	0.15–1.21
Hispanic	0.67	0.26–1.72
Native North American	1.12	0.26–4.74
Asians as comparator group		
White	2.41	1.15–5.02
Hispanic	1.09	0.34–3.46
Black/AA	1.60	0.73–3.51
Native North American	1.80	0.37–8.88
Whites as comparator group		
Black/AA	0.67	0.48–0.93
Asian	0.29	0.10–0.80
Hispanic	0.45	0.18–1.13
Native North American	0.75	0.18–3.12

* SLE = systemic lupus erythematosus; 95% CI = 95% confidence interval; AA = African American.
† Asian group includes Far East/Southeast Asia (N = 554, 4 cancers) and Indian subcontinent (N = 147, 2 cancers).

The Asian group included 554 subjects of Far East or Southeast Asian origin, and 147 subjects of Indian subcontinent origin. Analyses were performed both by including all of these subjects together and by separating out the Indian subcontinent subjects, with no appreciable difference in the results. Thus, for simplicity, the results are presented with the Asian group including all 701 subjects.

The mean ± SD age at the time of regional cancer registry linkage was 44.3 ± 17.1 years (median 43.0 years), and the mean duration of SLE was 11.7 ± 8.4 years (median 10.0 years). The person-years of followup for the 7,171 patients totaled 58,772.1 years. Over this period, a total of 301 cancers were ascertained in 298 subjects.

When controlling for age, sex, SLE duration, and geographic location, the white subjects with SLE appeared to have a higher risk of cancer occurrence compared with black/AA subjects (HR 1.49, 95% confidence interval [95% CI] 1.08–2.05) or Asian subjects (HR 2.41, 95% CI 1.15–5.02) (Table 1). In models where all white subjects were compared with all nonwhite subjects, the HR was 1.68 (95% CI 1.25–2.25) for all cancers and 1.25 (95% CI 0.62–2.51) for hematologic cancers only (including lymphoma).

Table 2 presents the race-specific SIRs, comparing the cancer experience for subjects with SLE versus the general population. Regarding the results for all cancers, the point estimates were quite variable and imprecise for all race/ethnicity groups except for white subjects, where the SIR was 1.14 (95% CI 1.00–1.30). In contrast, for lymphoma, the SIR point estimates for white, black/AA, and Asian races were all similar in magnitude, although the estimate was again most precise for whites (SIR 2.89, 95% CI 1.87–4.27).

Discussion

Interesting associations of cancer occurrence with race/ethnicity were present in this cohort. The white subjects

Table 2. Observed (O) and expected (E) malignancies, and standardized incidence ratio (SIR) by race/ethnicity groups*

	O	E	SIR	95% CI
All cancers				
White	231	202.7	1.14	1.00–1.30
Black/AA	56	57.0	0.98	0.74–1.28
Asian†	6	8.4	0.72	0.26–1.56
Hispanic	5	5.9	0.85	0.27–1.98
Native North American	3	0.9	3.48	0.70–10.2
Lung‡				
White	30	24.3	1.23	0.83–1.76
Black/AA	6	7.4	0.81	0.30–1.76
Asian	0	0.7	—	—
Hispanic	1	0.3	3.45	0.05–19.20
Native North American	0	0.1	—	—
Breast§				
White	52	59.5	0.87	0.65–1.15
Black/AA	7	17.8	0.39	0.16–0.81
Asian	0	2.7	—	—
Hispanic	0	2.0	—	—
Native North American	0	0.3	—	—
Total adjusted for age, sex, and race	59	82.2	0.72	0.55–0.93
Lymphoma¶				
White	25	8.7	2.89	1.87–4.27
Black/AA	5	2.0	2.45	0.79–5.72
Asian	1	0.3	3.33	0.07–29.3
Hispanic	0	0.3	—	—
Native North American	1	0.0	33.3	0.44–185
Total adjusted for age, sex, and race	32	11.3	2.83	1.94–3.99

* 95% CI = 95% confidence interval; AA = African American.
† Asian group includes Far East/Southeast Asia (N = 554, 4 cancers, SIR 0.77, 95% CI 0.21–1.97) and Indian subcontinent (N = 147, 2 cancers, SIR 0.64, 95% CI 0.07–2.30).
‡ No lung cancer cases observed in Asian or Native North American subjects.
§ No breast cancer cases observed in Asian, Hispanic, or Native North American subjects.
¶ No lymphoma cases observed in Hispanic subjects.

with SLE appeared to have a higher overall cancer risk than subjects with SLE of other races. However, it seems that the heightened risk of lymphoma in SLE may be fairly consistent regardless of race; our SIR point estimates across most race/ethnic groups were similar, suggesting a ~3-fold increased risk of lymphoma in SLE compared with the general population. The finding of increased risk for certain types of nonhematologic cancer in white (compared with black) subjects with SLE has been suggested in a previous report (6).

The variations in total cancer risk among individuals with SLE of different races may partly reflect particular genetic backgrounds inherited by a specific group of individuals with SLE (i.e., those of white race) that predispose to both autoimmunity and malignancy. However, our results may also be explained by different risk factor profiles (i.e., exogenous exposures) or competing risks. We note that Asian and black/AA populations with SLE are known to differ from white populations with respect to clinical severity or expression of SLE involvement (13,14), including nephritis. An important limitation of our study is that we are unable to present information about clinical subsets or disease severity in this sample. This is potentially important for several reasons, which are discussed below.

First, if a particular racial group is at risk for more severe SLE, subjects of that race may die of SLE- or treatment-related complications relatively early, and thus never manifest malignant complications. This issue, sometimes termed "competing risk," might not be that important of an influence in our results because available data suggest that malignancy risk in SLE is highest early in the course of SLE, not only later (1,2).

The differences in SLE severity between persons of different racial groups might alter cancer risk in other ways. For example, although the factors driving the association between SLE and lymphoma are unknown, it is suspected that either lupus activity or medication exposure may be mediating factors. Although we were not able to examine the issue in this study, data on medication use and other clinical factors are being collected in a project that is currently underway with the partnership of the Systemic Lupus International Collaborating Clinics and the Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus.

We acknowledge that our current study is limited in the ability to explore specific cancer types in all but the most frequent types of malignancies. Because lung and breast cancer are 2 of the most common malignancies worldwide (15), we aimed to generate race-specific estimates for these tumor types. In addition, because of the increased incidence of lymphoma in our study population, we had a sufficient number of subjects with lymphoma to allow the

presentation of race-specific estimates. However, invasive cases of other types of cancers (such as ovarian, breast, and cervical) are much less common than breast or lung cancer; therefore, we had few cases to analyze in our data. In the sample presented in this study, we found 9 invasive cervical cancers (5 occurring in white women), 7 ovarian (all occurring in white women), and 5 uterine (3 occurring in white women). We are therefore unable to comment definitively on race-specific risk for these types of cancer, although as a group these female reproductive tract malignancies may be slightly more frequent among the white subjects with SLE compared with the nonwhite subjects (adjusted HR 1.04, 95% CI 0.99–1.10).

We also recognize that there are limitations with respect to our SIR estimates; although we had an international cohort, we had to rely on North American SEER data for our race-specific population comparison. However, sensitivity analyses using only the North American centers produced similar findings across race/ethnic groups, but with wider confidence intervals due to the smaller subject pool.

We conclude that there appears to be an association of white race with total cancer risk in persons with SLE. This finding may partly reflect different baseline cancer rates among ethnic groups, but may also represent different risk factor profiles, or competing risks. Although white subjects with SLE appeared to have a higher overall cancer risk than subjects of other races with SLE, the heightened risk of lymphoma in SLE compared with the general population may be relatively uniform across racial and ethnic groups.

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REFERENCES

1. Bernatsky S, Boivin JF, Joseph L, Rajan R, Zoma A, Manzi S, et al. An international cohort study of cancer in systemic lupus erythematosus. Arthritis Rheum 2005;52:1481–90.
2. Bjornadal L, Lofstrom B, Yin L, Lundberg IE, Ekbom A. Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. Scand J Rheumatol 2002;31: 66–71.
3. Cibere J, Sibley J, Haga M. Systemic lupus erythematosus and the risk of malignancy. Lupus 2001;10:394–400.
4. Mellemkjaer L, Andersen V, Linet MS, Gridley G, Hoover R, Olsen JH. Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:761–8.
5. Pettersson T, Pukkala E, Teppo L, Friman C. Increased risk of cancer in patients with systemic lupus erythematosus. Ann Rheum Dis 1992;51:437–9.
6. Ramsey-Goldman R, Mattai SA, Schilling E, Chiu YL, Alo CJ, Howe HL, et al. Increased risk of malignancy in patients with systemic lupus erythematosus. J Investig Med 1998;46:217–22.
7. Sweeney DM, Manzi S, Janosky J, Selvaggi KJ, Ferri W, Medsger TA Jr, et al. Risk of malignancy in women with systemic lupus erythematosus. J Rheumatol 1995;22:1478–82.
8. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25: 1271–7.
9. National Institutes of Health. NIH policy on reporting race and ethnicity data: subjects in clinical research. Bethesda (MD): NIH; 2001 Aug. Report No.: NOT-OD-01-053.
10. Preston D, Lubin J, Pierce D, McConney M. Epicure release 2.10. Seattle (WA): Hirosoft International Corporation; 1998.
11. McCrohan KF, Harvey JW. A comparison of dummy variable versus traditional multiple discriminant function analysis. Health Mark Q 1989;6:147–57.
12. National Cancer Institute. US surveillance, epidemiology, and end results (SEER) program. URL: www.seer.cancer.gov.
13. Samanta A, Feehally J, Roy S, Nichol FE, Sheldon PJ, Walls J. High prevalence of systemic disease and mortality in Asian subjects with systemic lupus erythematosus. Ann Rheum Dis 1991;50:490–2.
14. Uribe AG, McGwin G Jr, Reveille JD, Alarcon GS. What have we learned from a 10-year experience with the LUMINA (Lupus in Minorities; Nature vs. Nurture) cohort? Where are we heading? Autoimmun Rev 2004;3:321–9.
15. Ferlay J, Bray F, Pisani P, Parkin D. GLOBOCAN 2000: cancer incidence, mortality and prevalence worldwide, version 1.0. In: IARC CancerBase No. 5. Lyon, France: IARCPress; 2001.