AUTOIMMUNE DISEASES AND CANCER CO-MORBIDITY IN THE U.S. ELDERLY, 1979 TO 2001

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ABSTRACT

It is believed that co-morbidity monotonically increases with age. But little is known about autoimmune diseases and cancer as co-morbid conditions in the US elderly. Even less is known about gender differences in the co-morbidity of autoimmune disease and cancer in the US elderly. Using Multiple Cause of Death data produced by the National Center for Health Statistics (NCHS), this study investigates the proportion of cancer deaths where a) autoimmune disease was the underlying cause of death and b) autoimmune disease deaths where cancer was the underlying cause of death in the elderly U. S. population age ≥65 for the years 1979-2001. Male and female proportions were found to be different with females demonstrating higher levels of co-morbidity when the underlying cause of death is cancer, and lower levels of co-morbidity, when the underlying cause of death is autoimmune disease. Possible reasons for these results are discussed.

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INTRODUCTION

Profound and complex changes in the immune response occur during the aging process. The deterioration of immune function with age is called immune senescence, which is reflected by the sum of dysregulation of immune system components and their interaction with other organ systems. Many of the changes appear to implicate age-related deficiencies of immune responses. Therefore, the term immunosenescence is believed to manifest itself in the increased risk of autoimmune phenomena, incidence of neoplasia, and predisposition to infections (Ginaldi L, 1999).

Autoimmune diseases begin to develop at young ages, but their physical consequences tend to increase with age, ultimately becoming major factors affecting the health and quality of life of the elderly. Frequent atypical presentation of autoimmune diseases, higher morbidity and mortality and association with neoplasic processes are three possible specific characteristics of autoimmune diseases in the elderly (Ramos-Casals, 2003).

Aging is characterized by increased co-morbidity and functional decline. The "frail elderly", who have problems in a variety of areas, including physical, cognitive, psychological, social and economic domains, represent an emerging demographic and epidemiologic reality (Lattanzio et al., 1997). Cancer may cause a number of co-morbid conditions (Hersh et al., 1965; Inagaki, Rodriquez, and Bodey, 1974)—especially in elderly individuals whose organ reserves have suffered age-related declines (Strehler, 1977). The association of cancer with autoimmune disease has been a subject of investigation for years, but little is known about mortality in autoimmune diseases and

cancer as co-morbid conditions in the US elderly and even less is known about mortality of gender differences in the co-morbidity of autoimmune disease and cancer in the US elderly.

What is known is what lymphomas occur more frequently in the course of autoimmune disease and that autoimmune rheumatic manifestation occur often in the course of lymphocytic malignancies (Cornoni-Huntley, et al., 1991). Autoimmune disease and cancer thus appears to be related with the association being bidirectional.

Autoimmune disease in cancer

Large Granular Lymphocyte (LGL) leukemia is a disease of the elderly, with a median age at diagnosis of 60 years. It is associated with many autoimmune disorders, including RA, autoimmune thrombocytopenia and hemolytic anemia, Sjogren's syndrome, Hashimoto's thyroiditis, autoimmune polyglandular syndrome, and others (McIntosh et al., 1997; Bowman, 2002; Ergas et al., 2002; Starkebaum, 2002; Coakley, 2002). Multiple serologic abnormalities have been described in this disorder, including rheumatoid factor, antinuclear antibody, either hyper- or hypogammaglobulinemia, monoclonal gammopathies (a potential precursor also to multiple myeloma), antiplatelet antibodies, and antineutrophil antibodies.

Rose and Berliner (2004) pointed out that up to one-third of patients with LGL leukemia has RA. Concomitant autoimmune thrombocytopenia, autoimmune hemolytic anemia, and other autoimmune diseases have been frequently reported. LGL leukemia has also been associated with many B-cell lymphoproliferative disorders. However, most follow-up studies of patients with RA demonstrate no increase in the incidence of cancer apart from an approximate doubling of the incidence of lymphoproliferative

malignancies. No association was found between RA and subsequent development of cancer at any site, either in a consecutive series of 1832 Japanese patients with RA at the center (Miyamoto, 1996).

Cancer in autoimmune disease

There are numerous case reports that associate autoimmune disorders with malignancies, cancers that usually occur several years after the onset of the autoimmune disease, but a true incidence rate is difficult to establish because of the protracted course and variable degree of immunosuppression. There is an increased incidence of lymphoid proliferation, mostly of B-cell origin, in patients with Sjogren's syndrome. The incidence of malignant lymphomas has been calculated to be 44 times greater than in the general population. Patients with celiac disease also have an increased cancer risk, with a tendency to acquire either lymphomas or carcinomas of the gastrointestinal tract (Penn, 1990). In addition, there are many reports of patients in whom cancers develop during therapy with immunosuppressive agents given for diseases such as psoriasis, ulcerative colitis, and other autoimmune states (Mueller and Pizzo, 1995).

Recently, a meta-analysis showed non-hodgkin lymphoma (NHL) is more common in patients with autoimmune disease than in the general population, especially in patients with primary Sjogren syndrome (pSS) and systemic lupus erythematosus (SLE). The studies (20) chosen for the meta-analysis included 6 for SLE, 9 for RA, and 5 for pSS (Zintzaras et al., 2005). An increased incidence of malignant lymphocytic diseases is present in patients with rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, and autoimmune thyroid disease. Descriptions of lymphocytic malignancies among other autoimmune rheumatic disease have been published (Ehrenfeld, 2001).

However, data supporting an association of RA with increased overall malignancy risk and cancer-related mortality are inconsistent (Moritomo et al., 1995; Cibere J, Sibley J & Haga M, 1997). There is far more compelling evidence linking RA with an increased risk of lymphoproliferative malignancy, particularly Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). Several independent groups have reported significantly increased NHL risk estimates for RA patients, with observed relative risks ranging from 2 to as high as 23 (Gridley et al., 1993; Macfarlane G & Black R. 1996; Mellemkjaer et al., 1996; Prior et al., 1984). Similarly, relative risks for HD in the context of RA have been reported to range from approximately 2 to 7 (Mikuls, 2003).

The objective of this study is to investigate gender in selected autoimmune diseases and cancers as co-morbid conditions for deaths (when the underlying cause of death is either cancer or autoimmune disease) among the elderly population by analysis of the multiple cause of death data. We seek to improve our understanding of the role of immunosenescence in age-related changes in human autoimmune diseases. This is done by examining the recording of co-morbid conditions on the death certificate.

MATERIALS AND METHODS

Data

The National Center for Health Statistics Multiple Cause of Death (MCD) data sets include data on all recorded deaths that occur in the United States, Puerto Rico, Guam, and the US Virgin Islands each year between 1968 to 2001 (currently being updated with 2002 mortality data).

For this paper, we use the data beginning 1979 to coincide with use of ICD-9 for cause of death coding. Each record includes information from the decedent's death certificate about the underlying cause of death, multiple conditions that contributed to the death, and the place and date of death, as well as demographic data on the decedent. Each record may contain up to 20 causes of death that were coded using the international diseases classification system (ICD).

There are different coding systems for the mortality files 1979-1998 or 1999-2001, because the international disease classification system used to code cause-of-deaths changed in 1999. The Ninth Revision of the International Classification of Diseases (ICD-9) was used to code causes-of-death for deaths occurring in the United States 1979 to 1998. The Tenth Revision of the ICD (ICD-10) was used to code underlying cause-of-death for deaths that occurred in the United States after 1998. Every U.S. death is recorded in these data sets. Deaths that occurred outside of the 50 states, such as in Guam, the Virgin Islands, and Puerto Rico, were excluded.

Methods

The MCD data were categorized by decedent age, sex, and then searched for reports of selected autoimmune diseases (e.g., rheumatoid arthritis, Hashimoto's thyroiditis) in U.S. residents aged 65 and greater who died 1979-2001. Two ICD-9 and ICD-10 categories based on the disease classification were used in the analysis. "Selected autoimmune diseases" and "Cancer" include decedents whose death certificates mentioned the ICD-9 and ICD-10 codes in Table 1 either as the underlying cause of death or as a secondary, or immediate, cause.

Table 1. Selected Autoimmune Diseases and Cancer ICD-9 and ICD-10 Codes.

Diseases	ICD-9	ICD-10
Rheumatoid arthritis and other inflammatory polyarthropathies	714	M05.0,M05.3,M06.4,M06.9,M08, M12.0, M12.3, J99.0
Systemic lupus erythematosus	710.0	M32_
Systemic sclerosis / Scleroderma	710.1_	M34_
Sjögren's syndrome/ Sicca syndrome	710.2	M35.0
Goodpasture's syndrome/Hypersensitivity angiitis	446.2	M31.0
Wegener's granulomatosis	446.4	M31.3
Polymyalgia rheumatica	725	M35.3
Giant cell arteritis /Temporal arteritis/ Horton's disease	446.5	M31.6
Hashimoto's disease/Chronic lymphocytic thyroiditis	245.2	E06.3
Graves' disease /Primary thyroid hyperplasia	242.0_	E05.0
Celiac disease	579.0	K90.0
Regional enteritis or Crohn's disease	555_	K50_
Ulcerative colitis	556_	K51_
Multiple sclerosis	340	G35
Guillain-Barre syndrome/Acute infective	357.0	G61.0

polyneuritis		
Cushing's syndrome	255.0	E24.9
Biliary, cirrhosis	571.6	K74.5
Cholangitis, sclerosing	576.1	K83.0
Raynaud's Syndrome	443.0	I73.0
Cancer	140-208	C00-C96

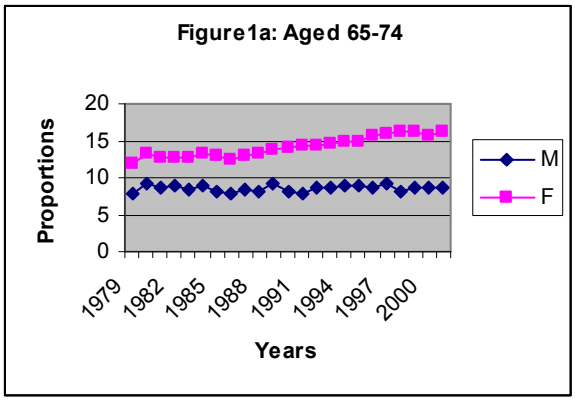
The proportion of cancer deaths where an autoimmune disease was the underlying cause of death, and the proportion of autoimmune diseases deaths where cancer was the underlying cause of death was calculated in the U.S. elderly population age ≥65 by sex between 1979 to 2001. Statistical analyses were performed using chi-square tests. Confidence intervals were calculated using t statistics.

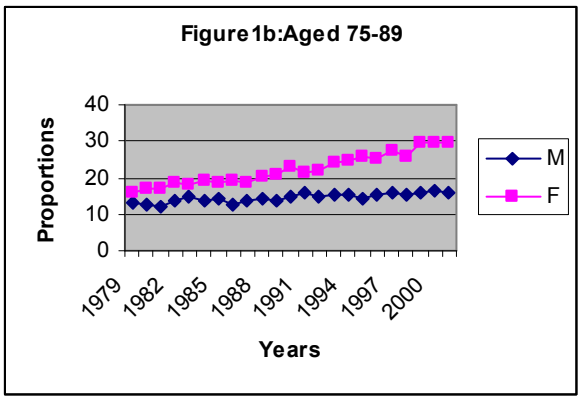
RESULTS

We used our large data set to examine trends in autoimmune disease reported as the underlying cause of death (Table 2) for the age categories 65-74, 75-89, and 90+ specific to genders. We examined gender differences in mortality rates in each age group one of the autoimmune diseases in Table 1 was the underlying cause of death between 1979 and 2001. Mortality increases for select autoimmune diseases with age were found for both males and females.

Table 2. Age-specific number of deaths for selected autoimmune diseases on UCD (1979-2001) by population rate (100,000).

Year	65-74 M	65-74 F	75-89 M	75-89 F	90+ M	90+ F
1979	7.94	11.92	13.26	15.84	14.65	14.51
1980	9.24	13.14	12.48	16.91	16.07	19.25
1981	8.63	12.61	11.90	17.21	13.98	18.49
1982	8.80	12.73	13.81	18.86	17.68	15.40
1983	8.46	12.58	14.94	18.07	14.83	20.38
1984	9.04	13.30	13.94	19.23	18.18	18.18
1985	7.98	12.87	14.27	18.59	14.88	20.39
1986	7.83	12.56	12.72	19.20	19.98	19.76
1987	8.46	13.05	13.45	18.85	20.89	24.23
1988	8.20	13.13	14.10	20.17	20.71	24.00
1989	9.09	13.72	13.54	21.00	17.86	24.41
1990	7.99	13.96	14.69	22.75	18.24	25.62
1991	7.85	14.22	15.62	21.64	23.50	21.87
1992	8.78	14.25	14.96	21.86	24.65	27.88
1993	8.74	14.51	15.16	24.32	15.06	25.08
1994	8.94	14.95	15.27	24.58	15.27	23.97
1995	8.90	14.82	14.47	25.82	22.91	26.88
1996	8.77	15.56	15.21	25.46	20.90	29.05
1997	9.19	16.08	15.99	27.44	22.27	29.63
1998	8.18	16.14	15.37	25.77	19.56	29.78
1999	8.68	16.28	15.75	29.78	22.57	31.68
2000	8.74	15.77	16.29	29.34	22.53	31.79
2001	8.75	16.23	16.11	29.41	20.42	34.30





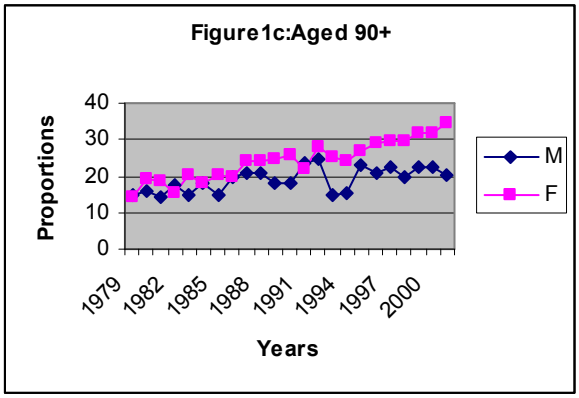


Figure 1. Specific age-specific rates for selected autoimmune diseases as the UCD (1979-2001).

There was a consistent increase in the rate of selected autoimmune disorders reported as an underlying cause of death by U.S. residents age 65+ from 1979 to 2001. The autoimmune disease death rate per 100,000 persons for females aged 65-74 was 11.92 in 1979. This increased to 16.23 in 2001; a 36.2% increase. The increase for males aged 65 to 74, 10.2 %, was smaller. For females aged 75-89, the rate was 15.84 in 1979, This increase to 29.41 in 2001, was an 85.67% increase. The increase for males, 21.49%, was smaller. The rate for females aged 90+ was 14.51 in 1979 and 34.30 in 2001, a 136% increase. Similar to other male age groups, the increase was smaller (39.39%) than for females. This reflects an annual increase of 1.35, 2.73, and 3.81% for the female age-groups 65-74, 75-89, 90+; and 0.42, 0.85, 1.45% for males of the same ages respectively (See figure 1a,b,c).

The proportion of deaths with autoimmune disorders reported as an underlying cause occurring at advanced ages (90+) increased significantly from 14.65% for males; 14.51% for females (1979) to 20.42% for males; and 34.30% for females (2001), reflecting that the oldest–old population is the fastest growing age group in the U.S. It also suggests that even though most autoimmune diseases usually affect young to middle aged persons, they are frequently associated with higher rates of morbidity and mortality in elderly populations (Ramos-Casals, 2003).

Autoimmune diseases and cancer co-morbidity (percentages) in the elderly age ≥65 between 1979 and 2001 in U.S. are shown in Table 3.

Table 3. Co-morbidity: Autoimmune diseases and Cancer (percentages).

Year	Male Ai among Ca (AiCa/Ca*)	Female Ai among Ca (AiCa/Ca)	Male Ca among Ai (CaAi/Ai)	Female Ca among Ai (CaAi/Ai)**
1979	0.28	0.44	4.42	2.57
1980	0.27	0.43	3.39	3.49
1981	0.29	0.47	3.73	1.72
1982	0.26	0.45	4.18	2.74
1983	0.30	0.47	4.31	2.92
1984	0.31	0.52	4.35	2.33
1985	0.30	0.49	4.09	2.96
1986	0.27	0.46	4.40	2.59
1987	0.30	0.52	4.02	2.62
1988	0.31	0.50	4.64	3.06
1989	0.32	0.51	4.49	2.53
1990	0.34	0.53	4.36	3.04
1991	0.33	0.54	6.16	2.71
1992	0.35	0.56	5.01	3.13
1993	0.33	0.59	4.69	2.59
1994	0.35	0.58	5.91	2.51
1995	0.34	0.59	5.16	2.41
1996	0.35	0.62	4.81	2.76
1997	0.34	0.58	4.32	2.82

1998	0.33	0.57	5.23	2.85
1999	0.32	0.53	4.29	2.12
2000	0.34	0.53	4.66	2.52
2001	0.32	0.53	4.38	2.57
Mean	0.31	0.52	4.57	2.68

Ai: Autoimmune diseases; Ca: Cancer
*Number of autoimmune diseases and cancer co-morbid condition in the multiple cause of death divided by number of cases where cancer is the underlying cause of death.
** Number of autoimmune diseases and cancer co-morbid conditions in the multiple cause of death divided by the number of cases where autoimmune diseases were the underlying cause of death.

Autoimmune diseases and cancer co-morbidity (percentages) in persons aged ≥65 between 1979 and 2001 in U.S. are shown in Figures 2 and 3.

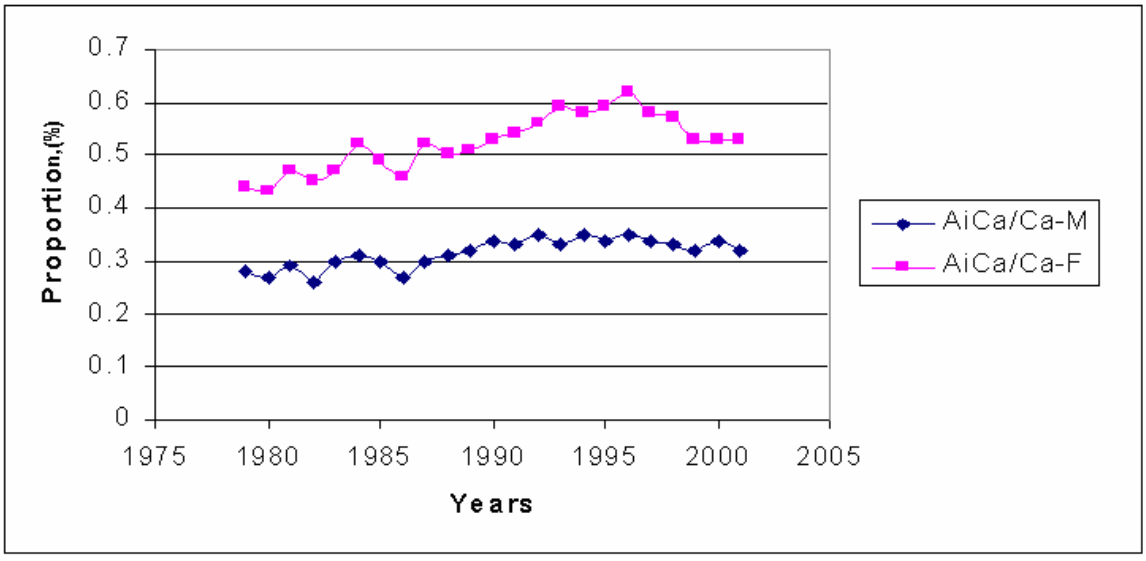


Figure 2. Co-morbidity: Autoimmune diseases and Cancer in U.S. 65+, 1979-2001(underlying cause of death was cancer).

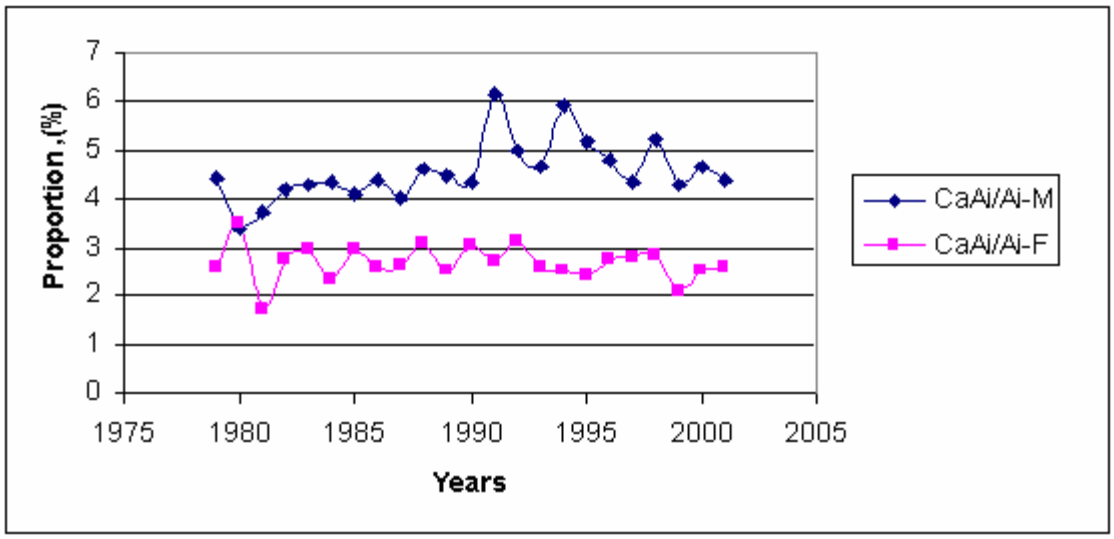


Figure 3. Co-morbidity: Autoimmune diseases and Cancer in U.S. 65+, 1979-2001(underlying cause of death was autoimmune disease).

When the underlying cause of death is cancer, cancer and autoimmune disease co-morbidity in the elderly age ≥65 in the U.S. increased from 0.44 to 0.62 between 1979 and 1995. After 1995, it showed a slight decrease to 0.53 for females; lower levels of co-morbidity and a smaller increase (0.28--0.32) is found for males (Figure 2). When the underlying cause of death is autoimmune disease, the data for the elderly age ≥65 between 1979 and 2001, shows that co-morbid conditions happen more often for males than for females. No clear changes can be seen for females in 1979-2001; there is fluctuation for males (Figure 3).

Male and female proportions were compared and found to be different with females having higher levels of co-morbidity when the underlying cause of death is cancer (difference = -0.21 (95%CI: 0.19, 0.23), $p<0.001$) and lower levels of co-morbidity when the underlying cause of death is autoimmune diseases (difference = 1.89 (95%CI: 1.57, 2.21), $p<0.001$) in the elderly age ≥65 between 1979 to 2001 (see Table 4).

Table 4. Autoimmune Disease and Cancer Co-Morbidity in the U.S. Aged ≥ 65.

Co-morbidity	Male	Female	Difference	95% CI	p Value
Ai among Ca	0.31%	0.52%	-0.21	0.19,0.23	<0.001
Ca among Ai	4.57%	2.68%	1.89	1.57,2.21	<0.001

Ai: Autoimmune diseases; Ca: Cancer; CI: Confidence interval.

Co-morbidity levels with different underlying causes of death were compared for men and women. The proportion of cancer deaths where autoimmune diseases was the underlying cause of death is larger than the proportion for autoimmune disease deaths where cancer was the underlying cause of death in both men (4.26, 95%CI: 3.99- 4.51, $p < 0.001$) and women (2.16, 95%CI: 1.99- 2.31, $p< 0.001$) (see Table 4) in those age ≥ 65.

The proportions of cancer deaths in persons aged 65+ where autoimmune diseases was the underlying cause of death, and autoimmune diseases deaths where cancer was the underlying cause of death were compared for males and females and found to be different. Females demonstrated higher levels of co-morbidity when the underlying cause of death is cancer and lower levels of co-morbidity when the underlying cause of death is autoimmune diseases.

DISCUSSION

Using Multiple Cause of Death Data produced by the National Center for Health Statistics (NCHS), our study investigates the proportion of cancer deaths where a) autoimmune disease was the underlying cause of death and b) autoimmune disease deaths

where cancer was the underlying cause of death, in the elderly U. S. population age ≥65 for 1979-2001. Male and female proportions were found to be different with females demonstrating higher levels of co-morbidity when the underlying cause of death is cancer, and lower levels of co-morbidity, when the underlying cause of death is autoimmune disease.

Even though the higher female prevalence of autoimmune diseases has been recognized for over 100 years, attention has only recently been focused on this relation. Studies have shown that, compared with men, women are at greater risk for autoimmune diseases, including lupus, rheumatoid arthritis, and multiple sclerosis. About 75% of autoimmune disease occurs in women during childbearing years (Jacobson, 1997). The reasons for the high prevalence in women are unclear. Researchers have long suspected that sex hormones such as estradiol may account for the increased risk. Hormonal factors, and their age fluctuation, play a major role in the onset of many autoimmune diseases in females. The mechanisms underlying this effect are poorly understood.

Most of our understanding of gender differences in an immune response comes from work done in animal models (Fairweather and Rose, 2004). For some time, the basic immune response between men and women has been known to differ, with women producing a more vigorous immune response and increased antibody production (Whitacre, 2001 and Da Silva., 1995). Females of many species more readily produce auto-antibodies and, therefore, are more likely to develop autoimmune disease than males (Olsen and Kovacs, 1996). However, autoimmune diseases that develop in men are more often severe (Klein, 2000). A higher relative risk of lymphoma was reported among both men (RR = 10.9) and women (RR = 6.9) with RA (Gridley et al., 1993; Prior, 1985) and

among men with Felty's syndrome (RR = 8.05) (Gridley et al., 1994). These reports suggest men with more severe disease have a higher risk of lymphoma but this may reflect the higher risk of lymphoma in men compared to women in the general population without rheumatic diseases (Ehrenfeld, 2001). Our analyses of elderly mortality in the U.S.1979-2001 also supports this point (see figure 2), where there are higher levels of cancer is among autoimmune disease in males ($P<0.001$). In contrast, higher levels of autoimmune diseases is among cancer in females ($P<0.001$). This suggests men with autoimmune diseases are at greater risk for cancer; women with cancer are at greater risk for autoimmune diseases compared to men with cancer. The former is inconsistent with the higher prevalence of autoimmune diseases in women. The latter is consistent with females higher prevalence of autoimmune disease.

So far no satisfactory explanation has been proposed for the increased risk of cancer in autoimmune diseases (Ehrenfeld, 2001). A more plausible alternative is the existence of an immunological predisposition for developing malignancies in patients with autoimmune diseases. It appears that immune dysregulation plays a role in the pathogenesis of autoimmunity and cancer. According to our analysis, we at least can speculate on the mechanism of downregulation of immune surveillance in autoimmune diseases and cancer co-morbidity.

The strength of our study is the extremely large number of cases in national mortality data covering more than 20 years for elderly persons. Analyses focused on cancer mortality for all sites combined and selected autoimmune diseases. Higher morbidity, mortality of autoimmune disease, and association with neoplasic processes, are possible characteristics of autoimmune diseases in the elderly. The limitation of our

study is the lack of a younger age group for comparison. Furthermore, we didn't analyze all autoimmune diseases. We are going to report analyses in a subsequent paper on associations between several specific autoimmune diseases and specific cancers.

In conclusion, gender differences were found in the co-morbidity autoimmune disease and cancer in the U.S.1979-2001. Findings were discussed with respect to the nature of immunosenescence, downregulation of immune surveillance and the complex roles that sex hormones may play in autoimmunity. The findings enhance our understanding of the mechanisms by which autoimmune diseases work and of sex differences in co-morbidity involving autoimmune diseases.

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