Incidence and prevalence of multiple sclerosis in Saskatoon, Saskatchewan

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ABSTRACT

Objective: To determine the incidence of multiple sclerosis (MS) in a longitudinal surveillance over 35 years and to estimate the prevalence rate in Saskatoon, Saskatchewan, on January 1, 2005.

Methods: A population-based registry was established in 1969, and identification of cases continued to 2005, from medical records, physicians, neurologists, community and provincial resources. A modified classification of Allison and Millar and the Schumacher diagnostic criteria were originally applied, and patients with definite and probable MS were included. The rates were age- and sex-adjusted to the US, European, and world 2000 populations.

Results: From 1970 to 2004, there were 558 incidence cases identified, 402 women and 156 men, for a sex ratio of 2.6:1 The average annual incidence rate was 9.5 in 100,000 (95% CI 8.8 to 10.4) and was stable over the three decades. The innate risk or residence at onset rate was 197 in 100,000 (95% CI 170 to 226). The crude prevalence rate for the living 587 cases on January 1, 2005, was 298.3 in 100,000 (95% CI 274.7 to 323.6).

Conclusions: The incidence and prevalence rates adjusted to the standardized populations were statistically higher than the longitudinal European studies and similar to North American studies. Our incidence study confirms the high risk of multiple sclerosis (MS) in Saskatoon, and these rates seem to be stable over the past 35 years. The high crude prevalence rate results from an accumulation of incidence and nonresident cases over time. Long-term follow-up studies and comparison with standardized populations are recommended to estimate reliable incidence and the true risk of MS in the world. ***Neurology*® 2007;69:1224–1229**

GLOSSARY

MS = multiple sclerosis.

There are few long-term surveillance studies over 30 years to determine the true incidence and prevalence rates of multiple sclerosis (MS) throughout the world. Only three prospective registries have been developed for longitudinal registrations of MS patients. The registry in Olmstead County, Minnesota, originated in 1905,[1] the registry in Norway originated in 1953,[2] and the registry in Denmark originated in 1948.[3] There were two 30-year surveys from Padova, Italy,[4] and one in a Northern Sardinia province.[5] Previous studies in Saskatoon have reported incidence rates of 8.3 in 100,000 from 1970 to 1979; 9.2 in 100,000 from 1980 to 1989[6]; and 8.7, 10.0, and 8.3 in 100,000 each decade from 1970.[7] The innate risk or residence at onset rate was 171 in 100,000, and the overall prevalence was 245 in 100,000 for the population.

The aims of this population-based prospective study were to determine the incidence of MS over the past 35 years; to estimate the innate risk or the resident at onset rate of MS on January 1, 2005; to identify potential factors influencing the incidence and prevalence rates; and to compare rates with the standardized Canadian, US, European, and world populations. Saskatoon is located at 52° 10′ north latitude and 106° west longitude. The population size was 126,445 in 1970, and it was increased to 196,810 in 2001. In 1962, universal medical

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Table 1 Incidence of multiple sclerosis in Saskatoon, 1970 to 2004

	Men			Women			Total		
Age, y	Population	Cases	Rate*	Population	Cases	Rate*	Population	Cases	Rate*
0–14	20,115	—	—	19,285	2	0.3	39,400	2	0.15
15–24	15,960	23	4.1	16,975	109	18.3	32,935	132	11.5
25–34	14,182	57	11.5	14,123	128	25.9	28,305	185	18.7
35–44	14,748	44	8.5	16,122	113	20.0	30,875	157	14.5
45–54	12,665	26	5.9	13,370	36	7.7	26,030	62	6.8
55–64	7,160	4	1.6	7,795	13	4.8	14,955	17	3.2
65–74	5,415	2	1.1	6,680	1	0.4	12,095	3	0.7
≥75	4,370	—	—	7,845	—	—	12,210	—	—
Total	94,615	156	4.7	102,195	402	11.2	196,815	558	8.1

* Incidence rate per 100,000 Saskatoon population, 2001.

insurance coverage became available for the physician and hospital services for all residents of Saskatchewan. The ethnic origins are 83.9% British and continental European, 9.8% aboriginal, and 6.3% visible minorities. The population is 92% Canadian born and 8% foreign born.

METHODS An MS registry was established in 1969 in the Royal University Hospital and transferred to the Saskatoon City Hospital Multiple Sclerosis Rehabilitation Clinic in 1993. A retrospective search of all medical records of three local hospitals commenced in 1969, and identification of cases continued for the next 35 years. The "spider approach"[8] was used in case ascertainment. Case information was obtained from nursing homes, the Home Care Program, MS Society Saskatoon, MS Rehab Clinic, family physicians, and neurologists and through a search of provincial records from 1984 through 1994. A review of medical records from Hospitals Medical Records Inventories was conducted every 5 years until 1990. Repeat surveys were performed in 1986, 1996, and 2003 to update the status of cases on whether they were alive, deceased, moved, or unable to be located.[6,7] Identification of cases continued until 2005. The medical records for admissions (340 cases) and emergency visits (204 cases) from 2001 to 2005 of all three local hospitals were screened, and all cases were in the registry. There were 19 single visits with a monosymptomatic complaint that remained for follow-up. There were 4 possible cases with insufficient information. The diagnostic classification, modified from Allison and Millar,[9] included clinical definite, possible, and suspect MS. The diagnostic criteria were adapted from Schumacher et al.[10] for the probable category. The revised diagnostic criteria of Poser[11] were introduced in 1983. MRI investigations were available since 1993 in this region. Formal alterations in diagnostic criteria with the availability of the MRI have changed the classification. Definite MS based on clinical criteria remains unchanged,[11] and further diagnosis requires supportive MRI evidence of MS according to recent revisions.[12] The possible and clinical isolated syndrome cases were excluded in this study. In 1997, an MS Treatment Database was established for all eligible patients referred by neurologists for disease-modifying therapies. The drug costs are covered by a provincial drug plan. The database has become a prime source for new case identification.

The original questionnaire and index cards have been maintained and included demographic information on sex, place of birth, date of birth, place of onset, age at onset, age at diagnosis, ethnic origin, family history, and date of death. The status of cases was updated for the prevalence date January 1, 2005. All incidence and nonresident cases were entered into a computerized database.

Statistical analysis. Analysis was performed using SPSS version 13.0. The annual incidence and prevalence rates[13] were estimated using the Statistics Canada 2001 population census.[14] The crude prevalence rate was estimated for January 1, 2005. Only clinical definite and probable cases were included in the analysis. Incidence rates were calculated for three 10-year intervals from 1970 to 1999 and the 5-year interval from 2000 to 2004. We used the χ^2 test for trend, equivalent to simple linear regression, to examine evidence for a linear trend in the ratio of female to male average annual incidence in the four time periods: 1970 to 1979, 1980 to 1989, 1990 to 1999, and 2000 to 2004. We compared the family histories of the incidence and nonresident cases to determine any genetic susceptibility.

The age- and sex-specific rates were calculated using the direct method with 5-year age intervals.[15,16] The rates were adjusted to the standard populations for the year 2000 of the United States, Europe, and the world.[17,18] The Saskatoon rates were compared with Canadian, Olmstead County, and the four European long-term reports. Confidence intervals (95% CI) were calculated using the method proposed by Schoenberg.[19]

RESULTS **Incidence.** In the 35-year period from January 1, 1970, to December 30, 2004, there were 558 incidence cases identified in Saskatoon, 402 women and 156 men, for a sex ratio of 2.6:1 (table 1). There is clear evidence of an increasing trend in the ratio of female to male average annual incidences from 1970 to 2004 ($\chi^2 = 23.64$, $df = 1$; $p <$

Table 2 Average annual incidence of multiple sclerosis in Saskatoon

	Men			Women			Total			
Interval	Population	Cases	Rate	Population	Cases	Rate	Population	Cases	Rate†	Sex ratio
1970–1979	64,677	40	6.2	68,131	84	12.3	132,808	124	9.3 (7.8–11.2)	2.0
1980–1989	84,764	50	5.9	91,095	130	14.3	175,859	180	10.2 (8.8–11.9)	2.4
1990–1999	92,285	47	5.1	99,177	129	13.0	191,462	176	9.2 (7.9–10.7)	2.6
2000–2004*	94,615	19	4.0	102,200	59	11.6	196,815	78	7.9 (6.2–9.9)	2.9

* The period 2000 to 2004 is 5 years.
† Incidence rate per 100,000 population (95% CI). The average annual incidence rate 9.5 in 100,000 (95% CI 8.8 to 10.4) population, 1970 to 2004.

0.00001). The female to male sex ratio increased from 2.0 to 2.9 (table 2).

The crude annual incidence rates were 4.7 in 100,000 for males, 11.2 in 100,000 for females, and 8.1 in 100,000 overall (table 1). This rate became 8.01 in 100,000 (95% CI 7.37 to 8.71) when adjusted to the 2001 Canadian population, 7.84 in 100,000 (95% CI 7.21 to 8.52) when adjusted to the US 2000 population, 7.89 in 100,000 (95% CI 7.26 to 8.58) when adjusted to the European 2000 population, and 7.90 in 100,000 (95% CI 7.27 to 8.59) when adjusted to the world 2000 population. For the three 10-year intervals starting from 1970, the incidence rates showed a stable trend (table 2). The rate adjusted to the Saskatoon 2001 white population was 9.8 in 100,000 (95% CI 9.0 to 10.7). There is a lower incidence rate in the 5-year period from 2000 to 2004.The time to diagnosis in incidence cases is 3.3 years, and that results in a incomplete case ascertainment in this time period.

Prevalence. On January 1, 2005, there were 587 living prevalence cases, 416 women and 171 men, for a sex ratio of 2.4:1. The 21 possible MS cases and 14 cases with missing information were excluded. The overall crude prevalence rate was 298.3 in 100,000 (95% CI 274.7 to 323.6) (table 3). The prevalence rate was 329 in 100,000 when age- and sex-adjusted to the Canadian 2001 population, 309.9 in 100,000 when adjusted to the US 2000 population, 336.9 in 100,000 when adjusted to the European 2000 population, and 240.4 in 100,000 when adjusted to the world 2000 population. The prevalence rates were significantly higher for women than for men, in all age groups, except that they were nearly equal in the group older than 75 years (table 3). On prevalence day, 402 incidence cases were still living, 54 had deceased, 59 had moved, and 43 were unable to be located. The innate risks of clinical definite cases was 182 in 100,000 (95% CI 157 to 212), and 197 in 100,000 (95% CI 170 to 226) including probable cases.

The average age at onset of the incidence cases was 32.4 (SD 10.3) years for women and 35.4 (10.5) years for men. The mean duration to diagnosis was 3.3 (4.3) years. The mean age of the living patients was 49.3 (11.9) years for men and 47.6 (11.1) years for women. The duration of disease of the living patients was 15.0 (9.1) years.

Table 3 Prevalence of multiple sclerosis in Saskatoon, January 1, 2005

	Men			Women			Total		
Age, y	Population	Cases	Rate	Population	Cases	Rate	Population	Cases	Rate*
0–14	20,115	—	—	19,285	—	—	39,400	—	—
15–24	15,960	1	6.3	16,975	6	35.3	32,935	7	21.3
25–34	14,182	16	112.8	14,123	40	283.2	28,305	56	197.8
35–44	14,748	29	196.7	16,122	85	527.2	30,875	114	369.2
45–54	12,665	55	434.3	13,370	138	1,032.2	26,030	193	741.5
55–64	7,160	41	572.6	7,795	87	1,116.1	14,955	128	855.9
65–74	5,415	20	369.3	6,680	43	643.7	12,095	63	520.9
≥75	4,370	19	205.9	7,845	17	216.7	12,215	36	294.7
Total	94,615	171	180.7	102,195	416	407.1	196,815	587	298.3

* Rate per 100,000 Saskatoon population, 2001.

The average age at death was 60.1 (11.5) years for men and 58.7 (13.5) years for women. The duration of disease for the deceased patients was 19.0 (6.2) years for men and 19.0 (8.2) years for women.

Of the 558 incidence cases, 155 cases (27.8%) were born in Saskatoon, 284 (50.9%) were born in the province of Saskatchewan, 56 (10.0%) were from other provinces, 20 (3.6%) were foreign born (14 Europe, 5 United States, and 1 Middle Eastern country), and 43 (7.7%) had no place of birth available. Four of the 558 cases with partial aboriginal heritage had onset in Saskatoon, indicating a low susceptibility to MS. A total of 70 cases (12.5%) were of British origin, 343 (61.5%) were of continental European origin, 18 (3.2%) were of non-European origin, and 127 (22.8%) were of unknown origin.

Of the 558 cases, 154 (27.6%) had at least one family member affected with MS (104 females and 50 males), and 129 of 154 (83.8%) were first-degree/second-degree relatives. Three of 5 identical twin sisters had MS, and 3 identical twin brothers were not affected, for a 37.5% concordance rate. Of the 182 nonresident cases, 18 men and 32 women (27.5%) had a family history of MS, of which 74% were first-degree/second-degree relatives. There were no identical twins in this group.

DISCUSSION We compared our results to other long-term incidence studies, including the three registries[1-3] and two epidemiologic surveys.[4,5] When adjusted to the US 2000 population, the Saskatoon incidence was 7.84 in 100,000 (95% CI 7.21 to 8.52), and it was comparable to that of Olmstead County, 7.3 in 100,000 (95% CI 6.0 to 8.6), which is located southeast of Saskatoon at 44° north latitude and 92° west longitude. When adjusted to the white population and compared with Olmstead County, the Saskatoon incidence rate was 9.8 in 100,000 (95% CI 9.0 to 10.67), and this indicates a significant difference in these two regional populations located in this wide latitude.

In a meta-analysis report of 69 prevalent and 22 incidence studies, from 1990 to 1998 the mean incidence rates adjusted to the world and European populations were 2.8 in 100,000 (95% CI 2.6 to 3.0) and 3 in 100,000 (95% CI 2.8 to 3.2).[20]

The four European studies[2-5] report recent increased incidence rates that range from 4.2 to 6.0 per 100,000, with two studies[2,5] adjusted to the standard European population and one adjusted to an Italian standard population.[4] The Olmstead study is adjusted to the US 2000 standard population. The incidence rate of the current study is comparatively higher than the adjusted rates reported in the meta-analysis and the five longitudinal studies (table 1). Most longitudinal studies have reported increased rates of MS over time, which are beginning to stabilize.[1,2] The enhanced ascertainment in this study is due to the recent technological advances (MRI), awareness, and availability of new drug treatments. The rate of MS is plateauing as determined over the past three decades. The etiologic factors that determine the incidence of MS may be stable.

In Canada for the period of 1980 through 1989, an incidence of 7.26 in 100,000 is reported in Weslock County, Alberta,[21] 5.6 in 100,000 is reported in Newfoundland,[22,23] 8.8 in 100,000 is reported in Nova Scotia,[24] and 3.4 in 100,000 is reported in London, Ontario.[25] These rates show regional variations, but Nova Scotia and Saskatoon have similar rates. For more accurate comparison, rates from different studies need to be adjusted to standardized populations.

There are time intervals and regional variations of high incidence. In Southeast Scotland from 1992 through 1995, the rate was 12.2 in 100,000 (95% CI 10.8 to 13.7).[26] In Alberta, a mean annual incidence of 22.2 in 100,000 was found for the period of 1998 to 2000.[27] A high rate of 12.1 in 100,000 (95% CI 9.98 to 14.7) occurred in Saskatoon from 1985 to 1989, and an exceptional high rate of 16.3 in 100,000 (95% CI 11.0 to 23.3) occurred in 1989 when there were 31 incidence cases (12 men and 19 women). Short-term studies may not determine the overall risk, as is shown in our study. The Canadian rates are not strictly comparable because of the difference in methodologies and incidence case identification. In comparison with our previous report,[7] there has been a slight increase in the incidence rate, which reflects more case ascertainment over time with repeated surveys. The high incidence rates in the shorter-term Canadian studies cover a wide range of values and may suggest that even in this northern temperate climate, there are a wide variety of factors that may have been acted as triggers of MS.[28] Our study shows a significant increasing trend in the female to male sex ratio of MS over the past three decades that concurs with the recent report of the substantial increase of the sex ratio in Canada, calculated by birth year and implicating environmental–gene interaction for the rapid change.[29] The equivalent high familial rates in the incidence and nonresident cases, and the twin concordance in our study support a genetic susceptibility to MS.[30] The Saskatoon population

is mainly of European descent, and the high familial aggregation strongly suggests a racial/genetic determination.

Epidemiologic studies have found a greater prevalence in northern and southern temperate climates ranging from 5 to 100 in 100,000 between the 37° and 52° north latitude.[31] There are regional variations of MS prevalence in Canada, and a reported rate of 340 in 100,000 for the prairie provinces is similar to our crude prevalence rate.[32] Urbanization and immigration of nonresident cases inflate the overall crude prevalence rates in this and other regional areas. These persons are immigrating to the city for the medical and rehabilitation services, for family work and educational opportunities, and for the lower cost of housing, and some are returning for closer family relationships. The regional variations and prevalence rates do not reflect the true risk of MS, which is dependent on incidence only. Some regional prevalence rates in Canada may vary as a result of the accumulation and influx of nonresident cases. The adjusted incidence rate of 8.01 in 100,000 indicates a high-risk area, and the innate risk or prevalence based on the incidence rate remains high at 197 in 100,000. The place of onset and date of onset must be determined to identify incidence cases. Our incidence is an estimate because there has been a large emigration of the younger population from age 20 to 35 years from this city and replaced by immigration from other provinces and elsewhere.

The incidence rates over the past three decades (1970 through 1999) with the repeated surveys have become stable (table 2). The slight increase compared with our previous reports is due to the repeated surveys and more case ascertainment. Continued long-term surveillance studies are necessary to determine reliable incidence rates and the innate prevalence rate of MS. The use of age- and sex-adjusted standard populations is recommended for meaningful comparisons of incidence and prevalence rates with other geographic population studies. The implementation of the year 2000 standard populations has been recommended.[33]

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