No increase in age-specific incidence of myelodysplastic syndromes

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A B S T R A C T

Backgrounds and Objectives. Epidemiological data on myelodysplastic syndromes (MDS) are sparse. However, the available evidence indicates that MDS are among the most common hematologic diseases.

Design and Methods. In a previous study, we showed that incidence rates rose from 1 to 4.1 in the period 1976-1990, with no increase between 1986 and 1990. We extended our study, covering the years 1991 through 2001. Diagnostic criteria and cytomorphology remained the same, with the criteria of the FAB classification being applied consistently.

Results. Three-hundred and eight new cases of MDS were identified in the town district of Düsseldorf, which provides the reference population for calculating incidences. There was no further rise in MDS incidence. The crude incidence in the period 1991-2001 was 4.9 (5.52 in males, 4.36 in females), which is similar to that in the 1986-1990 period. Age-specific incidences were 8.7, 24.5, and 31.3 for the age groups 60-70, 71-80, and 80-90 years, respectively. The incidence of MDS in the age group >70 years was significantly higher among males (42.3) than among females (19.0). The preponderance of males was found among patients with refractory anemia with excess blasts (16 vs 3), refractory anemia with excess blasts in transformation (7 vs 2), refractory anemia (15 vs 6) and chronic myelomonocytic leukemia (7 vs 2), whereas, somewhat surprisingly, the age-related incidence of refractory anemia with ringed sideroblasts was similar for males and females (4 vs 5). The data on MDS incidence in the town district of Düsseldorf showed a plateau since 1986.

Interpretation and Conclusions. Interpreting our data covering a 26-year period, we feel that the increase in the early years primarily reflected improved case ascertainment, whereas our new data may provide a good approximation of the true incidence of MDS. There is no evidence that the age-adjusted incidence of MDS is rising.

Key words: myelodysplastic syndromes, FAB classification, age-related incidence, descriptive epidemiology.

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Since the World Health Organization (WHO) only recently recognized myelodysplastic syndromes (MDS) as disease entities,[1,2] epidemiological data on MDS cannot be obtained from official statistics on morbidity and mortality, but have to be extracted from specialized registers such as regional cancer surveys and hospital-based registries. The MDS Registry in Düsseldorf provides a good opportunity to examine the incidence of MDS. The MDS Registry has established a network ensuring close co-operation with hospitals and private physicians in town. The purpose of this study was to examine epidemiological characteristics of MDS with special reference to variations of the incidence rates over time and to incidences in different age groups. We compared the findings with incidences rates obtained in a previous study[3] covering the years 1975-1990.

Design and Methods

For the study period from 1991 to 2001 we used exactly the same methods of identifying patients with MDS as in our previous study. The blood and bone marrow smears of all MDS patients included in the registry, including those with tentative diagnoses, were re-evaluated and classified according to French-American-British (FAB) criteria.[4] Minimal diagnostic criteria for MDS included the presence of single or multiple cytopenias or just macrocytosis without anemia, along with clear morphologic evidence of dysplasia in the bone marrow. The morphologic assessment was performed centrally according to the FAB classification, taking into account all the dysplastic parameters described in the initial FAB proposals. Since their publication, the

WHO proposals were also taken into consideration. All cytological diagnoses in the present study were made by C.A. or U.G., who applied the FAB criteria consistently, thereby ensuring comparability with the previous study. In the rare instances of uncertain cases or divergent classification, a joint effort was made to arrive at a final conclusion, giving priority to C.A.´s judgement, because of his superior experience. The proportion of cases reviewed by each of the two reviewers did not change significantly, as C.A. reviewed 90% of all cases in both series.

The clinical and laboratory results in the patients' records were reviewed. In particular, special care was taken to identify exclusion criteria for MDS, such as vitamin B12 and folic acid deficiency, alcoholism, hypersplenism, paroxysmal nocturnal hemaglobinuria, antibody-mediated cytopenia, solid tumors, chronic inflammatory diseases, severe metabolic disorders and acute toxicity from myelotoxic substances or radiation.

The Düsseldorf MDS registry contains data on all patients with MDS that are brought to our attention. The number of new patients has risen significantly over the last 25 years. Currently, 150–160 newly diagnosed patients are entered into the registry each year. We are not able to define the catchment area, in terms of administrative regions, for the whole population of patients. However, the town district of Düsseldorf, with approximately 575,000 inhabitants, is a clearly defined area for which exact demographic data are available. These data are provided by the *Landesamt für Statistik* of North-Rhine-Westphalia. There was no significant change with respect to the sex and age distribution in Düsseldorf over the observation period. MDS incidence data were adjusted for age and sex using the regional demographic data for age and sex of the entire town district population. As far as the incidence of MDS is concerned, we can state with confidence that very few patients from this area will be given a diagnosis of MDS without their bone marrow being reviewed in our laboratory. All blood and marrow slides of patients with anemia, bicytopenia or pancytopenia which were initially seen in one of three other hospitals in Düsseldorf were re-evaluated in our laboratory. We performed active case ascertainment by visiting archives and reviewing blood and bone marrow slides from patients with cytopenia, diagnosed at co-operating institutions.

Results

Among a total of 21,895 bone marrow specimens examined between 1991 and 2001, 1,302 cases of MDS were identified (5.9%). Of these, 1,219 patients (93.6%) had primary MDS. In 83 patients (6.4%), MDS
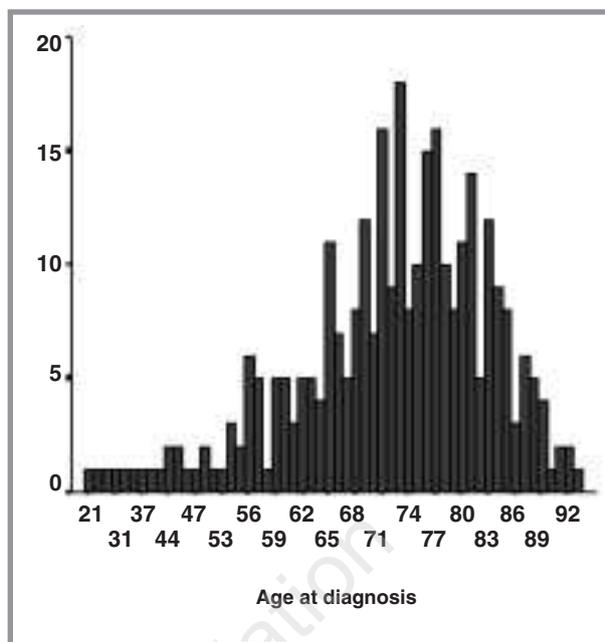

Figure 1. Age distribution of 308 MDS patients.

developed as a late complication of antineoplastic chemotherapy and/or radiotherapy (secondary MDS). Among the 1,302 patients with MDS, 308 (23%) lived in the town district of Düsseldorf.

FAB subtypes

Patients with refractory anemia (RA) and RA with ringed sideroblasts (RARS) accounted for 52% of all cases, 33% had RA with excess blasts (RAEB) or RAEB in transformation (RAEB-T), and 15% had chronic myelomonocytic leukemia (CML). Although there were annual variations, there was no substantial change in subtype distribution. We found no significant increase in new MDS diagnoses. The average number of new cases per year was 28, ranging from 21 to 35.

Age distribution

Figure 1 shows the age distribution. The median age at diagnosis was 72 years (20-93) and did not differ significantly between FAB types: RA 72 (20-91), RARS 75 (32-87), RAEB 75 (43-90), RAEB-T 71 (26-92), CMML 76 (56-93). Eighteen patients were under 50 years of age (5.8%), and 26% of patients were older than 80 years. The proportion of octogenarians did not change over the study period.

Gender

There was a preponderance of males among the patients with CMML (male/female: 1.58) and RAEB (1.45). In RARS, there was a preponderance of females (0.69). In the other FAB types, the gender ratio was rel-

Table 1. MDS incidence rates in the town district of Düsseldorf over an 11-year period.

Year	Total incidence	women	men	<50 years	50-70 years	>70 years
1991	4.50	3.5	5.5	0.27	3.3	29
1992	5.19	4.5	5.9	0.27	7.2	26.0
1993	4.35	3.2	5.5	0.56	3.2	26.4
1994	3.49	2.9	4.4	0.56	2.6	20.2
1995	3.85	2.3	5.5	0.28	4.0	21.7
1996	3.50	3.3	4.1	0.56	3.3	18.8
1997	5.61	4.4	6.6	0.28	8.8	25.7
1998	4.76	4.6	4.8	0.28	4.1	28.4
1999	5.91	5.6	6.3	0.86	9.5	21.6
2000	6.08	4.6	7.8	0.17	4.1	40.3
2001	4.17	4.3	4.1	0.17	6.8	18.7

Table 2. MDS incidence rates, according to age-groups and gender.

Age group	Total	Men	Women
<30	0.36	0.5	0.24
30-40	0.43	0.34	0.53
40-50	1.29	1.2	1.37
50-60	2.83	3.49	2.2
60-70	8.68	11.41	6.18
70-80	24.5	38.81	17.81
80-90	31.3	53.58	23.64
all ages	4.9	5.52	4.36

atively balanced (RA: 1.03, RAEB-T: 1.25). We diagnosed 19 patients with treatment-related MDS (6.2%); the number of new cases per year varied between 0 and 7, with no significant trend.

Incidences

Table 1 shows the incidence of MDS over an 11-year period in the town district of Düsseldorf. Marked annual variations can be attributed to the small numbers of patients in the different age groups. The annual incidence in patients over 70 years of age varied between 18 and 40 cases per 100,000 population. To compensate for annual variations, we calculated the crude and age-specific incidences for the entire 11-year time period, using average annual case numbers (Table 2).

The crude annual incidence of MDS was 4.9/100,000. The relation to age was obvious, with age-specific incidence rates lower than 0.4/100,000 for individuals younger than 30 years, and as high as 31.3/100,000 for people aged between 80 and 90 years.

Sex-specific incidence data show that MDS was more frequent in males than in females. This was particularly true for the older age groups (>70 years), in which high incidence rates were mainly attributable to male patients. This was similar for all FAB types except RARS (Figures 2-4). Figure 2 additionally shows the numbers of patients in the different age groups. On statistical analysis, the null hypothesis, that sex ratio was equal in all age groups, had to be rejected since the difference between the male and female incidences of MDS was significantly different for all age groups >50 years, even though there were very few patients over 90.

Long-term numbers

Figure 5 shows the total number of diagnoses per year covering the whole study period from 1976 to 2001. The number of MDS cases did not rise significantly from the mid-eighties.
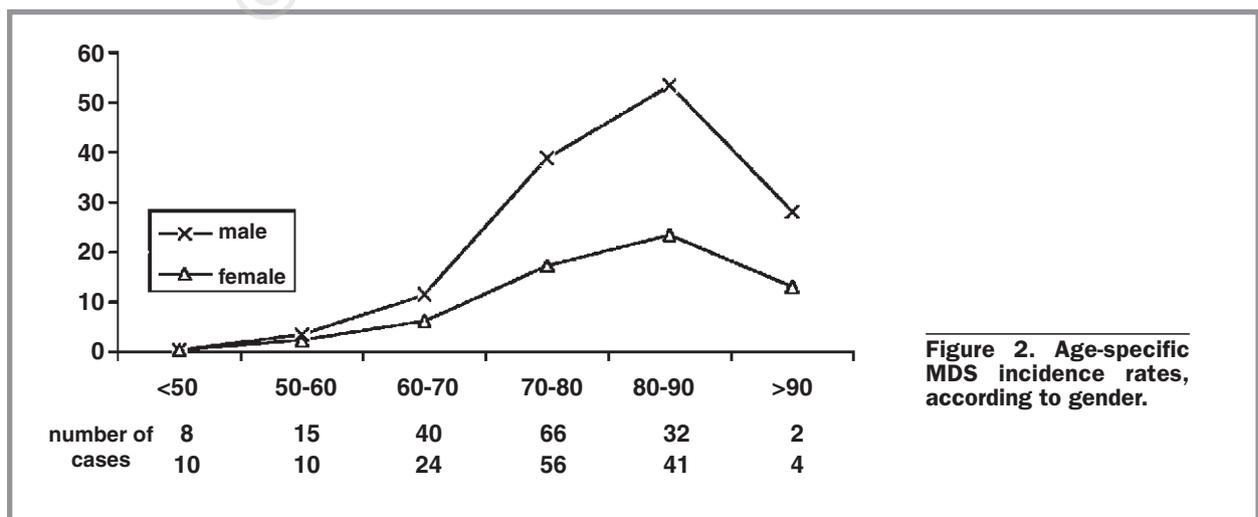

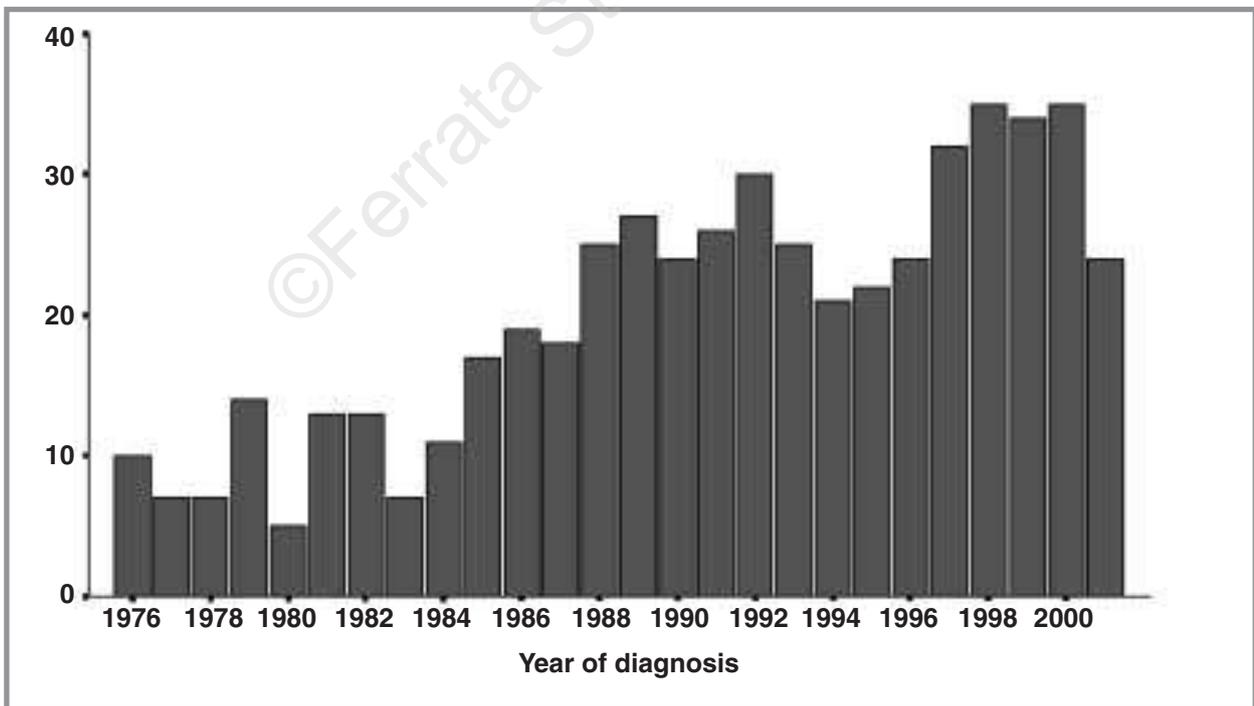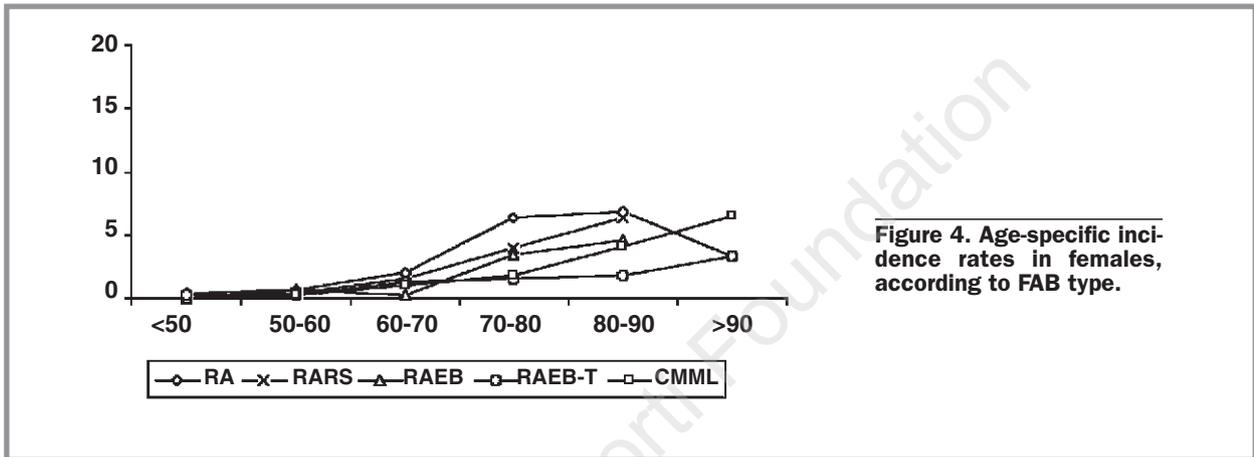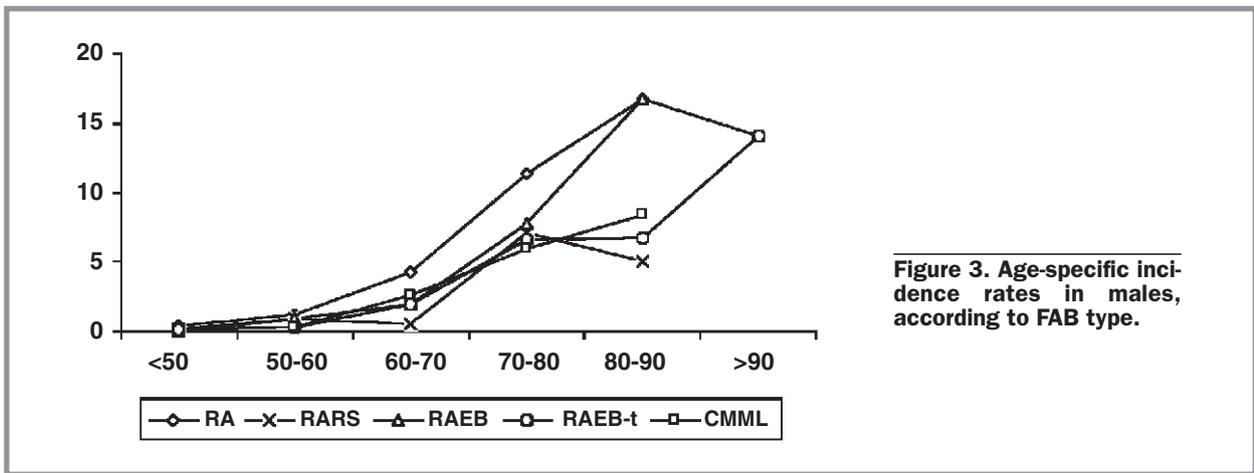Figure 2. Age-specific MDS incidence rates, according to gender.

number of cases	<50	50-60	60-70	70-80	80-90	>90
	8	15	40	66	32	2
	10	10	24	56	41	4

Figure 3. Age-specific incidence rates in males, according to FAB type.

Figure 4. Age-specific incidence rates in females, according to FAB type.

Figure 5. Numbers of MDS diagnoses in the town district of Düsseldorf from 1976 to 2001.

Table 3. Incidence of MDS: review of the literature.

Study	Cartwright	Cartwright	Phillip	Shimizu	Giralt	Radlund	Williamson	Bauduer	Maynadié	Carli	Carli	Aul	This study
Country	UK/Wal.	UK/Wal.	UK	Jap.	Spa.	Swe.	UK	Fra.	Fra.	Fra.	Fra.	Ger.	Ger.
OP	1984-86	1984-93	9 years	1991	1998	1978-92	1981-90	1993-96	1980-90	1980-95	1980-97	I:1976-80 II: 1981-85 III: 1986-90	1991-2001
Pop.	16 Mio.	16 Mio.	/	160 Mio.	1,18 Mio.	310,000	452,000	290,000	493,000	493,000	493,000	575,000	575,000
Inc.	3.6	m 4.31 w 3.62	9.3	1	8.1	3.5	12.6	7.7	3.2	m 2.6 w 1.3	m 2.9 w 1.5 III: 4.1	I: 1.4 II: 2.1	4.9 m 5.5 w 4.3
Remarks	no CM	no CM men: 50-54: 1.16 55-59: 2.76 60-64: 6.19 65-69: 11.26 70-74: 20.31 74-79: 35.60 80-84: 50.24 women: 50-54: 1.05 55-59: 1.72 60-64: 3.75 65-69: 6.40 70-74: 9.88 74-79: 18.22 80-84: 25.39	no CM	no CM	<60: 0.7 >60: 31.2 men: 9.6 women: 6.6	<50: 0.7 50-70: 1.6 >70: 15	** <50:0.5 50-60:5.3 60-70:15 70-80:49 >80:89	>65: 31.4	men: 50-59: 3.5 60-69: 8.2 70-79: 30 >80: 45 women: 50-59: 1 60-69: 6 70-79: 10 >80: 22	men: urban: 3.5 rural: 1.5 women: urban: 1.5 rural: 1.1	°°	I: <50: 0.1 50-70: 1.1 >70: 8.7 II: <50: 0.05 50-70: 3.1 >70: 11.0 III: <50: 0.2 50-70: 4.8 >70: 22.8	50-60: 3.4 60-70: 11.4 70-80: 38.8 80-90: 53.8 >90: 28.1 women: 50-60: 2.2 60-70: 8.1 70-80: 17.1 80-90: 23.6 >90: 13.0

*OP: observation period. Pop: population. Inc.: incidence. CM: central morphology. **Not always confirmed by biopsy. °°Regional disparities.*

Incidence according to WHO classification

Finally, we calculated the incidence of MDS on the basis of the WHO classification,[2] excluding CMML or RAEB-T with more than 20% bone marrow or peripheral blasts. Accordingly, 85 patients (28%) were excluded, which led to a crude MDS incidence of 3.5 cases/100,000 per year.

Discussion

The present study examined the incidence of MDS over an 11-year period, with the reference population, diagnostic criteria, and cytomorphologists being the same as in a previous study.[3] Taking both studies together, we have now surveyed a 26-year period using standardized acquisition of patients with MDS. In our previous study, we found a significant increase in the incidence of MDS between 1976 and 1986, from 1.4 to 4.1/100,000 per year. This increase was not attributable to changes in demographic or environmental factors, or to an increase in the frequency of treatment-related MDS. The main reason for the increased incidence was a higher frequency of bone marrow examinations in elderly patients. In addition, physicians' awareness was augmented, at least during the first years of that study, through publication of the FAB criteria for classifying MDS . Within the last quinquennium (1986 to 1990) of

the previous study, we found no further increase. Case ascertainment seems to have become more or less complete since the late 1980s. No consistent change in disease incidence was discernible over the new study period. Both the crude and age-specific incidences were almost identical with those calculated for the last quinquennium (1986 to 1990) of the first study. The high incidence of MDS in older age groups was mainly attributable to male patients, suggesting that occupational exposure of men to *myelodysplastogenic* substances may play a role in the etiology of MDS. However, if occupation is part of the explanation for the higher incidence in men, the induction-latency times appear to be much longer than those usually assumed for treatment-induced MDS.

Treatment-related MDS accounted for about 6% of the MDS cases in the registry. We found no increase in treatment-related MDS within the study period, but an increase may be anticipated for the future, due to improved survival after cancer treatment.[5] Life-style factors, such as smoking and alcohol consumption, which are more prevalent in the male population, may also play an etiological role. Exposure to these types of agents usually lasts over decades and may therefore contribute to the development of MDS in old individuals. However, there are no data on this topic as yet.

A small number of other epidemiological studies have calculated the incidence of MDS[3,6-16] (Table 3). Only three

of them are based on time periods long enough to look for trends. The study by Williamson[6] covered a 10-year period without finding a significant change in incidence rates. The crude incidence was as high as 12.6, perhaps due to the fact that 38% of the patients were at least 80 years old. Furthermore, not all diagnoses were confirmed by bone marrow biopsy. Radlund[7] examined the incidence of MDS in a Swedish county over a 15-year period. The incidence rate of MDS did not change significantly (from 3.2 to 4.1). The study by Maynadie[8] covered a 10-year period and showed an incidence rate of 3.2 which did not change over time. Two follow-up studies on the same population, covering 16 years[9] and 18 years,[10] again failed to show an increase in the incidence of MDS. Bauduer[11] presented epidemiological data from a 4-year period, calculating an incidence rate of 7.7. Cartwright[12] published a study covering 2 years and reported an incidence rate of 2.1, excluding patients with RAEB-T. That study was based on collecting locally diagnosed cases, rather than performing centralized cytomorphology. A large study covering the years 1984–1993, published by Cartwright[13] and based on the same method, calculated incidences of 4.31 for males and 3.62 for females. Giralt[14] and Shimizu[15] calculated incidence rates of 8.1 and 1.0, respectively. Each study covered 1 year and relied on reports from hospitals involved in making the diagnosis, without central review of blood and bone marrow slides. It was not possible to evaluate changes over time in the latter studies. Our previous investigation was the only epidemiological study demonstrating an increase in MDS incidence. However, we feel that the increase in the early years primarily reflected improved case ascertainment. Our new data, on the other hand, may provide a good approximation of the true incidence of MDS.

In conclusion, MDS are frequent hematologic disorders, with a crude incidence of about 5 cases per 100,000 population per year. In people over 70 years of age, incidence rates are about 20-40/100,000, suggesting that MDS are at least as common as chronic lymphocytic leukemia or multiple myeloma. At present, we have no evidence that the age-adjusted incidence of MDS is rising. However, with the *aging of the populations* in Western civilizations, we might see more MDS patients in the future.

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