Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs

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Reporting of myelodysplastic syndromes (MDSs) and chronic myeloproliferative disorders (CMDs) to population-based cancer registries in the United States was initiated in 2001. In this first analysis of data from the North American Association of Central Cancer Registries (NAACCR), encompassing 82% of the US population, we evaluated trends in MDS and CMD incidence, estimated case numbers for the entire United States, and assessed trends in diagnostic recognition and reporting. Based on more than 40 000 observations, average annual age-adjusted incidence rates of MDS and CMD for 2001 through 2003 were 3.3 and 2.1 per 100 000, respectively. Incidence rates increased with age for both MDS and CMD ($P < .05$) and were highest among whites and non-Hispanics. Based on follow-up data through 2004 from the Surveillance, Epidemiology, and End Results (SEER) Program, overall relative 3-year survival rates for MDS and CMD were 45% and 80%, respectively, with males experiencing poorer survival than females. Applying the observed age-specific incidence rates to US Census population estimates, approximately 9700 patients with MDS and 6300 patients with CMD were estimated for the entire United States in 2004. MDS incidence rates significantly increased with calendar year in 2001 through 2004, and only 4% of patients were reported to registries by physicians' offices. Thus, MDS disease burden in the United States may be underestimated. (Blood. 2008;112:45-52)

Introduction

Myelodysplastic syndromes (MDSs) comprise morphologically distinct disorders characterized by dysplastic and ineffective hematopoiesis. Although historically MDS has not been defined as a cancer, MDS results from the clonal expansion of an hematopoietic progenitor and progresses to acute myeloid leukemia in approximately 30% of patients.[1] Incidence rates for MDS and chronic myeloproliferative disorders (CMDs) in the United States were unavailable prior to the addition of these stem cell malignancies to central cancer registries in 2001. Description of national incidence rates provides an important baseline for future studies of secular trends and allows for the examination of rates by selected demographic factors to define risk profiles of these hematologic malignancies in the American population.

Estimated incidence rates of MDS for the United States in 2001 to 2003 were recently published based on initial data reported from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program.[2] Incidence rates increased with age and were higher among males than females,[2] although rates were not analyzed for MDS subtypes or for CMD. SEER covers approximately 26% of the US population, and given the recent incorporation of MDS to cancer registry surveillance, we sought to extend national estimates to 33 additional geographic areas that are not included in SEER and assess possible patterns in diagnostic recognition that might affect reporting frequency. To investigate MDS and CMD incidence overall and by disease subtype, evaluate trends in incidence by demographic factors, estimate total numbers of cases expected to be diagnosed in the entire United States, and examine incidence and survival data updated through 2004, we conducted an extensive analysis of data obtained through both SEER and the North American Association of Cancer Registries (NAACCR), based on more than 40 000 patients, the largest number ever available for analysis of MDS and CMD.

Methods

Frequencies of reported MDS, CMD, and chronic myelomonocytic leukemia (CMML) cases were obtained from US state and regional population-based cancer registries. (Although CMML is classified as an MDS subtype in the French, American, British [FAB] system, CMML is not coded as MDS in the system by which cancer cases are reported to central cancer registries. Therefore, CMML was included as a disease entity separate from MDS in the present analysis.) These cancer registries collect information on new cancer diagnoses through the National Cancer Institute's SEER Program, Centers for Disease Control Prevention's National Program of Cancer Registries (NPCR) Program, or both.[3] All cancer registries are members of NAACCR. The source of data in this paper for all analyses, except survival, is NAACCR's research data file, Cancer in North America (CINA); the December 2005 submission of the CINA Deluxe 1995 to 2003 file was used, and diagnosis years from 2001 to 2003 were included. To be

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included in the CINA deluxe database, registry data are required to meet specific certification criteria, details of which have been previously described.[4]

In the CINA Deluxe database, SEER data are composed of 9 state areas (California, Connecticut, Hawaii, Iowa, New Mexico, Utah, Kentucky, Louisiana, and New Jersey) and 3 metropolitan areas (Atlanta, Detroit, and Seattle). The other state registries in the CINA Deluxe file include Alabama, Alaska, Arizona, Colorado, Delaware, Washington, DC, Florida, Georgia, Idaho, Illinois, Indiana, Maine, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nebraska, Nevada, New Hampshire, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Texas, Washington, West Virginia, and Wisconsin. Since the SEER metropolitan areas of Atlanta, Detroit, and Seattle are also included in the Georgia, Michigan, and Washington registries, we excluded these 3 metropolitan areas from their respective states, thus avoiding double counting of patients and facilitating the comparison of incidence rates for MDS and CMD across 3 groups: SEER registries, NAACCR excluding SEER registries, and total registries.

Patients diagnosed between 2001 and 2003 were identified by International Classification of Diseases for Oncology Third Edition (ICD-O-3) codes (MDS: 9980-9989; CMD: 9950-9964; and CMML: 9945). ICD-O-3 includes codes for both topography and morphology and was implemented for data collection in cancer registries worldwide in 2001.[5] Although ICD-O-3 was developed by the World Health Organization (WHO), there are subtle differences between ICD-O-3 and the "WHO classification" of myeloid neoplasms, published in 1997 by WHO in conjunction with the European Association of Hematopathologists and the Society for Hematopathology.[6,7] As previously described,[2] the WHO classification includes the following MDS subtypes: refractory anemia (RA), RA with ringed sideroblasts (RARS), refractory cytopenia with multilineage dysplasia (RCMD), RCMD with ringed sideroblasts (RCMD-RS), RA with excess blasts-1 (RAEB-1), RAEB-2, MDS associated with isolated 5q deletion, and MDS, unclassified. The ICD-O-3 similarly includes RA, RARS, RAEB (RAEB-1 and -2 combined), MDS associated with isolated 5q deletion, RCMD, and MDS, not otherwise specified. Additional codes exist in ICD-O-3 for RAEB in transformation (retained from the original FAB classification) and therapy-related MDS. Categories of myeloproliferative disease (or CMDs in ICD-O-3) also differ from the WHO classification. The WHO classification includes 7 CMD categories: BCR/ABL$^+$ chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, hypereosinophilic syndrome, polycythemia vera, chronic idiopathic myelofibrosis (synonymous with myelosclerosis with myeloid metaplasia), essential thrombocythemia, and CMD, unclassifiable. The same categories are included in ICD-O-3 with the exception of BCR/ABL$^+$ CML, which is grouped with the leukemias in ICD-O-3. Incidence rates for CML have been previously reported from SEER,[8] and are therefore not included in this report.

Patterns in case reporting were described for SEER, NAACCR minus SEER registries, and all registries combined, including the distribution of patients by reporting source and diagnostic confirmation of the malignancy. Incidence rates were expressed as the number of new primary cancers per 100 000 persons at risk per year and age-adjusted according to the 2000 US standard population based on 5-year age groups.[9] To investigate patterns in MDS and CMD risk, incidence rates were stratified by demographic characteristics, including year of diagnosis, sex, age, and race (white, black, and other) and ethnicity (Hispanic vs non-Hispanic). (There were too few patients with CMML to conduct stratified analyses.) At the time of this analysis, data from 2004 were available from SEER Program but not from the CINA Deluxe file. Therefore, all analyses of incidence were based on the years 2001 through 2003. Statistical significance of the differences in age-adjusted incidence rates was assessed using analysis of variance (ANOVA).

To examine the national burden of disease, numbers of newly diagnosed patients with MDS, CMD, and CMML in 2004 were estimated for the entire US population based on the respective incidence rates calculated from the CINA Deluxe file for 2001 through 2003 and population estimates obtained from the US Census Bureau for 2004.[10] Specifically, MDS, CMD, and CMML incidence rates, stratified by 5-year age groups and sex, were multiplied by corresponding stratified census counts and divided by 100 000. Numbers of cases were then summed across all age groups and both sexes to obtain the total projected count for 2004.

To evaluate patterns in survival, 3-year relative survival rates were calculated using the SEER limited-use database consisting of SEER-17 registries, for which data are available from 2001 to 2004.[11] Relative survival rate is calculated by comparing observed survival with

Table 1. Reporting characteristics of patients with MDS and CMD in the SEER and NAACCR registries, 2001-2003

	SEER*		NAACCR − SEER†		Total	
	Count	%	Count	%	Count	%
MDS	7 076	100.0	17 722	100.0	24 798	100.0
Diagnostic confirmation						
Positive histology	6 202	87.6	14 272	80.5	20 474	82.6
Positive laboratory test/marker study	266	3.8	1 070	6.0	1 336	5.4
Clinical diagnosis/others	308	4.4	705	4.0	1 013	4.1
Unknown	300	4.2	1 675	9.5	1 975	8.0
Reporting source						
Hospital inpatient/laboratory	6 526	92.2	16 35	92.7	22 961	92.6
Physicians office/nursing, etc	416	5.9	572	3.2	988	4.0
Death certificate/autopsy only	134	1.9	715	4.0	849	3.4
CMD	4 226	100.0	11 893	100.0	16 119	100.0
Diagnostic confirmation						
Positive histology	3 355	79.4	7 893	66.4	11 248	69.8
Positive laboratory test/marker study	429	10.2	2 167	18.2	2 596	16.1
Clinical diagnosis/others	229	5.4	612	5.1	841	5.2
Unknown	213	5.0	1 221	10.3	1 434	8.9
Reporting source						
Hospital inpatient/laboratory	3 872	91.6	11 284	94.9	15 156	94.0
Physicians office/nursing, etc	304	7.2	357	3.0	661	4.1
Death certificate/autopsy only	50	1.2	252	2.1	302	1.9

Data source: NAACCR's CINA December 2005 submission of 1995 to 2003 patients.

*Excludes Arizona Indians.

†NAACCR registries minus SEER registries; excludes Seattle from Washington, Detroit from Michigan, and Atlanta from Georgia.

Table 2. Incidence rates for MDS and CMD by state, NAACCR 2001-2003

		MDS		CMD	
State	Population size*	Count†	Rate‡	Count†	Rate‡
Alabama	13 452 835	298	2.15	198	1.42
Alaska	1 921 510	31	2.88	25	1.79
Arizona	10 735 936	314	2.93	241	2.27
California§	104 983 136	2791	3.06	1,500	1.60
Greater Bay	19 699 167	430	2.37	217	1.15
Los Angeles	29 280 659	788	3.36	462	1.88
Colorado	13 472 998	339	3.20	273	2.35
Connecticut	10 379 209	244	2.10	144	1.27
Delaware	2 419 904	84	3.38	20	0.81
Washington, DC	1 691 671	30	1.81	26	1.58
Florida	50 033 890	2630	3.94	1,238	1.98
Georgia§	25 607 477	504	2.52	385	1.76
Atlanta	9 092 312	137	2.47	101	1.63
Hawaii	3 705 280	113	2.79	88	2.22
Idaho	4 031 456	174	4.69	154	4.07
Illinois	37 752 732	1186	3.23	749	2.04
Indiana	18 485 630	681	3.71	323	1.75
Iowa	8 808 345	422	4.01	268	2.67
Kentucky	12 275 955	475	3.90	283	2.27
Louisiana	13 437 239	425	3.38	285	2.20
Maine	3 893 588	145	3.26	127	2.86
Massachusetts	19 228 325	539	2.55	431	2.09
Michigan§	30 129 569	1229	4.09	825	2.74
Detroit	12 158 589	670	5.55	432	3.60
Minnesota	15 074 919	675	4.54	447	3.04
Missouri	17 041 549	522	2.87	252	1.40
Montana	2 735 068	100	3.34	106	3.54
Nebraska	5 182 752	145	2.62	121	2.19
Nevada	6 505 746	87	1.52	113	1.83
New Hampshire	3 823 495	116	3.08	141	3.69
New Jersey	25 725 929	942	3.46	614	2.27
New Mexico	3 687 478	89	2.55	112	3.09
New York	57 449 353	2239	3.71	1500	2.51
North Carolina	24 931 345	357	1.50	311	1.27
Ohio	22 798 256	431	1.78	368	1.54
Oklahoma	10 461 203	192	1.77	126	1.15
Oregon	10 561 772	276	2.51	144	1.33
Pennsylvania	36 997 707	1943	4.21	1117	2.56
Rhode Island	3 203 585	82	2.18	102	2.82
South Carolina	12 315 801	277	2.32	213	1.72
South Dakota	2 283 574	65	2.54	34	1.41
Texas	65 161 449	1920	3.70	1794	3.19
Utah	6 953 023	154	3.16	86	1.65
Washington§	18 191 211	848	4.98	459	2.65
Seattle	12 474 150	614	5.36	313	2.64
West Virginia	5 418 494	266	4.11	116	1.84
Wisconsin	16 320 562	418	2.42	260	1.53

Data source: NAACCR's CINA December 2005 submission of 1995 to 2003 patients.
*Sum of the population estimates in the indicated areas for the years 2001, 2002, and 2003.
†Total number of cases observed for the years 2001, 2002, and 2003.
‡Rates per 100 000; age-adjusted based on 2000 US standard population.
§Includes the one or more metropolitan SEER registries listed under the state.

expected survival from a set of people with the same characteristics as the patient cohort with respect to age, race, sex, and calendar period.[12] We used patients with MDS, CMD, and CMML diagnosed in 2001 through 2003 and followed through 2004 for 3-year relative survival rate calculations. Survival rates were stratified by sex, age and race, and 95% confidence interval (CI) are presented for each group. Survival by MDS subtype within SEER has been previously described[2]; thus, subtype analyses are presented only for CMD. The SEER*Stat program (version 6.2.4; National Cancer Institute) was used for all analyses in this paper, except for the statistical significance testing with ANOVA, which was conducted using SAS (Cary, NC).

Results

Reporting characteristics are presented in Table 1 for patients with MDS and CMD ascertained by SEER registries, by NAACCR registries that were not included in SEER (referred from here on out as "NAACCR minus SEER"), and for all patients combined. Between 2001 and 2003, 7076 and 17 722 patients with MDS were reported to SEER and NAACCR minus SEER registries, respectively, for a total of 24 798 patients with MDS overall. Roughly

Table 3. Age-adjusted incidence rates of MDS by demographic characteristics, 2001-2003

	SEER			NAACCR − SEER*			Total		
	Rate†	Count	%	Rate†	Count	%	Rate†	Count	%
Total	3.42	7 076		3.22	17 722		3.27	24 798	
Year of diagnosis‡									
2001	3.29	2 246	31.7	3.02	5 641	31.8	3.10	7 887	31.8
2002	3.38	2 349	33.2	3.25	6 159	34.8	3.29	8 508	34.3
2003	3.58	2 481	35.1	3.38	5 922	33.4	3.45	8 403	33.9
Sex‡									
Male	4.51	3 803	53.7	4.4	9 715	54.8	4.43	13 518	54.5
Female	2.71	3 273	46.3	2.47	8 007	45.2	2.53	11 280	45.5
Age‡									
Less than 40 y	0.14	186	2.6	0.14	406	2.3	0.14	592	2.4
40 to 49 y	0.71	246	3.5	0.58	482	2.7	0.62	728	2.9
50 to 59 y	2.05	524	7.4	1.90	1 203	6.8	1.95	1 727	7.0
60 to 69 y	7.57	1 135	16.0	6.98	2 796	15.8	7.14	3 931	15.9
70 to 79 y	20.94	2 393	33.8	19.72	6 170	34.8	20.05	8 563	34.5
80 y and older	36.41	2 592	36.6	35.14	6 665	37.6	35.49	9 257	37.3
Race									
White	3.48	6 068	86.9	3.28	16 239	93.1	3.33	22 307	91.4
Black	3.02	500	7.2	2.13	984	5.6	2.36	1 484	6.1
Asian/Pacific Islander	2.63	400	5.7	2.25	171	1.0	2.51	571	2.3
AI/AN	1.02	13	0.2	1.3	40	0.2	1.22	53	0.2
Ethnicity§									
Hispanic	2.79	516	7.3	2.85	635	4.2	2.83	1 151	5.2
Non-Hispanic	3.47	6 560	92.7	3.13	14 457	95.8	3.23	21 017	94.8

Data source: NAACCR's CINA December 2005 submission of 1995 through 2003 patients.

AI/AN indicates American Indian/Alaska Native.

*NAACCR registries minus SEER registries; excludes Seattle from Washington, Detroit from Michigan, and Atlanta from Georgia.

†Rate per 100 000; age-adjusted based on 2000 US standard population.

‡Differences in incidence rates across demographic categories (year of diagnosis, sex, or race) were statistically significant ($P < .05$) within SEER registries, NAACCR minus SEER registries, and all registries combined

§Differences in incidence rates by ethnicity were statistically significant ($P < .05$) within NAACCR minus SEER registries, and all registries combined, but not for SEER registries alone.

two-thirds as many patients with CMD were reported during the same time period (n = 16 119). As compared with patients with CMD, a greater proportion of patients with MDS were confirmed by positive histology in both SEER registries and NAACCR minus SEER registries (88% and 79% of patients with MDS and CMD, respectively, for SEER; 81% and 66% for NAACCR minus SEER). Conversely, a greater proportion of patients with CMD than with MDS were confirmed by a positive laboratory test (Table 1). The proportion of patients confirmed only by clinical diagnosis or other means was similar for MDS and CMD in both SEER and NAACCR minus SEER registries (4%-5%). Among patients with CMD and MDS reported to SEER registries, 92% were reported by a hospital or laboratory, as compared with 93% to 95% of patients with CMD and MDS in NAACCR minus SEER registries.

Age-adjusted incidence rates for MDS and CMD are presented in Table 2 for individual US states and geographic regions represented in NAACCR. MDS rates ranged from 1.5 per 100 000 in North Carolina to 5.6 per 100 000 in Detroit, while CMD rates ranged from 0.8 per 100 000 in Delaware to 4.1 per 100 000 in Idaho. The average annual age-adjusted incidence rate for MDS in 2001 through 2003 was 3.3 per 100 000, based on 24 798 cases reported by SEER and NAACCR minus SEER registries combined (Table 3). A slight but statistically significant increase in MDS incidence rates was observed with calendar year, ranging from 3.1 per 100 000 in 2001 to 3.5 per 100 000 in 2003 in all registries combined. Data for 2004 were available only for SEER at the time of this analysis, and the increase in MDS incidence continued through 2004, with an incidence rate of 3.8 per 100 000 based on 2720 reported patients ($P < .05$). Age-adjusted incidence of MDS was significantly higher among males (4.4 per 100 000) than females (2.5 per 100 000; $P < .05$; Table 3). A sharp increase in MDS incidence rates was observed with age, especially among the elderly: rates were 5 times greater among those aged 80 years and older (35.5 per 100 000) as compared with those aged 60 to 69 years (7.1 per 100 000). While no significant differences in MDS incidence rates were observed by race, non-Hispanics had a statistically significant increased risk of MDS compared with Hispanics. MDS incidence rates were highest among whites and non-Hispanics. Similar trends in MDS incidence rates with calendar year, sex, age, and race/ethnicity were observed between SEER and NAACCR minus SEER registries.

Incidence rates for CMD were lower than those for MDS, with an average annual age-adjusted incidence rate of 2.1 per 100 000, based on 16 119 reported patients in 2001 through 2003 (Table 4). No differences in incidence rates were observed by calendar year. (The incidence of CMD for 2004 in SEER was 2.1 per 100 000, based on 1561 patients.) CMD incidence rates were significantly higher in males (2.5 per 100 000) than females (1.8 per 100 000; $P < .05$). CMD incidence rates also significantly increased with age, although to a lesser extent than MDS incidence rates. Among individuals aged 80 years and older, the CMD incidence rate was 13.3 per 100 000. Statistically significant differences in CMD incidence rates were observed by race in all registries combined, with whites being at highest risk. No differences were observed by ethnicity. Trends in CMD incidence were similar in SEER and NAACCR minus SEER registries.

Frequencies and age-adjusted incidence rates are presented by disease subtype in Table 5. The distributions of disease subtypes were similar for SEER and NAACCR minus SEER registries. Refractory anemia (RA) comprised 16.8% and 13.4% of patients with MDS

Table 4. Age-adjusted CMD incidence rates by demographic characteristics, 2001-2003

	SEER			NAACCR – SEER*			Total		
	Rate†	Count	%	Rate†	Count	%	Rate†	Count	%
Total	2.01	4 226		2.17	11 893		2.12	16 119	
Year of diagnosis									
2001	2.09	1 451	34.3	2.24	4 157	35.0	2.20	5 608	34.8
2002	1.99	1 410	33.4	2.15	4 065	34.2	2.11	5 475	34.0
2003	1.94	1 365	32.3	2.11	3 671	30.9	2.06	5 036	31.2
Sex‡									
Male	2.44	2 250	53.2	2.58	6 190	52.0	2.54	8 440	52.4
Female	1.68	1 976	46.8	1.84	5 703	48.0	1.80	7 679	47.6
Age‡									
Less than 40 y	0.21	277	6.6	0.29	871	7.3	0.27	1 148	7.1
40 to 49 y	1.22	422	10.0	1.31	1 082	9.1	1.29	1 504	9.3
50 to 59 y	2.53	648	15.3	2.65	1 673	14.1	2.62	2 321	14.4
60 to 69 y	5.63	848	20.1	6.02	2 420	20.3	5.92	3 268	20.3
70 to 79 y	10.18	1 163	27.5	10.42	3 259	27.4	10.36	4 422	27.4
80 y and older	12.19	868	20.5	13.64	2 588	21.8	13.25	3 456	21.4
Race§									
White	1.99	3 462	84.6	2.17	10 527	91.0	2.12	13 989	89.4
Black	2.09	378	9.2	1.67	857	7.4	1.78	1 235	7.9
Asian/Pacific Islander	1.38	238	5.8	1.36	143	1.2	1.38	381	2.4
AI/AN	0.75	13	0.3	0.95	37	0.3	0.89	50	0.3
Ethnicity									
Hispanic	1.46	324	7.7	1.85	542	5.1	1.67	866	5.8
Non-Hispanic	2.07	3 902	92.3	2.21	10 113	94.9	2.17	14 015	94.2

Data source: NAACCR's CINA December 2005 submission of 1995 to 2003 patients.

AI/AN indicates American Indian/Alaska Native.

*NAACCR registries minus SEER registries; excludes Seattle from Washington, Detroit from Michigan, and Atlanta from Georgia.

†Rate per 100 000; age-adjusted based on 2000 US standard population.

‡Differences in incidence rates across demographic categories (sex and age) were statistically significant ($P < .05$) within SEER registries, NAACCR minus SEER registries, and all registries combined.

§Differences in incidence rates by race were statistically significant ($P < .05$) within NAACCR minus SEER registries, and all registries combined, but not for SEER registries alone.

reported to SEER and NAACCR minus SEER registries, respectively. RA with sideroblasts and RA with excess blasts were the next most commonly reported MDS subtypes. More than half of all patients with MDS reported in SEER and NAACCR registries combined were of unspecified subtype. Polycythemia vera comprised 45% of patients with CMD, and 24% patients had essential thrombocythemia. Approximately

Table 5. MDS, CMD, and CMML patient counts and rates by subtype for both sexes, 2001-2003

Disease type according to ICD-O-3	ICD-O-3 morphology code		SEER			NAACCR – SEER*			Total	
		Rate†	Count	%	Rate†	Count	%	Rate†	Count	%
Total‡	—	5.43	11 311	—	5.40	29 637	—	5.40	40 948	—
MDS	998	3.42	7 076	100.0	3.22	17 722	100.0	3.28	24 798	100.0
RA	9980	0.57	1 186	16.8	0.43	2 375	13.4	0.47	3 561	14.4
RA with sideroblasts	9982	0.40	819	11.6	0.30	1 662	9.4	0.33	2 481	10.0
RA with excess blasts	9983	0.47	968	13.7	0.34	1 850	10.4	0.37	2 818	11.4
RA with excess blasts in transformation	9984	0.06	129	1.8	0.05	257	1.5	0.05	386	1.6
Refractory cytopenia with multilineage dysplasia	9985	0.13	262	3.7	0.06	342	1.9	0.08	604	2.4
MDS with 5q deletion	9986	0.06	119	1.7	0.06	311	1.8	0.06	430	1.7
Therapy-related MDS	9987	0.06	126	1.8	0.09	484	2.7	0.08	610	2.5
MDS, not otherwise specified (NOS)	9989	1.67	3 467	49.0	1.89	10 441	58.9	1.84	13 908	56.1
CMD§	995-996	2.01	4 226	100.0	2.17	11 893	100.0	2.13	16 119	100.0
Polycythemia vera	9950	0.79	1 679	39.7	1.01	5 504	46.3	0.95	7 183	44.6
Myelosclerosis with myeloid metaplasia‖	9961	0.25	514	12.2	0.21	1 160	9.8	0.22	1 674	10.4
Essential thrombocythemia	9962	0.53	1 108	26.2	0.51	2 766	23.3	0.51	3 874	24.0
Chronic neutrophilic leukemia	9963	0.01	10	0.2	0.01	32	0.3	0.01	42	0.3
Hypereosinophilic syndrome	9964	0.03	71	1.7	0.03	158	1.3	0.03	229	1.4
Chronic myeloproliferative disease, NOS	9960	0.41	844	20.0	0.41	2 273	19.1	0.41	3 117	19.3
Chronic myelomonocytic leukemia (CMML), NOS¶	9945	0.37	751		0.34	1 850		0.34	2 601	

Data source: NAACCR's CINA December 2005 submission of 1995 to 2003 patients.

*NAACCR registries minus SEER registries; excludes Seattle from Washington, Detroit from Michigan, and Atlanta from Georgia.

†Rate per 100 000; age-adjusted based on 2000 US standard population.

‡Includes 9 and 22 patients with other malignant hematologic disorders (ICD-O-3 code 9970-9975) in SEER and NAACCR minus SEER, respectively.

§Synonymous with myeloproliferative neoplasms; does not include BCR/ABL$^+$ chronic myelocytic leukemia.

‖Synonymous with chronic idiopathic myelofibrosis (WHO classification) or primary myelofibrosis.

¶CMML is considered MDS in the FAB classification, but it is grouped with the leukemias in the WHO classification and ICD-O-3.

Table 6. Estimated numbers of patients with MDS, CMD, and CMML for the total US population in 2004

Demographic characteristic	MDS			CMD			CMML		
	Total	Male	Female	Total	Male	Female	Total	Male	Female
Total	9730	5329	4400	6328	3329	2999	1039	638	401
By age									
Less than 40 y	223	116	107	432	245	187	13	7	6
40 to 49 y	284	135	149	586	335	251	21	9	12
50 to 59 y	709	370	339	950	572	378	84	59	25
60 to 69 y	1583	912	671	1319	729	590	163	113	50
70 to 79 y	3212	1884	1328	1656	866	790	388	249	139
80 y and older	3718	1913	1805	1384	582	802	370	201	169
By race									
White	8549	4710	3839	5463	2886	2577	914	564	350
Black	821	419	402	598	299	299	86	50	36
Other	359	200	159	268	144	124	39	25	14

Data source: Based on US Census population estimates for 2004 and age-specific rates for 2001 to 2003 from NAACCR's CINA December 2005 submission of 1995 to 2003 patients.

20% of patients with CMD were of unspecified subtype. The age-adjusted incidence rate for CMML was approximately one-tenth that of MDS, at 0.3 per 100 000.

Applying the observed incidence rates from combined SEER and NAACCR registries to the total US Census population estimates for 2004, the estimated numbers of patients with MDS, CMD, and CMML diagnosed in the total US population for 2004 were 9730, 6328, and 1039, respectively (Table 6). Approximately 7000 patients with MDS and 3000 patients with CMD were estimated to occur in individuals aged 70 years and older.

Trends in survival based on SEER data are presented in Table 7. Relative to the general population, 3-year survival with MDS was poorer than survival with CMD (45% vs 80%, respectively), while the worst 3-year survival was observed for CMML (21%). Males experienced poorer 3-year survival than did females for MDS, CMD, and CMML, a difference that was statistically significant for MDS (males, 41%; females, 50%). Survival for patients with MDS and CMD decreased with age: among those younger than 50 years of age at diagnosis, relative 3-year survival was greater than 60% and greater than 90% for MDS and CMD, respectively, while relative 3-year survival among those 80 years and older dropped to 37% and 66% for MDS and CMD, respectively. Although a similar inverse association between age at diagnosis and survival was observed for CMML, patients in the youngest age category for which there were reportable data (50-59 years) still experienced an extremely poor prognosis, with a relative 3-year survival of 33%. The 3-year survival was greatest for the most common CMD subtypes, polycythemia vera (n = 1615 patients; 88% 3-year survival) and essential thrombocythemia (n = 1028 patients, 92% 3-year survival). Similar survival was observed among 464 patients with hypereosinophilic syndrome (85%), while the poorest survival among patients with CMD was observed for myelosclerosis with myeloid metaplasia (synonymous with primary myelofibrosis; n = 464 patients; 53% 3-year survival) and CMD, not otherwise specified (n = 730; 63% 3-year survival).

Discussion

The current analysis is the first to be based on NAACCR data, encompassing approximately 82% of the US population.[13] Based on more than 40 000 observations, average annual age-adjusted incidence rates in the United States were highest for MDS, followed by CMD and CMML, for the years 2001 through 2003, with corresponding rates of 3.3, 2.1, and 0.3 per 100 000, respectively. Incidence rates were similar whether they were based on

Table 7. The 3-year relative survival rates for MDS, CMD, and CMML among cases diagnosed in 2001 through 2003 and followed through 2004 in SEER

Demographic characteristic	MDS		CMD		CMML	
	No. patients	3-year relative survival, % (95% CI)	No. patients	3-year relative survival, % (95% CI)	No. patients	3-year relative survival, % (95% CI)
Total	5597	45 (43-47)	3916	80 (78-82)	580	21 (16-26)
Sex						
Male	3001	41 (38-43)	2099	79 (77-82)	345	18 (12-23)
Female	2596	50 (47-53)	1817	81 (78-84)	235	27 (18-35)
Age at diagnosis						
Less than 40 y	159	63 (54-72)	281	92 (88-96)	—	—
40 to 49 y	212	66 (58-73)	429	90 (86-94)	—	—
50 to 59 y	442	54 (48-60)	654	89 (86-92)	35	33 (13-53)
60 to 69 y	951	48 (44-53)	807	80 (76-84)	116	28 (17-39)
70 to 79 y	1909	43 (40-46)	1007	73 (69-77)	212	22 (15-30)
80 y and older	1924	37 (34-41)	738	66 (63-70)	202	12 (5-20)
Race						
White	4740	44 (42-46)	3216	80 (78-82)	510	21 (16-26)
Black	422	49 (42-56)	344	72 (65-78)	33	15 (0-32)

Data source: SEER Program based on November 2006 NCI SEER data submission.
— indicates statistic could not be calculated due presence of fewer than 15 observations.

SEER or NAACCR minus SEER registries, with results from NAACCR minus SEER registries confirming the positive trends in MDS incidence with increasing age and male sex previously reported from SEER.[2]

MDS may be misdiagnosed and/or underreported to population-based cancer registries. Elderly patients presenting to primary care physicians with anemia may not be assessed for a possible MDS diagnosis, and the likelihood of accurate MDS diagnoses may vary, depending on pathology expertise, physician, and patient characteristics. Although 88% of MDS diagnoses were confirmed by positive histology or laboratory test in NAACCR and SEER registries, 56% of diagnoses were of unspecified subtypes. Therefore, the observed subtype distribution may not be representative of the true MDS patient population if some subtypes were more likely to be characterized than others. No information or estimates are available on the number of patients in whom a possible diagnosis of MDS is not investigated by bone marrow studies.

Incidence rates for MDS increased with calendar year in 2001 to 2003 among the combined registry data, with the most recent 2004 SEER data indicating a rate of 3.8 per 100 000. Since MDS became a reportable malignancy only in 2001, it is possible that the increase in incidence rates over time reflect acclimation of those involved in the reporting process to the new guidelines resulting in rising capture rates. For example, only 4% of patients with MDS in NAACCR were reported by physicians' offices in 2001 through 2003. Since MDS is more commonly diagnosed and managed outside of hospitals compared with other cancers, it is possible that many of these cases are unreported to population-based registries. Although independent laboratories are also responsible for reporting MDS cases to local registries, the completeness of case reporting by out-of-state laboratories is unknown. As recently described by De Roos and colleagues,[14] case-finding methods may affect the completeness of MDS case reporting; registries that rely on passive case-finding (ie, cases are reported to the registry by hospitals and other diagnostic facilities) may not capture as many patients with MDS as those that use active case-finding methods (ie, surveying billing, pathology, and cytogenetic and other laboratory testing records). Surveys of private physicians' offices and central referral laboratories are needed to estimate the proportion of patients with MDS not captured by hospital registries. Nevertheless, the incidence rate of MDS estimated for the United States in 2001 through 2003 (3.3 per 100 000) is remarkably similar to those previously reported from European countries,[15] including England and Wales (3.6 per 100 000),[16] Germany (4.1 per 100 000),[17] Sweden (3.6 per 100 000)[18] and France (3.2 per 100 000).[19] Therefore, if substantial underreporting of MDS to cancer registries exists, the phenomenon is most likely not isolated to the United States. As clinicians, laboratories, and cancer registrars become more accustomed to reporting and recording MDS cases, incidence rates may continue to rise in the upcoming years.

In this first report of population-based incidence rates of CMD for the United States, demographic risk factors for CMD were similar to MDS, including older age, male sex, and white race. Although the CMD incidence rates did not increase with calendar year in 2001 through 2004 as they did for MDS, underreporting of CMD to population-based registries cannot be excluded. A recent analysis of medical claims data estimated the prevalence of polycythemia vera and essential thrombocythemia in the United States to be 136 000 patients as of 2003,[20] far greater than what would be expected based on the incidence rates reported here from SEER and NAACCR.

The 3-year relative survival was greater in patients with CMD (80%) than patients with MDS (45%), even among those aged 80 years and older at diagnosis. In contrast, survival with CMML was extremely poor (21%), even among younger patients. These data suggest that treatments with potential to alter the natural history of disease or curative strategies such as hematopoietic stem cell transplantation should be considered for patients with CMML who are appropriate candidates.

In conclusion, continued surveillance of MDS, CMD, and CMML through population-based registries will be useful for investigating trends in incidence and survival so that future prevention and treatment strategies may be developed. Concurrent assessment of potential misdiagnosis and underreporting of these malignant conditions is paramount for the elucidation and interpretation of these rates and trends.

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Authorship

Contribution: A.F.L., B.K.E., L.R., W.D.M., S.S.S., M.S., and D.E.R. designed the research; N.H. analyzed the data, and D.E.R. wrote the paper with contributions from A.F.L., B.K.E., L.R., W.D.M., S.S.S., M.S., and N.H.

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