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Mortality in Neurofibromatosis 1: An Analysis Using U.S. Death Certificates

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Although neurofibromatosis 1 (NF1) is a relatively common autosomal dominant condition, information about its effect on mortality is limited. We used Multiple-Cause Mortality Files, compiled from U.S. death certificates by the National Center for Health Statistics, for 1983 through 1997. We identified 3,770 cases of presumed NF1 among 32,722,122 deaths in the United States, a frequency of 1/8,700, which is one-third to one-half the estimated prevalence. Mean and median ages at death for persons with NF1 were 54.4 and 59 years, respectively, compared with 70.1 and 74 years in the general population. Results of proportionate mortality ratio (PMR) analyses showed that persons with NF1 were 34 times more likely (PMR = 34.3, 95% confidence interval [CI] 30.8–38.0) to have a malignant connective or other soft-tissue neoplasm listed on their death certificates than were persons without NF1. Overall, persons with NF1 were 1.2 times more likely than expected (PMR = 1.21, 95% CI 1.14–1.28) to have a malignant neoplasm listed on their death certificates, but the PMR was 6.07 (95% CI 4.88–7.45) for persons who died at 10–19 years of age and was 4.93 (95% CI 4.14–5.82) for those who died at 20–29 years of age. Similarly, vascular disease was recorded more often than expected on death certificates of persons with NF1 who died at <30 years of age (PMR = 3.26, 95% CI 1.31–6.71 at age <10 years; PMR = 2.68, 95% CI 1.38–4.68 at age 10–19 years; and PMR = 2.25, 95% CI 1.46–3.32 at 20–29 years) but not in older persons. This study supports previous findings of decreased life expectancy for persons with NF1 and, within the limitations of death certificates, provides population-based data about NF1 morbidity and mortality that are useful to clinicians caring for patients with NF1.

Introduction

Neurofibromatosis 1 (NF1 [MIM 162200]) is a relatively common autosomal dominant disorder, with a frequency of 1/3,000–4,000 persons (Poyhonen et al. 2000; Rasmussen and Friedman 2000). Cardinal features include multiple café-au-lait spots, benign neurofibromas, and Lisch nodules of the iris. Other common features include learning disabilities, mild shortness of stature, and skeletal abnormalities. An increased risk of malignancy has also been observed in patients with NF1 and may be related to the proposed tumor-suppressor role of the *NF1* gene (Shen et al. 1996).

Despite the high prevalence of NF1, information about its effect on mortality is limited. Sørensen and associates (1986) studied a cohort of 212 patients with NF1 who had been identified 42 years earlier in Denmark. Because probands were identified through hospitals (and therefore may have been more severely affected), the Sørensen group analyzed data on both probands and affected relatives. Survival of people with NF1 was significantly lower than that of the general population, and more so in probands than in affected relatives. Malignant neoplasms were significantly increased, primarily in probands (Sørensen et al. 1986; Neerup and Jensen et al. 1998).

A 12-year follow-up of 70 adult patients with NF1 (Zöller et al. 1995) found a decrease in life expectancy of ~15 years. Malignancy was the cause of death for more than half the patients, and hypertension was significantly associated with mortality. A third study used data from Japanese vital statistics for 1968–1992 on 605 deaths in which neurofibromatosis was listed as the underlying cause of death. The mean age at death in this study was 43 years (Imaizumi 1995). However, the authors did not distinguish between persons with NF1 and neurofibromatosis 2 (NF2), and no data were available on causes of death other than neurofibromatosis. In addition, because only case subjects in which neurofibromatosis was listed as the underlying cause of death were included, neurofibromatosis was believed to be underascertained in this population (Imaizumi 1995).

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In the present investigation, we used data from U.S. death certificates to study rates of NF1-associated deaths. Our population-based study includes data on >3,700 deaths of people with NF1 during 1983–1997. We used these data to examine mean and median ages at death and the most common conditions associated with death in persons with NF1 compared with the general U.S. population.

Methods

We used the Multiple-Cause Mortality Files (MCMFs), which are compiled from U.S. death certificates by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. MCMFs include demographic and geographic information and codes from the *International Classification of Disease, Ninth Revision* (ICD9) for the underlying cause of death and for as many as 20 conditions listed on the death certificate as "other significant conditions" (Israel et al. 1986). The ICD9 coding system has been used for mortality statistics since 1979; however, because of incomplete collection of death certificates for 1981 and 1982, the NCHS partially replicated data for these years (Israel et al. 1986). We were concerned about the effect of this case duplication on our small subset of case subjects with neurofibromatosis, so we limited our study to 1983–1997.

The codes in the MCMFs are in two formats: entity axis and record axis. The entity-axis format provides a separate code for each disease listed, whether it is an underlying cause of death or a contributory condition. The record-axis format uses linkage rules to combine some listings of conditions on the death certificates. We selected all cases listing the ICD9 code for "neurofibromatosis (von Recklinghausen's disease)" (237.7) in the record axis. This code may also include cases of the much less common but generally more severe condition NF2. We therefore excluded case subjects with the codes for "sensorineural deafness" (389.1), "benign neoplasms of cranial nerves" (225.1), "benign neoplasms of cerebral meninges"(225.2), and "benign neoplasms of spinal meninges" (225.4) as more likely to have NF2. For the remaining case subjects, we determined mean and median ages at death to approximate the survival of persons with NF1 overall and by sex and race. Race is classified as "white," "black," or "other" in the MCMFs; however, given the small number of case subjects of other races, we grouped subjects into two racial categories, "white" and "other." Because the distribution of age at death was skewed, a logarithmic transformation was applied to these data to obtain the geometric mean age at death and the associated 95% confidence intervals (CIs). We used the nonparametric-median-scores method to test the differences between median age at death in various categories. Version 8.0 of the SAS program was used for all analyses.

To investigate the relation of NF1-associated deaths to other medical conditions, we calculated the proportionate mortality ratio (PMR) for deaths of persons with NF1 for several conditions. The PMR was calculated as the observed number of deaths among persons with NF1 who also had a specific condition divided by the expected number of deaths of all persons with the specific condition. The expected number of deaths associated with a particular condition was calculated on the basis of the proportion of death certificates in the U.S. population listing that condition during 1983–1997, adjusted for decedent's age, sex, race, and death-cohort (Hennekens 1987). Because the complete file containing >32 million deaths was too large for convenient computation, we used a randomly selected subset containing 25% of U.S. deaths during 1983–1997 to calculate the expected number of deaths for each condition. We calculated 95% CIs by assuming that the number of deaths associated with both NF1 and another medical condition was distributed as a Poisson variable (Ahlbom 1993). PMR enables determination of whether a specific medical condition is more or less likely in deaths in which NF1 is listed on the death certificate than in deaths in the general population. If the medical condition is more likely in persons with NF1, the PMR will be >1; if the medical condition is less likely, the PMR will be <1. We selected 90 conditions for PMR analysis, because they are frequently listed as causes of death in the general population or because of their known association with NF1 morbidity or mortality (Sørensen et al. 1986; Zöller et al. 1995; McGaughran et al. 1999). For selected conditions, we also evaluated PMRs by age group at death (<10, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, or ⩾70 years). For this study, we defined vascular disease as hypertensive disease (ICD9 401–405), cerebrovascular disease (ICD9 430–438), or a disease of the arteries or arterioles (ICD9 440–449). This range includes renal artery stenosis (ICD9 440.1) but does not include heart disease, which we considered separately. We defined "heart disease (adult)" as ischemic heart disease (ICD9 410–414), diseases of the pulmonary circulation (ICD9 415–417), and other forms of heart disease (ICD9 420–429).

Results

We identified 3,829 case subjects with the code for neurofibromatosis listed on the death certificate. We excluded 59 case subjects as likely to have NF2. Of these, 24 cases were coded with "benign neoplasms of cranial nerves" (225.1), 32 were coded with "benign neoplasms

of cerebral meninges"(225.2), and 3 were assigned both these codes. No case subjects had been coded for neurofibromatosis and "sensorineural deafness" (389.1) or "benign neoplasms of spinal meninges" (225.4). The mean and median ages at death of the excluded case subjects were 40.1 and 32 years, respectively.

Among 32,722,122 deaths in the United States, 3,770 presumed NF1-associated deaths remained, a frequency of NF1-associated death of 1/8,700 deaths. The mean age at death of persons with NF1 was 15.7 years lower than the mean age at death in the general population (table 1). Although the mean age at death of females with NF1 was >3 years higher than that of males with NF1, the difference between the mean ages at death of persons with NF1 and of the U.S. general population was greater for females. The mean age at death of persons of other races who had NF1 was earlier than that of whites, but the difference between the mean ages at death of persons with NF1 and of the general population was greater for whites than for those of other races. The difference between mean ages at death of persons with NF1 and the general population increased during each of the three 5-year periods studied.

The median age at death of persons with NF1 was 59 years, whereas the median age at death of the U.S. population was 74 years (fig. 1). The median age at death was decreased more, compared with the general population, among females with NF1 than among males with NF1. The median age at death of persons of other races with NF1 was decreased more than that of whites with NF1, compared with the general population. The difference between median ages at death of NF1 case subjects and of the general population increased during each of the three 5-year periods studied.

Because we wondered whether the effect of NF1 mortality was restricted to younger patients, we also evaluated the mean and median age at death of persons who died at age ⩾40 years. The mean age at death of persons with NF1 who survived ⩾40 years was 65.6 years, whereas the mean age at death for this subset of the U.S. population was 74.5. The median age at death of persons with NF1 who died at age ⩾40 years was 67 years, compared with 76 years for the U.S. population.

Malignant neoplasms (all), vascular disease, cerebrovascular disease (a component of vascular disease), scoliosis, epilepsy, and mental retardation were reported more frequently than expected on death certificates of persons with NF1 (table 2). Diabetes mellitus and suicide were reported much less often than expected on death certificates of persons with NF1, and heart disease (adult) and diseases of the arteries and arterioles were reported slightly less often than expected.

Among NF1-associated deaths (table 3), malignant neoplasms of connective and other soft tissue were reported 34 times more frequently than expected, and neoplasms of the brain were reported 5.5 times more frequently than expected. Other neoplasms were less likely to be listed on the death certificates of persons with NF1 than on those of the general population, and this decrease reached statistical significance for malignant neoplasms of the lymphatic/hematopoietic system, breast (in women), trachea/bronchus/lung, pancreas, large bowel, prostate, uterine cervix, and skin. The PMR for all malignant neoplasms, excluding those of connective and other soft tissue and brain, was significantly <1 (PMR = 0.69; 95% CI 0.64–0.75).

Malignant neoplasms as a group occurred more frequently than expected among case subjects <39 years of age (table 4). When connective and other soft-tissue and brain neoplasms were excluded from malignant neoplasms, the PMR for other neoplasms was elevated for persons who died at <20 years of age. The PMR for myeloid leukemia was substantially increased for children aged <10 years, but malignant neoplasms of the lymphatic and hematopoietic system as a group were reported significantly less often than expected among persons with NF1 aged 20–49 years. Malignant neoplasms of connective and other soft tissue were listed much more frequently than expected among persons with NF1 at all ages, and the PMR was >50 for persons who died at age 20–39 years. Malignant neoplasms of the brain were reported more often on death certificates of persons with NF1 at all ages <70 years.

Vascular disease was reported more often than expected among persons with NF1 who were aged <29 years, but not in those who were older. The pattern was similar for cerebrovascular disease considered alone, but the PMR for hypertensive disease increased only among case subjects who died at 20–29 years of age, and the PMR for diseases of the arteries and arterioles decreased among case subjects aged >60 years.

Table 1

Geometric Mean Age, at Death, of Persons with NF1 and of the U.S. General Population, 1983–97

Category	No. of Deaths	Mean Age, at Death, of (years)		Difference between Means [95% CI] (years)
		Persons with NF1	U.S. Population	
All	3,770	54.4	70.1	15.7 [15.0–16.3]
Males	1,874	52.7	66.4	13.7 [12.8–14.6]
Females	1,896	56.1	74.0	17.9 [17.1–18.7]
Whites	3,150	55.4	71.5	16.1 [15.4–16.7]
Other races	620	49.6	61.3	11.7 [9.7–13.4]
1983–87	1,183	54.9	69.2	14.3 [13.2–15.4]
1988–92	1,247	53.9	69.8	15.9 [14.8–17.0]
1993–97	1,340	54.5	71.0	16.5 [15.5–17.6]

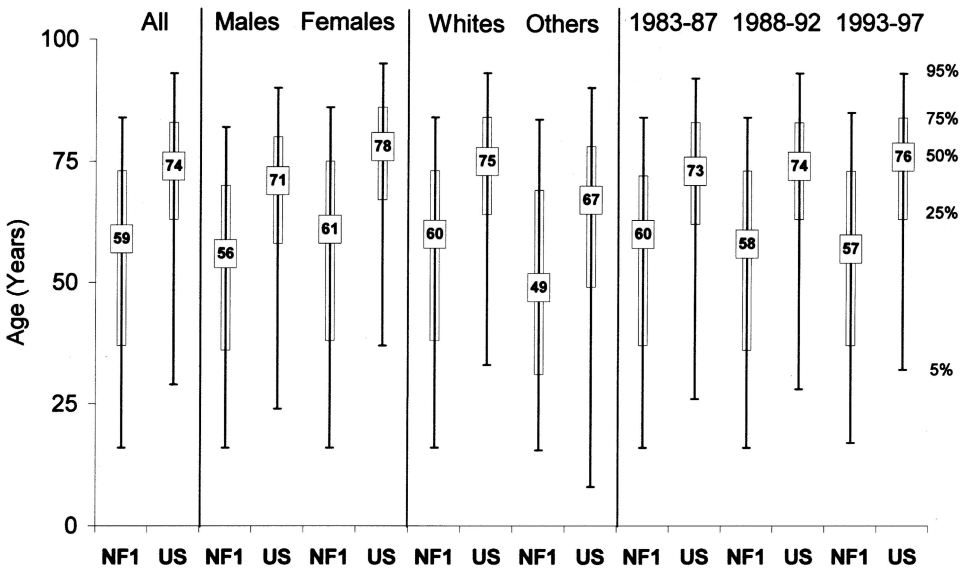

Figure 1 Median (in box) and 5th, 25th, 75th, and 95th percentiles of ages at death of persons with NF1 and of the U.S. general population, for all subjects and by sex, race, and time period.

Discussion

Our finding that survival, as estimated by mean and median age at death, is ~15 years less than expected in persons with NF1 is consistent with the results of previously reported smaller studies. Zöller et al. (1995) monitored 70 adults with NF1 for 12 years and estimated that the mean length of life for persons with NF1 was ~15 years shorter than expected. Inclusion of persons with NF1 presenting in childhood probably would have lowered the life expectancy even further (Zöller et al. 1995). The study by Imaizumi (1995) found that, in a Japanese population, the mean age at neurofibromatosis-associated death was 43 years, much lower than that seen in our study. However, Imaizumi's study included only case subjects for whom "neurofibromatosis" was listed as the underlying cause of death, whereas our study included all case subjects for whom neurofibromatosis was mentioned anywhere on the death certificate and excluded case subjects who were more likely to have NF2 than NF1. Neurofibromatosis was likely to be significantly underascertained in Imaizumi's study, resulting in a larger proportion of severe cases than in ours. Thus, our study population is more likely to be representative of all people with NF1.

Examination of mean and median ages at death suggests that survival of females with NF1 is more severely affected than that of males, in comparison with population expectations. Results of the study by Zöller et al. (1995) also suggested that women with NF1 may be more severely affected than men. In the study by Sørensen et al. (1986), female probands had the lowest survival rate, but the survival of female relatives with neurofibromatosis was only slightly less than that of the general population. Another possible explanation is that NF1 is likely to be diagnosed earlier in females, and thus NF1 may be listed more often on death certificates of females with NF1 who die earlier. In support of this, the frequency of deaths for which NF1 was listed on the death certificate is somewhat greater among females than among males (1/8,343 deaths for females vs. 1/9,019 for males). Further study is needed to determine whether NF1 affects survival more strongly in females than in males.

Evaluating the effect of race on NF1 mortality is more difficult. When subjects are stratified according to race, a comparison of mean age at death of persons with NF1 with mean age at death in the general population suggests that whites may be more severely affected than are other races; however, a comparison of median ages at death suggests that other races are more severely affected. When we compare mean and median ages at death by time period, the effect of NF1 on mortality appears to be increasing. However, these results could be secondary to earlier ascertainment of NF1 cases in more recent years.

The highest PMR in our study was for malignant neoplasms of connective and other soft tissue, a category that includes malignant tumors of the peripheral nerve sheath. These results are consistent with the rarity of such tumors in the general population, their poor prognosis, and their greatly increased frequency among persons with NF1 (Woodruff 1999; King et al. 2000). This type of tumor was identified as a major cause of

Table 2

Likelihood of Selected Medical Conditions Being Listed on NF1-Associated Death Certificates, 1983–97

Condition	ICD9 Code(s)	No. of Cases		PMR (95% CI)
		Observed	Expected	
Malignant neoplasms (all)	140–208	1,170	965	1.21 (1.14–1.28)
Heart disease (adult)	410–414, 415–417, 420–429	1,365	1,571	.87 (.82–.92)
Heart disease (congenital)	745–747	19	19.9	.95 (.57–1.49)
Vascular disease	401–405, 430–438, 440–447	658	597	1.10 (1.02–1.19)
Hypertensive disease	401–405	244	219	1.11 (.98–1.26)
Cerebrovascular disease	430–438	398	327	1.22 (1.10–1.34)
Diseases of arteries and arterioles	440–447	123	157	.78 (.65–.93)
Diabetes mellitus	250	64	239	.27 (.21–.34)
Curvature of spine[a]	737	66	2.72	24.3 (18.8–3.9)
Epilepsy	345	35	10.3	3.40 (2.37–4.73)
Mental retardation	317–319	43	9.00	4.78 (3.46–6.44)
Suicide	E950–E959	7	137	.05 (.02–.11)

[a] Includes scoliosis and kyphosis.

death in previous studies as well. In the study by Zöller et al. (1995), 3 of the 22 patients who died during the period of observation had soft-tissue sarcomas.

We also found a significantly increased PMR for malignant neoplasms of the brain. A significant excess of brain tumors was also found in the study by Sørensen et al. (1986). Of 212 patients with malignant tumors, 21 (10%) had tumors of the CNS; however, some of these persons may have had NF2 (Zöller et al. 1995). A high proportion of brain tumors was also seen in a follow-up study of NF1 patients who had been previously evaluated in a neurofibromatosis clinic (Airewele et al. 2001).

Malignant neoplasms are a major cause of death in people with NF1: ~55% of the cohort studied by Zöller et al. (1995) died of a malignancy, a rate higher than expected on the basis of data from a cancer registry (Zöller et al. 1995). Our study also shows an increased PMR for malignancy among persons with NF1, but the excess was seen only among subjects who died at <40 years of age. This increased PMR appears to result primarily from brain tumors and malignant neoplasms of connective and other soft tissue. When these types of cancer are excluded, the PMR for malignant neoplasms among persons with NF1 is lower than expected (PMR = 0.69; 95% CI 0.64–0.75).

The PMR for myeloid leukemia was significantly elevated among children with NF1 who died at <10 years of age. This observation is consistent with the known relation between juvenile chronic myelogenous leukemia and NF1 and the age at which this malignancy occurs (typically diagnosed at <4 years of age) (Hess et al. 1996). Myeloid leukemia was no more frequent than expected among persons who died with NF1 at other ages.

A number of reports have described life-threatening or fatal vascular abnormalities in young patients with NF1. The most frequently described manifestations are severe hypertension, usually associated with renal artery stenosis, and cerebrovascular disease associated with moyamoya disease (Sobata et al. 1988; Muhonen et al. 1991; Hattori et al. 1998; Kwong and Wong 1999; Fossali et al. 2000). Zöller and colleagues (1995) found that hypertension was significantly associated with NF1 mortality in a series of 70 adult patients monitored for 12 years. PMR for vascular disease was slightly higher than expected among persons with NF1 than among others, and this effect was especially prominent among persons who died at <29 years of age. Most of this increase in the PMR appears to be related to cerebrovascular disease, rather than to hypertensive disease or other diseases of the arteries or arterioles.

On the basis of our evaluation of PMRs by age group, we concluded that the impact of NF1 on mortality from vascular disease and malignancy appears to be focused on persons aged <40 years. However, even among persons with NF1 who survive to age 40, the mean and median ages at death are decreased by ~9 years when compared with the overall U.S. population. This is in contrast to the 15-year decrease observed among all persons with NF1 and suggests that NF1 affects mortality even at older ages, although less so than in earlier years.

This study has several important strengths. The use of MCMFs allows a population-based analysis and a comparison with data from the general population. The study is based on data from recent years, and data are available on deaths of 3,770 people with NF1, many more than all previous studies combined. In addition, our study provides data on deaths at all ages, whereas most previous studies have been limited to deaths among adults.

Our study also has several important limitations. First, the data are based on death certificates, which

Table 3

Likelihood of Selected Malignant Neoplasms Being Listed on NF1-Associated Death Certificates, 1983–97

Type of Malignant Neoplasm	ICD9 Code(s)	No. of Cases		PMR (95% CI)
		Observed	Expected	
Connective and other soft tissue	171.0–171.9	353	10.3	34.3 (30.8–38.0)
Brain	191.0–191.9	181	32.8	5.52 (4.74–6.38)
Lymphatic/hematopoietic system	200–208	69	113	.61 (.48–.77)
Myeloid leukemia	205.0–205.9	20	20.9	.96 (.58–1.48)
Female breast	174.0–174.9	79	120	.66 (.52–.82)
Trachea/bronchus/lung	162.0–162.9	132	236	.56 (.47–.66)
Stomach	151.0–151.9	22	23.5	.94 (.59–1.42)
Liver and intrahepatic bile ducts	155.0–155.9	11	16.1	.68 (.34–1.22)
Pancreas	157.0–157.9	24	39.4	.61 (.39–.91)
Colorectal[a]	153.0–154.9	38	94.6	.40 (.28–.55)
Ovary	183.0	21	28.8	.73 (.45–1.11)
Prostate	185.0–185.9	16	42.6	.38 (.21–.61)
Cervix uteri	180.0–180.9	4	18.7	.21 (.06–.55)
Body (or unspecified part) of uterus	179.0–179.9, 182.0–182.9	11	12.0	.92 (.46–1.64)
Skin (malignant melanoma)	172.0–173.9	12	23.2	.52 (.27–.90)
All neoplasms, excluding connective and soft tissue and brain	140–208, excluding 171 and 191	638	922	.69 (.64–.75)

[a] Includes colon, rectum, rectosigmoid junction, and anus.

previous studies have demonstrated to be both incomplete and, in some instances, inaccurate (Sirken et al. 1987; Lloyd-Jones et al. 1998). The low PMR observed for suicide may be related to this issue; physicians completing death certificates of persons who died of suicide may be less likely to also list NF1. Second, ICD9 does not allow for distinction between NF1 and NF2. We excluded cases coded as neurofibromatosis that had features more characteristic of NF2 than of NF1; but some cases of NF2 probably have been included, and some cases of NF1 may have been excluded from our study. NF1 cases appear to be underascertained in our study population. The proportion of death certificates listing neurofibromatosis is one-third to one-half the estimated population prevalence of NF1 (Poyhonen et al. 2000; Rasmussen and Friedman 2000). This underascertainment could introduce a critical bias if NF1 is more likely to be listed on the death certificates of persons who had severe disease or complications that are well known to be associated with NF1.

In addition, the ICD9 coding system used for mortality statistics is often not specific enough to provide all the information needed for a study of this kind. This limited our analysis of benign tumors; for example, plexiform neurofibromas are designated under the code 215 (other benign neoplasm of connective and other soft tissue), but this code may also include other tumors, such as cutaneous neurofibromas, thereby making analysis of this category impossible.

Another limitation is that our analyses of PMR used multiple comparisons, increasing the likelihood of demonstrating a statistically significant association when one may not exist (Rothman and Greenland 1998). We initially selected 90 codes on which to perform PMR analyses, and we subsequently performed additional analyses on eight age groups. However, the codes were not selected randomly, but focused instead on known associations with NF1 and common causes of death in the general population. It is reassuring that our PMR analyses generally confirm associations that have been previously well recognized in NF1.

Without information about the number of persons with NF1 living in the United States during each year of the study, we cannot be certain that our PMRs actually reflect altered disease-related survival among persons with NF1. A PMR could be lower than expected if competing causes of death eliminated patients who would have developed a particular disease if they had lived long enough (Kupper et al. 1978; Hennekens 1987). However, such effects would have to be differential to affect the PMR; that is, for competing causes of death to produce a lower PMR, persons with NF1 who would have died from one condition later in life would have to die from something else earlier, and persons with NF1 who are unlikely to die from that condition later in life would rarely die from these alternative causes earlier.

Because the PMR is a ratio, an increase in one cause of death results in a decrease in all other causes (Decoufle et al. 1980). The PMR could therefore be reduced if the rate of a particular condition is unchanged but the death rate associated with other medical conditions is greatly increased. The PMR calculation is based on the assumption that the overall rate of death from all causes is the same in the two groups being compared. This is unlikely to be true in the comparison between people with and people without NF1. To the extent that death from all causes is more likely among people with

Table 4

Likelihood of Selected Medical Conditions Being Listed on NF1-Associated Death Certificates, by Age Group, 1983–97

Condition	PMR (95% CI) for Subjects who Died at Age							
	<10 Years	10–19 Years	20–29 Years	30–39 Years	40–49 Years	50–59 Years	60–69 Years	⩾70 Years
Malignant neoplasms:								
All	3.94 (2.60–5.73)	6.08 (4.88–7.45)	4.93 (4.14–5.82)	2.13 (1.83–2.47)	1.18 (1.00–1.37)	.89 (.76–1.05)	.77 (.67–.89)	.84 (.74–.96)
Excluding those of connective and soft tissue and brain	3.15 (1.76–5.19)	1.76 (1.07–2.71)	1.27 (.86–1.82)	.55 (.39–.75)	.58 (.45–.73)	.67 (.55–.81)	.59 (.50–.69)	.75 (.65–.87)
Connective and soft tissue	16.1 (5.24–37.6)	38.3 (27.8–51.7)	52.4 (41.8–65.2)	5.2 (4.3–62.0)	31.5 (23.5–41.3)	22.1 (14.7–31.9)	22.9 (15.6–32.3)	18.3 (11.6–27.4)
Brain	3.94 (1.58–8.10)	11.4 (7.53–16.4)	9.32 (6.14–13.5)	7.99 (5.86–1.7)	5.73 (3.96–8.00)	2.99 (1.68–4.94)	3.44 (2.07–5.38)	1.47 (.48–3.42)
Lymphatic and hematopoietic	2.35 (.94–4.84)	.28 (.03–1.01)	.20 (.02–.72)	.07 (.002–.39)	.43 (.16–.93)	.64 (.29–1.22)	.74 (.42–1.20)	.91 (.59–1.33)
Myeloid leukemia	10.4 (3.38–24.3)	1.26 (.15–4.54)	.00 (.00–1.51)	.27 (.007–1.51)	.64 (.08–2.32)	.00 (.00–1.51)	1.20 (.33–3.08)	1.60 (.59–3.48)
Vascular disease:								
All	3.26 (1.31–6.71)	2.68 (1.38–4.68)	2.25 (1.46–3.32)	1.04 (.70–1.50)	1.02 (.75–1.35)	1.12 (.87–1.42)	1.19 (1.00–1.40)	1.01 (.90–1.12)
Hypertensive disease	.00 (.00–28.4)	6.32 (.76–22.6)	3.27 (1.32–6.74)	.32 (.07–.93)	1.07 (.68–1.59)	1.01 (.69–1.43)	1.19 (.91–1.53)	1.13 (.93–1.35)
Cerebrovascular disease	3.63 (1.46–7.47)	2.76 (1.32–5.07)	2.09 (1.19–3.39)	1.20 (.74–1.83)	.85 (.53–1.30)	1.54 (1.12–2.07)	1.46 (1.16–1.81)	1.06 (.92–1.22)
Diseases of arteries and arterioles	.00 (.00–26.3)	.00 (.00–5.51)	2.48 (.80–5.78)	1.15 (.37–2.69)	1.42 (.71–2.55)	.62 (.27–1.23)	.57 (.34–.90)	.78 (.61–.97)

NF1, the PMRs we calculated will underestimate the true cause-specific standardized mortality ratio (Roman et al. 1984). An alternative method that is not subject to this limitation is the use of the standardized mortality odds ratio (SMOR) (Miettinen and Wang 1981) to analyze death-certificate data. We also performed SMOR analyses on these data, and the results were similar to those reported here for PMR (data not shown).

In conclusion, on the basis of our analysis of data from U.S. death certificates, persons with NF1 appear to have a decrease in life expectancy of ~15 years, compared with the general population. However, because NF1 may have been significantly underascertained in our study population, our analysis may overestimate the difference in life expectancy between persons with NF1 and the general population. Certain kinds of malignancy (especially brain tumors and malignant neoplasms of connective and other soft tissues) appear to occur more frequently than expected in people who die with NF1, but other kinds of cancer do not. Such malignancies and vascular disease (especially cerebrovascular disease) appear to contribute disproportionately to mortality in children and young adults with NF1.

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Electronic-Database Information

The accession number and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for NF1 [MIM 162200])

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