VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS: A CLINICAL/PATHOLOGIC REVIEW WITH SPECIAL EMPHASIS ON COMPARATIVE MORTALITY BASED ON A 39-YEAR RETROSPECTIVE SURVIVAL STUDY

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Abstract

von Recklinghausen's Neurofibromatosis (NF-1) is a multisystem impairment. A comprehensive clinical/pathologic review is presented, followed by a comparative mortality analysis of a 39-year retrospective study of probands and relatives. Neurofibromatosis showed increased geometric average annual mortality ratios (MR) and excess death rates (EDR) in both probands and relatives at the end of the 39-year follow up. Female probands have the highest excess mortality, EDR 31, MR 295 percent, nearly double that of male probands, EDR 15, MR 188 percent. Female relatives have less excess mortality, EDR 5, MR 128 percent, than male relatives, EDR 16, MR 176 percent. Probands are, as a group, at least moderately substandard. Relatives are low substandard life insurance risks.

Introduction

My interest in von Recklinghausen's Neurofibromatosis (NF-1) began over 40 years ago. As a young boy, I would clandestinely observe a local personality with bumps all over his body, an enlarged head and mildly retarded behavior. He remained a social oddity until I reached medical school and made my clinical diagnosis. Whenever I visit my hometown, Cortland, New York, this gentleman is still walking up and down Main Street. His bumps have dramatically increased in extent and size; one on his right hand is the size of a lime. Few of us have a 40 year follow-up of NF-1; however a one-person observation is not an adequate mortality study. The purpose of this paper is to review NF-1 and present comparative mortality from a 39-year survival study.

Historical background

NF was initially described by Tilesius in 1793[1] and Smith in 1849.[2] In 1882, Friedrich Daniel von Recklinghausen in honor of Rudolf Virchow's sixtieth birthday formally described NF-1.[3] Quasimodo, the hunchbacked bell-ringer of Notre Dame is suspected of having NF-1.[4] Joseph Merrick, the Elephant Man, was originally believed to have NF-1.[3,5,6] Current belief is he was afflicted with the Proteus syndrome, a disease manifested by cutaneous pigmentation, subcutaneous nodules, intracranial tumors and mental retardation.[7,8,9,10] von Recklinghausen named hemochromatosis. The bone disease bears his name.

Genetics

NF-1 is transmitted as an autosomal dominant gene designated as nf 1.[9] Population frequency is estimated between 1:3000 and 1:4000.[5,10,11] It is the most common genetic mutation with 50 percent of index cases representing new mutations.[5,7] It is linked to DNA markers in the centromeric region and to the nerve growth factor receptor on the distil long arm of chromosome 17.[9,12] Although NF-1 begins in the fetus, if not the embryo, how mutations at the neurofibromatosis-1 locus manifest themselves is unknown.[12] The disease affects males and females equally and has no racial, ethnic or national restrictions.[5] NF-1 has a 100 percent penetration with a markedly variable expressivity.[5] Due to this, there is no correlation in severity between parents and siblings.[7] Maternal transmission appears to increase severity.[13] Once manifested, the disease is usually progressive. There is a minimum risk of 25 to 30 percent for the development of moderate to severe disease.[5] A first degree relative who is postpubertal and has no café-au-lait spots, neurofibromas or Lisch nodules is extremely unlikely to carry the gene.[5]

Pathogenesis

The café-au-lait spots, neurofibromas and various tumors of the endocrine and central nervous system ultimately derive from stem cells of neural-crest origin.[5,8] Whether these cells have a genetic tumorigenic potential or are influenced by extra-cellular factors is unknown. It does appear these tumors arise from multiple cell-site origins.[14] Currently, it is postulated the primary defect in NF-1 resides in the neural-crest-related secretory-membrane system of the Golgi complex and endoplasmic reticulum.[5] The presence of large numbers of mast cells in neurofibromas has led to speculation of their involvement in tumorigenesis.[5,8] One investigator had initial favorable results treating NF-1 with Ketoifen, a mast cell stabilizer.[15]

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Clinical manifestations

There are three forms of NF: classical neurofibromatosis (NF-1), bilateral acoustic neurofibromatosis (NF-2) and a segmental form. Bilateral acoustic neurofibromatosis (NF-2) is characterized by the almost invariable presence of bilateral acoustic neuromas and generally the absence of café-au-lait spots and dermal tumors.[16] The genetic abnormality is on chromosome 22.[17]

In the segmental form, café-au-lait spots and neurofibromas are limited to circumscribed body segments, usually right or left upper dermatomes. Segmental intra-thoracic or intra-abdominal neurofibromas are also present.[5] NF-1 has three cardinal features: café-au-lait spots, neurofibromas and Lisch nodules. Café-au-lait spots are present in nearly one hundred percent of patients with NF-1.[5] To establish the diagnosis in an adult, six or more greater than 15 millimeters in greatest diameter must be present.[6] One or two spots is a common finding in a normal population.[7] The café-au-lait spots are usually present at birth, but may take up to one year to develop.[5] Commonly, they increase in size and number through the first decade. By the end of the first decade virtually all patients destined to develop NF-1 will have café-au-lait spots.[2] There is no correlation between the number of spots and the severity of the disease.[10] Various other forms of hyperpigmentation are noted including the intertriginous areas and concordant with the borders of underlying neurofibromas.[5] Neurofibromas are the second diagnostic feature of NF-1. In contradistinction to café-au-lait spots, neurofibromas are absent at birth,[5] usually appear at puberty[2] and continue development and progression into adulthood.[7] Pregnancy can lead to a dramatic increase in size and number.[7] Deeper peripheral nerves and nerve roots can be involved and large plexiform neurofibromas which interfere with contiguous organ function can form.[5,7]

Table One

Neurological manifestations of neurofibromatosis

Central nervous system
- intracranial tumors
- headaches
- seizures
- macrocephaly
- cerebral vascular accident
- spinal tumors
- other spinal abnormalities (scoliosis, syringomyelia, etc.)

Peripheral nervous system
- subcutaneous neurofibromas
- plexiform neuromas

Autonomic nervous system
- Lisch nodules
- ganglioneuromas

Cognitive/language/psychosocial
- mental retardation
- learning disabilities
- attention deficit disorder
- depression/anxiety

The central nervous system as well as viscera and blood vessels innervated by the autonomic nervous system are also involved.[5,7] Neurofibromas are histologically benign, nevertheless they often cause functional compromise and cosmetic disfigurement due to size and location.[5] Isolated neurofibromas are not diagnostic of NF-1. Their incidence of malignant degeneration, discussed in a subsequent section, is a subject of considerable controversy. The third part of the diagnostic triad is Lisch nodules (iris hamartomas). They are present in 94 percent of patients age six or older. Their number usually increases with age; they remain asymptomatic.[6,12] Histopathologically, they consist of discrete masses of melanocytes.[9]

The National Neurofibromatosis Foundation has proposed the following diagnostic criteria for NF-1.[6] The presence of two or more in an individual will establish the diagnosis:

- On examination in room light, at least five major café-au-lait macules over five millimeters in greatest diameter, if prepubertal; six café-au-lait macules over 15 millimeters in greatest diameter, if postpubertal. Neurofibromatosis Conference Statement recommends at least six café-au-lait macules regardless of age.[18]
- Two or more neurofibromas of any type, or one plexiform neurofibroma
- Multiple freckles in the axillary or inguinal regions
- Sphenoid wing dysplasia or congenital bowing or thinning of long bone cortex, with or without pseudarthrosis
- Optic nerve glioma
- Two or more iris Lisch nodules on slit lamp examination
- A first-degree relative (parent, sibling, or offspring) with NF-1 by the above criteria.

NF-1 has features that involve nearly every organ system. Endocrine abnormalities are frequent. Pheochromocytomas have a reported prevalence between one and 23 percent.[2,5,19] Delayed sexual maturation,[2,5] precocious puberty,[7,19] medullary thyroid carcinoma,[2,5] thyromegaly,[2] and hyperparathyroidism[2,5] all are noted in association with NF-1. Neurological manifestations, listed in Table One, are found in nearly 50 percent of individuals with NF-1.[19] (Reprinted with permission)

Nineteen percent of hospitalized children with NF-1 had malignancy. Optic nerve gliomas accounted for 57 percent. The remainder were fifth cranial nerve neuromas, ependymomas and meningiomas. Most occurred in the first decade of life.[13]

Several non-neoplastic central nervous system manifestations of NF-1 deserve comment. Macrocephaly is noted in about 30

percent of patients, but is not necessarily associated with any other structural abnormalities.[5,19] Intellectual impairment of varying degrees has a prevalence of about 40 percent;[5,19] the median IQ is between 85-90.[2] Frank retardation accounts for only two to five percent of those involved.[5] Seizures have a tenfold increased prevalence.[19] Asymptomatic, abnormal EEG changes are common.[5,19] Rodriquez reported the prevalence of syringomyelia in 20 percent of cases.[1] A feature of NF-1, recognized only with the advent of magnetic resonance imaging, is "bright lesions" in brains of affected children. These are noted primarily in the basal ganglia and internal capsule but also can be visualized in other areas. Their significance is unknown although some may represent low grade gliomas or their precursors.[9]

Considerable controversy exists concerning the frequency of malignant or sarcomatous degeneration of peripheral nerve tumors in NF-1. One series of patients revealed 19 percent developing a malignant schwannoma by age 40; the overall incidence of malignant schwannomata was 29 percent.[2] The authors leave open the question whether a malignant schwannoma arises de novo or originates from a benign schwannoma or neurofibroma. Knight and associates reported sarcomatous degeneration in 4.4 percent of pre-existing cutaneous neurofibromas and reviewed three other studies which revealed prevalences of 3.1, 2.4, and 16.5 percent.[20] The peak age range of sarcomatous degeneration in NF-1 is 21 to 50 years.[13] Constant trauma and previous surgical manipulation appear to predispose to malignant transformation.[5,21] Alterations at the p53 locus on the short arm of chromosome 17 appear to be critical for the progression of a neurofibroma to a neurofibrosarcoma.[12] In contradistinction, The Neurofibromatosis Foundation states that dermal neurofibromas rarely, if ever, become cancerous. Such a change may occur, although very rarely, in plexiform tumors.[6] They also state there is no evidence surgical manipulation of neurofibromas can cause a change from benign to malignant. Robbins notes in his textbook of pathology "schwannomas (neurilemmomas) virtually never undergo malignant transformation." Malignant change in superficial, cutaneous neurofibromas is rare; however such change in large neurofibromas attached to large nerve trunks of the neck and extremities occurs in 10-15 percent of cases.[22] No attempt will be made to reconcile the large discrepancies among the various studies on the incidence of malignant degeneration of peripheral tumors except to note that selection bias of populations studied likely had a major influence.

Prominent non-neurological features of NF-1 include constipation, pruritus and kyphoscoliosis.[5] Congenital defects of bone development have been extensively reviewed.[23] Renal artery stenosis occurs in two percent of patients.[24]

Malignant associations in other organs: Hope and Mulvihill presented on extensive review of neoplasia associated with NF-1.[13] Although neoplasm is beyond question part of NF-1, reliable estimates of the frequency are unreliable owing to a lack of formal epidemiologic studies. Maternal transmission appears to increase the severity of the disease including the probability of malignancy. Tumors associated with NF-1 usually arise from cells of neural crest origin and include neuroblastoma, pheochromocytoma and medullary thyroid carcinoma. Malignant melanoma does not have an increased incidence. Malignancies of non neural crest origin include rhabdomyosarcoma and a weak association with Wilms tumor.

Sorenson and colleagues extensively analyzed the prevalence of malignant tumors in NF-1.[25] Before proceeding, the authors definition of "malignant tumor" deserves special note. It included all malignant neoplasms as well as benign central nervous system neoplasms such as gliomas, meningiomas and acoustic neuromas; benign peripheral nerve tumors, e.g., neurofibromas are excluded. The authors' reason for classifying gliomas as malignant was their potentially lethal anatomic sites in the central nervous system. Observed new malignant neoplasms were compared with expected numbers calculated from Danish national year-, age- and sex-specific incidence rates according to males and females. These two were then further subdivided into probands and relatives. Although the prevalence of neoplasms in NF-1 was similar to the general population, the site was dramatically different. Nervous system tumors were most common, totaling 47 percent, with gliomas accounting for 84 percent. The authors state that none of the peripheral nerve tumors could confidently be said to have arisen from a benign neurofibroma. In the general population, a second tumor developed in four percent of persons with cancer. In probands the incidence of second tumors, mainly central nervous system, was approximately nine times that noted in the general population. Relatives had no excess second malignancies.

A weak relationship exists between NF-1 and childhood leukemia.[13,26] The ratio of acute lymphocytic to nonlymphocytic leukemia is reversed with an excess of the latter. The prevalence of unusual subtypes of nonlymphocytic leukemia in children such as chronic myelogenous and acute myelomonocytic is increased.

A 39-year retrospective study of individuals with NF-1 (probands) and their relatives is the basis for this comparative mortality study.[25] The source cases, 84 probands, were located from a previous study that had searched nearly all Danish hospitals and identified all patients diagnosed with NF-1 from January 1, 1924 to January 1, 1944.[27] The criteria for the diagnosis of NF-1 was consistent with contemporary standards. Fifty eight percent of the probands were sporadic cases. The authors discussed the limitations of their analysis which included the possibility of chance unrepresentativeness (type II error). They noted the unfavorable survival of probands could have been biased by the fact that each was identified in-hospital and therefore represented an initially sicker population. The relatives, 128 patients, were located by reconstruction of family registers through the Danish Center Personal Register, church registers and other sources. Only two relatives who immigrated to the United States could not be found for follow-up. The authors did not note their sex nor whether they had already been excluded from the data. I elected to exclude these two individuals from the analysis. Ob-

served deaths were determined from death certificates and where possible from hospitalizations and postmortem examinations. Total deaths of probands and relatives at the end of the 39-year observation period were noted.

Published survival curves were prepared by standard life-table methods. Expected cumulative survival was based on age-, year- and sex- specific mortality data from the Danish vital statistics. Whether the expected survival data was based on initial age distribution or age distribution of survivors is unknown. For expected mortality, a single decrement table was created using cumulative survival percentages for each interval and an assumed 1,000 lives at start of follow-up. The recalculated expected interval survival rates (p') were not graduated (smoothed).

Refer to Table Two for definitions of abbreviations used in the following text and tables. Each survival curve was enlarged to facilitate measurement. Cumulative survival percents, observed (P) and expected (P'), were calculated for intervals 0-10, 11-20, 21-30, 31-39 and 0-39 years. Cumulative survival is difficult to measure directly and accurately from the small, published survival curves. Errors are inherent due to optical distortion in production of originals and enlargements. ECG calipers and the method of proportions were utilized to maximize accuracy. Since the cumulative survival curves had a vertical scale with 100 percent survival only 22mm, P and P' were rounded to the nearest 0.005. Single decrement mortality tables, observed and expected, were then constructed (Tables 3-14) and calculated values (q, p, P, $\breve{q}$) were rounded to the nearest 0.001. Carrying out calculations to three decimal places may appear inappropriate. However, when the initial life tables were constructed to two places, inaccuracies of rounding produced unacceptable inconsistencies in much of the data, especially deaths. I therefore elected to use three decimal places. All deaths (d) were rounded to the nearest whole number. Mortality ratios (MR) were rounded as follows: 0-199 to one percent, 200-995 to five percent. Excess death rates (EDR) were rounded to the nearest whole digit(s).

For comparative analysis, average annual excess death rates (EDR) and average annual mortality ratios (MR) were calculated from the geometric average annual mortality rates ($\breve{q}$), observed and expected.

Data inconsistencies in construction of the tables deserve note. Male probands, observed (Table Three): The source document noted 26 deaths. In construction of the life table, deaths (d) were calculated from the product (1) (q_i) and rounded upward or downward to the nearest whole number. The sum of all interval deaths was only 25; therefore, I rounded 4.4 deaths upward to five in the final interval 31-39 to achieve the correct number of total deaths. Combined probands observed (Table Seven): For interval 31-39, the product of $p_{(0\text{-}10)}$, $p_{(11\text{-}20)}$ etc. is .210. Direct life table calculation of $P_{(0\text{-}39)}$ is .211. Male relatives observed (Table Nine): As in male probands observed, the sum of total calculated deaths for each interval did not equal the source number of deaths. For interval 31-39 the number of deaths was rounded upward from 5.4 to six.

Comparative mortality data on the survival of von Recklinghausen's disease is presented in two formats. The first, males and females, probands and relatives are illustrated and discussed separately (Tables 3-6, 9-12). Secondly, males and females are combined as relatives and probands (Tables Seven, Eight, 13, 14). Finally, comparative mortality of all groups is presented (Table 15).

Due to the small number of observed deaths in each proband/relative group individually as well as combined one may question the potential value of this study. The reviewed article would rate an A, highest value (top priority). The existing mortality sources are almost nil and the deaths are in the range of 26-100.[28] Underwriting manuals usually do not separate males and females. By combining data, more accurate and meaningful comparative mortality information is produced.

For each single group the comparative mortality analysis reveals the following:

- Male probands: The 39-year observation period reveals an EDR of 15 and MR of 188 percent. There appears to be no consistent trend through succeeding intervals.
- Female probands: Compared to male probands the EDR is slightly more than double (31/15). The MR is about 50 percent greater (295/188).
- Combined probands: For the duration of observation the EDR is 22 and the MR 230 percent.
- Male relatives: The EDR and MR for male relatives, 16, 176 percent over the entire observation period is nearly identical to that of male probands, 15, 188 percent.

Table Two
Definitions of abbreviations used in the text and Tables 3-15

l:	living entrants
d:	deaths, observed
d':	deaths expected
P:	cumulative survival rate, observed
P':	cumulative survival rate, expected
q:	interval mortality rate, observed
q':	interval mortality rate, expected
p:	interval survival rate, observed
p':	interval survival rate, expected
$\breve{q}$:	geometric average annual mortality rate, observed
$\breve{q}$':	geometric average annual mortality rate, expected
MR:	geometric average annual mortality ratio
EDR:	geometric average annual excess death rate

- Female relatives: Compared to all other cohorts, this group has a superior survival with only a slightly excessive EDR 5 and MR 128 percent.
- Combined relatives: The EDR 9 and MR 147 percent are about 50 percent of the combined probands. Nevertheless, this group does exhibit excess mortality.

Not surprisingly, the EDR and MR of the combined probands is considerably greater than those of the combined relatives. The combined probands had a moderately elevated EDR, 22 and MR, 230 percent for the interval 0-39. Compared to the combined probands, the relatives had a much lower EDR, 9 and MR, 147 percent over the same interval. Relatives do not have a standard mortality compared to the reference Danish population.

This mortality analysis is based on expected Danish population mortality rates. The authors did not disclose whether the expected rates and subsequent cumulative survival curves were based on age distribution of survivors or initial age distribution in each group at the start of each interval. If expected survival had been based on the latter, q' values may be progressively overestimated with increasing duration leading to underestimation of excess mortality. The average annual increase in q' for male probands is about eight percent. When life tables are constructed, the average annual increase in mean q' is often as low as one or two percent per year, rather than the 10 percent per year average in population life tables from about age 35 to 75 or 80 (letter from RB Singer, MD, March 1988). If the overestimation for q' is in a similar range for all probands and relatives, comparative mortality data may again underestimate the true mortality picture. When we consider the additional factor that these results are based upon expected population rates, it is obvious that NF-1, both probands and relatives, have excess mortality. Were expected rates based upon industry select/ultimate rates, the comparative mortality would be even more adverse.

Those individuals (probands) afflicted with NF-1 are, as a group, insurable risks although at least moderately substandard. Individuals in this group no doubt comprise the entire spectrum of insurability including some who are uninsurable to those who may be low substandard risks.

Underwriting relatives of those with NF-1 is problematic. By objective analysis, there is at least a low substandard excess mortality. However, how relatives who have only a genetic association with NF-1 are underwritten is a complex decision. My personal sense is the legal and onerous politically correct consequences of making an adverse underwriting decision on a relative whose excess mortality is relatively small may not be worth the mortality savings. However, were one to make an adverse decision, objective data is presented to substantiate solidly the action was based on the dictum that a decision must be based on sound actuarial principles reasonably related to actual or anticipated loss experience. Whether relatives belong in a preferred category depends upon individual company rules. Objective data argue strongly against this classification.

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Table Three

Male probands, observed, by single decrement mortality table

t+t	*P*	p_t	q_t	ℓ	*d*	q_t	p_t	*P*	$\check{q}_t$
0-10	.880	.880	.120	36	4	.111	.889	.889	.012
11-20	.655	.744	.256	32	8	.250	.750	.667	.028
21-30	.405	.618	.382	24	9	.375	.625	.417	.046
31-39	.285	.704	.296	15	5	.333	.667	.278	.044
0-39	.285	.285	.715	36	26	.722	.278	.278	.032

Table Four

Male probands, expected, by single decrement mortality table

t+t	*P'*	p'_t	q'_t	ℓ	*d'*	q'_t	p'_t	*P'*	$\breve{q}'_t$
0-10	.955	.955	.045	1,000	45	.045	.955	.955	.005
11-20	.875	.916	.084	955	80	.084	.916	.875	.009
21-30	.715	.817	.183	875	160	.183	.817	.715	.020
31-39	.515	.720	.280	715	200	.280	.720	.515	.036
0-39	.515	.515	.485	1,000	485	.485	.515	.515	.017

Table Five

Female probands, observed, by single decrement mortality table

t+t	*P*	p_t	q_t	ℓ	*d*	q_t	p_t	*P*	$\breve{q}'$
0-10	.705	.705	.295	40	12	.300	.700	.700	.35
11-20	.475	.674	.326	28	9	.321	.679	.475	.038
21-30	.285	.600	.400	19	8	.421	.579	.275	.053
31-39	.145	.509	.491	11	5	.455	.545	.150	.065
0-39	.145	.145	.855	40	24	.85	.150	.150	.047

Table Six

Female probands, expected, by single decrement mortality table

t+t	*P'*	p'_t	q'_t	ℓ	*d'*	q'_t	p'_t	*P'*	$\breve{q}'_t$
0-10	.930	.930	.070	1,000	70	.070	.930	.930	.007
11-20	.820	.882	.118	930	110	.118	.882	.820	.013
21-30	.675	.823	.177	820	145	.177	.823	.675	.019
31-39	.530	.785	.215	675	145	.215	.785	.530	.027
0-39	.530	.530	.470	1,000	470	.470	.530	.530	.016

Table Seven

Combined male and female probands, observed, by sinqle decrement mortality table

t+t	ℓ	*d*	q_t	p_t	*p*	$\breve{q}_t$
0-10	76	16	.211	.789	.789	.023
11-20	60	17	.283	.717	.566	.033
21-30	43	17	.395	.605	.342	.049
31-39	26	10	.385	.615	.210	.053
0-39	76	60	.789	.211	.211	.039

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Table Eight

Combined male and female probands, expected, by sinqle decrement mortality table

t+t	ℓ	*d'*	q_i'	p_i'	*p'*	$\breve{q}_i'$
0-10	2,000	115	.058	.942	.942	.006
11-20	1,885	190	.101	.899	.847	.011
21-30	1,695	305	.180	.820	.694	.020
31-39	1,390	345	.248	.752	.522	.031
0-39	2,000	955	.478	.522	.522	.017

Table Nine

Male relatives, observed, by single decrement mortality table

t+t	*P*	p_i	q_i	ℓ	*d*	q_i	p_i	*P*	$\breve{q}_i$
0-10	.875	.875	.125	31	4	.129	.871	.871	.014
11-20	.660	.754	.246	27	7	.259	.741	.645	.030
21-30	.420	.636	.364	20	7	.350	.650	.420	.042
31-39	.245	.583	.417	13	6	.462	.538	.226	.066
0-39	.245	.245	.757	31	24	.774	.226	.226	.037

Table 10

Male relatives, expected, by single decrement mortality table

t+t	*P'*	p_i'	q_i'	ℓ	*d'*	q_i'	p_i'	*P'*	$\breve{q}_i'$
0-10	.880	.880	.120	1,000	120	.120	.880	.880	.013
11-20	.760	.864	.136	880	120	.136	.864	.760	.015
21-30	.605	.796	.204	760	155	.204	.796	.605	.023
31-39	.445	.736	.264	605	160	.264	.736	.445	.034
0-39	.445	.445	.555	1,000	555	.555	.445	.445	.021

Table 11

Female relatives, observed, by single decrement mortality table

t+t	*P*	p_i	q_i	ℓ	*d*	q_i	p_i	*P*	$\breve{q}_i$
0-10	.840	.840	.160	48	8	.167	.833	.833	.018
11-20	.630	.750	.250	40	10	.250	.750	.625	.028
21-30	.485	.770	.230	30	7	.233	.767	.479	.026
31-39	.405	.835	.165	23	4	.174	.826	.396	.021
0-39	.405	.405	.595	48	29	.604	.396	.396	.023

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Table 12

Female relatives, expected, by single decrement mortality table

t+t	P'	p_i'	q_i'	ℓ	d'	q_i'	p_i'	P'	$\breve{q}_i'$
0-10	.905	.905	.095	1,000	95	.095	.905	.905	.010
11-20	.770	.851	.149	905	135	.149	.851	.770	.016
21-30	.620	.805	.195	770	150	.195	.805	.620	.021
31-39	.485	.782	.218	620	135	.218	.782	.485	.027
0-39	.485	.485	.515	1,000	515	.515	.485	.485	.018

Table 13

Combined male and female relatives, observed, by single decrement mortality table

t+t	ℓ	d	q_i	p_i	p	$\breve{q}_i$
0-10	79	12	.152	.848	.848	.016
11-20	67	17	.254	.746	.633	.029
21-30	50	14	.280	.720	.455	.032
31-39	36	10	.278	.722	.329	.036
0-39	79	53	.671	.329	.329	.028

Table 14

Combined male and female relatives, expected, by single decrement mortality table

t+t	ℓ	d'	q_i'	p_i'	p'	$\breve{q}_i'$
0-10	2,000	215	.108	.892	.892	.011
11-20	1,785	255	.143	.857	.764	.015
21-30	1,530	305	.199	.801	.612	.022
31-39	1,225	295	.241	.759	.465	.030
0-39	2,000	1,070	.535	.465	.465	.019

Table 15

Comparative mortality of all study group by duration

	Male probands		Female probands		Combined probands		Male relatives		Female relatives		Combined relatives	
Interval	EDR	MR	EDR	MR	EDR	MR	EDR	MR	EDR	MR	EDR	MR
0-10	7	240	28	500	17	385	1	108	8	180	5	145
11-20	19	310	25	290	22	300	15	200	12	175	14	193
21-30	26	230	34	280	29	245	19	183	5	124	10	145
31-39	8	122	38	240	22	171	32	194	-6	78	6	120
0-39	15	188	31	295	22	230	16	176	5	128	9	147

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