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The Clinical and Screening Age-at-Onset Distribution for the MEN-2 Syndrome

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Summary

The decision to screen for multiple endocrine neoplasia type 2 (MEN-2) is generally based on family history, the rationale for this approach being the presumed 100% penetrance of the disease. To determine the validity of this presumption we have estimated—by applying modifications of the life-table method—the clinical and screening age-at-diagnosis distributions for MEN-2, using families from the Cancer Research Campaign Medullary Thyroid Cancer Register and one large American family. The clinical penetrance of MEN-2 is shown to be incomplete, an estimated 41% of gene carriers not presenting with symptoms by age 70 on the basis of clinical history. Screening by the standard tests for detecting the earliest manifestations of the syndrome increases the penetrance to an estimated 93% by age 31. There is no evidence of a difference in the age-at-diagnosis distributions between maternal and paternal transmission, or among different families, but there is some suggestion of an earlier onset of medullary thyroid cancer in female gene carriers, and of a tendency of pheochromocytoma to cluster in families. These results can be used to calculate risks to relatives of affected individuals, which in turn can be used to guide decisions on which individuals to screen.

Introduction

Multiple endocrine neoplasia type 2 (MEN-2) is a rare autosomal dominant cancer syndrome (Schimke 1984). The distinguishing features of the syndrome are either medullary thyroid carcinoma (MTC) or pheochromocytoma or both, the diseases usually occurring in middle age. Once the syndrome is recognized, other family members can be screened for early evidence of hyperplasia of the thyroid C-cells (from which MTC originates) by detecting a raised serum calcitonin level. Screening for pheochromocytoma is based on raised catecholamine production.

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The majority of patients with MTC probably have sporadic (nonhereditary) disease (Chong et al. 1975). Although there are some criteria for separating hereditary from nonhereditary MTC—in particular, the presence of C-cell hyperplasia on pathology (Block et al. 1980)—it is frequently difficult to decide which patients presenting with MTC should have their families screened, since a negative family history can only be interpreted with knowledge of the proportion of gene carriers who have yet to manifest the disease by a given age. We have therefore attempted to estimate the distributions of the age at clinical onset of disease and of the age at first positive screening test in MEN-2 gene carriers by using data from a large series of MEN-2 families.

Families

The Cancer Research Campaign Medullary Thyroid

Register began in 1983. It records clinical details of cases of medullary thyroid cancer, both hereditary and apparently sporadic, contributed by a number of clinicians in the United Kingdom and Europe. Contributing clinicians are asked to provide a first-degree family history for all cases submitted to the register. Since each of the participating clinics would be referred the majority of MTC cases within the hospital catchment area, the register should contain a reasonably representative sample of MEN-2 families, without gross overrepresentation of more or less impressive families.

Families affected with MEN-2 are identified by (*a*) a history of MTC or pheochromocytoma in a relative of the index case, (*b*) a positive screening result in a relative, or (*c*) previous or subsequent contraction of pheochromocytoma in the index case. Where a second relative is affected (as ascertained either clinically or by screening), the first-degree relatives of this individual are then considered as part of the family (for the purposes of this study) and this process is repeated until no more affected individuals can be identified.

At the time of this analysis, 44 index cases in the register met these criteria for MEN-2. For 31 of these the family history had been confirmed by one of us by interview with family members and by review of hospital records and death certificates where appropriate. The 31 families consist of 20 identified by a history of MTC or pheochromocytoma in first-degree relatives of the index case, eight identified by screening, and three identified because the index case had pheochromocytoma and MTC. The individuals analyzed in this study are members of these 31 families. They consist of 207 affected individuals (90 diagnosed at clinical presentation, 84 diagnosed at first screen, and 33 who converted from a negative to a positive screen) and 322 unaffected first-degree relatives. All screening for MTC in these families was by the standard pentagastrin-stimulation test (Telenius-Berg et al. 1977), using a dose of 0.5 or 0.6 μg pentagastrin/kg body weight. Screening for pheochromocytoma was by measurement of urine or plasma catecholamines. By virtue of suitable repetition of suspicious results, these tests are essentially 100% specific. About half the affected individuals are members of one large pedigree originally ascertained as nine separate families with branches in Sweden (the S kindred; Telenius-Berg et al. 1984) and the United States (the J kindred; Graze et al. 1978; Gagel et al. 1988); the remaining families each contain 1–13 affected members. (Note that the J kindred, though not ascertained through the CRC register, is included since it is a branch of the S kindred.)

Methods

The statistical methods used for calculating the age-at-onset distribution will be described in more mathematical detail elsewhere and are only outlined here. Similar methods have been used by Newcombe (1981) and Newcombe at al. (1981) for analyzing data on families with Huntington chorea.

Let $F(t)$ be the probability that an MEN-2 gene carrier has not become clinically affected by age t. We shall refer to $F(t)$ rather loosely as the "age-at-onset distribution," in keeping with terminology of genetics; however, the time of biological "onset" is impossible to ascertain, and the results here are based on the age at diagnosis. Moreover, we must allow the possibility that some gene carriers may never become affected, so the term "cumulative incidence distribution" would be a more accurate description. Given a cohort of gene carriers followed up to time t, we could calculate the usual life-table estimate of $F(t)$ (Kaplan and Meier 1958):

$$F(t) = \prod_{k=1}^{t} \frac{r_k - C_k/2 - O_k}{r_k - C_k/2},$$

where r_k is the number of gene carriers at risk at age k, C_k the number of individuals lost to follow-up at age k, and O_k the number of individuals who became affected at age k.

Unfortunately, we cannot identify a cohort of gene carriers unambiguously, because first-degree relatives of affected individuals who themselves do not become affected may or may not be gene carriers. To solve this problem, we let P_j be the probability that j is a gene carrier, given the observed data, and then redefine

$$r_k = \sum_{j \in R_k} P_j,$$

where R_k consists of individuals at risk at age k; in other words, individuals are weighted by the probabilities P_j that they may be gene carriers in any risk sets into which they fall. C_k is adjusted similarly.

The probabilities P_j are calculated according to the usual method for genetic risks (Emery 1976). Thus, P_j is clearly 1 for an affected individual. For a first-degree relative of an affected individual who is unaffected at age t, the probability is

$$P = \frac{F(t)}{1 + F(t)}.$$

For the unaffected mother and father of an affected offspring who are unaffected at ages t_m and t_t, respectively, the probabilities that either is a gene carrier are

$$P_m = \frac{F(t_m)}{F(t_m) + F(t_f)} \text{ and } P_f = \frac{F(t_f)}{F(t_m) + F(t_f)},$$

and so on. Since these probabilities depend on $F(t)$, estimation proceeds iteratively. This is an example of the EM algorithm (Dempster et al. 1977) and will thus converge to the maximum likelihood estimate for $F(t)$.

To avoid ascertainment bias, carefully chosen criteria must be used to define the risk period for each individual. These criteria are as follows:

1. The index case for each family is not considered at risk since he or she is by definition affected.
2. If the index case has MTC only, at least one first-degree relative of the index case must be affected (as ascertained either clinically or by screening) for the family to be included. The first such case is called the second index case and is also excluded from the life-table calculations.
3. All other first-degree relatives of the index case are at risk from the date of diagnosis of the second index case.
4. Once a first-degree relative (including the second index case) of the index case is identified as affected, the relative's first-degree relatives also become at risk *from birth* (except if they are first-degree relatives of the index case). If any of these individuals are affected, then their relatives are at risk, and so on. These additional relatives can be followed from birth without bias because ascertainment of the family does not depend on whether or when they were affected. (Such individuals could be validly considered only from the age of the index case—and when this was done similar results were obtained—but information is lost unnecessarily.)
5. For estimating the clinical age-at-onset distribution, an individual ceases to be at risk when first screened.
6. To avoid problems of poor diagnosis, risk is not considered prior to January 1, 1950. For similar reasons, no attempt is made to examine the age-at-onset distribution beyond age 70.
7. If the index case has pheochromocytoma diagnosed prior to or concurrently with MTC, this is sufficient to classify the family as MEN-2. In this situation no second index case is required and all first-degree relatives are at risk from birth (unless criterion 6 applies). If pheochromocytoma is diagnosed subsequently, this also is sufficient to classify the family as MEN-2 if a second index case has not occurred by this date; however, in this situation first-degree relatives are at risk only from the data of pheochromocytoma. The presence of parathyroid disease together with MTC would also have been sufficient to indicate an MEN-2 family, and would have been treated in the same way as pheochromocytoma. In fact, however, none of the index cases did present in this way.

For the purposes of defining individuals at risk, the S + J family is regarded as nine separate families, each with its own proband. To estimate the distribution of age at onset by screening, we proceed similarly, but define the period at risk from the date of first screening. An added complication, however, is that many individuals are found to be affected when *first* screened (as opposed to converting). This situation is dealt with by adjusting the life-table method to allow for left censoring (Cox and Oakes 1984).

In some families, where both parents of an affected individual are unaffected, the calculations of genetic risk would be affected by the possibility of new mutation. Unfortunately, for MEN-2 the rate of new mutations is not known; but since no clear examples of new mutation have ever been described, the rate is generally assumed to be low. In principle it would be possible to use the information from the pedigrees in this study to estimate the new mutation rate, but in practice the number of informative individuals is so small that such

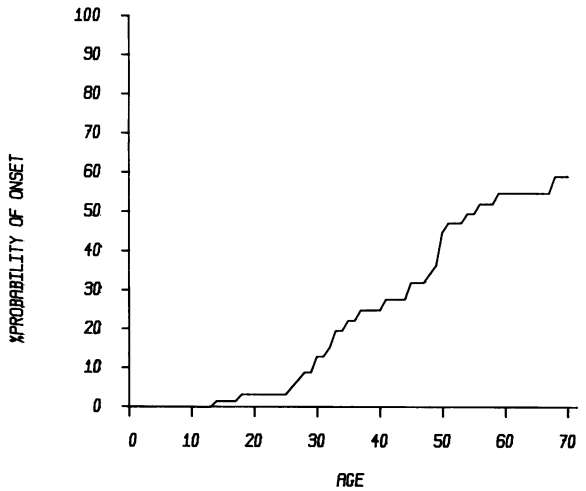

Figure 1 Probability of MEN-2 onset in an MEN-2 gene carrier by a given age, in the absence of screening. (A detailed discussion of the clinical application of this figure is given in Ponder et al. 1988.)

an estimate would be very imprecise. However, allowance for a variety of new mutation rates was found to make very little difference in the resulting age-at-onset distribution, and for simplicity the calculations presented here assume no new mutations.

To determine whether the distribution of age at clinical onset differs between males and females, or between families, we use a modification of the log-rank test (Peto and Peto 1972) in which the expected numbers of events are calculated using the estimated number of individuals at risk at a given age (Newcombe et al. 1981). To compare screening onset distributions, a further modification is required in which observed and expected numbers of events at first screen are calculated separately, as in the standard analysis of animal carcinogenesis experiments (Gart et al. 1986). For this purpose, the age at first screen is divided into 5-year periods up to age 30, ages 30–40, and ages 40 and over.

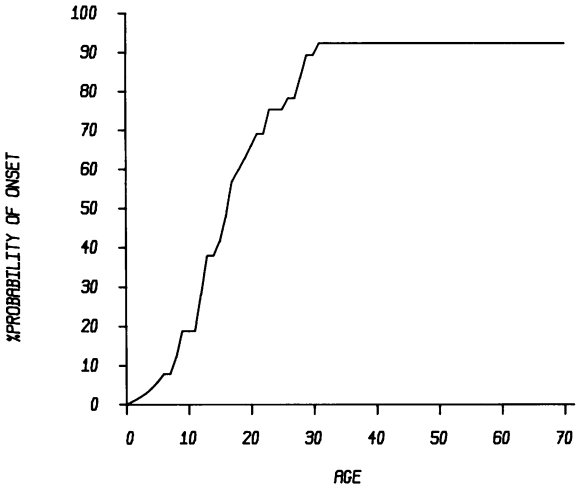

Figure 2 Probability of a positive screen in an MEN-2 gene carrier by a given age. Screening consists of a pentagastrin stimulation test for MTC and assay of urinary catecholamines for pheochromocytoma.

Results

Figure 1 shows the clinical onset distribution obtained from the above method by using all available families. The estimated proportion of gene carriers with clinical onset is 45% by age 50 and 59% by age 70, with 95% confidence limits 30%–59% at age 50 and 43%–75% at age 70. By applying the same methods we can obtain an estimate of 28% (95% confidence limits 14%–42%) for the risk to age 50 of medullary thyroid cancer and of 23% (95% confidence limits 9%–37%) for pheochromocytoma. (In these latter analyses only the first presenting tumor is considered for each individual, the analysis being censored at that point, since many individuals presented with MTC would be screened for pheochromocytoma, and vice versa.)

The corresponding screening onset curve is given in figure 2. An estimated 93% of gene carriers would have converted by age 31. No increase in this estimate is observed after age 31; but the number of individuals at risk at older ages is low (only five individuals are estimated to be at risk at age 35), so this apparent plateau

Table 1

Log-Rank Comparisons of Clinical Age at Onset

	MTC		Pheochromocytoma		MEN-2	
Variable	Observed	Expected	Observed	Expected	Observed	Expected
Sex:						
Male	4	7.56*	6	6.57	10	14.13**
Female	10	6.44	6	5.43	16	11.87
Transmission:						
Father	6	3.97	1	2.22	7	6.18
Mother	4	6.03	5	3.78	9	9.82
Family:						
A	5	6.16	6	4.37	11	10.53
Other	9	7.84	6	7.63	15	15.47

Note.—"Expected" denotes log-rank expected numbers, adjusted to allow for genetic risks (see text).
* $p < .05$.
** $p < .10$.

Table 2

Comparisons of Screening Onset Distributions

	MTC		Pheochromocytoma		MEN-2	
Variable	Observed	Expected	Observed	Expected	Observed	Expected
Sex:						
Male	59	61.60	21	22.96	61	63.66
Female	35	32.40	13	10.04	37	34.34
Transmission:						
Father	31	30.99	6	6.18	32	32.01
Mother....	46	46.01	17	16.82	48	47.99
Family:						
S + J.....	59	56.02	26	21.01**	61	57.89
A	6	6.30	0	3.35	5	6.08
B	4	4.85	0	1.35	4	5.11
C	4	4.83	1	1.29	4	4.92

Note.—"Expected" denotes log-rank expected numbers, adjusted to allow for genetic risks (see text). "Observed" and "expected" numbers are the sum of those calculated separately for first screen and subsequent screens (see text).

** $p < .10$.

may be spurious. The distribution is qualitatively and quantitatively similar to that given by Gagel et al. (1982).

Tables 1 and 2 give details of the log-rank comparisons of clinical and screening onset, respectively, by sex, sex of affected parent, and family. In each table the observed number of events (clinical diagnosis or positive screen) in each group is given together with the number expected on a log-rank basis, using the estimated number of individuals at risk at each age. To provide a test with reasonable power for the comparison of screening onset between families, only the four families with more than four expected MEN-2 events are compared; for clinical onset, only family A contains more than three events, and the only test of heterogeneity with reasonable statistical power is that comparing family A with the other families combined.

There is some suggestion of an earlier clinical onset in females ($P = .10$); this difference is most apparent in the MTC incidence ($P = .05$), with no difference in the pheochromocytoma onset. No significant difference in clinical onset between paternally and maternally transmitted cases is observed, and no difference in the age-at-onset distribution of MEN-2, MTC, or pheochromocytoma is observed between family A and all other families combined. No significant differences are observed between the screening onset distributions for males and females and paternally and maternally transmitted gene carriers (table 2), though the number of events and hence the power of these comparisons is low. There is a slight suggestion of heterogeneity in the pheochromocytoma incidence between families ($P < .10$), with two of the families (A and B) having no observed cases of pheochromocytoma as compared with 4.70 expected. However, in one of these families (A) the index case and several of the relatives affected before the follow-up period did have pheochromocytoma, so that this family is clearly not an example of a "pheochromocytoma-free" family. No significant difference in MTC incidence is observed between families.

Two widely held clinical impressions are (1) that some MEN-2 families have few if any cases of pheochromocytoma while others have many and (2) that families without many cases of pheochromocytoma tend to have less aggressive MTC. The above analysis failed to produce convincing evidence of low-incidence pheochromocytoma families, but the analysis is very weak statistically because the number of cases of pheochromocytoma expected in one family during the period of the study is so low. A more useful analysis is to compare pheochromocytoma incidence in those families where the index cases had pheochromocytoma with that in families where the index case had MTC only. As shown in table 3, there is some evidence that the incidence is higher in those families where the index case had pheochromocytoma ($\chi^2 = 5.70$, $P = .017$). Table 4 compares MTC incidence in families with or without pheochromocytoma. A slightly lower incidence is seen

Table 3

Comparisons of Pheochromocytoma Incidence in Families according to Whether the Index Case Had Pheochromocytoma

	Pheochromocytoma Events in Family					
	Clinical Onset		Screening Onset		Total	
Index Case	Observed	Expected	Observed	Expected	Observed	Expected
MTC only	1	3.69	3	7.19	4	10.88*
MTC + pheochromocytoma	11	8.31	31	26.81	42	35.12

Note.—"Expected" denotes log-rank expected numbers, adjusted to allow for genetic risks (see text).
* $p < .05$.

in the families without pheochromocytoma compared with families with pheochromocytoma, though this difference is not significant.

Discussion

This study provides evidence that the clinical penetrance of the MEN-2 gene is not complete even by age 70. Some of this could be due to underdiagnosis, but it seems unlikely that this could account for the entire lack of penetrance, since the majority of families are known to clinicians with a particular interest in the syndrome. No cases of clinical onset were observed beyond the age of 70, but few individuals were at risk at these ages and here the problems of underdiagnosis are more severe. Thus, no useful statement can be made about the completeness of clinical penetrance beyond age 70.

This lack of penetrance contrasts with nearly complete penetrance of the screening tests in MEN-2 gene carriers, with 93% of gene carriers having converted to a positive screen by age 31. The estimated screening onset distribution is very similar to that obtained by Gagel et al. (1982) in 11 families. Only a small part of the present study (less than 10%) overlaps that of Gagel et al. (1982), and the studies have used somewhat different statistical methods, so that the present study provides independent confirmation of the shape of screening onset distribution. It should be emphasized that the screening onset distribution applies only to the standard pentagastrin-stimulation test with minor modifications; a lower penetrance would obtain if the less sensitive basal calcitonin test (Telenius-Berg et al. 1977) were used. The discrepancy between the screening and clinical age-at-onset distributions is partly explained by the relatively slow growth rate of MTCs, but also suggests that one or more further genetic or epigenetic events, occurring at a low rate, are required to convert a hyperplastic C-cell into an MTC cell, or to convert a hyperplastic adrenal medullary cell into a pheochromocytoma cell. A more complete understanding of the biology of these tumors will be needed to resolve this issue.

Some evidence of a higher (or earlier) incidence of medullary thyroid cancer in females as compared to male gene carriers has been obtained. This evidence,

Table 4

Comparisons of MTC Incidence in Families with or without Pheochromocytoma

	MTC Events in Family					
	Clinical Onset		Screening Onset		Total	
Family Type	Observed	Expected	Observed	Expected	Observed	Expected
Pheochromocytoma present	13	11.49	83	78.85	96	90.34
Pheochromocytoma absent	1	2.51	11	15.15	12	17.66

Note.—"Expected" denotes log-rank expected numbers, adjusted to allow for genetic risks (see text).

though not strong, is supported by examination of all the cases of MTC in these families (including index cases). Of the 33 cases presenting clinically with MTC before the age of 40, 20 (61%) were female. However, although thyroid cancer in general is about twice as common in females as in males in most Western countries (Waterhouse et al. 1982), this does not appear to apply to medullary thyroid cancer in particular—unpublished data on MTC registrations from the Mersey and South Thames registries gives an age-standardized female:male incidence ratio of 0.81:1.

No clear evidence for heterogeneity of MTC incidence between families was obtained. The majority of the families in the study were, however, quite small, which makes this comparison very weak statistically. There was, however, some evidence of heterogeneity in pheochromocytoma incidence. Farndon et al. (1986) have described two large families in which there is inheritance of MTC without pheochromocytoma and in which the disease is apparently less aggressive (measured in terms of survival) than usual. No families as distinct as these were found in the present study: although 12 of the 31 families had no reported cases with clinical pheochromocytoma or with raised catecholamines, all were small families in which no more than 1 clinically detectable pheochromocytoma would have been expected. A more extensive study of the prevalence of pheochromocytoma in different families by uniformly applying modern screening techniques would be worthwhile.

The incomplete clinical penetrance of MEN-2 has important implications for family screening, both in known MEN-2 families and in the families of cases of apparently sporadic MTC, and these implications are discussed in detail in Ponder et al. (1988). The MEN-2 gene has now been localized to chromosome 10 by genetic linkage (Mathew et al. 1987; Simpson et al. 1987), and once closely linked polymorphic DNA markers become available it will be possible to estimate the age-at-onset distributions more precisely. More important, risk estimation in families will become much more accurate since it will be possible to identify gene carriers with near certainty. The major clinical problem of determining which apparently sporadic cases of MTC are in fact familial will, however, remain. This will not be completely resolved until the genetic defect causing MEN-2 has been identified. In the meantime, genetic risk estimates based on the age-at-onset distribution offer the best guide to identifying the families most likely to benefit from screening.

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