Mortality Rates among Carriers of Ataxia-Telangiectasia Mutant Alleles

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Background: Mutations at the ataxia-telangiectasia locus cause a distinctive autosomal recessive syndrome in homozygotes and predispose heterozygotes to cancer and ischemic heart disease.

Objective: To examine mortality rates among persons carrying a mutated ataxia-telangiectasia gene.

Design: Retrospective cohort study.

Setting: The United States and Canada.

Participants: 405 grandparents of patients with ataxia-telangiectasia.

Measurements: Ages at death and risk for death (from all causes, cancer, ischemic heart disease, and other causes) among carriers and noncarriers of ataxia-telangiectasia mutations.

Results: Compared with noncarriers, carriers of a mutated ataxia-telangiectasia allele had a significantly increased risk for death at 20 through 79 years of age (relative risk, 1.9 [95% CI, 1.3 to 2.8]) ($P < 0.001$). On average, carriers died 7 to 8 years earlier than noncarriers. Cancer caused most of the excess deaths, and ischemic heart disease caused the remainder. Among carriers, relative risk for death from cancer and ischemic heart disease before 80 years of age was 2.6 (CI, 1.4 to 4.7; $P = 0.002$) and 2.0 (CI, 1.0 to 4.0; $P = 0.062$), respectively. Compared with noncarriers, carriers who died of cancer were a mean of 4 years younger ($P > 0.2$) and carriers who died of ischemic heart disease were a mean of 11 years younger ($P = 0.006$).

Conclusion: Carriers of mutations at the ataxia-telangiectasia locus, who make up 1.4% to 2% of the general population, have a higher mortality rate and an earlier age at death from cancer and ischemic heart disease than noncarriers.

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Ataxia–telangiectasia, a clinically distinctive autosomal recessive syndrome with early childhood onset, is characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, and hypersensitivity to ionizing radiation (1). Patients with ataxia-telangiectasia, who carry two mutant alleles at the ataxia-telangiectasia locus, develop new cases of cancer at approximately 100 times the age-specific population rate and have a median age at death of approximately 20 years (2). More than 85% of cancer cases observed in children with ataxia-telangiectasia are acute lymphocytic leukemia or lymphoma (1). The proportion of new cancer cases that are epithelial rather than lymphocytic increases steadily with age. In patients older than 20 years, fewer than 50% of cancer cases are acute lymphocytic leukemia or lymphoma. Solid tumors include, in order of decreasing frequency, stomach cancer, breast cancer, medulloblastoma, basal-cell carcinoma, ovarian dysgerminoma, hepatoma, and uterine leiomyoma.

Ataxia-telangiectasia heterozygotes, who carry one mutated allele at the ataxia-telangiectasia locus, make up approximately 1.4% to 2% of the general population (3, 4). Studies of blood relatives of patients with ataxia-telangiectasia have shown that such carriers have an increased risk for cancer, especially breast cancer in women, and possibly ischemic heart disease (5–14). From a public health standpoint, it is important to know whether the millions of ataxia-telangiectasia heterozygotes in the general population have an excess risk for death because of their higher disease-specific risks.

Studies that have compared identified ataxia-telangiectasia carriers with noncarriers from the same families provide reliable estimates of excess disease or mortality for ataxia-telangiectasia heterozygotes (12, 14). In families of such persons, the carrier status of each family member can be reliably determined by using direct mutation detection or haplotype analyses (12, 14, 15). Using molecular genotyping and systematically collected clinical data, we compared the mortality rates and mean ages at death of carrier and noncarrier grandparents of ataxia-telangiectasia homozygotes.

Methods

Study Sample

During the past 28 years, families of patients with clinically confirmed ataxia-telangiectasia have been recruited from the United States and Canada into our continuing study of ataxia-telangiectasia blood relatives. Detailed descriptions of methods and selection criteria have been published elsewhere (5, 6, 8). Briefly, all first-, second-, and third-degree nonhomozygous blood relatives alive on 1 January 1930 or later were eligible for inclusion in the

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study. We selected 1930 because it was the first year in which all states used death certification. Initial contacts were sought through the parents of patients with ataxia-telangiectasia, and a four-generation pedigree was constructed. Relatives were excluded if they had lost contact with the family and could not be located, declined to give consent for the study, did not reside in the United States, or had died so long ago that adequate health or death information could not be obtained.

According to these criteria, 112 grandparents were excluded from the initial cohort. For our study, an additional 407 decedents were excluded because no DNA sample could be obtained from either person in a grandparental pair. We also excluded 31 persons whose familial mutations or haplotypes were unknown at the time of the study and 45 living persons who did not provide blood samples.

Of the 405 grandparents included in our study, all but 4 carriers and 1 noncarrier were paired. The results did not change significantly when we excluded unpaired grandparents; therefore, they were included in the final analysis. Informed consent was obtained from all study participants or from their closest relatives under protocols approved by the appropriate institutional review boards.

Genotyping

Since 1989, we have requested blood samples from each living relative and tissue samples for those who have died. Genotyping was performed by using mutation or haplotype analysis. Genomic DNA was isolated from peripheral blood (16) or paraffin-embedded tissues as described elsewhere (12). Blood samples were used to perform genotyping for 138 carriers and 144 noncarriers. Archival tissue samples were used to perform genotyping for 17 carriers and 17 noncarriers whose blood was unavailable.

One hundred eighty-five grandparents (94 carriers and 91 noncarriers) underwent genotyping by mutation analyses. Mutations present in the patients with ataxia-telangiectasia were identified through direct sequencing of the ataxia-telangiectasia locus by using genomic DNA from the patient or his or her parents. Each exon of the ataxia-telangiectasia gene and its splicing sites was amplified from genomic DNA by polymerase chain reaction (PCR) using a GeneAmp PCR system 9600 (Applied Biosystems, Foster City, California). The PCR products were directly sequenced by the BigDye PrimerSequencing Kit using the ABI PRISM 877 Integrated Thermal Cycler and the ABI PRISM 377 DNA Sequencer (Applied Biosystems). A variation from the ataxia-telangiectasia DNA sequence in GenBank (accession number U33841) was determined to be a true mutation if it would lead to a protein truncation or deletion or was a known missense mutation (17). After a specific mutation was identified in the parental DNA, the appropriate region of the ataxia-telangiectasia gene was then amplified and sequenced for the related grandparents. Grandparents who showed the ataxia-telangiectasia mutations of the related parents were considered carriers. Among the 94 carrier grandparents, we found 41 frameshift insertions or deletions (44%), 20 nonsense mutations (21%), 19 splicing mutations (20%), 2 in-frame deletions (2%), 1 mutation that disrupted the initiation codon (1%), and 11 missense mutations (12%).

One hundred thirty-one grandparents (61 carriers and 70 noncarriers) had genotyping by haplotype analysis. For the 34 persons for whom only tissue samples were available, a previously reported method was used (12). The remaining samples were analyzed by using the ABI PRISM 377 GeneScan Analysis software and Genotyper fragment analysis software. The haplotypes associated with the ataxia-telangiectasia allele in each family member were determined by analyzing three microsatellite markers on chromosome 11q near or within the ataxia-telangiectasia locus: D11S1778 (telomeric), D11S1819 (centromeric), and D11S2179 (intragenic) (12, 14, 15, 18). A grandparent was determined to be a carrier if he or she carried either of the haplotypes associated with the patient's two mutant alleles. An additional 41 carriers and 42 noncarriers were also initially genotyped by haplotype analyses. Later mutation analyses confirmed the results.

The carrier status of 89 grandparents without DNA samples (49 carriers and 40 noncarriers) was inferred on the basis of the genotypes of their spouses and their a priori probability of carrying an ataxia-telangiectasia mutant allele (12). Before genotyping, the a priori probability of carrying an ataxia-telangiectasia mutant allele was 0.5 for each grandparent. Therefore, if one member of a grandparental pair was a carrier, it was almost certain that the other member was not, and vice versa. When DNA was available from one member of a grandparental pair, we performed genotyping for this member and inferred the genotype of the other member accordingly. This approach, which was used to include grandparents who otherwise would have been excluded because of missing DNA samples, reduced

Table 1. **Characteristics of Grandparents of Patients with Ataxia-Telangiectasia**

Characteristic	Noncarriers	Carriers
Total	201	204
Women, *n (%)*	92 (46)	111 (54)
Median year of birth (range)	1923 (1879–1948)	1924 (1886–1951)
Median year of death (range)	1986 (1949–1998)	1984 (1935–1998)
Smoking history, *n (%)*		
Ever	116 (58)	114 (56)
Never	72 (36)	74 (36)
Unknown	13 (6)	16 (8)
Genotyping method, *n (%)*		
Haplotype analysis only	70 (35)	61 (30)
Mutation analysis only	49 (24)	53 (26)
Haplotype and mutation analysis	42 (21)	41 (20)
Inferred	40 (20)	49 (24)

potential selection bias. Overall, the observed proportion of ataxia-telangiectasia carriers agreed remarkably well with that expected from the a priori probability of heterozygosity in each family. Mutations or haplotypes were concordant in all related carriers.

Vital Information

At the beginning of enrollment and periodically thereafter (for those who were living), health questionnaires were sent to study participants or, if study participants were deceased, to their closest relatives. The questionnaires asked for health-related information (such as smoking status) as well as past and present medical history, including all major hospitalizations.

Death certificates and records of all major medical visits were obtained as described elsewhere (6, 8). Underlying causes of death were coded according to the International Classification of Diseases, Eighth Revision (ICD-8). Cancer included ICD-8 codes 140 through 209 for malignant neoplasms. Ischemic heart disease included acute myocardial infarction (code 410) and other forms of acute or chronic ischemic heart disease (codes 411 to 414). All deaths from causes other than cancer and ischemic heart disease were analyzed as other deaths.

Statistical Analyses

The cumulative probabilities of death were estimated by using the Kaplan–Meier method (19) and were compared between carriers and noncarriers by using the Mantel–Haenszel log-rank test or the exact log-rank test for small numbers (20). Nonparametric estimates of median ages of death were also obtained by using this method. Sex-adjusted parametric estimates of relative survival times between carriers and noncarriers were obtained by using a Weibull regression model in which the hazard increased with age. The mean age at death for deceased grandparents was compared by using the *t*-test when appropriate. To restrict the study to adult mortality rates only, each grandparent was entered into the observation period on his or her 20th birthday. The closing date was his or her date of death or the last date of contact when the person was known to be alive.

For carriers, hazard ratios for death and 95% CIs were calculated by using the Cox regression model (21). Cause-specific risks were estimated according to the method recommended by Kalbfleisch and Prentice (22). Carrier status and sex were included as independent predictors of death. On the basis of previous studies (8) and information about the accuracy of death certificates for different diseases and different age groups (23), we also examined the hazard ratios for carriers at various age cut-points, as well as the averages for all ages. These age-dependent hazard ratios were estimated through an extended Cox model that allowed nonproportional hazards (24, 25). Subgroup analyses were also performed by using carrier status, sex, smoking status, and age–carrier status interaction as independent predictors of death for the 376 grandparents with known smoking information. Year of birth and the interaction terms of carrier status with sex and smoking, respectively, were initially tested in the models and were found to have no significant independent effect on death. They were therefore excluded from subsequent analyses for efficiency. Risk estimates for paired grandparents were calculated by using stratified Cox regression analyses according to Kalbfleisch and Prentice (26).

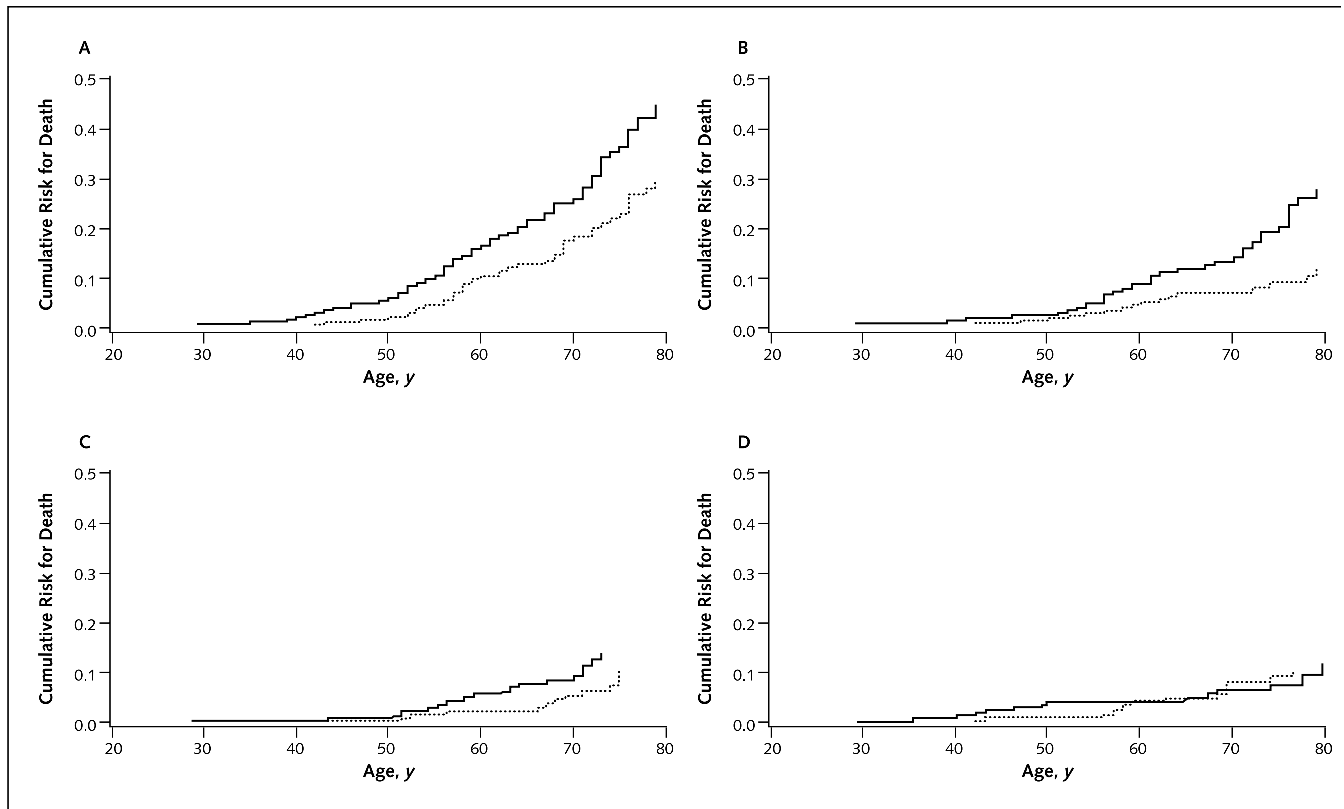
All *P* values were two-sided. The exact log-rank test was performed by using Proc-StatXact (Cytel Software Corp., Cambridge, Massachusetts). All other statistical analyses were performed by using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Overall Deaths

Of the 405 grandparents included in the study (**Table 1**), 144 died during the period of observation. Three carriers died early, in their 20s and 30s, but all noncarrier deaths occurred after 40 years of age. Most carrier deaths occurred before 80 years of age; 22 of the 65 noncarrier

Figure. **Kaplan–Meier curves for the cumulative risk for death from 20 through 79 years of age in grandparents of patients with ataxia-telangiectasia, according to carrier status.**



A. Risk for death from all causes (67 of 204 carriers, 43 of 201 noncarriers) ($P = 0.006$). **B.** Risk for death from cancer (35 of 204 carriers, 16 of 201 noncarriers) ($P = 0.003$). **C.** Risk for death from ischemic heart disease (19 of 204 carriers, 13 of 201 noncarriers) ($P = 0.175$). **D.** Risk for death from other causes (13 of 204 carriers, 14 of 201 noncarriers) ($P > 0.2$). Solid lines represent carriers, and dotted lines represent noncarriers. All P values were determined by using the two-sided log-rank test.

deaths (34%) and only 12 of the 79 carrier deaths (15%) occurred afterward.

The Kaplan–Meier survival curve showed a clear excess risk for death among carriers (**Figure**). The sex-adjusted relative risk for death was 1.9 (95% CI, 1.3 to 2.8) before 80 years of age (**Table 2**) and 1.1 afterward, with an estimate of 1.7 for all ages (CI, 1.2 to 2.4) ($P = 0.002$).

After adjustment for sex, the carriers' relative risk for death over all ages was somewhat higher with stratified Cox analyses for paired grandparents (relative risk, 1.9 [CI, 1.2 to 3.0]; $P = 0.007$). In subgroup analyses of the 376 grandparents with known smoking information (**Table 1**), the relative risk for carriers remained unchanged and the relative risks for smoking and male sex were 2.2 (CI, 1.4 to 3.4; $P < 0.001$) and 1.8 (CI, 1.2 to 2.7; $P = 0.003$), respectively. Year of birth (**Table 1**), dichotomized at 1924 (the median for all participants) in the Cox regression model, was not a significant predictor of death (data not shown).

Carriers were a mean of 7 years younger at death than noncarriers (64 years vs. 71 years, respectively) ($P = 0.005$). The Kaplan–Meier estimate of the median age at death was 8 years younger for carriers than for noncarriers in both men and women (74 years vs. 82 years in men, respectively, and 86 years vs. 94 years in women, respectively). The sex-adjusted Weibull estimate of expected lifespan for carriers was only 92% of the estimate for noncarriers ($P = 0.003$).

Causes of Death

From the cause-specific Kaplan–Meier analyses (**Figure**), it is evident that the excess mortality rate among carriers was due in large part to cancer and to ischemic heart disease. Of the 3 deaths that occurred in the carriers'

20s and 30s, 2 were caused by cancer (1 by melanoma in a 29-year-old carrier and 1 by breast cancer in a 39-year-old carrier). The third death was caused by acute uremia in a 35-year-old carrier. Of note, all 8 deaths from breast cancer (6 in persons younger than 80 years of age) occurred in the 111 female carriers; none occurred in the 92 female noncarriers ($P = 0.005$ [exact log-rank test]) (**Table 3**). Among carriers, the relative risk for death from cancer was 2.6 (CI, 1.4 to 4.7) before 80 years of age ($P = 0.002$) (**Table 2**) and only slightly lower at all ages (relative risk, 2.2 [CI, 1.3 to 3.8]); $P = 0.002$). The mean age at death from cancer was 65 years for carriers and 69 years for noncarriers ($P > 0.2$).

Most deaths among carriers from ischemic heart disease occurred at young ages: Forty-one percent occurred before 60 years of age and 65% occurred before 70 years of age, compared with only 19% and 33%, respectively, among noncarriers. Not surprisingly, the mean age at death from ischemic heart disease was 11 years younger for carriers than for noncarriers (64 years vs. 75 years, respectively) ($P = 0.006$). However, 12 of 15 deaths from ischemic heart disease after 75 years of age and all 7 deaths from ischemic heart disease after 85 years of age occurred among noncarriers. Only 3 of 12 noncarriers had a diagnosis of ischemic heart disease confirmed in medical records; 6 others did not, and the remaining 3 did not have medical records available. On the basis of diagnoses on death certificates, carriers' relative risk for death from ischemic heart disease was 3.0 (CI, 0.9 to 9.6; $P = 0.06$) before 60 years of age, 2.5 (CI, 1.2 to 5.4; $P = 0.02$) before 75 years of age, 2.0 (CI, 1.0 to 4.0; $P = 0.062$) before 80 years of age (**Table 2**), and 1.6 (CI, 0.8 to 2.9; $P = 0.15$) for all ages.

Table 2. **Risk for Death between 20 and 79 Years of Age among Carrier Grandparents of Patients with Ataxia-Telangiectasia**

Cause of Death	Deaths among Noncarriers	Deaths among Carriers	Relative Risk for Carriers Compared with Noncarriers (95% CI)*	*P* Value
	n			
All	43	67	1.9 (1.3–2.8)	<0.001
Cancer	16	35	2.6 (1.4–4.7)	0.002
Ischemic heart disease	13	19	2.0 (1.0–4.0)	0.062
Other	14	13	1.1 (0.5–2.4)	>0.2

* Adjusted for sex.

Table 3. **Deaths from Cancer between 20 and 79 Years of Age among Grandparents of Patients with Ataxia-Telangiectasia**

Type of Cancer*	Deaths among Noncarriers	Deaths among Carriers
	n	
Breast	0	6
Ovarian	1	1
Lung	8	12
Stomach	1	3
Pancreatic	1	1
Salivary gland	0	1
Bladder	0	2
Melanoma	0	2
Colorectal	4	0
Prostate	0	1
Lymphoreticular system	0	3
Central nervous system	1	0
Endocrine glands	0	1
Unspecified	0	2
Total	16	35

* Types of cancer not listed were found to cause no deaths.

No excess deaths from other causes were observed among carriers. For deaths from causes other than cancer and ischemic heart disease, no known single disease category predominated among carriers. Carriers' relative risk for death from other causes was 1.1 (CI, 0.6 to 2.1; $P > 0.2$) at all ages and 1.1 (CI, 0.5 to 2.4; $P > 0.2$) before 80 years of age (**Table 2**).

DISCUSSION

In this study, comparison of molecularly genotyped ataxia-telangiectasia carriers and intrafamilial noncarriers showed that carriers had a clear excess risk for death. From 20 through 79 years of age, risk for death among carriers of an ataxia-telangiectasia mutant allele was nearly twofold greater than that among noncarriers. Consequently, ataxia-telangiectasia carriers died, on average, 7 to 8 years earlier than noncarriers. A previous study showed that from 20 to 59 years of age, blood relatives of patients with ataxia-telangiectasia had higher mortality rates than spouse controls; however, only approximate estimates of such risks were provided because carriers and noncarriers could not be distinguished among the blood relatives of patients with ataxia-telangiectasia (8).

It is difficult to evaluate the carriers' relative risk for death at 80 years of age and older because almost everyone who survives to 80 years of age dies before reaching 100 years of age. Therefore, for both carriers and noncarriers,

the increasing risk for death with advancing age could dominate the differential effect of ataxia-telangiectasia mutations in later years. In addition, risk estimates for later years may be unreliable because they are based on a relatively small number of observations (27). In our study, the excess risk for death caused by the presence of an ataxia-telangiectasia mutation was most clearly seen before 80 years of age.

Cancer was the underlying cause of most excess deaths among carriers, and ischemic heart disease caused the remainder. Carriers had an increased risk for death from cancer throughout life. Their risk for death from ischemic heart disease was highest before 60 years of age; however, this risk was of only borderline significance because of the smaller number of deaths available for analysis. Risk for death from ischemic heart disease seemed to decrease with age. The decrease was especially clear after 75 years of age; the number of deaths and the magnitude of risk were large enough for the relative risk to reach statistical significance only for deaths from ischemic heart disease before this age cutoff.

This trend for ischemic heart disease coincides with the tendency of death certificates to list ischemic heart disease more frequently as the cause of death among older decedents. In a recent report from the Framingham Heart Study, Lloyd-Jones and colleagues found that death certificates attributed 30% more deaths to coronary heart disease (ischemic heart disease) in decedents between 75 and 84 years of age and twice as many in decedents 85 years of age or older compared with clinical records (23). Nondifferential misclassification results in bias toward the null (28–30). As the authors clearly demonstrated, such misclassification of cause of death substantially affects the ability of a study to detect differences between groups of participants at risk (23). The overrepresentation of coronary heart disease was substantially lower at younger ages (an average of 13% for decedents 45 to 74 years of age).

Lloyd-Jones and colleagues found that, unlike ischemic heart disease, cancer has high positive and negative predictive values when listed on a death certificate as the cause of death (>95% in the Framingham Study) (23). This finding is consistent with those of other studies, which found discrepancies of approximately 1.5% between medical records and death certificates for assigning a diagnosis of cancer (31). Risk estimates for cancer were therefore less affected by possible diagnostic imprecision. Further studies based on more reliable ascertainment of ischemic heart disease are needed to confirm the findings in the current study.

Increased incidence of, or reduced clinical survival with, cancer or ischemic heart disease (or both) may have contributed to the overall high mortality rates among ataxia-telangiectasia carriers. Previously, blood relatives of patients with ataxia-telangiectasia were found to have an increased risk for breast cancer (6, 8–10), which led to estimates that female ataxia-telangiectasia heterozygotes had a five- to sevenfold increased risk. The proportion of ataxia-telangiectasia carriers is therefore predicted to be higher in patients with breast cancer than in the general population. Studies that failed to find this increase were based on inadequate techniques of mutation detection. Three studies (4, 32, 33) exclusively used protein truncation tests, which can miss more than 35% of expected mutations even in patients with ataxia-telangiectasia (34, 35), in whom most mutations are truncating. In the general population, it seems that most ataxia-telangiectasia mutations are splicing or missense mutations that usually do not result in protein truncations (36, 37). Two other studies dismissed missense mutations as rare polymorphisms (38, 39). All of these studies used poorly selected controls and lacked sufficient statistical power to detect the range of risks for breast cancer found in ataxia-telangiectasia carriers (34, 40). Studies with better techniques of mutation detection and ascertainment confirmed the original finding that carriers of a mutant ataxia-telangiectasia allele have an increased risk for breast cancer (estimated range, 3- to 13-fold) (12–14, 41, 42). In a series of patients with breast cancer in the general population, 8% to 10% were found to be carriers (43–47).

However, the increased incidence of breast cancer does not itself account for all excess deaths in carriers. The incidence of cancer at other sites and the incidence of ischemic heart disease may also be increased (6, 7, 11, 36). Cancer of the colon and rectum, however, may be an exception. The absence of any deaths among carriers from these types of cancer before 80 years of age in our study and similar observations in previous studies (8, 48) suggest that ataxia-telangiectasia mutations may offer some protection. A reduced risk for colorectal cancer may have offset the increased risks for other types of cancer and resulted in a somewhat more modest increased risk for death from all cancer.

In addition, it is possible that cancer or ischemic heart disease progresses more rapidly in ataxia-telangiectasia car-

riers, resulting in poorer clinical survival. If this is true, more aggressive treatments and closer surveillance may be indicated for ataxia-telangiectasia carriers. Further characterization of the associations of ataxia-telangiectasia mutations with various types of cancer and ischemic heart disease may lead to new and effective measures to reduce the incidence and improve the survival of carriers with these diseases.

The mechanisms by which ataxia-telangiectasia mutations produce their clinical effects are unclear. A region of the ataxia-telangiectasia gene has substantial homology to phosphatidylinositol 3-kinases (15, 49). Enzymes of this class, and the ataxia-telangiectasia gene product itself, have been implicated in cell cycle regulation, DNA repair, and responses to ionizing radiation. It has been conjectured that abnormalities of these functions explain the increased cancer risk associated with ataxia-telangiectasia mutations (50–52). However, the primary cellular role of the ataxia-telangiectasia gene product and the role of mutations at this locus in causing clinical diseases remain uncertain.

Some evidence suggests that both cancer and atherosclerosis may share certain risk factors and follow a common pathway in the early stages of development (53, 54). A mutated ataxia-telangiectasia gene itself may be one of these factors. Also, a mutated ataxia-telangiectasia allele may cause excess sensitivity to environmental agents, such as ionizing radiation, that predispose persons to cancer or ischemic heart disease (8).

Because of our study design, bias as a result of missing data is unlikely. Both carriers and noncarriers were included or excluded equally in pairs because genotypes could be inferred reliably. Therefore, spouses who would have been excluded for missing DNA samples or nonparticipation were included because living status, medical records, and death certificates could always be obtained through their relatives. As demonstrated persuasively by Kalbfleisch and Prentice, who used statistical inference for paired survival data, there is no bias involved in restricting the study to pairs in which both members were available for inclusion (26). For this reason, the observed difference in mortality rates between ataxia-telangiectasia carriers and noncarriers is likely to apply to the general population, because any potential selection bias in recruiting the participating families would apply equally to both carriers and noncarriers.

The chance of error that a grandparent inferred to be a noncarrier actually carried a random mutation at the ataxia-telangiectasia locus was too small to influence the results. Since 1.4% to 2% of the general population have ataxia-telangiectasia mutations and we included 40 inferred noncarriers (**Table 1**), the possible number of misclassified genotypes due to inference was unlikely to be more than 1. In any case, any resulting misclassification would bias results toward the null hypothesis if at all (28–30).

It is not likely that the excess deaths observed among carriers in our study were caused by systematic differences in other risk factors between carrier and noncarrier grandparents. The carrier and noncarrier in each grandparental pair shared many risk factors, such as ethnic origins, socioeconomic status, access to medical care, and environmental exposures. Birth years and smoking history, for example, were similar in the two groups. Therefore, the noncarrier grandparents as a group are an excellent comparison group for the carrier grandparents.

It would not be as effective to compare the mortality rates of ataxia-telangiectasia carriers in ataxia-telangiectasia families with some "standard" population by using standardized mortality rates. Many risk factors that affect mortality rates, such as socioeconomic status and smoking history, would not be similar between the two groups. This would make it difficult to attribute any difference or lack of difference in mortality rates to a single risk factor, including carrier status.

The length of follow-up and the cost of mutation screening limit the practicality of demonstrating excess mortality rates in a population-based study in which carriers identified from the general population are compared with a group of similarly ascertained matched noncarriers. Between 10 000 and 20 000 people would have to be screened to identify 200 carriers, the number of carriers in our study. Furthermore, because the deaths observed in our study spanned a total of 63 years (**Table 1**), a prolonged period of prospective follow-up or a much larger number of carriers would be required to attain equal statistical power. Given the large size of the ataxia-telangiectasia gene, the extremely diverse spectrum of ataxia-telangiectasia mutations (17, 55), and the currently available mutation detection techniques, such a study is clearly unrealistic at this time. In contrast, ataxia-telangiectasia families provide a unique, numerically enriched source of ataxia-telangiectasia mutation carriers and noncarriers who are similar in many other risk factors for disease.

Ataxia-telangiectasia carriers in the general population cannot be identified through clinical examination or con-

ventional laboratory tests. The most efficient methods of DNA analysis, which use complete exon-by-exon screening, have detected 70% to 86% of expected ataxia-telangiectasia mutations (45, 47, 56, 57). With these methods, mutations at the ataxia-telangiectasia locus have been found in 8% to 10% of patients with breast cancer in three independent series (43, 45, 47); in contrast, the proportion of such mutation carriers in the control population is estimated to be 1.4% to 2% (3, 4). Furthermore, the overall effect of ataxia-telangiectasia mutations on mortality rates is similar to that of smoking and sex. New technology to improve mutation detection and new measures to prevent high mortality rates among ataxia-telangiectasia carriers could therefore benefit a substantial proportion of the general population and have a substantial impact on public health.

The observed high mortality rates among ataxia-telangiectasia carriers may cause concern among blood relatives in ataxia-telangiectasia families who already know or suspect that they carry a single mutant ataxia-telangiectasia allele. However, not every carrier in our study died early of cancer or ischemic heart disease. These diseases are most likely to arise from the interaction of genetic predisposition and environmental risk factors. Identifying and minimizing exposure to such environmental risk factors may effectively decrease the high mortality rates among carriers of ataxia-telangiectasia mutations. Early vigorous surveillance for cancer or ischemic heart disease, and more aggressive treatment if a need for it is demonstrated, may also lead to improved survival. However, to change the course of diseases associated with ataxia-telangiectasia mutations, a thorough understanding of the molecular mechanisms and clinical circumstances related to high mortality rates among carriers will be necessary.

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