Public Health Burden of Cancer in Ataxia-Telangiectasia Heterozygotes

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Knowing that mutations of a specific gene predispose to certain cancers is an important step toward more effective preventive or therapeutic measures for those cancers. The history of ataxia-telangiectasia (A-T) research illustrates how advances in genetic and molecular genetic technology are clarifying and quantifying the role of mutations at this genetic locus in common diseases and mortality in the general population.

An exceptionally high incidence of cancer was observed in patients with the rare autosomal recessive syndrome A-T (1) shortly after Boder and Sedgewick (2) published their remarkably complete initial characterization of this disorder in 1958. I hypothesized (3) that mutations at the A-T locus (sometimes referred to as the ATM, for “ataxia-telangiectasia mutated,” locus) might contribute substantially to the public health burden of cancer, despite the rarity of A-T homozygotes, because individuals who carry a single mutation at this locus—A-T heterozygotes—are relatively common in the general population according to the genetic Hardy–Weinberg principle.

When we began to test this hypothesis in 1970, A-T heterozygotes could not be identified through molecular testing; they still cannot be distinguished by physical examination or by conventional laboratory tests. Such carriers are, however, a high proportion of blood relatives in A-T families. In the first study of 26 A-T families, we found substantially more deaths from cancer among the blood relatives than among the spouse control subjects (3).

The public health implications of our initial findings and the interest expressed by other scientists led my research group in 1981 to undertake a comprehensive nationwide study of A-T families. From a retrospective comparison of cancer incidence in blood relatives and spouse control subjects in 110 A-T families, female breast cancer emerged as the leading cancer associated with A-T heterozygosity (4). A prospective analysis of newly incident cancers in these and additional families, published in 1991 (5), confirmed this specific association as well as the overall predisposition of A-T heterozygotes to cancer.

Although prospective studies are the “gold standard” in epidemiology, the interpretation of data from A-T families was limited by the fact that only the parents, and certain grandparents in consanguineous families, were definite—obligate—carriers of the A-T mutations segregating in these families. Reliable methods for determining carrier status, originally through marker haplotypes, made it possible to measure the relative risk of breast cancer for A-T heterozygotes (6) by use of a statistically powerful bias-resistant approach (7) that is now called the “index-test method.” This method uses highly reliable intrainfamilial genotyping to compare cancer incidence rates in carriers with those in noncarriers in the same families, the best possible comparison group in terms of matching for important confounders.

Studies of A-T families in the U.K. (8), in France (9), and now in the Nordic countries by Olsen et al. (10) reporting in this issue of the Journal have confirmed the association of A-T heterozygosity with breast cancer risk. The most reliable and informative data in these three studies come from the obligate heterozygotes, the mothers. The relative risk estimates of breast cancer for these mothers were 3.37, 3.32, and 7.1, respectively, based on comparisons with population mortality or incidence rates. With the index-test method, we had estimated the relative risk of breast cancer for A-T heterozygotes to be 3.8 (6). Our recently reported comparison of the mortality of carrier and noncarrier grandparents in A-T families (11), which is based on comprehensive data collection and genotyping, is consistent with these findings. The relative risk of death from all cancers for male and female carriers was 2.6.

A relative risk of breast cancer greater than 3 is compatible with three recent studies (12–14), which found the proportion of A-T mutation carriers to be 8%–10% in populations of breast cancer patients. Two of these studies (12,13) employed exon-by-exon screening, and one (14) used the protein truncation test. Earlier studies that had yielded lower estimates of the heterozygote frequency in narrowly selected populations had detected only truncating mutations (15,16) or had dismissed missense mutations as neutral polymorphisms (17).

These data may be compared with those of “control” population samples. In two studies in the United States (12,15), approximately 1% of the population has been found to be A-T mutation carriers. Even though only a single truncating A-T mutation was sought in a sample from the general Dutch population, it was found in 0.7% of this sample (14). Estimates (10,18) of the population frequency of A-T heterozygotes based on the Hardy–Weinberg principle are inevitably too low because this calculation depends on accurate measurement of the birth incidence of the homozygotes, which is not currently feasible. The important point is that prevalence surveys (10,18) typically underestimate the birth incidence of genetic syndromes severalfold.

Therefore, reliable estimates of the frequency of A-T heterozygotes in the general population and in groups of breast cancer patients will require highly sensitive, specific, and cost-effective methods of mutation screening. Mutation detection at the A-T locus is challenging because the gene has 66 exons that span 150 kb of genomic DNA. Exon-by-exon screening methods have detected mutations in 57%–85% of the specific chromosomes 11 that must be mutated because they were found in patients with A-T (19,20). It is likely that many of the “missing” mutations are due to sequence changes deep within introns that lead to splicing errors that produce an altered gene product. On the positive side, hundreds of different mutations—truncating, missense, splicing, and in-frame insertions or deletions—have already been found in the DNA of A-T patients or their parents. In all reported studies of A-T patients, truncating mutations constituted more than 50% of all identified mutations.

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Remarkably, missense mutations at the A-T locus were found at a high frequency in three series of breast cancer patients from the general population (11,12,21) and at a relatively high frequency in one set of population control subjects (21) but not in two others (11,12). Truncating mutations predominated in breast cancer patients in another population study (14). In my unpublished data from A-T families, the proportion of missense and truncating mutations in relatives with breast cancer is not substantially different from the proportion of each type in the entire sample.

It is important to recognize that some missense mutations may not produce clinically recognizable A-T in homozygotes or compound heterozygotes but may increase the risk of breast cancer in heterozygotes. Stankovic et al. (22) reported that patients homozygous for the 7271T→G missense mutation had extremely mild neurologic symptoms, leading to the diagnosis of A-T only in adult life. Breast cancer was present in two female homozygotes in this family and in a total of three relatives in this family and another family with this mutation. The finding that A-T patients who are compound heterozygotes for a missense mutation are taller and live longer (20) is further support for the concept that such mutations lead to a mild A-T phenotype.

At this time, all statistical estimates demonstrating an elevated risk of breast cancer for A-T heterozygotes derive from studies that included diverse mutations. To estimate disease risks for specific mutations or groups of mutations, appropriate samples and research designs must be selected.

In summary, individuals heterozygous for a mutation at the A-T locus, who constitute at least 1% of the general population, have a risk of developing female breast cancer that is more than threefold greater than that of noncarriers. Hypotheses about predisposition to other cancers remain to be tested through genotyping of cancer cases within families of A-T homozygous probands. Clinical testing to determine who carries an A-T mutation and measurements of heterozygote frequency in groups of cancer patients and the general population will become increasingly practical and reliable as methods of mutation detection and evaluation improve.

REFERENCES


