Ionizing Radiation, Breast Cancer, and Ataxia-Telangiectasia

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It is well established that genetic predisposition (1) and environmental exposure to ionizing radiation (2) each play an important role in the etiology of breast cancer. In this issue of the Journal, Lavin et al. (3) address the important possibility that some individuals are predisposed to breast cancer because they are more susceptible than the rest of the population to the carcinogenic effects of ionizing radiation. The reasoning in their report is based on extensive information about ataxia-telangiectasia (4-15), an autosomal recessive syndrome in which the homozygous affected individuals have both very high cancer rates and an exquisite sensitivity to ionizing radiation (5,6).

In childhood and adolescence, ataxia-telangiectasia homozygotes develop new cancers, predominantly lymphoid, at a rate of one for every 100 person-years (5). Severe, often lethal, necrosis of normal tissue develops rapidly when an ataxia-telangiectasia patient with leukemia or lymphoma is treated with radiotherapy at conventional doses (6). Cells from ataxia-telangiectasia patients respond abnormally to ionizing radiation in vitro, with excess cell killing as a virtual hallmark of the disorder (7).

The genetic abnormality in ataxia-telangiectasia has a direct impact on cancer in the general population; an estimated 1.4% of the population carries a single ataxia-telangiectasia gene (8). Ataxia-telangiectasia heterozygotes are predisposed to breast and other cancers (9-12). The risk of breast cancer for ataxia-telangiectasia heterozygotes appears to be at least fivefold greater than that of noncarriers (9-12). Seven percent or more of all breast cancer patients are likely to carry a single ataxia-telangiectasia gene (10). This gene appears to predispose carriers to breast cancer primarily with onset before age 65 or 70 years (9,10). Thus, the proportion of ataxia-telangiectasia heterozygotes among women with early breast cancer onset may be substantially greater than 7%.

Ataxia-telangiectasia heterozygous cells as a group are killed at a higher rate than cells in the control group after exposure to ionizing radiation under selected experimental conditions (13,14). These conditions do not define a useful test to detect ataxia-telangiectasia heterozygotes in populations, since there is considerable overlap between carriers and noncarriers (13,14). Because ionizing radiation can produce an excess of breast cancers in the general population, we examined the role that ionizing radiation under selected experimental conditions (13,14) has in detecting ataxia-telangiectasia heterozygotes among women with early breast cancer onset may be substantially greater than 7%.

Ataxia-telangiectasia heterozygous females to such exposures. Lavin et al. (75) previously reported that heterozygous carriers of a gene for ataxia-telangiectasia could be distinguished from those in the control group by an assay that measures, by flow cytometry, the proportion of cultured lymphoblasts in G2 arrest after exposure to ionizing radiation. In this issue of the Journal, they (3) report that 8% of 24 age-matched control women and 20% of 108 patients with diagnosed breast cancer had elevated values on this assay that were comparable to those they had observed previously in obligate ataxia-telangiectasia heterozygotes. Lavin et al. (3) also found an elevated proportion of high values in their assay in a group of women who had severe immediate reactions to radiation treatment of their breast cancers. How can these results be interpreted? These and other important questions must be answered.

For example, we do not yet know that having an excessive immediate reaction to radiation therapy or having a high value in the assay of Lavin et al. (3,15) are genetic characteristics. Evidence must be sought in family studies. Only when it is clearly established that these are genetically influenced characteristics will it be possible to search for specific genes controlling them. Further, do we know that ataxia-telangiectasia heterozygotes are reliably identified by this assay? The proportion of control individuals scoring abnormally high was about 8% (3), considerably higher than even the most generous estimate of the frequency of ataxia-telangiectasia heterozygotes in the general population (8). Can this assay be replicated in other laboratories? How reliable is it as a population test for the ataxia-telangiectasia heterozygote under stringent blinded conditions? My previous experience with proposed cell biological tests for the ataxia-telangiectasia heterozygote has been discouraging, with random or almost random results when blinded samples were sent to several different laboratories that had proposed an ataxia-telangiectasia heterozygote assay (16; unpublished data).

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Although ataxia-telangiectasia homozygotes invariably have severe immediate reactions to conventional radiation therapy (6), there is, as yet, no evidence that ataxia-telangiectasia heterozygotes are predisposed to such reactions. My personal informal review of the medical records of ataxia-telangiectasia blood relatives who had breast cancer and radiation therapy did not reveal any data in support of this heterozygote reaction, a question that should be addressed systematically.

It is likely that population screening for ataxia-telangiectasia gene carriers will become a clinical reality when the gene is cloned and a test based on DNA and RNA abnormalities associated with ataxia-telangiectasia mutations can be developed. According to the presentations given by investigators at the Sixth International Workshop (Birmingham, England) on ataxia-telangiectasia in May 1994, at least three laboratories are searching for complementary DNAs (cDNAs) in a narrow region defined by genetic linkage analysis. We have shown that there is no recombination between the ataxia-telangiectasia locus and the marker locus D11S384 (17); cDNAs are abundant around this locus.

Many important questions will be answered rapidly when the ataxia-telangiectasia gene is cloned. The frequency of each mutation at this locus will be determined from the hundreds of ataxia-telangiectasia chromosomes available in many laboratories. Efficient assays to detect the most common mutations will be developed, so that the frequency of these mutations can be measured in the general population and in subpopulations of cancer patients. Several cancer sites appear to be associated with ataxia-telangiectasia heterozygosity (9,10), although these associations are not as well established as that with breast cancer. Each of these hypothesized associations will be tested using the statistically powerful unbiased index-test method (18), which uses the DNA samples we have already collected from cancer patients in ataxia-telangiectasia families.

The expression of the wild-type and mutant genotypes at the ataxia-telangiectasia locus will be studied in cultured cells and transgenic animals. What cancers will these animals develop spontaneously? What cancers develop in response to specific environmental agents? Will certain drugs prevent these cancers? I am optimistic that we will be able to prevent many ataxia-telangiectasia–associated cancers, since there is evidence (9,10,19) that these cancers result from the interaction of environmental factors with the specific genotype.

Much remains to be learned about genetic susceptibility to ionizing radiation and to cancer. At present, the ataxia-telangiectasia gene offers the best, perhaps the only, insight into this area. We owe our knowledge of this gene to the thousands of patients with the severe autosomal recessive syndrome ataxia-telangiectasia, which leads to progressive disability and early death (4,5). It would be fitting if current molecular research led to an effective treatment to arrest the disability and prolong the lives of the affected homozygous individuals.

References


Note

Manuscript received September 20, 1994; accepted September 29, 1994.
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