ABSTRACT

DNA rearrangement rather than point mutation is an emerging hypothesis for human carcinogenesis. Although there is no direct evidence for this hypothesis, indirect evidence is provided by cancer cytogenetics and genetics. It has been suggested that patients with Bloom's syndrome, a disorder of spontaneous chromosomal rearrangement, develop the common fatal internal cancers and that genetic rearrangements, rather than chemical mutagens, cause most internal human cancers.

To test this observation, we have derived age- and sex-adjusted cancer incidence rate ratios for specific organ sites in patients with three chromosomal instability disorders (Bloom's syndrome, xeroderma pigmentosum, and dyskeratosis congenita) and have found that the increased incidence of cancer in all three disorders is limited to specific and often uncommon organ sites. We conclude that chromosomal instability disorders do not predispose patients to the common fatal internal cancers. Although DNA rearrangement remains a promising concept in human carcinogenesis, the organ site specificity of cancers associated with Bloom's syndrome, xeroderma pigmentosum, and dyskeratosis congenita cannot be used as evidence to implicate this mechanism.

INTRODUCTION

An emerging concept in oncology is that DNA rearrangement rather than point mutation is a more likely cause of cancer. This hypothesis may explain the specific chromosomal rearrangements seen in cancer cells, the greater frequency and decreased latency of transformation by carcinogens when compared to point mutation, and the apparent reversibility of some tumors (2, 5, 10, 15, 17, 22, 24, 32, 35). Although there is as yet no direct evidence for DNA rearrangement as a cause of human cancer, indirect evidence is derived from cancer cytogenetics. Nonrandom chromosomal rearrangements were first observed in chronic myelogenous leukemia cells (18), and other rearrangements have now been identified in a wide variety of cancers (17, 23, 25). However, at present, it is not known whether the rearrangements seen in the chromosomes of cancer cells cause the malignant state or result from it.

Another indirect argument for DNA rearrangement rather than point mutation as a cause of human cancer is derived from Cairns' recent epidemiological study. Cairns examined published data on mortality from fatal internal cancers among patients with 2 inherited disorders that predispose to cancer, Bloom's syndrome and xeroderma pigmentosum. He pointed out that patients with xeroderma pigmentosum show a markedly deficient capacity to repair DNA damage caused by UV and that the resulting mutations are associated only with skin cancer and not with fatal internal cancers. In contrast, patients with Bloom's syndrome, whose cells manifest an increase in DNA rearrangements, demonstrate a markedly increased mortality from the common fatal internal cancers but have not shown a single case of skin cancer (2). From his analysis, Cairns concluded that, for people without these disorders, the main source of mutagenic lesions in DNA is UV, which produces nonfatal skin cancer, and that genetic rearrangements rather than chemical mutagens cause most internal human cancers (2).

Are Bloom's syndrome patients and patients with other chromosomal instability disorders predisposed to the common fatal internal cancers, as Cairns suggests? We have derived age- and sex-adjusted incidence rate ratios of specific types of cancer by organ site in 3 chromosomal instability disorders (Bloom's syndrome, xeroderma pigmentosum, and dyskeratosis congenita). Cells from patients with all 3 disorders show increased chromosomal aberrations and sister chromatid exchanges, spontaneously in Bloom's syndrome, on exposure to UV in xeroderma pigmentosum, and on exposure to cross-linking agents in dyskeratosis congenita. The types of cancer seen in these patients should indicate whether chromosomal instability disorders predispose to the common fatal internal cancers or to specific relatively uncommon cancers.

MATERIALS AND METHODS

Comparison of Observed and Age-adjusted, Sex-adjusted Expected Cancer Incidence Rates. The expected numbers of cancer cases at specific organ sites were derived for 3 chromosomal instability disorders that predispose to cancer, xeroderma pigmentosum, Bloom's syndrome, and dyskeratosis congenita. These disorders were selected because there was a sufficient number of clinical cases reported in the literature for adequate study. Data on patients with Bloom's syndrome were derived from 2 sources, (a) a published registry of 72 cases (12, 13) and (b) 27 unpublished cases generously provided by Dr. James L. German of the New York Blood Center, for a total of 1715 person-years at risk of cancer. A recent collation of the published world literature on dyskeratosis congenita (30) and the few cases published subsequently (3, 11) provided data from a total of 54 cases comprising 1169 person-years at risk. Published case series describing the clinical features of xeroderma pigmentosum patients provided 164 cases (1, 6–9, 14, 16, 19, 21, 26, 28, 29, 34), comprising 2741 person-years at risk; series designed solely to illustrate cancer cases were excluded. An estimate of skin cancer incidence in xeroderma pigmentosum (20, 33) is provided in Table 1. A precise determination of skin cancer incidence cannot be made, since nonmelanoma skin cancer is underreported in the general population and shows marked secular and geographical variation (27). However, the expected incidence of melanoma was calculated and is of interest because of the serious nature of that form of skin cancer. (Among dyskeratosis congenita patients, only one case of skin cancer has been reported; no cases have been reported...
among Bloom’s syndrome patients.) For each syndrome, the total number of years each patient lived or, if still alive at the time of the original report, until the date of the report, was calculated. These data were used to derive, for each 5-year age range, the total number of years the patient population was at risk of developing cancer. The age- and sex-specific total number of person-years at risk was multiplied by known age- and sex-specific cancer incidence rates in the general population in order to calculate the expected numbers of cases of cancer by organ site. These age- and sex-specific numbers were then summed to determine the total number of expected cases of cancer at specific organ sites. For each type of cancer, the probability of the observed or greater number of cases was determined by an exact test using the Poisson distribution (31). Age- and sex-specific cancer incidence rates were taken from the recent National Cancer Institute Surveillance, Epidemiology, and End Results Program, which pools data from 11 United States cancer registries (37).

RESULTS AND DISCUSSION

Age- and Sex-adjusted Cancer Incidence Rate Ratios by Organ Site. The observed and age- and sex-adjusted expected numbers of cases of cancer at specific organ sites were compared in 3 chromosomal instability disorders: Bloom’s syndrome; xeroderma pigmentosum; and dyskeratosis congenita (Table 1). In all 3 disorders, cancers that are relatively uncommon for the age range of these patients are seen. For example, Bloom’s syndrome manifests an increased incidence of leukemia, lymphoma, and cancers of the pharynx and digestive tract, despite the fact that brain, endocrine, and bone cancer occur more frequently than do pharynx and digestive tract cancers in the general population in the age range of these patients. Dyskeratosis congenita also shows a narrow range of tissue susceptibility to cancer, with an increased incidence of pharynx and digestive tract cancers but not of leukemias, lymphomas, or other cancers. Cancers do not necessarily arise in those tissues disturbed by other clinical features of these disorders.

Cancer incidence rate ratios derived by this analysis are limited by the following problems. (a) Selection bias is unavoidable in an analysis of reported cases. For example, milder forms of these diseases might go undiagnosed or might not be published in the literature or reported to registries, and some types of cancer could be relatively overreported in the Bloom’s syndrome registry because of selective patient referral or ascertainment. (b) The patients in different studies may not be comparable, particularly if the therapy for one cancer is itself potentially carcinogenic. However, the comparison we performed is of organ sites for cancer within each of the 3 disorders, rather than of cancer incidence rates between disorders. The person-years method assumes that 10 people followed for 1 year are equivalent to one person followed for 10 years, which may not be true if a subpopulation of patients developed multiple cancers and accounted for most of the cases. However, when we excluded patients from the analysis after the development of their first cancer, the results were essentially the same as those reported here. The cancer incidence rates we have used for the general population may not be applicable to the patients studied, particularly since geographical and racial data were not available for use. However, calculations of expected cancer incidence in these patients were similar to those presented here when other sources of cancer incidence rates in the general population (4, 36) were used. An exact determination of the relative risk of cancer in
these patients will require further investigation. Nevertheless, this type of analysis provides a more precise estimate of cancer incidence than anecdotal experience, since it controls for patient age and sex and provides a relative estimate of cancer incidence at various organ sites.

As noted by Cairns (2), xeroderma pigmentosum manifests an increased incidence of skin cancer but not internal cancers, which are more common in Bloom’s syndrome. However, combining all internal cancers into one category (2) may mask the fact that patients with Bloom’s syndrome and dyskeratosis congenita, like those with xeroderma pigmentosum, show a surprisingly narrow range of tissue susceptibility to cancer (Table 1).

The major result of this study is that, in patients known to have an increased rate of chromosomal rearrangement, cancer incidence is significantly increased only at specific organ sites, which are often not the most common sites for cancer in the general population in the age range of these patients. Although DNA rearrangement remains a promising concept in human carcinogenesis, the organ site specificity of cancers associated with Bloom’s syndrome, xeroderma pigmentosum, and dyskeratosis congenita cannot be used as evidence to implicate this mechanism. For each chromosomal instability disorder studied here, we observe a different pattern of organ site specificity for cancer. At present, it is not known whether this observation is due to tissue differences in chromosomal rearrangement, oncogene activation, or mutagenic susceptibility. However, any proposed mechanism of carcinogenesis must explain this organ site specificity.

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Organ Site Specificity for Cancer in Chromosomal Instability Disorders

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