Radiation and Non-Hodgkin's Lymphoma

John D. Boice, Jr.2

Radiation Epidemiology Branch, Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland 20892

Abstract

Lymphomas are rarely, if ever, found to be in excess following exposure to ionizing radiation. Hodgkin's disease has never been linked to radiation, and the evidence for non-Hodgkin's lymphoma (NHL) is very weak. Low doses of radiation from diagnostic X-ray procedures or from occupational exposures do not appear to cause NHL. Mortality studies of atomic bomb survivors in Japan and other epidemiological studies with quantitative estimates of radiation dose also fail to find dose-response relationships. NHL may arise infrequently following high-dose, possibly near lethal, radiation treatments. Immunosuppression associated with the disease being treated, such as Hodgkin's disease, may contribute to the development of NHL. If radiation does not cause NHL, at least not by its accepted mechanism of action of breaking chromosomes, creating rearrangements, gene deletions, and mutations, perhaps other environmental mutagens and clastogens should not be considered likely causes of NHL.

Introduction

In contrast to leukemia, which is the most commonly identified cancer following exposure to ionizing radiation, lymphomas are rarely, if ever, found to be in excess. NHL, like chronic lymphocytic leukemia, is a cancer of B-lymphocytes in which tumor cells proliferate primarily in the lymph nodes. Chronic lymphocytic leukemia and Hodgkin's disease have never been linked to radiation. At present, there is no consistent evidence that ionizing radiation induces lymphoma in humans (1, 2).

Overview of Epidemiological Studies

Table I lists epidemiological studies of populations exposed to ionizing radiation and the reported risks of leukemia and NHL. The single most informative study is that of the Japanese survivors of the atomic bombs. Leukemia was a major effect, with the relative risk at 1 Gy (100 rads) body-wide exposure estimated to be 6. For lymphoma, the relative risk at 1 Gy was 0.95 (i.e., no effect), despite nearly 110 cases available for dose-response analyses (3). Early studies of atomic bomb survivors suggested positive associations between NHL and radiation (4, 5), but were based on incomplete dosimetry and relied heavily on autopsy diagnoses. Because autopsies were performed more frequently among those with the highest exposures, it is conceivable that the early reports reflected differences in autopsy rates by exposure category rather than differences in radiation risks.

Radiation Therapy. The limited evidence linking radiation with malignant lymphoma comes from patient populations given very high doses of radiation therapeutically. The most compelling evidence comes from a study of patients treated with radiation for ankylosing spondylitis, an arthritic condition of the spine (6). However, there were only 16 cancer deaths observed (versus 7.1 expected), the dose to lymphatic tissue was not determined, and an underlying immune defect might have been responsible for part of the reported increase. A nonsignificant increase in NHL was seen among cervical cancer patients receiving radiotherapy, but there was no evidence for a dose-response relationship (7). Patients irradiated for cancer of the uterine corpus were not at increased risk for NHL (8). NHL is frequently found to be excessive after treatment for Hodgkin's disease (9). This increase, however, appears independent of radiotherapy and is likely due to immunosuppression or altered immunity, such as seen following renal transplants. Patients irradiated for benign menstrual disorders or for ringworm of the scalp were not at increased risk for NHL, although significant increases in leukemia were reported (10, 11). Large population studies of patients with multiple primary cancers find little evidence linking NHL to radiotherapy overall, or for any particular site (12). Among 600,000 cancer patients treated in Connecticut and Denmark, 586 secondary lymphomas were reported, which was very close to the number expected (563) based on population rates in both countries. This implies, perhaps, that the incidence of secondary lymphoma must be increasing at nearly the same rate as that seen for initial lymphomas in the population, and that treatment for primary disease causes few, if any, NHL.

Diagnostic X-Ray Procedures. There have been no reported associations between non-Hodgkin's lymphoma and exposure to low level diagnostic X-ray procedures. Among tuberculosis patients who received frequent chest X-ray fluoroscopies (average, 77) during lung collapse treatment, no excess of lymphoma was observed in 6285 patients followed for up to 40 years (13). In a case-control study of 318 patients with lymphoma, no association with diagnostic X-rays was found (14). Interestingly, there was a hint that lymphoma risk increased with increasing number of X-rays. However, when exposures near the time of diagnosis were excluded, the trend disappeared. These data were interpreted to suggest that persons with lymphoma may undergo X-ray procedures frequently just prior to diagnosis for conditions related to the development, or natural history, of their disease. Although leukemia has been frequently linked to prenatal X-ray exposure, there is no convincing evidence that NHL is similarly increased (15).

Radionuclides. Studies in Sweden of over 45,000 patients given diagnostic or therapeutic doses of radioactive iodine have failed to find increases in lymphoma, despite a wide range of administered activities (16–18). On the other hand, Thorotrast, a radiographic contrast media used extensively in the 1930s and 1940s for angiography, has been related to a nearly 3-fold non-significant risk of NHL (19). Thorotrast (radioactive thorium dioxide) emits α-particles and remains in the body for life. This is one of the few studies for which radiation exposure may have contributed to a lymphoma excess; conceivably from the internally deposited α-particle emitters, which resulted in extremely high radiation doses to lymph nodes.

Occupational Exposures. Studies of occupational groups provide little evidence for an association with radiation. American radiologists who practiced in the 1920s and 1930s have been reported to be at increased risk for lymphosarcoma, but

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2 To whom requests for reprints should be addressed, at EPN/408, 6130 Executive Boulevard, Rockville, MD 20852.
3 The abbreviation used is: NHL, non-Hodgkin's lymphoma.
Discussion

Similar to chronic lymphocytic leukemia and Hodgkin’s disease, the evidence that NHL is increased following radiation exposures is weak and inconsistent (Table 2). Associations, when seen, are only following very large therapeutic doses and even here the evidence is equivocal and based on small numbers. Immunosuppression probably plays a contributing role in some of the excesses, such as those observed following treatment for Hodgkin’s disease. One speculative immunological mechanism might be that high, near lethal, doses of radiation kill off suppressor T-cells, which are known to be quite radiosensitive (24), and this depletion might permit an unregulated proliferation of B-lymphocytes leading to lymphoma in rare instances. Evidence that low doses of radiation do not cause lymphoma comes from the atomic bomb survivor study, and from several large-scale studies of patients undergoing diagnostic X-ray procedures or administered radioactive iodine. Finally, while many studies find leukemia to be increased following radiation exposure, there is not a single study for which a dose-response relationship has been demonstrated for non-Hodgkin’s lymphoma. Interestingly, the one leukemia never linked to radiation, chronic lymphocytic leukemia, appears etiologically and clinically as a lymphoma and is distinct from other forms of leukemia (1). Overall, it seems unlikely that ionizing radiation is responsible for even a portion of the apparent increases in NHL reported in the general population during the last several decades. To speculate on the implications of these radiation studies, if radiation does not cause NHL, at least not through its normal mechanism of breaking chromosomes, creating rearrangements, gene deletions, and mutations, then perhaps other environmental factors with similar modes of action, i.e., mutagens and clastogens, may also turn out not to be major causes of NHL.

References


Table 1 Epidemiological studies of populations exposed to ionizing radiation and subsequent risk of leukemia and NHL, by type of exposure and strength of the association

<table>
<thead>
<tr>
<th>Type of exposure</th>
<th>Study</th>
<th>Leukemia</th>
<th>NHL</th>
</tr>
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<tbody>
<tr>
<td>Atomic bomb</td>
<td>Japanese survivors (3)</td>
<td>++±</td>
<td>±</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Cervical cancer (7)</td>
<td>++±</td>
<td>±</td>
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<tr>
<td></td>
<td>Endometrial cancer (8)</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Hodgkin’s disease (9)</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Ankylosing spondylitis (6)</td>
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<td></td>
<td>General patient exposures (14)</td>
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<td>±</td>
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<tr>
<td></td>
<td>Prenatal X-ray, twin cohorts (15)</td>
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<td>Radiologists, U.S. (20)</td>
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<tr>
<td></td>
<td>X-ray workers, China (21)</td>
<td>++±</td>
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</tbody>
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* +++*, highly significant finding; +++, meaningful association; +, suggested but unconfirmed; ±, equivocal; -, no evidence for an increase in risk.

Table 2 Some observations on exposure to ionizing radiation and NHL

1. Similar to chronic lymphocytic leukemia and Hodgkin’s disease, the evidence that ionizing radiation causes NHL is very weak.
2. NHL may arise infrequently following high-dose, possibly near lethal, radiation treatments.
3. Immunosuppression associated with the disease and/or treatment may play some role in subsequent NHL development.
4. Low doses of radiation have not been linked to NHL; studies of atomic bomb survivors and of patients exposed to diagnostic X-ray procedures are negative.
5. No epidemiological study has found a dose-response relationship for NHL.
6. Although speculative, perhaps carcinogens that act like radiation do not cause NHL?


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