

# Lymphoma Risks in Populations with Altered Immunity—A Search for Mechanism<sup>1</sup>

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## Abstract

There have been numerous studies of lymphoma incidence in patient populations having diseases or taking medications that result in altered immunity. While many of these have uncovered substantially elevated risks, little has been done to use these observations to gain insights into the mechanisms of lymphomagenesis. Speculation about mechanism has centered on either immunosuppression or immunostimulation. The patterns of risk among kidney transplant recipients (higher risks for those receiving cadaveric grafts, having multiple transplants, or having received transplants in the earlier years of transplantation) favor the immunostimulation hypothesis. Likewise, the higher lymphoma risk associated with indices of increasing severity of disease among patients with sicca syndrome also support the role of immunostimulation over that of immunosuppression. However, an ordering of many of the more extensively studied conditions with altered immunity on the basis of the relative risk of lymphoma associated with these conditions reveals a pattern of risk which is not completely consistent with the level of either immune suppression or immune stimulation. Perhaps we have reached a point where epidemiologists working with laboratory and clinical immunologists can discern a more sophisticated underlying mechanism than the crude concepts of immunosuppression or immunostimulation that would explain the markedly differing lymphoma risks seen in various groups with marked immune abnormalities. If so, markers of more subtle alterations in this mechanism might be profitably explored for their role in lymphoma in general and as a tool to define the environmental causes of the epidemic increases.

Immunoepidemiology, the study of populations with altered immune systems, has been an active area of cancer research for some time. This level of activity is probably due to two features of these studies. First of all, epidemiology tends to be an opportunistic science, studying groups that are easily studied. Patient groups with major immunological alterations tend to be easily identifiable and generally stay close to medical care systems and thus are relatively easily followed. Second, strikingly altered risks of certain cancers, particularly lymphomas, are frequently noted for these groups, fueling interest in further study. On the other hand, and perhaps for these same reasons, while epidemiologists have documented risk patterns, they have tended not to push beyond these observations into attempts at elucidation of the underlying mechanisms involved. Such efforts at a minimum involve two activities: looking in detail among high-risk groups for the characteristics of the patients who are at high risk of lymphoma compared to those who are not, and a synthesis of the findings from studies of different patient groups, in order to develop hypotheses for the varying patterns of risks seen.

Two examples of a search for risk factors among high-risk groups concern the determinants of lymphoma risk for kidney transplant recipients and for patients with sicca syndrome (Tables 1 and 2). The kidney transplant data come from the

study of the American College of Surgeons Kidney Transplant Registry, which has been described in detail elsewhere (1, 2). The data presented here, however, are new and reflect the complete experience of this registry, which went out of existence in the mid-1970s. Risk of lymphoma did not differ by type of primary renal disease, age at transplant, age of donor, or a number of other characteristics of the patients. Risk did appear to vary, however, according to the three variables in Table 1 (type of donor, year of transplant, and number of transplants). The relative risk of lymphoma was substantially lower in those receiving grafts from siblings than among those receiving cadaveric grafts; risk was higher for those having undergone multiple transplants as a result of rejection episodes than in those receiving just one graft; and there was a clear trend of decreasing lymphoma risk with increasing year at transplantation. Speculation about the mechanism of lymphoma risk in transplant recipients has focused on two possibilities, level of immunosuppression and resultant loss of immunological surveillance against oncogenic viruses and host cell changes, or level of antigenic stimulation to the immune system from the implanted graft and resultant opportunity for abnormal proliferation. While intensity of immunosuppression and level of antigenic stimulation tend to be correlated, the results in Table 1 would seem to favor the antigenic stimulation hypothesis. In this time period in particular, sibling grafts tended to be much closer matches than cadaver grafts; over time, there were improvements in typing, leading to much closer matching in later *versus* earlier time periods; and persons receiving multiple transplants will have been through the intensive antigenic storms of rejection episodes.

A very similar conclusion could be derived from the detailed analysis of lymphoma risk in patients with sicca syndrome. This disease, also known as Sjogren's syndrome, is a chronic, inflammatory, autoimmune disease in which the salivary and lacrimal glands are damaged, producing xerostomia and xerophthalmia. The condition involves only minor levels of immunosuppression. As indicated in Table 2, and described elsewhere (3), indices of disease severity among sicca syndrome patients are directly related to level of lymphoma risk. Patients with the disease but no parotid swelling have a 12-fold risk. Patients with parotid swelling not requiring radiation therapy have a 40-fold risk, and those with parotid swelling of a severity requiring radiation have a risk 300 times that of the general population. Boice (4) indicates that the excess risk is not due to the radiation but to the severity of the sicca syndrome itself.

However, this consistent story of excess lymphoma risk in immune-altered populations resulting from the level of antigenic stimulation becomes much less consistent when one attempts the second part of this search for clues to mechanisms, a synthesis of findings from studies of all groups with altered immunity. Table 3 categorizes a number of the more extensively studied conditions of altered immunity according to their approximate relative risk of lymphoma. If the findings from the risk group analyses of transplant recipients and sicca syndrome patients indicate that level of antigenic stimulation might

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Table 1 Observed number and relative risk<sup>a</sup> of lymphoma among kidney transplant recipients by selected characteristics of the transplantation

	Observed	Relative risk
Year of first transplant		
≤1967	16	25.0
1968-69	13	17.1
1970-71	13	12.0
≥1972	12	10.5
No. of transplants		
1	45	13.5
2	7	22.8
3+	2	100.0
Relationship of donor <sup>b</sup>		
Sibling	5	6.9
Parent	9	18.4
Cadaver	30	15.1

<sup>a</sup> Observed number of lymphomas divided by those expected based on applying age, sex, and time-specific incidence rates from general population to the corresponding person-years of follow-up of the transplant recipients.

<sup>b</sup> Limited to those receiving one transplant only with known donor.

Table 2 Observed number and relative risk<sup>a</sup> of lymphoma among women with sicca syndrome by degree of parotid gland involvement

	Observed	Relative risk
No parotid swelling	1	12.5
Parotid swelling, no radiation	3	37.5
Parotid swelling and radiation	3	300

<sup>a</sup> Observed number of lymphomas divided by those expected based on applying age, sex, and time-specific incidence rates from general population to the corresponding person-years of follow-up of sicca syndrome patients. Adapted from Reference 3.

Table 3 The relative risk<sup>a</sup> of lymphoma associated with selected conditions which entail altered immunity

Magnitude of relative risk of lymphoma		
High (RR <sup>b</sup> > 15)	Intermediate (RR > 2)	Low (RR ≤ 2)
Multiple transplants	Sibling transplant	Splenectomy
Cadaver transplant	Mild sicca syndrome	Sarcoidosis
Severe sicca syndrome	Nontropical sprue	Hyperimmunization
Wiskott-Aldrich syndrome	Crohn's disease	Asthma
Ataxia-telangiectasia	Short-term HIV infection	Hansen's disease
Long-term HIV infection	Rheumatoid arthritis	Cytotoxic drug Rx
		Systemic lupus

<sup>a</sup> Risk of lymphoma in patients with the condition relative to a risk of 1.0 to comparable individuals without the condition.

<sup>b</sup> RR, relative risk; HIV, human immunodeficiency virus.

dictate risk of lymphoma, several factors in Table 3 argue against this. For example, several studies have found no excess lymphoma risk among patients with systemic lupus. If there is an excess among these patients it is likely to be of a relatively low order of magnitude, perhaps 2-fold. This sort of critical

review leads to the conclusion that the concepts of "immunosuppression" and "immunostimulation" are probably much too crude to describe the immunological mechanisms of lymphomagenesis.

With the rapid and continuing evolution of our understanding of the immune system, perhaps we have reached the point where epidemiologists working with laboratory and clinical immunologists can discern a more sophisticated underlying mechanism that would explain the markedly differing lymphoma risks seen in various groups with marked immune abnormalities. A detailed immunological characterization of each of these conditions might reveal differences and similarities between some measures of immune function that would parallel the differences and similarities in lymphoma risks, and a unifying hypothesis would emerge. If this is too optimistic at this time, it is more likely that such an exercise could at least identify specific conditions such that if they were more extensively characterized immunologically they might provide key data to solving this puzzle. Alternatively, the immunologist might identify a specific condition for which lymphoma risk has not been determined, but if so evaluated epidemiologically could provide similarly seminal information as to mechanism. This sort of targeted approach seems appropriate at this time if we are to move from a quantification of risk to an understanding of possible mechanisms. This clarification of potential mechanism could then lead to identification-appropriate biomarkers associated with the mechanism, biomarkers which could be incorporated into studies of lymphoma in the general population. In this way it might then be possible to determine if more subtle alterations in these immunological pathways play a role in a more significant proportion of lymphoma than only that which occurs in these rare syndromes. It would then also be possible to investigate environmental influences on these immunological pathways and to assess whether changes in any of these environmental factors could explain the time trends for non-Hodgkin's lymphoma.

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