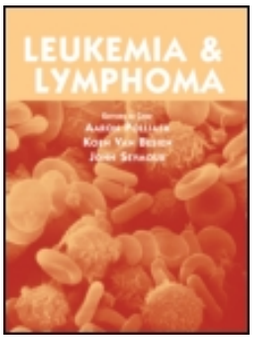

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COMMENTARY

Splenectomy and second malignancies in patients with Hodgkin lymphoma: is there a causal relationship?

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The spleen is a part of the reticuloendothelial system that plays an important role in immune surveillance [1]. Removal of the spleen has been shown to be associated with higher risks of infections and portal vein thrombosis in the short term, and a higher incidence of secondary cancers in the long term, although the exact mechanism remains unknown [1,2]. In patients who undergo splenectomy as a part of treatment for either hematological or non-hematological disorders, there exist conflicting data on whether: (1) the incidence of secondary cancers after splenectomy is truly higher, and (2) the risk of second cancer is higher when compared to a population of patients who undergo splenectomy as a part of non-cancer treatment [2–5].

Older *in vitro* animal studies showed an increased growth of inoculated tumor cells and a decreased circulating peripheral blood lymphocyte count after splenectomy [6,7]. tumor growth was also reversible with auto-transplant of the spleen, thus suggesting a role of the spleen in immune surveillance [6]. Similarly, splenic irradiation has been shown to cause atrophy of the red pulp of the spleen, fibrosis, loss of the sinusoidal pattern and reduced deformability of erythrocytes, which is a marker of functional asplenia [8,9]. Thus, splenectomy or splenic irradiation has been postulated to have similar short-term and longer-term pathological and clinical consequences.

In population-based observational studies, data from retrospective cohort studies also showed an increased incidence of secondary cancers in patients treated for Hodgkin lymphoma (HL) [4,5,10–12]. These included increased incidences of secondary leukemia, myelodysplastic syndrome, non-Hodgkin lymphoma and solid cancers [4,5,10–12]. Factors found to be associated with an increased risk of second cancers in patients with HL include the use of MOPP-based chemotherapy (mechlorethamine, vincristine, procarbazine and prednisone), being male, age $>$ 40 years, receiving extensive radiation therapy and combined multi-modality therapy [4,5,10]. The role of asplenia has also been addressed in a cohort study of 892 newly diagnosed patients with adult HL treated from 1960 to 1984 [4]. Patients who underwent splenectomy or splenic irradiation as a part of their HL treatment had an increased incidence of secondary cancers when compared to a population with functional or surgical asplenia. In a multivariate analysis controlling for age, gender, clinical stage, regional radiation therapy and type of chemotherapy regimen used, the following factors were significantly associated with increased risk of developing second cancers: age $>$ 40 years, combination of MOPP and regional/extended field radiation, and splenic irradiation/splenectomy [4]. Children with HL treated with radiation therapy between 1960 and 1999 were also more likely to develop second solid tumors in a separate study [13]. In another retrospective cohort study of 1939 patients with HL treated over two decades from 1966 to 1986, the overall incidence for developing secondary malignancies was 20% over a 20-year period, of which the most common types were hematological malignancies such as leukemia, non-Hodgkin lymphoma (NHL) and solid tumors [5]. Additionally, it was noted that 29% (564 patients) of the study population underwent splenectomy. In multivariate analysis, type of chemotherapy, older age (age $>$ 40 years), advanced stage and splenectomy were found to be significant risk factors for developing secondary leukemia. This risk of secondary leukemia was reduced for patients treated with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) in the 1980s, although the risk of solid cancers increased in general (10,12,14). In a more recent retrospective study of 5798 patients with HL treated from 1963 to 2001, those who received chemotherapy alone were associated with an increased risk for second cancer, but this was lower and affected fewer anatomic sites when compared to those who received multi-modality therapy [11]. This study failed to implicate the role of splenectomy as a risk factor for developing second cancers.

Functional or surgical asplenia has been recognized as a risk factor for the occurrence of secondary malignancies, assumed to be due to the loss of innate immune surveillance. Recent epidemiologic data suggest an increased risk of secondary cancers in patients who undergo splenectomy, irrespective of cause, emphasizing the role of the spleen [2].

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Replication of these findings can potentially strengthen the proof of causation, since both *in vitro* animal models and large observational studies have shown significant associations. Additionally, newer studies fail to mention the role of functional or surgical asplenia in HL, as treatment options currently used have now evolved to other types of chemotherapy. While the studies that implicated the association between splenectomy and second cancers were found in the context of exploratory analyses, none specifically focused on splenectomy. To address the causative role of splenectomy in patients with HL treated more recently, Kooistra *et al*. [15] in this issue of ***Leukemia and Lymphoma*** conducted a single-institution retrospective cohort study in 166 patients with HL treated from 1970 to 1996, of whom 90 underwent splenectomy. After controlling for the use of alkylating agents, the study failed to find differences in the incidence of second hematological or non-hematological cancers in the study population.

The strength of the current study comes from the ability of the authors to ascertain second cancers due to the completeness of follow-up data, despite the relatively smaller sample included compared to studies by Dietrich *et al*. [4] and van Leeuwen *et al*. [5]. However, the small sample size of this study may also have prevented them from having enough power to detect a difference. Additionally, it was a single-center study that lacked heterogeneity in treatment approaches and variation in the distribution of underlying risk factors. However, this homogeneity of the sample treated by a single center allowed for other risk factors also implicated as culprits of second cancers to be somewhat controlled. If the study findings are to be interpreted as true, one can hypothesize that second cancers after HL treatment may be a result of multiple factors, and not simply a direct effect of splenectomy. Since a prospective cohort study is not likely to be conducted to truly evaluate the causal relationship between splenectomy and second cancer, the role of asplenia in causing second cancer after HL treatment remains elusive.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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