response rates among controls (which could enrich for a positive history of transfusion), genuine differences among populations studied, or other sources of heterogeneity. Finally, although the cohort study is the strongest observational study design, the meta-analysis was based on only 5 cohort studies.

The second source of heterogeneity identified was by NHL subtype. NHL is known to be biologically and clinically heterogeneous, and the impact of this heterogeneity for etiologic risk factors is receiving renewed attention. Castillo et al found that of the common subtypes, an association with transfusion history was only observed for chronic lymphocytic leukemia/small lymphocytic lymphoma (meta-RR = 1.66) and not diffuse large B-cell (meta-RR = 1.06) or follicular (meta-RR = 1.02) lymphomas. It is important to note that these exploratory results were based on a much smaller subset of the studies.

One of the main limitations of this report relates to the limitations of meta-analysis itself relative to a pooled analysis of primary data. Beyond the statistical concerns of meta-analysis, a pooled study allows for more detailed analyses based on different exposure scenarios and selected subgroups, as well as adjustment for potential confounding factors across studies, evaluation of interactions, and a more robust and complete assessment of NHL subtypes. In this study, it was not possible to estimate meta-RRs based on latency, number of transfusions, types of transfusion (eg, specific component(s) transfused; autologous versus allogeneic transfusion), or indication for transfusion. Assessment of subtypes was limited to the most common ones for studies that published estimates; studies that did not include subtype estimates had to be excluded, and evaluation of rarer subtypes was not possible. However, even pooled analysis cannot overcome limitations in primary data collection, and many studies could not specifically document what was actually transfused.

Is the association of transfusion with NHL risk likely to be causal? There are insufficient data at this time to decide. Although a randomized trial would be the strongest study design to directly assess this question, such a study would be both unethical and impractical. Thus, we will need to rely on observational data in humans supplemented by laboratory insights. The meta-analysis here raises more questions than it “meta-answers,” but it does move the field forward by identifying where we are and the types of additional data that we need. Castillo and colleagues’ conclusion supporting a conservative approach to transfusion is prudent. Ultimately, any association of transfusion and NHL risk is more likely to impact our understanding of lymphomagenesis than it is to specifically impact transfusion practice, where risk and benefit considerations remain extremely complex.

**Conflict-of-interest disclosure:** The author declares no competing financial interests.

---

**REFERENCES**


---

**HEMATOPOIESIS & STEM CELLS**

Comment on Sun et al, page 2932

**Hemangioblasts: back to the future?**

Bruno Peault

**UNIVERSITY OF EDINBURGH; UNIVERSITY OF CALIFORNIA AT LOS ANGELES**

In this issue of *Blood*, Sun and collaborators report the existence of a population of hemangioblasts in the adult mouse uterus, adding substance to the long-lasting debate on the persistence of these ancestral progenitor cells in the developed organism.

Florence Sabin, the first woman to be elected to the American National Academy of Sciences, needed no more than a primitive microscope and chicken embryos kept alive in culture to conclude in 1917 the existence of a unique origin for both emerging endothelial and blood cells.¹ The term hemangioblast was coined 15 years later to name such progenitors, but did not gain wide popularity until the end of the 20th century when the existence of angio-hematopoietic stem cells became one of the most challenging concepts in developmental hematology. Sabin’s brilliant intuition was confirmed when hemangioblasts were identified among the progeny of mouse and human embryonic stem cells²,³ and in early mouse and fish embryos.⁴,⁵

Genuine hemangioblasts are commonly defined as founders of the blood and vascular system in early embryonic life. Hemangioblasts derived from the extraembryonic mesoderm are at the origin of coupled vasculogenesis and primitive blood formation in the yolk sac, whereas those born to intraembryonic (splanchnoeural) mesoderm generate definitive hematopoietic cells in the dorsal aorta through a hemogenic endothelium intermediate, a sequence that may also apply to yolk sac hemangioblasts (see figure).⁶,⁷ Besides these documented key roles in the incipient blood and vascular systems, some investigators have evoked the possibility that hemangioblasts persist and function at later stages of development, and even during postnatal and adult life. Candidate hemangioblasts marked by the coexpression of CD34 and KDR (the receptor 2 for vascular endothelial growth factor) were identified in human umbilical cord blood and adult bone marrow, albeit at the infinitesimal frequency of approximately 1 in $2 \times 10^5$.

---

From www.bloodjournal.org by guest on June 12, 2017. For personal use only.
The hemangioblast (A) is defined as a mesodermal progenitor cell committed to the generation of endothelial cells (B) and blood cells (C), sometimes—perhaps always—via a hematogenous endothelium intermediate (D). Professional illustration by Marie Dauenheimer.

Hemangioblasts: back to the future?

Bruno Péault