number of pulmonary metastases in VWF-null mice compared with control mice following intravenous injection of cancer cells. Restoration of VWF plasma levels by injection of VWF inhibited metastasis. These experiments conducted by Mochizuki et al. (2) are consistent with the concept that inactivation of VWF is required in the initial establishment of metastatic foci, independently of its role in hemostasis.

Now, how are we to integrate the elegant preclinical studies of Mochizuki et al. (2) to expand our understanding of clinical metastasis? Let us go back to the basics. The mouse pulmonary colonization model used by Mochizuki et al. (2) is considered the "gold standard" in analyzing cancer dissemination. The fact that mouse lung metastasis occurs within weeks, whereas human metastases develop over years, is cause for concern. Furthermore, the extensive proliferation of metastatic cancer cells intravascularly in mouse lungs (8) appears different from pathological examination of human metastases.

What other data is needed to "nail down" the role of ADAM28 cleavage of VWF in cancer? An association of VWF levels in blood and tissues and ADAM28 levels in patient tumor tissue with indolent vs aggressive cancers would be revealing. One area of concern deals with an old observation that humans with type O blood group have substantially lower plasma levels of VWF than other ABO groups (9), which, according to Mochizuki et al. (2), might lead to diminished tumor cell apoptosis, hence more aggressive cancers. But, on the contrary, patients with type O blood do not display enhanced tumor aggressiveness (9–11). Other investigators reported increased serum levels of VWF antigen and multimers in patients with cancer, but the issue of correlation of VWF with prognosis is disputed (12).

From a wider perspective, how are we to make sense of the enlarging number of genes being implicated in the metastatic process? Will it turn out that individual human tumors require different proteins to complete the metastatic process or will a small panel of “driver genes” be identified? We have the cell and molecular technology, animal models, and clinical tools to solve the problem, but the path to drug discovery for treatment of metastasis and the dream of turning cancer into a “chronic disease” (13) might turn into quite an obstacle.

References

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Non-Hodgkin Lymphoma in Early Life
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The non-Hodgkin lymphomas (NHLs) are a heterogeneous group of B-cell and T-cell neoplasms that vary by morphological appearance, etiology, biology, and clinical manifestations. Worldwide, the incidence of NHL began to increase circa 1950 (1,2), approximately doubling in the United States between 1975 and 2000 (3,4), and then stabilizing with an age-standardized rate near 20 per 100000 person-years (3). The age-standardized incidence rate, however, is an age-specific weighted average that may...
mask important age-related trends (5,6), especially among younger persons. Additionally, whereas recent trends for NHL overall may be related to HIV/AIDS and changes in classification systems or diagnostic practice patterns (2), perinatal and family risk factors also may be important for NHL in early life. Therefore, in this issue of the Journal, Crump et al. (7) conducted a national cohort study in Sweden among young persons aged 0–37 years, who were newly diagnosed with NHL between 1973 and 2008 and followed through 2009. The authors linked Swedish birth and cancer registries data for NHL, family characteristics, and the perinatal period (variously defined as the days immediately before and after birth). Linkage to the national birth and cancer registries was nearly 100% complete. More than 99% of the original cohort remained after exclusions for missing data regarding gestational age at birth and/or birth weight. There were 936 NHL patients with 66.3 million person-years of follow-up. The overall incidence rate was 1.4 per 100,000 person-years (1.7 for men and boys and 1.1 for women and girls). Age-specific incidence rates rose with advancing age at diagnosis, like rates of epithelial carcinomas (8).

For a similar period, incidence rate patterns were slightly higher among young persons in the United States than in Sweden (Figure 1), using the National Cancer Institute’s Surveillance, Epidemiology, and End Results 9 Registries Database (SEER, 1973–2008) (9). There were 15,089 NHL patients with 527 million person-years of follow-up among persons of the youngest nine of 19 SEER age groups (ie, ages 00, 01–04, 05–09, … 35–39 years). The age-standardized incidence rate (adjusted to the World Standard Million population) for these nine age intervals combined was 2.37 per 100,000 person-years (3.15 for men and boys and 1.58 for women and girls) (Figure 1, A). The estimated annual percentage change for the age-standardized rate was 1.26% and 1.91% among men and boys and women and girls, respectively. Age-specific rates rose continuously with advancing age (Figure 1, B), as in Sweden.

In the Swedish study (7), relative risks of non-Hodgkin lymphoma were presented as hazard ratios (HRs) unadjusted and adjusted for sex, birth year, fetal growth, gestational age at birth, twinning, birth order, maternal age at delivery, maternal and paternal education level, and family history of NHL. Independent risk factors were family history of NHL, high fetal growth, older maternal age, low birth order, and male sex. Based on small numbers, the strongest risk factor was for family history of NHL in either a sibling (HR = 9.84) or parent (HR = 2.36) with a greater risk for a same-sex sibling or parent. High fetal growth weight that was two standard deviations or more from the reference birth weight, by gestational age and sex, was associated with increased risk of NHL (HR = 1.64). Maternal age was an important confounder for low birth order with an inverse relationship between NHL and birth order after adjusting for maternal age. Male sex was an age-specific effect modifier, with a twofold increase in NHL among boys who were aged younger than 15 years but not older. In the United States, there was also a relative excess of NHL among younger men compared with women (Figure 1, B) with a male to female incidence rate ratio of 2.7 (95% CI = 1.9 to 3.7) between ages 5–9 years and 2.3 (95% CI = 1.7 to 3.0) between ages 10–14 years. When incidence of NHL subtypes was examined (7), family history and older maternal age were associated with increased risk for diffuse B-cell subtypes. Family history was not estimable for the
other subtypes. Older maternal age was associated with a borderline increased risk for T-cell tumors. A reciprocal birth cohort effect was observed with decreasing risk by year of birth for diffuse B-cell and increasing risk for other B-cell and T-cell tumors. Although it is important to determine whether the etiology of NHL differs by subtype, subtype trends in this study are somewhat uncertain because of small sample sizes and missing data (35% missing subtype, 332 of 936 subjects). Additionally, although the distinction between B-cell and T-cell tumors is generally straightforward, the categorization for B-cell and T-cell subtypes has evolved over time, raising concern for calendar period effects due to changing classification systems or improved diagnostic techniques. The authors attempted to rule out calendar period effects and to confirm birth cohort or exposure effects by accommodating different patterns of missingness. First, they distributed the subjects with missing subtype data in the observed proportions of known subjects with diffuse B-cell tumors (50%), other B-cell tumors (40%), and T-cell tumors (10%) and then recalculated the subtype trends. Second, missing subtype data were redistributed by the observed proportions of known subjects for each year of birth, age at diagnosis, and sex. Birth cohort effects persisted and remained statistically significant in these sensitivity analyses. Alternatively, population-based birth cohort effects could have been assessed with age-period-cohort models (10). Notwithstanding the well-documented identifiability issues for the age-period-cohort framework (11), cohort deviations or changes are estimable functions that have the added value of being fully adjusted for age and period effects. In the United States SEER population (Figure 2), we could show statistically significant decelerating (concave parabola) cohort deviations or changes for diffuse B-cell tumors \( P < .001 \) and accelerating (convex parabola) deviations for T-cell tumors \( P < .001 \) but not for other B-cell tumors \( P = .28 \).

In conclusion, the study by Crump et al. (7) is a national cohort study of perinatal and family characteristics associated with the diagnosis of NHL among children and young adults in Sweden. Limitations included the unavailability of many host and environmental risk factors for NHL such as infectious exposures, radiation, environmental contaminants, and primary or inherited immune deficiencies. Nonetheless, their large-scale and population-based design minimized selection bias and maximized generalizable conclusions for associations between NHL in early life and family history, high fetal growth weight, older maternal age, low birth order, and male sex. However, risk estimates for family history were based on small numbers of case patients with an affected sibling \( n = 4 \) or parent \( n = 10 \). Pooled studies with larger sample sizes will be required to further assess the potential role of gene-environmental exposures for family history of NHL. In contrast to Crump et al. (7), a large meta-analysis showed no statistically significant association between high or low birth weight and NHL (12), and the authors concluded that birth weight might not be a good metric for an association between fetal growth and lymphoma (12). Advancing maternal age appears to be a risk factor for many childhood cancers possibly due to differential gene expression in cell cycle control and DNA damage repair mechanisms among older women, age-related mutations in oocyte genes, increasing use of fertility technology by older mothers, or changes in maternal hormonal exposures with advancing age (13). The association of low birth order after adjustment for maternal age is consistent with the hypothesis of “reduced or delayed exposure” to first viral or bacterial infection in infancy due to the absence of other siblings (14); however, others have found little support for an association between NHL and birth order or family size (15,16). Finally, though male predominance in the incidence of cancer is well established (17), the age interaction or effect modification by sex before age 15 years is not easily explained.

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