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Comment on "Association between Residential Proximity to Viticultural Areas and Childhood Acute Leukemia Risk in Mainland France: GEOCAP Case–Control Study, 2006–2013"

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The comprehensive article by Mancini et al. compared the residential location of 3,711 patients under age 15 who were diagnosed with acute leukemia between the years 2006 and 2013 to the place of residence of 40,196 controls.[1] The authors found no association between proximity to vineyards and acute leukemia; however, viticulture density within 1,000 m was detected to be positively associated with acute lymphoblastic leukemia (ALL). The authors concluded that there is a slight increase in the risk of ALL in children living in areas with high viticulture density. They hypothesized that environmental exposure to pesticides may be associated with childhood ALL.[1]

Although there is strong evidence that exposure to pesticides can cause cancer, other factors may be involved. A number of studies have revealed an increased rate of leukemias and cancer in individuals working in agriculture, forestry, and other occupations that are exposed to soil.[2–5] As a rule, soil contains a significant amount of fungi.[6–8] Accordingly, agricultural workers have a high rate of exposure to fungi. This likely includes those working in viticulture; a recently published article revealed that in a survey of 310 vineyards, 533 fungal strains belonging to 35 distinct genera were isolated from diseased vines.[3]

A two-hit hypothesis for the development of ALL combines genetic predisposition and exposure to an infectious agent. Although somewhat controversial, individuals with allergy-related diseases and asthma generally are reported to have a decreased rate of cancer, including acute myeloid leukemia and some solid tumors, as compared to the general population.[5,9–11] Epidemiological data points to a possible role for immunoglobulin E (IgE), allergy, and atopy in protecting against certain tumors. An increased risk of cancer in association with IgE immunodeficiency also has been reported.[12] Significant information regarding the inverse association between atopic conditions and glioma has been accumulated. In our study of 40 children with ALL, the plasma of patients was positive for antibodies against a mycovirus-containing *Aspergillus flavus*, whereas three groups of controls—including healthy individuals and patients with either solid tumors or sickle cell disease—were negative.[13] Separately, we exposed mononuclear cells from patients with ALL in complete remission to the products of the mycovirus-containing *A. flavus*. The result was the redevelopment of cell surface and genetic markers characteristic of ALL in the cells from patients but not controls.[14] Products of this organism can alter transcription factors.[15] It should be noted that existence of mycovirus within the fungi was proven by multiple electron microscopy examination, and this organism did not produce any aflatoxin.[13,14] The role of mycovirus-containing *Aspergillus flavus* in leukemogenesis needs to be further investigated.

With the above evidence, the finding described by Mancini et al. of an increased rate of ALL in children living in areas with high viticulture density may be more complicated than stated and may not be entirely related to the environmental exposure to pesticides.

Editor's Note: In accordance with journal policy, Mancini et al. were invited to respond to this letter. They chose not to do so.

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