TO THE EDITOR:

Obesity and neoplasms of lymphohematopoietic cells

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In countries such as the United States, where aggressive antismoking campaigns have led to a striking decrease in the fraction of the population who are tobacco smokers, obesity is an unwanted replacement as a preventable factor that increases the risk of cancer in multiple tissues, including the marrow.1 In a report of August 2016, the International Agency for Research on Cancer (IARC) Handbook Working Group summarized the relative risk of cancer of various tissues as a result of body fatness, based on published studies. They found sufficient evidence to ascribe an elevated risk of cancer in 13 tissues to overweight or obesity.2

Obesity has also been shown to increase the risk of lymphohematopoietic neoplasms.3 The IARC Working Group reaffirmed the data linking overweight and obesity to the risk of myeloma, the latter neoplasm originating in the transformation of a marrow B-lymphocytic progenitor cell. The evidence for an increased risk of myeloma as a result of overweight and obesity is compelling.3-11 Of special interest is whether the precursor of myeloma, essential monoclonal gammopathy (also known as monoclonal gammopathy of unknown significance), has an increased risk of occurrence in obese patients. An initial study indicated that it did,11 whereas a recent study has challenged that finding.12 The reason that this relationship is of particular interest is that it speaks to the question of the mechanism by which the consequences of obesity act. Obesity could be inductive, that is the metabolic, endocrine, and inflammatory effects of excess adipose tissue might contribute directly to the acquisition of oncogenic mutations during DNA replication or repair in the process of cell division and, thereby, establish a neoplastic clone. Alternatively, the varied and influential metabolic effects of fat tissue could act to select an established, but dormant, clone to undergo evolution to a malignancy.13 If essential monoclonal gammopathy is not increased in prevalence in overweight and obese subjects, this finding could be interpreted as favoring the selection hypothesis, at least as it applies to myelomagenesis.14

Among the alterations incurred in patients with obesity is the metabolic syndrome, the major manifestations of which are visceral (truncal) obesity, hyperglycemia, insulin resistance, hypertriglyceridemia, decreased high-density lipoprotein cholesterol, and hypertension.15 Although the studies of diabetes as a risk factor for myeloma are largely unconvincing, there is suggestive, preliminary evidence that the use of metformin (in patients with type 2 diabetes mellitus) may be associated with a decreased occurrence of essential monoclonal gammopathy and a decreased likelihood of progression from monoclonal gammopathy to myeloma.16,17

The IARC report did not comment, either affirmatively or negatively, on the evidence indicating that there is an increased relative risk of other neoplasms that originate in a marrow cell, as a result of antecedent overweight or obesity. There is evidence that myelodysplasia, acute myelogenous leukemia, and chronic myelogenous leukemia are increased in frequency in obese subjects. Acute promyelocytic leukemia, as a result of rearrangement of the RARα gene on chromosome 17, is a specific genotype of acute myelogenous leukemia associated with obesity.23,24

The possible mechanisms underlying the relationship of overweight and obesity to the incidence of myeloma and the myelogenous leukemias are under study.9,10,25-28 It is unclear whether the metabolic, inflammatory, and endocrine effects of obesity, including decreased serum adiponectin, elevated serum interleukin-6, elevated serum leptin, elevated serum insulin growth factor-1, upregulation of the promyelocytic leukemia protein, and other cytokines altered in the obese, play a role in this relationship. Several of the cytokines (eg, leptin and interleukin-6), increased in obese subjects, can act directly on myeloma and myeloid cells through ligand-receptor interactions regulating proliferative rate and or apoptosis.9,29,31,32

Clonal hematopoiesis of indeterminate potential is now an accepted concept.37-39 Individuals with such clones have an increased likelihood of progression to an overt myeloid malignancy, usually myelodysplasia or acute myelogenous leukemia. In obese individuals, preceding clonal hematopoiesis...
may undergo clonal evolution to a clinically significant malignancy (selection hypothesis), as a result of the metabolic and related effects of obesity.

Some but not all studies have associated obesity with shortened telomeres and elongation of telomeres after significant weight loss. Telomere shortening could be another pathway to the establishment of a hematopoietic clone. The reduction of that risk may occur with weight loss.

The concept of the later progression of nascent subclinical neoplasms by clonal evolution has been confirmed repeatedly as techniques to interrogate the human genome to identify driver and cooperating mutations in early neoplastic clones have become available. The ability to consider cancer progression within the framework of evolutionary biology has raised the possibility of stabilizing an indolent clone as a means of prevention of malignancy. It is possible that prevention or treatment of obesity, not easy tasks, could prove to be a way to decrease the risk of cancer initiation or progression, which could apply to a very large segment of the population.

Obesity in children and adults has been associated: with the incidence of other lymphoid neoplasms, with the issue of dose calculations for treatment of obese patients with hematological malignancies, as a sanctuary site for leukemic cells, as a factor in the outcome of hematopoietic stem cell transplant, and as a prognostic factor in the response to therapy, as well as other issues that are beyond the scope of this commentary.

**Contribution:** M.A.L. did the literature research and wrote the paper.

**Conflict-of-interest disclosure:** M.A.L. has served as a medical expert in toxic tort cases in which the matter of obesity as a risk factor for a hematological malignancy has been raised.

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**References**


DOI 10.1182/bloodadvances.2016001685

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