TO THE EDITOR:

Obesity and neoplasms of lymphohematopoietic cells

Marshall A. Lichtman

Division of Hematology-Oncology, Department of Medicine, and James P. Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY

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,^{8,18} acute myelogenous leukemia,^{3,8,19-21} and chronic myelogenous leukemia²² are increased in frequency in obese subjects. Acute promyelocytic leukemia, as a result of rearrangement of the *RAR α* 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,^{26,28} elevated serum interleukin-6,²⁹ elevated serum leptin,³⁰⁻³³ elevated serum insulin growth factor-1,^{34,35} upregulation of the promyelocytic leukemia protein,³⁶ and other cytokines altered in the obese,⁹ 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.⁴⁰ 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.⁴¹

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.

Correspondence: Marshall A. Lichtman, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642-0001; e-mail: mal@urmc.rochester.edu.

References

- Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet*. 2011;378(9793):815-825.
- Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer—viewpoint of the IARC Working Group. *N Engl J Med*. 2016;375(8):794-798.
- Lichtman MA. Obesity and the risk for a hematological malignancy: leukemia, lymphoma, or myeloma. *Oncologist*. 2010;15(10):1083-1101.
- Larsson SC, Wolk A. Body mass index and risk of multiple myeloma: a meta-analysis. *Int J Cancer*. 2007;121(11):2512-2516.
- Renahan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569-578.
- Wallin A, Larsson SC. Body mass index and risk of multiple myeloma: a meta-analysis of prospective studies. *Eur J Cancer*. 2011;47(11):1606-1615.
- Hofmann JN, Moore SC, Lim U, et al. Body mass index and physical activity at different ages and risk of multiple myeloma in the NIH-AARP diet and health study. *Am J Epidemiol*. 2013;177(8):776-786.
- Murphy F, Kroll ME, Pirie K, Reeves G, Green J, Beral V. Body size in relation to incidence of subtypes of haematological malignancy in the prospective Million Women Study. *Br J Cancer*. 2013;108(11):2390-2398.
- Carson KR, Bates ML, Tomasson MH. The skinny on obesity and plasma cell myeloma: a review of the literature. *Bone Marrow Transplant*. 2014;49(8):1009-1015.
- Lwin ST, Olechnowicz SW, Fowler JA, Edwards CM. Diet-induced obesity promotes a myeloma-like condition in vivo. *Leukemia*. 2015;29(2):507-510.
- Landgren O, Rajkumar SV, Pfeiffer RM, et al. Obesity is associated with an increased risk of monoclonal gammopathy of undetermined significance among black and white women. *Blood*. 2010;116(7):1056-1059.
- Boursi B, Weiss BM, Haynes K, Mamtani R, Yang YX. Reappraisal of risk factors for monoclonal gammopathy of undetermined significance. *Am J Hematol*. 2016;91(6):581-584.
- Merlo LM, Pepper JW, Reid BJ, Maley CC. Cancer as an evolutionary and ecological process. *Nat Rev Cancer*. 2006;6(12):924-935.
- Chang S-H, Luo S, O'Brian K, et al. Does obesity play a role in the development of multiple myeloma in patients with monoclonal gammopathy of undetermined significance? Using data from the Veterans Health Administration System. Society for Medical Decision Making 36th Annual Meeting. 18-22 October 2014. Miami, FL.
- Micucci C, Valli D, Matakchione G, Catalano A. Current perspectives between metabolic syndrome and cancer [published online ahead of print 24 March 2016]. *Oncotarget*. doi:10.18632/oncotarget.8341.
- Chang SH, Luo S, O'Brian KK, et al. Association between metformin use and progression of monoclonal gammopathy of undetermined significance to multiple myeloma in US veterans with diabetes mellitus: a population-based retrospective cohort study. *Lancet Haematol*. 2015;2(1):e30-e36.
- Sośnicki S, Kapral M, Węglarz L. Molecular targets of metformin antitumor action. *Pharmacol Rep*. 2016;68(5):918-925.
- Ma X, Lim U, Park Y, et al. Obesity, lifestyle factors, and risk of myelodysplastic syndromes in a large US cohort. *Am J Epidemiol*. 2009;169(12):1492-1499.
- Poynter JN, Richardson M, Blair CK, et al. Obesity over the life course and risk of acute myeloid leukemia and myelodysplastic syndromes. *Cancer Epidemiol*. 2016;40:134-140.
- Larsson SC, Wolk A. Overweight and obesity and incidence of leukemia: a meta-analysis of cohort studies. *Int J Cancer*. 2008;122(6):1418-1421.
- Castillo JJ, Reagan JL, Ingham RR, et al. Obesity but not overweight increases the incidence and mortality of leukemia in adults: a meta-analysis of prospective cohort studies. *Leuk Res*. 2012;36(7):868-875.
- Lichtman MA. Obesity and the risk of chronic myelogenous leukemia: is this another example of the neoplastic effects of increased body fat? *Leukemia*. 2012;26(1):183-184.
- Estey E, Thall P, Kantarjian H, Pierce S, Kornblau S, Keating M. Association between increased body mass index and a diagnosis of acute promyelocytic leukemia in patients with acute myeloid leukemia. *Leukemia*. 1997;11(10):1661-1664.
- Wong O, Harris F, Yiyang W, Hua F. A hospital-based case-control study of acute myeloid leukemia in Shanghai: analysis of personal characteristics, lifestyle and environmental risk factors by subtypes of the WHO classification. *Regul Toxicol Pharmacol*. 2009;55(3):340-352.
- Karmali R, Dalovisio A, Borgia JA, et al. All in the family: clueing into the link between metabolic syndrome and hematologic malignancies. *Blood Rev*. 2015;29(2):71-80.

26. Dalamaga M, Christodoulatos GS. Adiponectin as a biomarker linking obesity and adiposopathy to hematologic malignancies. *Horm Mol Biol Clin Investig*. 2015;23(1):5-20.
27. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. *Nat Rev Cancer*. 2011;11(12):886-895.
28. Hofmann JN, Liao LM, Pollak MN, et al. A prospective study of circulating adipokine levels and risk of multiple myeloma. *Blood*. 2012;120(22):4418-4420.
29. Cozen W, Gebregziabher M, Conti DV, et al. Interleukin-6-related genotypes, body mass index, and risk of multiple myeloma and plasmacytoma. *Cancer Epidemiol Biomarkers Prev*. 2006;15(11):2285-2291.
30. Considine RV, Caro JF. Leptin and the regulation of body weight. *Int J Biochem Cell Biol*. 1997;29(11):1255-1272.
31. Gainsford T, Willson TA, Metcalf D, et al. Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. *Proc Natl Acad Sci USA*. 1996;93(25):14564-14568.
32. Konopleva M, Mikhail A, Estrov Z, et al. Expression and function of leptin receptor isoforms in myeloid leukemia and myelodysplastic syndromes: proliferative and anti-apoptotic activities. *Blood*. 1999;93(5):1668-1676.
33. Bansal P, Ghalaut VS, Sharma TK, et al. Status of leptin in MBCR-ABL p210 positive chronic myeloid leukemia patients before and after imatinib therapy: a conflicting scenario. *Clin Lab*. 2014;60(11):1845-1852.
34. Werner H, Sarfstein R, LeRoith D, Bruchim I. Insulin-like growth factor 1 signaling axis meets p53 genome protection pathways. *Front Oncol*. 2016;6:159.
35. Vigneri R, Goldfine ID, Frittitta L. Insulin, insulin receptors, and cancer [published online ahead of print 1 July 2016]. *J Endocrinol Invest*. doi: 10.1007/s40618-016-0508-7.
36. Carracedo A, Rousseau D, Douris N, et al. The promyelocytic leukemia protein is upregulated in conditions of obesity and liver steatosis. *Int J Biol Sci*. 2015;11(6):629-632.
37. Genovese G, Kähler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med*. 2014;371(26):2477-2487.
38. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med*. 2014;371(26):2488-2498.
39. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood*. 2015;126(1):9-16.
40. Carulli L, Anzivino C, Baldelli E, Zenobii MF, Rocchi MB, Bertolotti M. Telomere length elongation after weight loss intervention in obese adults. *Mol Genet Metab*. 2016;118(2):138-142.
41. Harvie MN, Howell T. Could intermittent energy restriction and intermittent fasting reduce rates of cancer in obese, overweight, and normal-weight subjects? A summary of evidence. *Adv Nutr*. 2016;7(4):690-705.

DOI 10.1182/bloodadvances.2016001685

© 2016 by The American Society of Hematology