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http://dx.doi.org/10.1016/j.mayocp.2012.07.012

In reply: We thank Dr Redegeld and colleagues for their thoughtful letter in response to our original article on the use of nonclonal serum immunoglobulin free light chains (FLCs) to predict overall survival in the general population.[1] The authors introduce several interesting hypothesis-generating concepts regarding potential mechanisms and associations between excess serum immunoglobulin FLCs and inflammation. Works such as theirs may bring further meaning to our observation that excess FLC is associated with poorer survival outcomes in the general population, clarifying whether FLCs are merely markers for more ominous events or whether they actually contribute to pathology.

Angela Dispenzieri, MD
Mayo Clinic
Rochester. MN

1. Dispenzieri A, Katzmann JA, Kyle RA, et al. Use of nonclonal serum immunoglobulin free light chains to predict overall survival in the general population. *Mayo Clin Proc*. 2012;87(6):517-523.

http://dx.doi.org/10.1016/j.mayocp.2012.07.011

Changes in Serum Prostate-Specific Antigen Levels

To the Editor: I would like to comment on the study by Jacobsen et al[1] published in the January 2012 issue of *Mayo Clinic Proceedings* that documented the changes in serum prostate-specific antigen (PSA) values in a large group of men. The authors determined that the median annual change in PSA was about 4.8%, while the 95th percentile for PSA increase was about 50%. Interestingly, while the baseline PSA values and the absolute increases in PSA values increased with age, the increases in PSA were relatively constant across all ages when expressed as a percentage of the baseline value. They propose that PSA velocity, expressed as a percentage increase over the baseline PSA, may have more utility as an indication for biopsy than using a fixed annual increase in PSA. For example, men in their 50s had a median baseline PSA of 0.9 ng/mL, so the 95th percentile increase would be about 0.45. For men in their 70s, with a median baseline PSA of 2.1, the 95th percentile increase would be about 1.05. These examples show how using a percent increase in PSA as a biopsy threshold might prove more adaptive to age-related variations than using a fixed absolute annual increase of 0.75 points, as has been proposed in the past.

Much work needs to be done in this area to validate these findings. Many physicians will choose to follow the reasonable recommendation of the US Public Health Service not to screen for PSA in any category of healthy men until stronger evidence of benefit emerges.[2] But for those who believe that there is a useful signal buried in all the noise of PSA measurements, perhaps this study is the first step in developing a prostate cancer screening algorithm that will prove robustly beneficial for men across a range of ages and baseline PSA values. As a primary care physician who is stubbornly biased in favor of PSA testing, I would be interested to see further research into the utility of adaptive algorithms when testing PSA.

David L. Keller, MD
Providence Medical Group
Torrance, CA

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2. US Preventive Task Force. Screening for prostate cancer. http://www.uspreventiveservicestaskforce.org/prostatecancerscreening.htm. Accessed August 28, 2012.

http://dx.doi.org/10.1016/j.mayocp.2012.07.014

In reply: We thank Dr Keller for his comments regarding our study of longitudinal changes in serum PSA levels published in the January 2012 issue of *Mayo Clinic Proceedings*.[1] As Dr Keller notes, our article shows that using changes in serum PSA levels expressed as percent change per year yields more stable findings across different ages and also provides a nomogram to aid clinicians in interpreting changes in serum PSA levels observed in a normal clinical practice. Much controversy currently surrounds the use of serum PSA measurements, and while PSA is not a perfect test, at this time it is still the only widely available option for screening for prostate cancer. Using a single cut point for serum PSA level or changes in serum PSA level irrespective of age or baseline PSA level has often been noted as a drawback of using serum PSA testing.[2,3] In order to prevent PSA history from repeating itself, either in the continued use of serum PSA measurements or in the development of future prostate cancer biomarkers, it is important to focus on an algorithm that is robust across different ages and baseline levels.

Steven J. Jacobsen, MD, PhD
Kaiser Permanente
Pasadena, CA

Debra J. Jacobson, MS
Jennifer L. St. Sauver, PhD
Mayo Clinic
Rochester, MN

1. Jacobsen SJ, Jacobson DJ, McGree ME, et al. Sixteen-year longitudinal changes in serum prostate-specific antigen levels: the Olmsted County study. *Mayo Clin Proc*. 2012;87(1):34-40.
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Levamisole Toxicity

To the Editor: The review of levamisole toxicity by Lee et al[1] published in the June 2012 issue of *Mayo Clinic Proceedings* does not mention leukoencephalopathy as a well-

documented and serious complication of this drug (and cocaine adulterant). Patients may present with a variety of neurologic symptoms related to multifocal white matter lesions that can be identified on magnetic resonance imaging. The lesions do not appear to be vasculitic and are often reversible with cessation of levamisole exposure. In the setting of cocaine abuse, the clinical and magnetic resonance imaging features can be confused with other complications of cocaine abuse and high-risk lifestyles.[2-4]

Robert W. Graebner, MD
University of Wisconsin School of Medicine and Public Health
Madison, WI

1. Lee KC, Ladizinski B, Federman DG. Complications associated with use of levamisole-contaminated cocaine: an emerging public health challenge. *Mayo Clin Proc*. 2012;87(6):581-586.
2. Kimmel DW, Wijdicks EF, Rodriguez M. Multifocal inflammatory leukoencephalopathy associated with levamisole therapy. *Neurology*. 1995;45(2):374-376.
3. Xu N, Zhou W, Li S, Zhou G, Zhang N, Liang J. Clinical and MRI characteristics of levamisole-induced leukoencephalopathy in 16 patients. *J Neuroimaging*. 2009;19(4):326-331.
4. Graebner RW. Two rare leukoencephalopathies presenting with ataxia. Wisconsin Neurological Society, Madison, WI, November 11, 1995.

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In reply: We appreciate Dr Graebner's comments regarding levamisole-induced leukoencephalopathy, a well-documented complication of levamisole when used in high doses for treatment of conditions such as malignant melanoma or severe recurrent aphthous ulcers.[1,2] During the drafting of our manuscript,[3] the association between leukoencephalopathy and levamisole-contaminated cocaine had not been reported in the literature. Since then, one article has raised the possibility of multifocal inflammatory leukoencephalopathy resulting from levamisole-adulterated cocaine, suggesting that this complication can also occur with small amounts of levamisole found in cocaine.[4] We encourage health care professionals to add leukoencephalopathy to the growing list of complications resulting from this adulterant frequently detected in illicit drugs.

Kachiu C. Lee, MD
Brown University
Providence, RI

Barry Ladizinski, MD
Duke University Medical Center
Durham, NC

Daniel G. Federman, MD
VA Connecticut Healthcare System
West Haven, CT

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Benzodiazepine Oncogenesis as Mediated via Diminished Restorative Sleep Effected Sympathoadrenal Activation

The valuable cohort contribution by Kao et al[1] associating narcotic zolpidem consumption with heightened iatrogenic malignancy risks would be considerably more compelling if accompanied by proposition of a distinct plausible pathophysiologic mechanism. The most favorably received mechanism would define associations between the physiologic effects of zolpidem that are common to other pharmacologic agents and diagnoses that effect similar intermediary stepwise events epidemiologically linked to oncogenesis.

Though newer benzodiazepine controlled substances are marketed as "non-benzodiazepines," zolpidem activates identical benzodiazepine sleep modulation γ-aminobutyric acid type A receptors as classic benzodiazepines,[2] enhancing superficial stage 1/2 sleep interval at the expense of restorative rapid eye movement and stage 3/4 deep slow wave sleep (SWS).[2,3] Benzodiazepines thereby enhance sleep duration, but at the expense of restorative sleep. Similarly, all benzodiazepines suppress afferent carotid body[4] and medullary ventilatory centers, enhancing central sleep apnea perils.[5] Nocturnally ingested opioids are also well characterized as enhancing sleep duration but suppressing SWS[6] and inducing central sleep apnea,[5] with potential oncogenesis.

A 22-year study of obstructive sleep apnea has suggested that malignant lesions are potentially mediated by hypoxemic angiogenesis.[7] However, sleep apnea induced hypoxemia propagates awakenings, fragmenting SWS architecture,[8] alternatively explaining reported epidemiologic findings. Polysomnographic SWS findings were unreported. In addition, the authors did not discuss decreased oncogenesis in SWS preserved, chronically iron-depleted anemic hypoxemic, non-apnea conditions bereft of carcinogen exposure.[9]

Further challenging the angiogenesis hypothesis, non-hypoxemic circadian sleep impaired shift work decreases melatonin, which effects parallel rapid eye movement and SWS duration decrements,[10] diminishing sleep duration by 1 to 4 hours to compromise restorative sleep quality and concomitantly increase cancers.[11] In addition, without sleep apnea hypoxemia, 42,351 patients with sleep disorders with unknown extent of SWS deficit revealed a substantially elevated risk of cancer.[12]

Analogous to benzodiazepine and opioid impaired restorative SWS without decrement in overall sleep duration, experimentally laboratory simulated selectively fragmented SWS impairment without compromise of total sleep duration induced sympathoadrenal hyperactivity, increasing circulating cortisol and catecholamines[8] as well as hyperglycemic dyshomeostasis.[13]

Impaired restorative SWS effects daytime cognitive impairment and neurobehavioral anxiogenesis, with attendant augmentation of nocturnal sympathoadrenal hyperactivity,[14] perpetuating and magnifying hyperglycemia.

The constant aberrant serologic hyperglycemic environment detrimentally compromises white cell optimal cancer scavenging immunosurveillance, facilitating unimpeded microscopic tumor growth to macroscopic tumor bulk. Clinically expressed immunosuppression facilitates oncogenesis, as witnessed in patients with diabetes, those with human immunodeficiency