13. Mak S, Witte KK, Al-Hesayen A, Granton JJ, Parker JD. Cardiac sympathetic activation in patients with pulmonary arterial hypertension. *Am J Physiol Regul Integr Comp Physiol* 2012;302:R1153–R1157.
14. Rousseau MF, Gurné O, Duprez D, Van Mieghem W, Robert A, Ahn S, Galanti L, Ketelslegers JM, Investigators BR. Beneficial neurohormonal profile of spironolactone in severe congestive heart failure: results from the rales neurohormonal substudy. *J Am Coll Cardiol* 2002;40:1596–1601.

DOI: 10.1164/rccm.201205-0905ED

Sleep Apnea: A Common Mechanism for the Deadly Triad—Cardiovascular Disease, Diabetes, and Cancer?

The last decade has produced compelling data implicating sleep-disordered breathing (SDB) as a risk factor for hypertension, diabetes, stroke, coronary artery disease, and heart failure. Although SDB commonly occurs in obese individuals, these relationships have persisted even after considering potential confounding by adiposity (1–5). Potential mediators include SDB-associated oxidative stress, inflammation, insulin resistance, and endothelial dysfunction. Such evidence from epidemiological and translational research has stimulated efforts to understand how SDB interventions may improve metabolic function and reduce inflammation, with the goals of reducing cardiovascular disease and diabetes incidence and morbidity.

Obesity, a frequent co-conspirator with SDB, is associated not only with cardiovascular disease and diabetes, but also with an increased incidence of cancer and cancer mortality. The strength of associations linking obesity and cancer vary for population subgroups and for cancer type (6). Overall, obesity is estimated to account for 15 to 20% of cancer deaths (7). Associations between cancer incidence and obesity generally suggest dose–response relationships with progressively higher rates of cancer of the colon, prostate, esophagus, and breast (postmenopausal) occurring with increasing body mass index (8, 9). Increased visceral obesity may better predict cancer than body mass index (10), pointing to the importance of metabolic dysfunction in cancer biology. Components of the metabolic syndrome, including abnormalities in insulin and insulin-like growth factor-1 pathways, may play mediating roles in obesity-related cancer risk. The latter is supported by studies showing diabetics to have increased rates of cancers of the kidney, breast (postmenopausal), liver, pancreas, and endometrium (11).

Despite the high prevalence of obesity, diabetes, and metabolic dysfunction in individuals with SDB, there has been surprisingly little research that has addressed whether SDB is associated with cancer. The article in this issue of the *Journal* by Nieto and colleagues (pp. 190–194) provides important novel data implicating SDB as a significant contributor to all-cause and cancer-specific mortality (12). Specifically, the Wisconsin Sleep Cohort, which previously had provided the first population-based prevalence data for SDB in the United States (13), and critical data linking SDB to incidence of hypertension and diabetes (5, 14), now enriches the literature with new findings from a 22-year follow-up analysis of over 1,500 study participants. Baseline polysomnography was used to characterize SDB severity and many important potential confounders were adjusted for, including tobacco use, alcohol, and physical activity. Sleep duration, which has also been associated with colon polyps and breast cancer (7, 15), also was considered in analyses. A total of 112 deaths were identified over the follow-up period, including 50 cancer deaths. A statistically significant trend for increasing cancer mortality was observed with higher levels or SDB, measured either by the apnea–hypopnea index or degree of overnight hypoxemia. Furthermore, results appeared to be stronger in analyses of nonobese participants and in analyses that excluded participants who used continuous positive airway pressure during the follow-up period. The authors speculated that SDB may enhance angiogenesis within tumor tissues, leading to more aggressive tumor progression. Potential mediating pathways noted were those potentially stimulated by SDB-associated intermittent hypoxemia, including hypoxia-inducible factor, with its up-regulation of proangiogenic factors such as vascular endothelial growth factor (16). However, because the study did not have data on cancer incidence, it is unclear whether the observed association was due to a higher rate of cancers (which may be explained by metabolic and inflammatory mechanisms), rather than to a more aggressive cancer biology associated with angiogenesis or to other factors. Furthermore, because the total absolute number of cancers of any given type was small, it is difficult to determine whether the additional cancers were those known to be associated with metabolic dysfunction and obesity or were cancers that may occur or progress through pathways other than those associated with adiposity.

The authors noted that only baseline data were used to minimize the effects of reverse causality. However, it is known that in addition to adiposity, weight gain, reflecting changing metabolic and nutritional profiles, may influence the propensity for certain cancers. Furthermore, only limited data on nutrition and physical activity were available. Compared with those with less severe SDB, participants with SDB were more obese, had lower education, and had poorer overall health status. Thus, it is possible that despite the careful statistical modeling, there were unmeasured confounders that may have accounted for the observed associations.

Although the data provided by Nieto and colleagues suggest an intriguing link between SDB and cancer, it is only a first step. As noted by the authors, their study was underpowered to determine whether risks for cancer mortality differed among various types of cancer. Furthermore, although some of the analyses suggest a dose–response relationship between cancer mortality and severity of SDB, it is unclear whether there is a threshold value of SDB or hypoxemia that confers increased risk. Thus, additional adequately powered cohort studies are needed to address the aforementioned important questions as well as to determine whether the increase in cancer mortality is related to a greater incidence rate, more aggressive biology of prevalent disease, or both. Moreover, future studies are needed to elucidate whether hypoxia-induced angiogenesis, as hypothesized by the authors, is the mechanism underlying the increase in mortality, or another as yet unidentified factor.

Cardiovascular disease, cancer, and diabetes account for approximately two-thirds of all deaths in the United States, resulting in $700 billion dollars in direct and indirect economic costs. It is estimated that economic costs of SDB are $65–165 billion dollars (17). Thus, there are substantial personal and economic impacts of these conditions. In 2004, the American Heart Association, American Diabetes Association, and American Cancer Society issued a call for a collaborative effort to identify and treat common

Supported by the Harvard Transdisciplinary Research in Energetics and Cancer Center (1 U54CA155626-01).

risk factors for cardiovascular disease, cancer, and diabetes such as obesity, tobacco exposure, poor diet, and reduced physical activity (18). The findings by Nieto and colleagues suggest that in addition, SDB also may be a modifiable risk factor common to these other diseases with major public health burden, but additional confirmatory data are required.

Author disclosures are available with the text of this article at www.atsjournals.org.

SUSAN REDLINE, M.D., M.P.H.
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts
and
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

STUART F. QUAN, M.D.
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

References

1. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM, *et al.* Obstructive sleep apnea-hypopnea and incident stroke: The Sleep Heart Health Study. *Am J Respir Crit Care Med* 2010;182:269–277.
2. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, *et al.* Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: The Sleep Heart Health Study. *Circulation* 2010;122:352–360.
3. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, *et al.* Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009;6:e1000132.
4. Seicean S, Kirchner HL, Gottlieb DJ, Punjabi NM, Resnick H, Sanders M, Budhiraja R, Singer M, Redline S. Sleep-disordered breathing and impaired glucose metabolism in normal-weight and overweight/obese individuals: The Sleep Heart Health Study. *Diabetes Care* 2008;31:1001–1006.
5. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;342:1378–1384.
6. Stephenson GD, Rose DP. Breast cancer and obesity: an update. *Nutr Cancer* 2003;45:1–16.
7. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med* 2003;348:1625–1638.
8. Chow WH, McLaughlin JK, Mandel JS, Wacholder S, Niwa S, Fraumeni JF Jr. Obesity and risk of renal cell cancer. *Cancer Epidemiol Biomarkers Prev* 1996;5:17–21.
9. Rodriguez C, Patel AV, Calle EE, Jacobs EJ, Chao A, Thun MJ. Body mass index, height, and prostate cancer mortality in two large cohorts of adult men in the United States. *Cancer Epidemiol Biomarkers Prev* 2001;10:345–353.
10. Schoen RE, Tangen CM, Kuller LH, Burke GL, Cushman M, Tracy RP, Dobs A, Savage PJ. Increased blood glucose and insulin, body size, and incident colorectal cancer. *J Natl Cancer Inst* 1999;91:1147–1154.
11. Wideroff L, Gridley G, Mellemkjaer L, Chow WH, Linet M, Keehn S, Borch-Johnsen K, Olsen JH. Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. *J Natl Cancer Inst* 1997;89:1360–1365.
12. Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farré R. Sleep-disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med* 2012;186:190–194.
13. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230–1235.
14. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. *Am J Respir Crit Care Med* 2005;172:1590–1595.
15. Thompson CL, Larkin EK, Patel S, Berger NA, Redline S, Li L. Short duration of sleep increases risk of colorectal adenoma. *Cancer* 2011;117:841–847.
16. Almendros I, Montserrat JM, Ramirez J, Torres M, Duran-Cantolla J, Navajas D, Farre R. Intermittent hypoxia enhances cancer progression in a mouse model of sleep apnoea. *Eur Respir J* 2012;39:215–217.
17. The price of fatigue: the surprising economic costs of unmanaged sleep apnea. Boston, MA: Harvard Medical School Division of Sleep Medicine; c2010 [accessed April 2012]. Available from: https://sleep.med.harvard.edu/what-we-do/public-education
18. Eyre H, Kahn R, Robertson RM, Clark NG, Doyle C, Hong Y, Gansler T, Glynn T, Smith RA, Taubert K, *et al.* Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *Circulation* 2004;109:3244–3255.

DOI: 10.1164/rccm.201204-0657ED