DOI:10.1093/jnci/djt218
Advance Access publication August 13, 2013

Our Shifting Understanding of Factors Influencing Prostate-Specific Antigen

Eric A. Singer, Robert S. DiPaola

Correspondence to: Eric A. Singer, MD, MA, Rutgers Cancer Institute of New Jersey, Section of Urologic Oncology, Robert Wood Johnson Medical School, Rutgers University, 195 Little Albany St, New Brunswick, NJ 08903 (e-mail: singerea@cinj.rutgers.edu).

Prostate cancer continues to be a substantial burden on men's health with 238 590 new cases and 29 720 deaths expected in 2013, making it the most commonly diagnosed noncutaneous malignancy and the second leading cause of cancer mortality in men (1). Nonmodifiable risk factors such as age, race, and family history are known to contribute to a man's risk of developing prostate cancer. In this issue of the Journal, Flynn-Evans and colleagues examine the potential role of shiftwork as an additional prostate cancer risk factor (2).

Flynn-Evans and colleagues combined the results from three separate National Health and Nutrition Examination Surveys (NHANESs) to determine the impact of work schedule on the serum prostate-specific antigen (PSA) values (total and percentage free) of men aged 40 to 65 years (2). Although an imperfect biomarker, increased total PSA and low percentage free PSA are associated with a higher risk of prostate cancer. Because disruptions in circadian rhythms have been implicated in carcinogenesis, the authors sought to investigate the differences between the serum PSA values of men performing shiftwork (defined by the authors as regular night shifts or a rotating schedule) vs all other schedules (3). NHANES, which provides a representative sample of adult, noninstitutionalized American men, is a unique vehicle with which to perform this study. From the combined results of the 2005 to 2006, 2007 to 2008, and 2009 to 2010 surveys, a total of 2017 men had both occupational and PSA information available for analysis. The authors conclude that current shiftworkers aged 40 to 65 years had a statistically significant positive association with elevated PSA of 4.0 ng/mL or greater compared with nonshiftworkers (2).

Flynn-Evans and colleagues (2) provide supportive data for the hypothesis that shiftwork may affect serum PSA values, although with some limitations. Although the NHANES dataset is designed to represent the United States as a whole through extrapolation, the sample size of 2017 is small, and the work described by Flynn-Evans and colleagues required corrective measures to properly weight each of the three NHANESs used. For example, only 3% of men in this study had a total PSA value greater than or equal to 4.0 ng/mL, which was their a priori definition of elevated PSA. Although their multivariable model adjusted for age, body mass index, race/ethnicity, health insurance, average hours of sleep per night, and months on the current job, it did not consider other potential covariables, some of which are available through NHANES. For example, NHANES has been used to show an association between altered PSA levels and some medications, diet, and physical activity (4–7). It is possible to hypothesize that nonmedical determinants of health, such as opportunities to exercise, personal dietary preferences, and the availability of healthy eating choices, could vary based on whether a man is a day worker vs. shiftworker.

In contrast with the potential impact of shiftwork on PSA values, conclusions regarding increased risk of developing prostate cancer could not be tested by the authors' study design. NHANES is limited regarding information about surveyed men who are subsequently diagnosed with or treated for prostate cancer, so it is not possible to know the number of men who had concerning PSA values and developed prostate cancer. Furthermore, it is important to be mindful of the limitations of using a survey such as NHANES, which was not designed with the primary endpoint of PSA dynamics or prostate cancer, to draw conclusions about prostate cancer risk. Researchers have analyzed NHANES data from similar years only to reach conflicting conclusions, as seen when the 2001 to 2004 vs 2003 to 2006 datasets were used to examine the effects of exercise on PSA (6,7). Although conclusions regarding prostate cancer risk cannot be made with these data, we do agree with the authors that larger studies are needed to further elucidate the effects of shiftwork on PSA and prostate carcinogenesis.

Although NHANES data have inherent limitations, the survey is a useful and efficient method of hypothesis generation. Flynn-Evans and colleagues have provided important evidence in support of the potential link between circadian disruption and elevated PSA levels. Clearly there is a need for further exploration. As noted in their article, the existing literature on shiftwork and prostate cancer is limited by largely retrospective studies, small sample sizes, and few prostate cancer events. Cooperative, prospective, longitudinal cohort studies will be needed to provide the necessary statistical power and clinically meaningful endpoints (prostate cancer diagnoses, morbidity, and mortality) regarding circadian rhythms and prostate cancer carcinogenesis. If circadian rhythms and prostate cancer are examined in greater detail, it may help usher in a more nuanced approach to prostate cancer screening.

The recent debates regarding the known risks and potential benefits of prostate cancer screening have shifted the expectations about PSA testing and the information needed for shared decision making (8–11). A "grand unified theory" of factors affecting prostate cancer, encapsulating both modifiable and nonmodifiable risks, may allow for a more precise and holistic approach to prostate cancer screening. In addition to age, race, and family history, a novel predictive nomogram could include factors from domains such as physiology (PSA, percentage free PSA, body mass index, serum testosterone); lifestyle (sleep hygiene/occupation, exercise); nutrition (diet content and caloric intake); and medical conditions (prescription and over-the-counter medications, comorbidities) to produce both a risk score for prostate cancer as well an estimate of the likelihood that a man would live 10 to 15 years and thus potentially benefit from further screening or treatment (12). The United States Preventive Services Task

Force grade D recommendation for prostate cancer screening was intended to inform decisions about population-level screening for men without an increased risk of prostate cancer (13). Flynn-Evans and colleagues, as well as other investigators studying NHANES, have again reminded us that we do not fully understand many of the components that may influence a man's PSA level or his risk of developing prostate cancer (14). Additional research into modifiable and nonmodifiable prostate cancer risk factors is needed, as is the continued use of shared decision making and personalized counseling for this important aspect of men's health.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin*. 2013;63(1):11–30.
2. Flynn-Evans EE, Mucci L, Stevens RG, Lockley SW. Shiftwork and prostate specific antigen in the National Health and Nutrition Examination Survey. *J Natl Cancer Inst*. 2013;105(17):1292–1297.
3. Straif K, Baan R, Grosse Y, et al. Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol*. 2007;8(12):1065–1066.
4. van Wijngaarden E, Singer EA, Palapattu GS. Prostate-specific antigen levels in relation to cadmium exposure and zinc intake: results from the 2001–2002 National Health and Nutrition Examination Survey. *Prostate*. 2008;68(2):122–128.
5. Singer EA, Palapattu GS, van Wijngaarden E. Prostate-specific antigen levels in relation to consumption of nonsteroidal anti-inflammatory drugs and acetaminophen: results from the 2001–2002 National Health and Nutrition Examination Survey. *Cancer*. 2008;113(8):2053–2057.
6. Loprinzi PD, Kohli M. Effect of physical activity and sedentary behavior on serum prostate-specific antigen concentrations: results from the National Health and Nutrition Examination Survey (NHANES), 2003–2006. *Mayo Clin Proc*. 2013;88(1):11–21.
7. Parekh N, Lin Y, Marcella S, Kant AK, Lu-Yao G. Associations of lifestyle and physiologic factors with prostate-specific antigen concentrations: evidence from the National Health and Nutrition Examination Survey (2001–2004). *Cancer Epidemiol Biomarkers Prev*. 2008;17(9):2467–2472.
8. Singer EA, Kaushal A, Turkbey B, Couvillon A, Pinto PA, Parnes HL. Active surveillance for prostate cancer: past, present and future. *Curr Opin Oncol*. 2012;24(3):243–250.
9. Carter HB, Partin AW, Walsh PC, et al. Gleason score 6 adenocarcinoma: should it be labeled as cancer? *J Clin Oncol*. 2012;30(35):4294–4296.
10. Nam RK, Oliver TK, Vickers AJ, et al. Prostate-specific antigen test for prostate cancer screening: American Society of Clinical Oncology provisional clinical opinion. *J Oncol Pract*. 2012;8(5):315–317.
11. Singer EA, Penson DF, Palapattu GS. Prostate-specific antigen screening for prostate cancer: the added challenges of obesity. *J Hosp Ethics*. 2011;2(2):16–22.
12. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. *J Urol*. 2013;190(2)419–426.
13. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157(2):120–34.
14. Raghavan D. PSA: please stop agonizing (over prostate-specific antigen interpretation). *Mayo Clin Proc*. 2013;88(1):1–3.

Funding

This work is supported by a grant from the National Cancer Institute (P30CA072720).

Note

The authors have no conflicts of interest to disclose.

Affiliations of authors: Urologic Oncology, Department of Surgery (EAS) and Medical Oncology, Department of Medicine (RSD), Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ.

DOI:10.1093/jnci/djt220
Advance Access publication August 15, 2013

Potential to Link Dietary Patterns in the Food Supply and Populations to Health

Rachel Ballard-Barbash, Susan M. Krebs-Smith, Marian L. Neuhouser

Correspondence to: Rachel Ballard-Barbash, MD, Applied Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, NCI Shady Grove, Rm 3E406, 9609 Medical Center Dr, MSC 9762, Bethesda, MD 20892–9762 (e-mail: barbashr@mail.nih.gov).

The article by Arem et al. (1) on the association of dietary patterns as defined by the Healthy Eating Index (HEI)–2005 and pancreatic cancer contributes to a rapidly evolving literature on the association of dietary patterns with multiple disease outcomes. In summarizing the global literature on diet and cancer, the 2007 World Cancer Research Fund report concluded that the limited number of studies on dietary patterns and cancer outcomes prevented any conclusions on this topic and identified the need for more research to better define dietary patterns and examine their potential association with cancer (2). The study by Arem et al. is a well-designed and well-executed study that reflects efforts to advance research on dietary patterns. Such research is intended to address issues that have been well documented in nutrient or individual food or food group research, and these issues are clearly detailed by Arem and colleagues in their introduction: difficulty in disentangling the multicollinearity of nutrients and individual foods; inability to capture biologic interactions among different nutrients, foods, or nonnutritive components of diet; and improved distinction between individuals in terms of overall dietary patterns and quality at extremes of the distribution of a dietary pattern measure. In addition, just as foods and nutrients have been documented to be highly correlated, other health behaviors, such as energy intake and weight, alcohol intake, physical activity, and tobacco use, have been documented to be correlated with dietary patterns (3), as clearly demonstrated in the examination of