The concerning methodology in the study by Finkle et al. is the authors’ use of men taking PDE5-Is as a purported benign control group. PDE5-Is were originally developed as a treatment for cardiovascular diseases such as angina [3] and are currently approved by the US Food and Drug Administration as treatments for pulmonary hypertension. They also have known cardiovascular benefits [3] including findings from a recent randomized placebo-controlled trial that showed PDE5-I use in heart failure patients was associated with improvements in left ventricular ejection fraction, diastolic function, exercise tolerance, and overall clinical condition [4]. The potential cardiovascular benefits of PDE5-Is may have contributed to the differences in MI rates found in the study, and this limitation was not discussed in the publication. Neither Vigen et al. nor Finkle et al. evaluated serum testosterone levels after beginning TST. Consequently, it is difficult to ascertain whether these men were compliant with the medication or even responded to therapy.

Multiple previous studies have found that low testosterone is associated with an increased risk of cardiovascular disease [5] and that TST is associated with a reduction in mortality in hypogonadal men [6]. The increased rate of MIs in the TST cohort of the Finkle et al. study may have been the result of preexisting cardiovascular risk factors present within the low testosterone group that were not present in the PDE5-I group. As mentioned previously, it is also possible that PDE5-I use in the so-called control group provided some cardiovascular-protective effect.

The question now becomes how these results affect clinical practice. There is clearly a need for large prospective placebo-controlled randomized trials such as the Women’s Health Initiative to determine definitively the cardiovascular risks of TST. However, until this occurs, physicians should consider adding to their patient counseling a discussion about putative cardiovascular risks associated with TST including the limitations of the current studies. The recent publications described represent an opportunity for well-informed physicians to have thorough discussions with their patients about the risks and benefits of TST and, if prescribed, to enter into an agreement with the patient to enable appropriate oversight during treatment.

Conflicts of interest: Larry I. Lipshultz participates in clinical trials and is a consultant and speaker for both Auxilium and Endo. The other authors have nothing to disclose.

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Re: Global Effects of Smoking, of Quitting, and of Taxing Tobacco
Jha P, Peto R.

Experts’ summary:
In this outstanding review, Jha et al. [1] summarize the reasons and effects of smoking on global health, highlighting the benefits of smoking cessation and discussing reasons affecting tobacco consumption. Still approximately 50% and 10% of young men and women, respectively, take up smoking with relatively few ever stopping. This has led to a steady increase in the annual tobacco-attributable death toll. Interestingly, smoking patterns have changed over the last century. Initially, smoking rates increased substantially in many high-income countries, followed by increasing rates in the middle- and low-income countries. In addition increasing rates of daily cigarette consumption were observed during the last century with comparable changes according to the income classes.

The authors found that in middle age patients, mortality rates among cigarette smokers were 2–3 fold increased compared to never smokers. Throughout adulthood this likely leads to a reduction in life span by an average of about 10 years, which mainly impairs the life expectancy of those killed by smoking in the middle age, as those otherwise might have had a life expectancy of decades. In contrast, smoking cessation increases life expectancy. Tobacco taxes and consumption are clearly inversely related especially in low-income and less educated groups. Moreover, banning advertisement may further help decrease overall consumption. Although most former smokers quit unaided, physician support or multimedia based counseling can increase the likelihood of successful quitting. The authors estimated that decreasing smoking prevalence could prevent several tens of millions of tobacco-attributable deaths during the next few decades.

Experts’ comments:
Tobacco use is a major preventable cause of premature death and disease worldwide. Smoking is the best-established
individually amenable risk factor for development of over 18 types of cancer and cause of death of several non-malignant diseases. There is little doubt that reducing the morbidity and mortality from tobacco use remains one of the most important public health challenges of the last and current century. To achieve this, federal and institutional non-profit tobacco-control programs have tried to promote smoking-cessation and prevent initiation of smoking. Various approaches such as price (eg, tax increase) and non-price (eg, advertisement regulations) interventions in association with a better general education are used to inform about the harms and detrimental effects of smoking [1]. However, despite seemingly good smoking cessation success rates over the past decades, still the number of daily smokers and the number of cigarettes consumed worldwide significantly increased during the same period, confirming that the global tobacco market continued to grow. In addition, as the majority of smoking-related diseases (eg, cancer, cardiovascular diseases, cerebrovascular diseases, chronic lung disease, etc.) are diseases of the middle aged and elderly, people starting smoking at an early age are more likely to experience one of those conditions. Finally, smokers today have a much higher risk of developing smoking-related diseases than did smokers in the past, probably because of changes in the design and composition of cigarettes over time.

Over the past decades our understanding of the biologic mechanisms behind smoking-related disease emergence significantly improved. However, the evidence regarding the effects of cigarette smoking and other tobacco use on subsequent prognosis is by no means complete [2]. The socio-biological epidemiology of smoking-related diseases is rather complex with substantial variability between individuals, ethnicities, genders, inherent genetic and environmental impacts, as well as other social and lifestyle factors. In addition, it is important to notice that smoking is not just smoking! Several previous studies investigating the effects of smoking on disease outcomes and prognosis faced important methodological barriers. While most studies analyze the impact of cigarette smoking, other tobacco products (eg, cigars, pipes, and tobacco chewing) and different forms of tobacco exposure (eg, second-hand smoking and occupational exposure) are excluded. Smoking assessment is usually based on self-reported patient history and therefore subject to recall bias. Biochemical verification of the smoking status may be a goal for future investigations. Another important issue is the problem of the correct quantification of tobacco exposure. To quantify cumulative cigarette smoking exposure, the medical convention has favored pack-years. However, that measure assumes that duration and intensity (packs per day) have equivalent effects [2]. Growing evidence, however, suggests that this is not the case. Recently published studies in different cancer entities found clear dose–response relationships between smoking amount and duration as well as inverse relationships with time since smoking cessation [3–8]. Thus, at present, current research findings are difficult to compare between different groups or patient subpopulations.

The review article of Jha et al. is another plea to all healthcare practitioners to support smoking cessation efforts since this may increase the likelihood of successful quitting. Anyway, how does smoking affect us as urologists? The effects of smoking are apparently associated with several urological disorders. Smoking is an important risk factor for development of all major urological carcinomas including prostate [9], bladder [3–8] and renal cell [10] carcinoma, and is likely to effect oncological outcomes [3–8]. In addition, smoking leads to erectile dysfunction, and, although there is heterogeneous evidence, it seems to be associated with lower urinary tract symptoms including benign prostate hyperplasia, chronic prostatitis and chronic pelvic pain syndrome [11,12]. Thus, it should not be only our obligation to counsel our patients regarding the detrimental effects of smoking, but also assist our patients in smoking cessation attempts. For many patients cancer diagnosis represents a teachable moment to successfully quit smoking. In addition, urological patients are willing to quit smoking with some education and help of their physicians [13]. Although studies have shown that smoking cessation at time of cancer diagnosis may cause better outcomes than continuing smoking, still, our goal must be prevailing our patients on stopping smoking earliest possible. While brief physician encounters may provide an impetus for a patient to attempt to quit smoking, long-term cessation rates are improved by various medical and behavioral supports for smoking cessation, but only too few patients are offered any intervention to aid in cessation [14,15]. For example, nicotine replacement therapy, the use of bupropion or nortriptyline and/or, as an adjunct to medical therapy, individual and group counseling may help patients to achieve successful smoking cessation [15]. Research regarding the effects of smoking needs to continue to improve our understanding and answer many unanswered questions in the future. However, we as urologists must accept the responsibility and better counsel our patients about the detrimental effects of smoking and assist them in cessation efforts to improve their health and life today.

Conflicts of interest: The authors have nothing to disclose.

References

Re: Procalcitonin as a Diagnostic Marker for Sepsis: A Systematic Review and Meta-analysis

Wacker C, Prkno A, Brunkhorst FM, Schlattmann P

Experts' summary:
The authors evaluated the role of serum procalcitonin (PCT) as a diagnostic marker for sepsis and noninfectious systemic inflammatory response syndromes (SIRS). They performed a meta-analysis including 3244 critically ill patients of whom 1863 (57%) had sepsis and 1381 (43%) SIRS of noninfectious origin. In a subcohort of 1173 sepsis patients, severity of illness (sepsis, severe sepsis, septic shock) was classified. The sites and the sources of infection differed, and most patients were hospitalized in intensive care units. Most studies used a quantitative manual PCT assay, and 73% of the studies met currently available quality standards for PCT determination.

The cut-off for PCT concentrations differed between 0.5 ng/ml and 2.0 ng/ml, with a median of 1.1 ng/ml. Pooled sensitivity for testing was 0.77 (95% confidence interval [CI], 0.72–0.81), and pooled specificity was 0.79 (95% CI, 0.74–0.84). The area under the receiver operating characteristic curve was 0.85 (95% CI, 0.81–0.88). The authors concluded that the analysis of PCT can differentiate between sepsis and noninfectious SIRS, although due to initial antibiotic therapy, bacteremia occurs in only 30% of patients with sepsis. Unfortunately, although the best cut-off is not really settled due to the absence of a real threshold effect, it is suggested that a value between 1 ng/ml and 2 ng/ml may allow for discrimination between sepsis and other inflammatory diseases.

Experts' comments:
Urosepsis, defined as sepsis with clear infectious origin, is diagnosed according to clear clinical, laboratory, and organ dysfunction parameters [1]. Unfortunately, besides PCT, other mediators and molecules of the host response to infection, especially C-reactive protein, have been investigated without a breakthrough, as Wacker et al. note. In particular, the prediction of the presence of bacteremia and bacterial load in patients with febrile urinary tract infections (UTIs) would help identify inflammatory status with regard to diagnosing bacteremia as early as possible [2]. Using a PCT level of >0.25 ng/ml as a cut point to predict bacteremia in febrile UTIs [2], the sensitivity and specificity were calculated as 0.95 (95% CI, 0.89–0.98) and 0.50 (95% CI, 0.46–0.55) as criteria to initiate blood cultures in this clinical setting. In this study, the measurement of erythrocyte sedimentation rate and C-reactive protein was not helpful in predicting bacteremia. Considering these results and the data of the presented meta-analysis for sepsis, there is evidence for the significant role of PCT evaluation in a clinical setting to diagnose severely ill, infectious patients with febrile UTIs.

Conflicts of interest: The authors have nothing to disclose.

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