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Fall 2001

# Psychosocial Stress and Prostate Cancer: A Theoretical Model

Gary L. Ellison

*National Cancer Institute, ellisong@mail.nih.gov*

Ann L. Coker

*University of South Carolina - Columbia, ann.coker@uky.edu*

James R. Hebert

*University of South Carolina, jhebert@sc.edu*

Maureen Sanderson

*Meharry Medical College, msanderson@mmc.edu*

Charmaine D. Royal

*Duke University, charmaine.royal@duke.edu*

*See next page for additional authors*

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## Repository Citation

Ellison, Gary L.; Coker, Ann L.; Hebert, James R.; Sanderson, Maureen; Royal, Charmaine D.; and Weinrich, Sally P., "Psychosocial Stress and Prostate Cancer: A Theoretical Model" (2001). *CRVAW Faculty Journal Articles*. 101.  
[https://uknowledge.uky.edu/crvaw\\_facpub/101](https://uknowledge.uky.edu/crvaw_facpub/101)

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**Authors**

Gary L. Ellison, Ann L. Coker, James R. Hebert, Maureen Sanderson, Charmaine D. Royal, and Sally P. Weinrich

**Psychosocial Stress and Prostate Cancer: A Theoretical Model****Notes/Citation Information**

Published in *Ethnicity & Disease*, v. 11, p. 484-495.

Dr. Ann Coker had not been a faculty member of the University of Kentucky at the time of publication.

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## Psychosocial Stress and Prostate Cancer: A Theoretical Model

Gary L. Ellison, PhD; Ann L. Coker, PhD; James R. Hebert, ScD;  
Maureen Sanderson, PhD; Charmaine D. Royal, PhD; Sally P. Weinrich, PhD

African-American men are more likely to develop and die from prostate cancer than are European-American men; yet, factors responsible for the racial disparity in incidence and mortality have not been elucidated. Socioeconomic disadvantage is more prevalent among African-American than among European-American men. Socioeconomic disadvantage can lead to psychosocial stress and may be linked to negative lifestyle behaviors. Regardless of socioeconomic position, African-American men routinely experience racism-induced stress. We propose a theoretical framework for an association between psychosocial stress and prostate cancer. Within the context of history and culture, we further propose that psychosocial stress may partially explain the variable incidence of prostate cancer between these diverse groups. Psychosocial stress may negatively impact the immune system leaving the individual susceptible to malignancies. Behavioral responses to psychosocial stress are amenable to change. If psychosocial stress is found to negatively impact prostate cancer risk, interventions may be designed to modify reactions to environmental demands. (*Ethn Dis.* 2001;11:484-495)

**Key Words:** African American, Prostatic Neoplasms, Psychological Stress, Race

### Introduction

African-American men have a prostate cancer incidence rate 63 percent higher than European-American men and are more than twice as likely to die from the disease.<sup>1</sup> On average, African Americans are at a socioeconomic disadvantage when compared to European Americans. For example, poverty rates for African Americans are over three times those for European Americans.<sup>2</sup> Pov-

erty, alone, does not explain the racial disparity in incidence of prostate cancer. However, it sets the context in which social, psychological, and behavioral factors can be identified.<sup>3</sup> Economic disadvantage limits one's ability to access resources, can cause psychosocial stress, and may be linked to negative behaviors such as cigarette smoking, alcohol use, and physical inactivity, which can affect health and modulate stress through a variety of mechanisms. Moreover, individuals in society who are more economically robust are exposed to a variety of resources that may buffer the effects of social and environmental stress.<sup>4</sup> Thus, socioeconomic status (SES) may be considered a measure of coping resources. Historically African-American men, regardless of socioeconomic position, have been exposed to racism, which can be an added source of psychosocial stress.<sup>5</sup> Racial disparities in health must be examined within the context

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From the University of South Carolina, School of Public Health, Department of Epidemiology and Biostatistics, Columbia, South Carolina (GLE, ALC, JRH, SPW, MS); National Human Genome Center at Howard University, Washington, DC (CDR); University of Louisville Health Sciences Center, School of Nursing, Louisville, Kentucky (SPW).

Address correspondence and reprint requests to Gary L. Ellison, PhD; Cancer Prevention Fellowship Program; Division of Cancer Prevention, NCI; Executive Plaza South, Suite T-41; 6120 Executive Boulevard, MSC-7105; Bethesda, MD 20892-7105. 301-496-8640; 301-402-4863 (fax); ge48v@nih.gov

of the history and culture that shape the lives of African Americans. This observation has been most notable with studies investigating the racial disparities in high blood pressure prevalence.<sup>3,6</sup> James et al found that high John Henryism, a strong predisposition to cope actively with psychosocial stressors in one's environment, did not increase high blood pressure prevalence. However, when combined with limited economic resources, the prevalence was increased among African Americans.<sup>6</sup> This association did not hold true for European Americans. In other words, among African Americans, a strong desire to achieve what is valued in American society was thwarted by limited economic resources and proved to be stressful; this was not the case among European Americans.

In this manuscript, we develop and present a theoretical model for an association between psychosocial stress and prostate cancer and suggest that stress may explain the higher incidence among African-American, relative to European-American men. We begin by presenting the epidemiology of prostate cancer, in which relevant risk factors are discussed, followed by a theoretical framework that chronicles the psychological, social, and biological rationales for this association.

### **Epidemiology of Prostate Cancer**

Prostate cancer is the most frequently diagnosed cancer in the United States (US) and the second leading cause of cancer deaths among men.<sup>7</sup> A clear feature of prostate cancer is the disproportionate incidence and mortality rates among African-American men relative to men in other US racial groups. From 1988 to 1992, the age-adjusted incidence was 34 percent higher among African-American men compared to European-American men (180.6 vs 134.7 per 100,000, respectively) and mortality was more than twice as high (53.7 vs 24.1 per 100,000, respectively).<sup>1</sup> Even among men diagnosed at the same stage, the ratio of

African-American to European-American age-adjusted mortality rates range from 1.9 for men diagnosed at local stages to 2.4 for men diagnosed at distant stages.<sup>8</sup> Despite widely variable incidence rates, the prevalence of latent prostate cancer, defined as those lesions found during autopsy or surgical removal of the prostate, is similar around the world.<sup>9</sup> In addition, men migrating from countries where the incidence of prostate cancer is low assume the incidence rate of the host country.<sup>10</sup> Given the similar prevalence of latent prostate cancer in low- and high-risk countries, and the increasing incidence of prostate cancer resulting from migration, social and/or environmental factors may play an important role in promoting carcinogenesis.<sup>9,11</sup>

There are few known modifiable risk factors for prostate cancer, and factors responsible for the higher incidence among African-American men have not been identified. Age is the strongest risk factor for prostate cancer, and the occurrence of prostate cancer before 50 years of age is rare.<sup>1,10</sup> The genetic characteristics of prostate cancer are unclear. A genome-wide search provided evidence for prostate cancer susceptibility on chromosome 1 (HPC 1).<sup>12</sup> Family history of prostate cancer, which combines genetic risks and shared environmental experiences, has been associated with a two- to three-fold increase in prostate cancer risk in case-control studies.<sup>13-18</sup> Cohort studies have consistently reported a 65% to 70% increase in prostate cancer risk in sons of fathers diagnosed with prostate cancer.<sup>19,20</sup> These associations are homogeneous across cultures and thus do not explain the increased incidence among African-American men.

Studies investigating the effects of lifestyle behaviors, such as cigarette smoking, alcohol consumption, physical activity, and diet on the risk for prostate cancer have provided inconsistent results. Some case-control studies found an increased risk of prostate cancer for greater smoking

duration<sup>21,22</sup> while others found no association.<sup>23,24</sup> Prospective studies have reported a higher incidence of prostate cancer due to smoking.<sup>25,26</sup> Similar prostate cancer incidence and mortality rates due to smoking have been observed between African-American and European-American men.<sup>25,27,28</sup>

Few studies have investigated prostate cancer risk associated with alcohol consumption. A population-based case-control study reported a strong risk of prostate cancer associated with consuming large quantities of alcohol, independent of smoking.<sup>29</sup> Other case-control studies<sup>23,30</sup> and cohort studies<sup>25,31</sup> have not reported a statistically significant association between alcohol use and prostate cancer.

Physical activity is hypothesized to reduce the risk of prostate cancer. However, results of recent epidemiological studies have been equivocal. Leisure and occupational activities have been found to reduce the risk of prostate cancer in two case-control studies,<sup>32,33</sup> while physical activity was not associated in another case-control study.<sup>34</sup> Prospective studies have been equally inconsistent, with one study reporting no association between prostate cancer and physical activity,<sup>35</sup> while others reported a reduction in risk for prostate cancer at strenuous levels of physical activity.<sup>36,37</sup> Again, these studies do not explain the racial disparity in incidence of prostate cancer.

Several case-control studies have found an increased risk of prostate cancer to be associated with a diet high in fat,<sup>34,38–44</sup> but cohort studies have been inconsistent in affirming this finding.<sup>45,46</sup> Few studies of diet and prostate cancer risk have included a sufficient number of African-American men to study this association. However, one large case-control study, which included several ethnic groups concluded that a diet high in saturated fat accounted for approximately 10 percent of the difference in prostate cancer incidence between African-American and European-American men,<sup>34</sup>

suggesting that other factors, perhaps not yet measured, are responsible for the higher incidence among African Americans.

Results of studies addressing the effect of SES on the incidence of prostate cancer have been as inconsistent as the operational definition of SES itself. Individuals with 13 or more years of education had an increased risk of prostate cancer compared to men with zero to six years in both African-American (OR = 2.3; CI = 1.1–5.2) and European-American (OR = 1.5; CI = 1.2–1.9) men in a hospital-based case-control study.<sup>32</sup> Studies that used ecological measures of SES suggest that racial differences in incidence rates persisted even after accounting for SES.<sup>47–50</sup>

### **Psychological and Biological Stress Responses to Environmental Demands**

Psychosocial stress results when environmental demands tax or exceed the adaptive capacity of an individual, causing psychological and biological changes that may place persons at risk for disease.<sup>51</sup> Lazarus and Folkman developed a model of psychological stress that described how environmental demands could produce biological stress responses.<sup>52</sup> When confronted with environmental demands, individuals evaluate whether the demands are a threat and whether resources are available to cope with the demands. Individuals who evaluate these demands as threatening, and lack resources to cope adequately with them, perceive themselves as stressed.<sup>51,52</sup> Thus, individual appraisals of environmental demands determine the magnitude of psychological reactions and their resulting biological responses.<sup>53</sup>

The biological response to stressful stimuli involves the activation of two inter-related systems: the sympathetic-adrenal medullary system (SAM), and the hypothalamic-pituitary-adrenocortical (HPA) axis.<sup>51,54</sup> Activation of SAM is designed to assist the organism in dealing with acutely stressful situations. The adrenal medulla and/or sym-

pathetic nerve endings release epinephrine and norepinephrine, catecholamine hormones.<sup>51</sup> These hormones are released in an effort to maintain normal physiological functioning and to facilitate adaptive behavior of the organism when stressed.<sup>51,54,55</sup> Baum et al suggested that, in emergency situations, epinephrine is released to provide a biological advantage to the organism, and thus allow it to respond more rapidly to danger.<sup>54</sup> This physiological response to stress may be brief because the organism adapted quickly or the stressor itself was acute. Prolonged elevation of catecholamines may either enhance<sup>53</sup> or have a damaging effect on cellular immunity.<sup>54</sup>

In situations where adaptation of the organism is not achieved, as in the case of prolonged or chronic stress, the result is massive release of corticosteroids from the HPA axis.<sup>55</sup> The HPA axis is activated by the secretion of the corticotrophic releasing hormone (CRH) by the hypothalamus. CRH stimulates the anterior pituitary gland, which secretes adrenocorticotrophic hormones (ACTH). ACTH activates the adrenal cortex to secrete corticosteroids.<sup>53,55</sup> HPA axis activity was the basis of Selye's general adaptation syndrome (GAS), for which he defined three stages.<sup>56</sup> During the alarm stage, large amounts of corticosteroids are released to meet the initial demands of the stressor. The stage of resistance involves adaptation to the stressor, but output of corticosteroids remains high. The last stage, exhaustion, occurs during prolonged exposure to the stressor, rendering the HPA axis unable to mount a stress response; causing a breakdown of tissues and organs. In contrast to the effects of sympathetic activity and circulating epinephrine, corticosteroids (eg, cortisol in humans) may exert harmful effects on immune function, limiting the ability of the immune system to fight virally infected and cancerous cells.<sup>53</sup>

## Stress and Immune Functioning

Psychosocial stress causes a series of physiological changes and involves activation of a complex behavioral-neural-endocrine system.<sup>57</sup> The presence of corticosteroid hormones, released via the HPA axis, are increased in plasma as a result of chronic stress and a sustained increase in these hormones has an immunosuppressive effect.<sup>58,59</sup> Experimental models have demonstrated stress-induced corticosteroid hormone production resulting in a decrease in circulating lymphocytes and natural killer cell cytotoxicity.<sup>60</sup> Natural killer cells are important aspects of the immune system that are capable of recognizing and destroying newly forming tumor cells.<sup>61</sup> Consequently, environmental stressors perceived as severe in humans consistently have been related to increased urinary corticosteroid concentration<sup>62</sup> and low, natural-killer cell cytotoxicity.<sup>63,64</sup> The function of this behavioral-neural-endocrine system is to regulate immune responsiveness. Prolonged exposure to psychosocial stress diminishes that function.<sup>65,66</sup> This stress-mediated immunological impairment has a profound effect on cells and tissues and renders the individual susceptible to a number of diseases, including malignancies.<sup>57,67,68</sup>

## Stress and Cancer

Animal models have provided evidence that stress affects tumor growth and development.<sup>58,67,68</sup> Stress-induced tumor growth in animals also may be influenced by stress chronicity and coping. An experiment designed to assess the role of chronic stress on tumor growth and development found that a single episode of 60 inescapable six-second shocks at one-minute intervals inhibited tumor growth and development compared to these shocks given on five and 10 consecutive days, respectively.<sup>69</sup> This result was contrary to expectation. Another experiment assessed the health effects of coping with stress.<sup>69</sup> Mice were placed in

three identical Plexiglas boxes where they were exposed to inescapable electrical shock stress, escapable shock stress, and no shock stress. Mice that were exposed to inescapable shock formed tumors earlier and had larger tumors than mice that were able to escape the shock or mice that did not receive shock.<sup>69</sup> Thus, escaping the physical stressor as a means of coping inhibited tumor growth; mice that could escape controlled the physiological effects of shock. Animal studies are a useful guide to studies in humans, but extrapolation from animals to humans is of limited value.

Several epidemiologic studies have demonstrated an association between stressful life events and cancers of the lung,<sup>70</sup> breast,<sup>71–74</sup> and colon.<sup>75–78</sup> In a study of stress and its relationship to lung cancer, the proportion of men with malignant pulmonary disease and high scores of recent loss (eg, loss of a job or death of a spouse, parent, or sibling) was significantly greater than the proportion without cancer having high loss scores (68% vs 33% for any type of loss;  $P < .001$ ).<sup>70</sup>

Cancers of both the breast and prostate are believed to be hormone-responsive,<sup>79</sup> and the findings from breast cancer studies may be relevant to prostate cancer. The incidence of psychosocial stress, specifically the death of a close friend, was higher among 1,596 breast cancer patients than among 567 controls ( $P < .05$ ) in a British study of women presenting to a breast clinic for suspicious lumps.<sup>71</sup> Women with breast cancer who experienced the death of a close friend also perceived these events as more upsetting as compared to women without breast cancer.<sup>71</sup> In a later study, this research group found that women who experienced a major stressful life event were more likely to develop breast cancer than were women who did not experience the event.<sup>72</sup> The risk was even higher for women who were unable to externalize their emotions as a means of coping. In a matched case-control study, containing 87 matched pairs, a five-

fold increase in breast cancer risk was found among women reporting an important emotional loss prior to breast cancer diagnosis.<sup>73</sup> However, breast cancer patients were interviewed after surgery for breast cancer, which may have differentially biased their reporting of stress. A London case-control study with 41 breast cancer cases and 78 controls reported a high risk of breast cancer (OR = 11.6; 95% CI = 3.1–43.7) among women who experienced a threatening life event.<sup>74</sup> Women with breast cancer in this study perceived their events as great threats (OR = 7.8; 95% CI = 2.31–21.65). In addition, women who coped with adverse events by confronting them or focusing on them were more at risk of developing breast cancer (OR = 3.11; 95% CI = 1.18–8.19).

The relation of stressful life events to colon and colorectal cancer also has been investigated in epidemiologic studies.<sup>75–78</sup> In an early study of 40 colorectal and 14 gastric cancer cases, and ten normal controls, gastric cancer patients had significantly higher life change scores ( $P < .05$ ) in the two years prior to the onset of illness symptoms.<sup>78</sup> Life change in this study was assessed using the Social Readjustment Rating Scale<sup>79</sup> that measures the intensity and duration necessary to accommodate various desirable or undesirable life events (eg, marriage, death of a spouse, etc).

Death of a family member or a major family illness (OR = 1.24; 95% CI = 1.05–1.47), major family problems (OR = 1.32; 95% CI = 1.11–1.57), and major work problems (OR = 2.24; 95% CI = 1.60–3.15) were significantly more common among colorectal cancer cases compared to the controls in an Australian population-based case-control study.<sup>77</sup> Both male and female colorectal cancer patients reported being significantly more upset with their recent life events than did their controls (OR = 1.86; 95% CI = 1.46–2.37). Recent life events were one of four categories of events (death of a family member or major family

illness, major family problems, major work problems, or other problems) experienced over the five years prior to diagnosis for cancer cases, and five years prior to the interview for controls. In addition to population-based controls, this study included hospital controls (admitted for surgery) to reduce the possibility of recall bias. The magnitude of association between colorectal cases and hospital-based controls was similar to that observed when population-based controls were the reference group. Similar to the findings of Kune et al,<sup>77</sup> results from a Swedish population-based case-control study demonstrated a large relative risk for colorectal cancer cases for those who had work-related problems over the ten years prior to diagnosis, as compared to controls (OR = 5.5; 95% CI = 2.3–23.5).<sup>71</sup> In addition, change of residence (OR = 2.8; 95% CI = 1.1–7.1) and death of a spouse (OR = 1.5; 95% CI = 1.0–2.3) were significantly associated with the development of colorectal cancer in this study.

Karasek et al (1981, 1988) postulated that psychological strain results when individuals lack sufficient control over their work situation to adequately deal with the level of demands placed on them.<sup>81,82</sup> These individuals experienced prolonged or chronic stress, resulting in increased corticosteroid production via the HPA axis. To follow up on work-related stress, Courtney et al found a small increase in colon cancer risk for the highest compared to the lowest tertile of job control (OR = 1.3; 95% CI = 1.0–1.6) in an age-, sex-, and neighborhood-matched case-control study.<sup>76</sup> No association was found between risk and job demands. The effect of job control was independent of job demands, and may have the same physiological consequences of chronic stress.

Few studies have investigated psychosocial risk factors for prostate cancer. The few studies addressing psychosocial factors have focused on marital status, which may

be a crude measure of stress or social support. Newell et al found a lower risk of prostate cancer for all ages of single, separated, and divorced European Americans when compared to married European Americans, and a higher risk among single African Americans (aged 55 to 74) compared to their married counterparts.<sup>83</sup> A hospital-based case-control study, composed of 1,162 prostate cancer cases and 3,124 age-matched controls, found a significant reduction in risk of prostate cancer for never-married compared to married African-American men (OR = 0.3; 95% CI = 0.1–0.9).<sup>32</sup> Reduction in risk was found among never-married European-American men (OR = 0.7; 95% CI = 0.5–1.1); however, chance may explain the observed results. Counter to expectation, Johansen and Olsen did not find an increase in the observed incidence of prostate cancer among those who experienced losing a child to cancer.<sup>84</sup> This study of stress and the incidence rates of several cancers concluded that the human species is highly adaptable to stress. However, the psychological impact of the stressor was excluded from this study; the manner in which stress is perceived and coped with is an important indicator of the stress response.

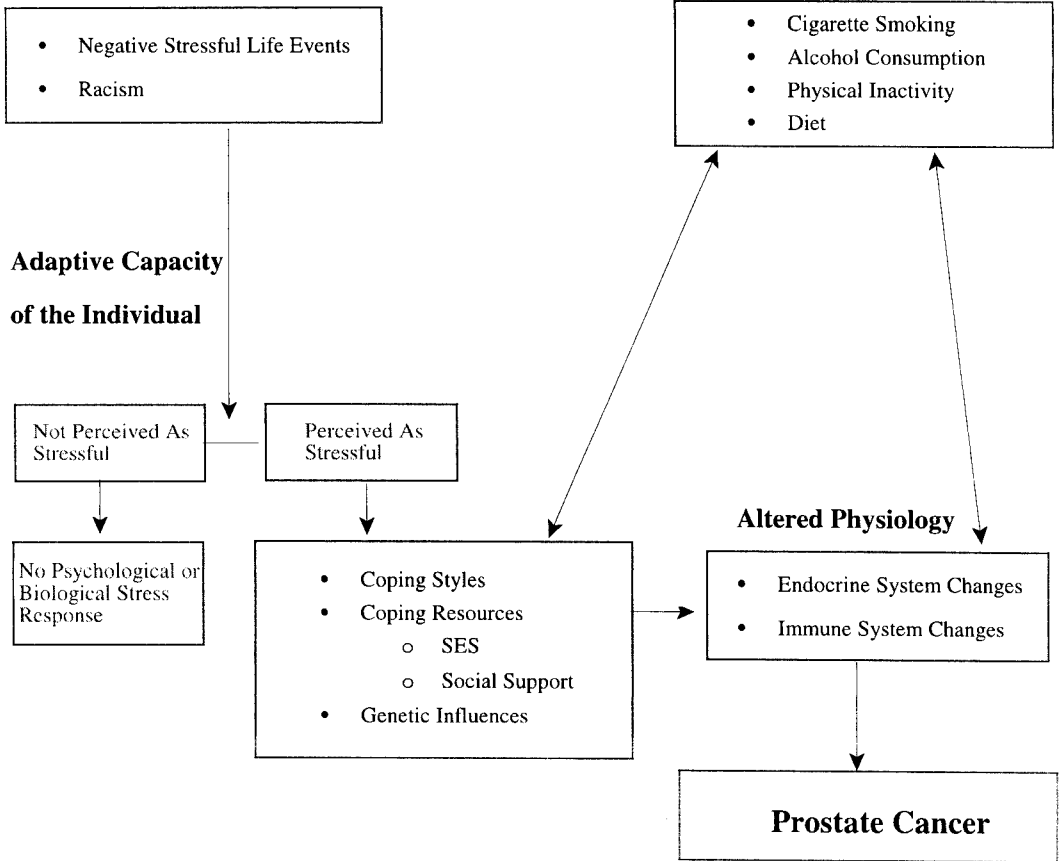
### Model of Stress and Prostate Cancer

Psychosocial stress involves a relationship between an individual and the environment that is appraised as taxing or exceeding his or her resources.<sup>52</sup> Repeated episodes of stress may leave the immune system ineffective and render the individual susceptible to malignancies.<sup>53,63,66</sup> This cumulative effect of stress and the subsequent diminution of endocrine and immune system responsiveness is called allostatic load.<sup>66</sup> An important feature of prostate cancer is the high incidence and mortality rates among African-American men. African-American men routinely experience psychosocial stress due to the historical effects of racism.<sup>85</sup> Racial differences exist in the



**Environmental Demands**

**Lifestyle Behaviors**



**Fig 1.** Model of psychosocial stress and prostate cancer (Adapted from Adler and Matthews, 1994).

quality of education, level of pay for the same level of education, employment stability, and purchasing power of income.<sup>85-87</sup> The perception of racism among African Americans frequently evokes psychological and physiological stress responses.<sup>88</sup> The high prevalence of repeated racism-induced stress among African-American men may negatively impact the immune system and may partially explain the higher incidence of many diseases, including prostate cancer.

Figure 1 illustrates a model in which psychosocial stress may lead to the development of prostate cancer. The terms, “environmental demands” and “stressors” will be used interchangeably throughout our de-

scription of the model. Psychosocial stress may lead to prostate cancer directly through physiological changes that accompany environmental demands. The arrow between *environmental demands* and the *adaptive capacity of the individual* illustrates the impact of the environment on the individual. The relationship between environmental demands and *altered physiology* is dependent on the adaptive capacity of the individual, which is a function of individual perception, coping styles, coping resources, and genetic influences.<sup>52,58</sup> Thus, individuals who perceive environmental demands as threatening and who lack appropriate coping styles and inadequate resources experi-

ence psychosocial stress. Additionally, the stress response to environmental demands (ie, activation of the HPA axis) that subsequently alters physiology is influenced, in part, by genetic factors.<sup>89</sup> Individuals unable to adapt to environmental demands may be more susceptible to prostate cancer because of an inability to mount an appropriate immunologic response to neoplastic cells.

The ability to cope with environmental demands is an important individual characteristic. Coping with environmental demands may be effective when coping resources are available (eg, sufficient socioeconomic status, adequate social support).<sup>52</sup> However, not all styles of coping are adequate for all stressors. For example, individuals of low socioeconomic status may perceive a wider range of events as stressful and also may lack the resources necessary to cope adequately with these environmental demands. In other words, given the same stressors, the method of coping that is adequate for individuals who have economic stability and adequate social support may be inadequate for individuals without these resources.<sup>52,90</sup> Individuals who lack the resources to cope adequately with environmental demands may have a greater risk of developing prostate cancer than do individuals with such resources, even if they perceive coping styles to be sufficient. Research has indicated that the relationship between John Henryism, a measure of active coping particularly relevant to African Americans, and blood pressure, is modified by socioeconomic status in that low socioeconomic individuals possessing high levels of this coping style experience higher blood pressure.<sup>6</sup> Evidence also exists to suggest that strong social support networks<sup>91,92</sup> and religious participation<sup>92</sup> among African Americans may reduce the deleterious effect of psychological stress on health.

The double-headed arrow in Figure 1 pointing from “adaptive capacity of the individual” to “lifestyle behaviors” empha-

sizes an interaction between psychosocial stress (failure to adapt to environmental demands) and lifestyle behaviors. An indirect effect of psychosocial stress on altered physiology and the promotion of prostate cancer may be participation in health-damaging behaviors. Individuals who experience stress may find it difficult to participate in health-promoting behaviors and may have unhealthy lifestyles.<sup>66,93</sup> Consequently, individuals under greater stress may be more likely to cope with this stress by smoking cigarettes, drinking alcohol, becoming physically inactive, or maintaining an unhealthy diet. Health-damaging behaviors may be an effective short-term coping style; however, long-term unhealthy behavior may result in greater stress.<sup>66</sup> Cigarette smoking,<sup>94–96</sup> alcohol use,<sup>97</sup> and a high-fat diet<sup>98</sup> all may contribute to impairment of the immune system that, in turn, increases susceptibility to disease. In contrast, physical activity may improve the immune system by increasing natural killer cell cytotoxicity.<sup>99,100</sup> Also, there is evidence that physical activity may improve adaptation to stress.<sup>101</sup> Although results from studies investigating lifestyle factors and prostate cancer risk have been inconsistent, a stronger effect of psychosocial stress on prostate cancer risk may be found among individuals who participate in unhealthy lifestyle behaviors.

Understanding that the etiology of prostate cancer is multifactorial, our model is not meant to be all-inclusive. Family history of prostate cancer is not indicated in our model; however, it may interact with lifestyle behaviors and psychosocial stress in an important way. Men in the same family may share lifestyle behaviors that potentially alter physiology and thus may increase risk of developing prostate cancer. Moreover, these men, when encountering persistent psychosocial stress, may engage in similar reactions to these demands, (ie, unhealthy lifestyle behaviors), thereby further increasing their risk. Family history of

prostate cancer must be considered in studies assessing the role of psychosocial stress in prostate carcinogenesis.

### Summary

We have provided a theoretical model for an association between psychosocial stress and prostate cancer. Physiological changes that result in increased corticosteroid production through the HPA axis due to stress provide plausibility for a stress-prostate cancer association. Stress-induced plasma corticosteroid has an immunosuppressive effect that leaves individuals susceptible to malignancies. African-American men, who experience a disproportionate burden of prostate cancer, routinely experience psychosocial stress due to racism. Environmental demands historically and culturally unique to African Americans may result in a pattern of persistent and chronic stress that compromises the immune system's ability to fight malignancies and may explain the high incidence of prostate cancer among African-American men.

The stress-prostate cancer hypothesis provides avenues that can be investigated and may prove promising. Numerous factors contribute to the development of prostate cancer, and the physiological responses to stress are complex. Our model suggests a route by which psychosocial stress may interact with other modifiable factors to create a higher risk for prostate cancer. Empirical investigations suggested by the model may address the following questions:

- 1) What is the relationship between perceived stress and prostate cancer? Does the relationship between perceived stress and prostate cancer differ among men of various racial and ethnic groups?
- 2) Do psychological responses to stress modify the relationship between lifestyle behaviors and prostate cancer?
- 3) Do the psychological or biological responses to stress differ according to the context of stress (ie, negative stressful

life events or racism)? How does this relate to the risk for prostate cancer?

If a relationship between stress and prostate cancer is discovered, subpopulations of individuals may be targeted for interventions to reduce this modifiable risk factor.

### Acknowledgements

This work was supported by a predoctoral fellowship (GLE) from the National Cancer Institute, F31 CA72126. The authors thank the reviewers for their valuable comments.

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