

---

### Prostate-specific Antigen and All-Cause Mortality: Results From the Baltimore Longitudinal Study On Aging

---

Benign prostatic hyperplasia (BPH) and prostate cancer are two common diseases in aging males. Age is the strongest known risk factor for the development of both diseases. The prevalence of BPH and prostate cancer increase exponentially with age (1,2).

Prostate-specific antigen (PSA) is a protein product of the prostate that is a recognized marker of both BPH and prostate cancer. Cross-sectional data suggest that PSA increases 4% per milliliter of prostate volume and that 30% and 5% of the variance in PSA can be accounted for by prostate volume and

age, respectively (3). The risk of a prostate cancer diagnosis in the 10 years after a baseline PSA measurement increases incrementally with increasing PSA levels (4).

Because PSA is a marker of two diseases that are closely related to aging, we wondered if PSA levels might serve as a proxy for the aging process. Our hypothesis was that men in whom prostate disease is present might be biologically more advanced in age than those without prostate disease. If so, all-cause mortality, as a surrogate for aging, should be directly related to PSA.

To investigate this relationship, we reviewed death records and autopsy data of men who were participants in the

**Table 1.** Age-adjusted relative risks (RR) with increasing prostate-specific antigen (PSA) level

Outcome	RR for each ng/mL increase in PSA level (95% CI)	P value*
All-cause mortality	1.03 (1.02–1.04)	<i>P</i> < .001
Cancer mortality†	1.05 (1.03–1.06)	<i>P</i> < .001
Cardiovascular mortality	1.02 (0.98–1.06)	<i>P</i> = .32
Development of cancer	1.04 (1.02–1.05)	<i>P</i> < .001

A cohort of 929 men who had participated in the BLSA with no history of prostate cancer and a median age of 50 years (range = 20–92 years) at first assessment for whom a total of 4152 PSA levels had been measured from frozen sera samples over three decades. Median follow-up was 15.5 years (range = 1.5–40.4 years) with 190 deaths (34% from cardiovascular disease and 22% from cancer other than prostate cancer). Proportional hazards analysis was used to determine longitudinally the association of PSA with all cause, cardiovascular, and cancer mortality and with cancer incidence using the survival functions developed by Therneau (6) and incorporated into S-PLUS (Insightful, Seattle, WA). The dependent covariates PSA and age used the Anderson-Gill (7) formulation as a counting process. For each subject, time was divided into intervals between evaluations, and the covariates were based on the evaluation at the start of the interval. Longitudinal models included age and PSA at each evaluation. The final model used the same statistical model with age and PSA to evaluate the risk of development of cancer (excluding prostate and non-basal/squamous cell skin cancer) during the follow-up period. The end point was either the diagnosis of cancer or cancer at death.

\*Derived using a Wald test with two-sided comparison.

†Cancer mortality refers to deaths from all cancers other than prostate cancer.

Baltimore Longitudinal Study of Aging (BLSA), a long-term, prospective study of aging conducted by the National Institute on Aging (5). This study on aging has institutional approval (MedStar Research Institute, Harbor Hospital - Johns Hopkins Hospital), and all human subjects give written informed consent for the study prior to participation. There were 1201 male subjects in the BLSA who had PSA measurements from frozen sera over three decades. After excluding all men who had undergone a simple prostatectomy before their first PSA measure (n = 61), men who had used finasteride (n = 42), and all men with a diagnosis of prostate cancer (n = 169), we were left with a cohort of 929 men who had no history of prostate cancer. Associations between PSA and mortality, and PSA and the development of cancer were evaluated by proportional hazards analysis.

We demonstrated a statistically significant direct relationship between PSA and all-cause mortality, cancer mortality, and the development of cancer (Table 1). For each ng/mL increase in PSA, there was a 3%–5% increase in the risk of an event. There was no statistically significant relationship between PSA and cardiovascular mortality, and this finding was not the result of the lack of events in the cardiovascular group because most deaths were from a cardiovascular event.

The inclusion of body mass index, testosterone, and free testosterone index as covariates in the analysis did not alter the findings in this study (data not shown). We cannot exclude the possibility that some men in our cohort may have had undiagnosed prostate cancer that could have resulted in elevated PSA levels. However, it is not likely that the cause of death was misclassified because of the careful review of death records and autopsy data. Therefore, it seems unlikely that the relationship between PSA and mortality from all cancers other than prostate could have been driven by the presence of occult prostate cancer.

A relationship between PSA and mortality from cancer other than prostate has not previously been reported. One possible explanation for our findings is that the development of prostate disease with age reflects a loss of growth-control mechanisms within the prostate that also occurs simulta-

neously in other tissues within the body. If so, men with prostate disease (and elevated PSA levels) would be at greater risk of non-prostatic neoplasia. Although we do not know why men with the highest PSA levels are at an increased risk of development and death from cancer other than prostate, the relationships between PSA and cancer mortality and between PSA and cancer development suggests that the events that lead to PSA elevations with age may be related to the development of cancer in non-prostate tissues.

H. BALLENTINE CARTER  
E. JEFFREY METTER  
JAMES WRIGHT  
PATRICIA LANDIS  
ELIZABETH PLATZ  
PATRICK C. WALSH

## REFERENCES

- (1) Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol* 1984;132:474–9.
- (2) Carter HB and Coffey DS. The prostate: an increasing medical problem. *Prostate* 1990;16:39–48.
- (3) Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. *JAMA* 1993;270:860–864.
- (4) Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA* 1995;273:289–294.
- (5) Shock NW, Greulich RC, Andres R, Arenberg D, Costa PT Jr, Lakatta EG, et al. Normal human aging: The Baltimore Longitudinal Study of Aging. Washington (DC): U.S. Government Printing Office; November 1984 Report No. NIH Publ No. (NIH)84–2450.
- (6) Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. 1<sup>st</sup> ed. New York (NY): Springer; 2000.
- (7) Anderson PK, Gill MD. Cox's regression model for counting processes: a large sample study. *Ann Stat* 1982;10:1100–20.

## NOTES

Supported by Prostate Spore NCI-CA58236, NIA Intramural Research Program.

*Affiliations of authors:* Department of Urology, The Johns Hopkins University School of Medicine, The James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore, Maryland (HBC, JW, PL); The Johns Hopkins Bloomberg School of Public Health (EP); National Institute on Aging, Gerontology Research Center (EJM), Baltimore, MD.

*Correspondence to:* H. Ballentine Carter, Department of Urology, 403 Marburg, The Johns

Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287-2101 (e-mail: hcarter@jhmi.edu).

DOI: 10.1093/jnci/djh111