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Inferior Cancer Survival for Men with Localized High-grade Prostate Cancer but Low Prostate-specific Antigen

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Results from the Surveillance, Epidemiology and End Results (SEER) Program and National Cancer Data Base (NCDB) indicate that among men with localized, high-grade prostate cancer, those with low prostate-specific antigen (PSA) levels at diagnosis have

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worse prognosis compared to men with intermediate PSA levels [1], This prior analysis was based on data with rather short median follow-up of only 2–4 yr, which is limited given the long natural history of prostate cancer, and only reported on a limited number of prostate cancer deaths. The aim of our analysis was to validate these findings among men with Gleason score 8–10 prostate cancer within the US Health Professionals Follow-up Study (HPFS). Gleason scores were re-reviewed by experienced genitourinary pathologists according to the most recent grading recommendations [2]. The primary endpoint was lethal prostate cancer, defined as death from prostate cancer or the development of metastases during follow-up. The association between PSA and lethal prostate cancer was modeled using restricted cubic splines with four knots and Cox regression.

Of 4908 men with localized prostate cancer diagnosed between 1988 and 2015 and data on PSA available at diagnosis and follow-up, 716 had Gleason score 8–10 tumors. The median age at diagnosis was 70 yr (interquartile range 66–77). Primary treatment included radical prostatectomy (43%), radiotherapy (33%), brachytherapy (8%), hormonal therapy (9%), and watchful waiting or other therapies (9%; Supplementary Table 1). Over median follow-up of 13 yr (interquartile range 8–19), 156 men (22%) experienced progression to lethal prostate cancer and 259 (36%) noncancer deaths occurred. The association between diagnostic PSA levels and lethal disease is presented in Fig. 1A. After adjustment for clinical stage, Gleason score, and treatment received, men with low PSA (<5 ng/ml) at diagnosis were at higher risk of lethal progression compared to men with intermediate PSA levels (5–8 ng/ml; hazard ratio [HR] 1.83, 95% confidence interval [CI] 1.05–3.20). Men with high PSA (>8 ng/ml) also had an excess risk of lethal prostate cancer (HR 2.14, 95% CI 1.35–3.40) compared to those with intermediate PSA. Competing-risk analyses revealed that all-cause mortality exceeded lethal cancer events among the whole cohort and that lethal prostate cancer was more common for men with low or high PSA at diagnosis (Fig. 1B).

These results suggest a J-shaped rather than a linear association between PSA and lethal disease among men with localized high-grade prostate cancer. Data from this prospective cohort with long-term follow-up confirm prior findings of worse oncological outcomes for men with high-grade prostate cancer and low PSA at diagnosis. Previous research suggested that altered neuroendocrine/small-cell histology and androgen receptor signaling might be a reason for the inferior oncological outcomes [1]. This may explain why men with high-grade prostate cancer and low PSA often respond differently to primary or salvage therapies [3]. Our data support the need for an amended clinical definition of “highest-risk” localized prostate cancer expanded to include men in the low PSA group. Further research is needed to explore genomic and/or genetic tests, lifestyle modification, and different treatment regimens for this group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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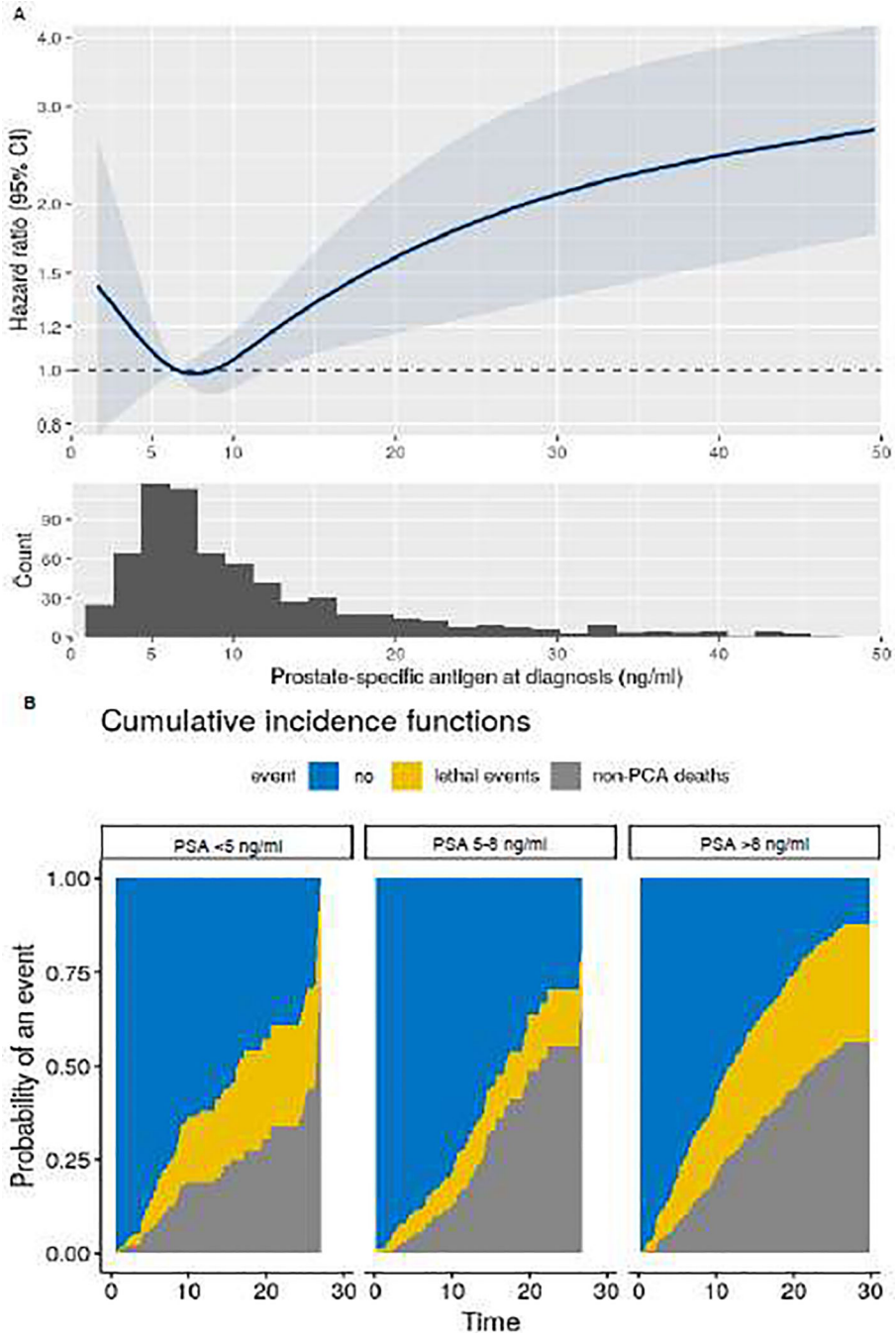

Fig. 1 –.

Lethal prostate cancer (PCA) according to prostate-specific antigen (PSA) levels at cancer diagnosis among men diagnosed with localized, Gleason score 8–10 PCA between 1986 and 2015 within the Health Professional Follow-up Study. (A) Multivariable hazard ratios from Cox proportional hazards regression, with PSA modeled as a restricted cubic spline, adjusted for clinical stage, Gleason score, and treatment received. The solid curve represents point estimates and the highlighted blue area the 95% confidence interval (CI). (B) Cumulative

incidence of lethal PCA (yellow) and all-cause mortality (gray) among men with high or low PSA levels compared to men with intermediate PSA levels.