

# Abstract

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## **A large prospective study of SEP15 genetic variation, interaction with plasma selenium levels, and prostate cancer risk and survival.**

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**BACKGROUND:** The role of selenium in prostate cancer (PCa) risk remains controversial, but many epidemiologic studies suggest an inverse association with more aggressive disease.

**OBJECTIVE:** A recently discovered selenoprotein, SEP15, which is highly expressed in the prostate, may play a role either independently or by modifying the effects of selenium.

**METHODS:** We genotyped four common single-nucleotide polymorphisms capturing common variation (frequency >5%;  $R(2) > 0.8$ ) within SEP15, as well as rs5859 in the 3' untranslated region, previously reported to reduce the efficiency of selenium incorporation into SEP15. We examined the association of these single-nucleotide polymorphisms with PCa risk and PCa-specific mortality, as well as their interactions with plasma selenium levels, in the Physicians' Health Study.

**RESULTS:** In this nested case-control study (1,286 cases and 1,267 controls), SEP15 polymorphisms were not significantly associated with PCa risk. However, among the cases, three variants were significantly associated with PCa-specific mortality [rs479341 hazard ratio (HR), 1.94; 95% confidence interval (95% CI), 1.15-3.25; rs1407131 HR, 2.85; 95% CI, 1.45-5.59; rs561104 HR, 1.54; 95% CI, 1.12-2.11] with a recessive model. Additionally, rs561104 significantly modified the association of plasma selenium with PCa survival ( $P(\text{interaction}) = 0.02$ ); an inverse relationship of high levels of selenium with PCa mortality was apparent only among those without the increased risk genotype.

**CONCLUSIONS:** This study provides evidence that SEP15 genetic variation may influence PCa mortality. Additionally, the association of selenium with PCa mortality was modified by a variant, suggesting the possibility that some men with PCa may benefit more from selenium than others, depending on their genotype.

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