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Cancer Epidemiology, Biomarkers & Prevention

Short Communication

Prediagnostic Circulating Anti-Müllerian Hormone Concentrations Are Not Associated with Prostate Cancer Risk

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Abstract

Despite considerable research, the pathogenesis of prostate cancer remains poorly understood. Meanwhile, PSA testing has shifted prostate cancer case populations for study to include a greater proportion of asymptomatic and indolent disease. Thus, efforts to identify prostate cancer biomarkers—particularly for aggressive disease—are required to elucidate pathogenesis and aid screening efficacy. Current evidence suggests that decreased circulating concentrations of the testis-derived, TGFβ family peptide hormone—anti-Müllerian hormone (AMH)—may be associated with prostate cancer pathogenesis. To test this hypothesis, we measured AMH concentrations in prediagnostic (cohort baseline) sera using the Beckman Coulter AMH Gen II ELISA in 1,000 cases and 1,000 controls nested within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Controls were frequency matched to cases on age at entry, enrollment year, and years of follow-up. Unconditional logistic regression models, adjusted for age at randomization, were used to estimate odds ratios (ORs) and 95% confidence intervals (95% CI). We found that prediagnostic serologic AMH concentrations were not significantly associated with total ($OR_{Q4\ vs.\ Q1} = 1.15$; 95% CI, 0.89–1.48; $P_{trend} = 0.13$), aggressive ($OR_{Q4\ vs.\ Q1} = 1.14$; 95% CI, 0.80–1.63; $P_{trend} = 0.51$), or nonaggressive ($OR_{Q4\ vs.\ Q1} = 1.22$; 95% CI, 0.91–1.63; $P_{trend} = 0.07$) prostate cancer risks. Different definitions of aggressive disease did not meaningfully alter these results. Despite *in vitro* studies linking AMH to prostate cancer, this first analysis of prediagnostic, circulating AMH concentrations in men provides no evidence for an association with prostate cancer risk. *Cancer Epidemiol Biomarkers Prev; 23(11); 2597–602. ©2014 AACR.*

Introduction

Prostate cancer is the most common noncutaneous cancer and the second leading cause of cancer-related death in U.S. men (1). Despite considerable research, the pathogenesis of prostate cancer remains poorly understood. The PSA test leads to many false-positive results and significant overdiagnosis (2), and it has changed prostate cancer case populations under study to include a greater proportion of asymptomatic and indolent disease. Thus, in the quest to identify novel prostate cancer biomarkers to elucidate pathogenesis and possibly aid diagnosis, it is imperative that studies are designed to enable robust analysis when stratified by disease aggressiveness.

Recent evidence suggests that anti-Müllerian hormone (AMH) may be a potential biomarker of prostate cancer risk. In males, AMH is produced by Sertoli cells within the testes and is instrumental for *in utero* apoptotic regression of Müllerian ducts to confer a male phenotype. AMH is a peptide hormone within the TGFβ family of growth factors that control cell proliferation, cell differentiation, and apoptosis in normal tissues (3). However, in advanced prostate cancer, TGFβ itself—the founding member of this family of structurally related proteins—is found at increased concentrations with loss of apoptotic regulation (4, 5). TGFβ dysfunction promotes immunosuppression, extracellular matrix degradation, angiogenesis, and metastasis to create a microenvironment favoring cancer development and progression (4, 5).

Several *in vitro* studies have demonstrated the inhibitory effects of AMH in prostate cancer cell lines through an NF-κB–dependent mechanism (6–8). The ligand-binding AMH type 2 receptor (AMHR2) is expressed in human prostate cancer cell lines, as well as in normal and cancerous prostate tissues (6). In a study comparing the effect of AMH on multiple human cancer cell lines, the most significant anti-proliferative activity was against a human prostate cancer cell line (9).

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There is evidence that AMH and testosterone negatively regulate one another—particularly during the pre- and immediately postpubertal periods (3, 6, 10, 11)—playing integral roles during prostate gland growth and differentiation. Before the onset of puberty, AMH concentrations are high, testosterone is low, and androgen receptors (AR) are not expressed in the testes. At pubertal onset, intratesticular testosterone concentration significantly increases which induces expression of AR, subsequently causing an AR-signaling cascade resulting in decreased AMH concentration and prostate gland growth and differentiation (3, 11). This interplay between AMH and testosterone may implicate a role for AMH in prostate carcinogenesis.

Despite basic science research linking AMH to prostate cancer in cell lines, epidemiologic studies on this potential association are lacking. Therefore, we investigated the association between prediagnostic serologic AMH concentrations and prostate cancer risk in a large, prospective cohort study—the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Materials and Methods

Study population

The PLCO Cancer Screening Trial randomized 37,000 eligible men ages 55 to 74 years at entry into two arms (control and intervention) at 10 U.S. screening centers to assess effects of cancer screening on disease-specific mortality endpoints (12). For the prostate cancer component, men in the control arm received usual medical care, whereas those in the intervention arm received annual screening with the PSA test (first 6 years) and digital rectal exam (DRE; first 4 years).

To date, the PLCO cohort has been followed up for more than 13 years. Diagnosed cancers and deaths were ascertained by annual mailings supplemented by linkage to the National Death Index. Cancer diagnoses were confirmed by medical record abstraction. Underlying causes of death were determined via a death review process using information from death certificates as well as medical documents (13).

For analysis, we randomly sampled 1,000 cases and 1,000 controls from the PLCO Cancer Screening Trial. Cases were restricted to incident first primary prostate cancers, and controls were selected from men without a diagnosis of prostate cancer. Controls were frequency matched to cases on age at entry in 5-year intervals, sex (all male), calendar year of enrollment, and number of years of follow-up. Men included in this analysis were non–Hispanic white from the intervention arm of the PLCO cohort, and had no prior history of cancer diagnosis (excluding nonmelanoma skin cancer) at baseline. Sera for the AMH measurement were collected at baseline (see www.plcostars.com). We excluded one control and two cases due to insufficient serum volume, providing 998 cases and 999 controls for analysis. Time between baseline sera collection and prostate cancer diagnosis ranged from 1 to 15 years (median, 3 years). Aggressive prostate cancers ($n = 367$) were defined as biopsy Gleason Score > 7, or clinical stage $\geq$ III, or prostate cancer as the underlying cause of death.

AMH assay

AMH quantitation was conducted using the Beckman Coulter AMH Gen II ELISA according to the manufacturer's updated "pre-mix" protocol. Given excellent reproducibility of this assay, samples and standards were run in single wells. Samples were randomized and tested blindly. High and low AMH PLCO quality control samples were run in triplicate in each batch to ensure assay reproducibility (overall CV, 6.42%; within-batch CV, 3.08%; and between-batch CV, 5.63%).

Statistical analysis

Pearson χ^2 tests were used to compare categorical characteristics by case–control status and by quartiles of AMH concentrations. Spearman correlations were used for circulating androgens (testosterone, androstenedione, 3α-androstanediol glucuronide, and free testosterone; available for 688 of our selected participants from a prior analysis; ref. 14) and age at entry in relation to AMH concentration. Unconditional logistic regression was used to determine the effect of AMH on overall prostate cancer risk with adjustment for age at randomization (continuous). AMH concentration was assessed as a continuous and as a categorical variable (quartiles based on AMH distribution in controls). Multinomial logistic regression was used to investigate the association between AMH and prostate cancer subtypes (aggressive/nonaggressive) compared with controls with adjustment for age at randomization. Prostate cancer cases that could not be classified to a subtype due to missing information were retained and modeled in an "unknown" category. We examined potential reverse causation due to latent disease by sequentially excluding prostate cancer cases diagnosed within 2, 3, and then 5 years after sera collection. In addition, we investigated associations between AMH concentrations and prostate cancer risk in a subgroup restricted to those with PSA < 4 ng/mL at baseline. P_{trends} were calculated through assessment of log-transformed AMH concentrations in relation to prostate cancer.

To test the robustness of associations obtained in the main analysis ("model 1"), three other definitions of prostate cancer "aggressiveness" were used for sensitivity analyses: "model 2": best Gleason (from prostatectomy or biopsy) $\geq$7, or best stage (pathologic or clinical) $\geq$ III, or fatal prostate cancer; "model 3": best Gleason $\geq$8, or best stage $\geq$III, or fatal prostate cancer; and "model 4": modified D'Amico criteria as low (biopsy Gleason $\leq$6, and cT1 to cT2a, and prediagnostic PSA within 6 months $\leq$10 ng/mL), intermediate (biopsy Gleason = 7, or cT2b, or prediagnostic PSA within 6 months >10 ng/mL and $\leq$20 ng/mL), and high risk (biopsy Gleason $\geq$8, or $\geq$cT2c, or prediagnostic PSA within 6 months >20 ng/mL, or fatal prostate cancer).

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Results

Participant characteristics and determinants of AMH in PLCO

Baseline characteristics by case status are shown in Table 1 and by AMH quartiles in Supplementary Table S1. AMH levels were significantly affected by age at randomization ($P < 0.001$) and body mass index (BMI) at baseline ($P = 0.001$), but these factors were not significantly related to prostate cancer and thus no potential confounders were identified using $P < 0.05$ in univariate

Table 1. Baseline characteristics by case status

Baseline characteristics	Controls ($n = 999$)	Cases ($n = 998$)					
		Total	*P*	Aggressive[a]	*P*	Nonaggressive[b]	*P*
AMH quartiles (ng/mL)			0.599		0.283		0.525
Q1 (0.04–2.64)	248 (24.8%)	222 (22.2%)		78 (21.3%)		134 (22.0%)	
Q2 (2.65–4.21)	249 (24.9%)	260 (26.1%)		107 (29.2%)		150 (24.6%)	
Q3 (4.22–6.74)	252 (25.2%)	260 (26.1%)		97 (26.4%)		159 (26.1%)	
Q4 (6.75–25.0)	250 (25.0%)	256 (25.7%)		85 (23.2%)		167 (27.4%)	
Age at randomization, y			1.000		0.180		0.462
≤59	151 (15.1%)	151 (15.1%)		40 (10.9%)		109 (17.9%)	
60–64	345 (34.5%)	346 (34.7%)		127 (34.6%)		211 (34.6%)	
65–69	327 (32.7%)	325 (32.6%)		124 (33.8%)		193 (31.6%)	
≥70	176 (17.6%)	176 (17.6%)		76 (20.7%)		97 (15.9%)	
Marital status			0.098		0.562		0.052
Married or living as married	861 (86.2%)	882 (88.4%)		319 (86.9%)		545 (89.3%)	
Single[c]	138 (13.8%)	113 (11.3%)		46 (12.5%)		64 (10.5%)	
First-degree relative(s) with prostate cancer			<0.001		<0.001		<0.001
No	924 (92.5%)	864 (86.6%)		320 (87.2%)		524 (85.9%)	
Yes	52 (5.2%)	114 (11.4%)		39 (10.6%)		74 (12.1%)	
BMI at baseline (kg/m^2)			0.411		0.538		0.399
<25	275 (27.5%)	265 (26.6%)		104 (28.3%)		152 (24.9%)	
25–30	505 (50.6%)	530 (53.1%)		192 (52.3%)		327 (53.6%)	
≥30	210 (21.0%)	190 (19.0%)		67 (18.3%)		122 (20.0%)	
History of diabetes			0.015		0.086		0.054
No	909 (91.0%)	937 (93.9%)		345 (94.0%)		571 (93.6%)	
Yes	85 (8.5%)	57 (5.7%)		21 (5.7%)		36 (5.9%)	
Cigarette smoking status			0.005		0.001		0.124
Never	394 (39.4%)	453 (45.4%)		181 (49.3%)		265 (43.4%)	
Current	96 (9.6%)	66 (6.6%)		21 (5.7%)		44 (7.2%)	
Former	509 (51.0%)	478 (47.9%)		164 (44.7%)		301 (49.3%)	
Food energy from diet (kcal/d)			0.429		0.604		0.487
Q1 (≤1707)	243 (24.3%)	217 (21.7%)		76 (20.7%)		135 (22.1%)	
Q2 (1718–2212)	244 (24.4%)	268 (26.9%)		97 (26.4%)		168 (27.5%)	
Q3 (2213–2804)	243 (24.3%)	235 (23.5%)		89 (24.3%)		142 (23.3%)	
Q4 (≥2805)	244 (24.4%)	249 (24.9%)		88 (24.0%)		153 (25.1%)	
Enlarged prostate			0.044		0.677		0.020
No	738 (73.9%)	696 (69.7%)		267 (72.8%)		417 (68.4%)	
Yes	261 (26.1%)	301 (30.2%)		100 (27.2%)		192 (31.5%)	
Biopsy of prostate			<0.001		0.008		<0.001
No	922 (92.3%)	864 (86.6%)		318 (86.6%)		529 (86.7%)	
Yes	56 (5.6%)	105 (10.5%)		35 (9.5%)		67 (11.0%)	

NOTE: Column percentages may not sum to 100% due to missings. *P* values were estimated by χ^2 tests using nonmissing values. There were 21 prostate cancer cases that could not be classified to a subtype due to missing tumor characteristics.

[a]Aggressive prostate cancer: biopsy Gleason ≥ 7, or clinical stage ≥III, or fatal.

[b]Nonaggressive prostate cancer: biopsy Gleason ≤ 6, and clinical stage I or II.

[c]Single: widowed/divorced/separated/never married.

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Table 2. Age-adjusted ORs and 95% CIs for AMH quartiles and prostate cancer risk

		Cases					
AMH quartiles (ng/mL)	Controls	Total		Aggressive[a]		Nonaggressive[b]	
Q1 (0.04–2.64)	248	222	1.00 (reference)	78	1.00 (reference)	134	1.00 (reference)
Q2 (2.65–4.21)	249	260	1.17 (0.91–1.50)	107	1.39 (0.99–1.95)	150	1.11 (0.83–1.48)
Q3 (4.22–6.74)	252	260	1.16 (0.90–1.49)	97	1.26 (0.89–1.78)	159	1.15 (0.86–1.54)
Q4 (6.75–25.0)	250	256	1.15 (0.89–1.48)	85	1.14 (0.80–1.63)	167	1.22 (0.91–1.63)
P_{trend}			0.134		0.512		0.074

NOTE: There were 21 prostate cancer cases that could not be classified to a subtype due to missing tumor characteristics.
[a]Aggressive prostate cancer: biopsy Gleason $\geq$ 7, or clinical stage $\geq$III, or fatal.
[b]Nonaggressive prostate cancer: biopsy Gleason $\leq$ 6, and clinical stage I or II.

analyses. Among controls, BMI ($P = 0.048$) and cigarette smoking ($P = 0.030$) were significantly inversely associated with circulating AMH concentrations (Supplementary Table S2).

The distribution of age-specific AMH concentrations by case status is shown in Supplementary Fig. S1. Median baseline AMH concentrations for cases (4.27 ng/mL) and controls (4.22 ng/mL) were comparable. When analyzed as a continuous variable in cases and controls combined, AMH levels were significantly negatively correlated with advancing age (rho $= -0.12$, $P < 0.0001$). AMH levels were inversely associated with age (Supplementary Fig. S2). No association was found between circulating AMH and androgen concentrations (Supplementary Table S3).

AMH levels and prostate cancer risk

We found no significant differences in prediagnostic circulating AMH concentrations between prostate cancer cases and controls (Table 2). In addition, we did not find any association between AMH concentrations and subtypes of prostate cancer in model 1. When we sequentially excluded cases diagnosed within 2, 3, and then 5 years of sera collection, the estimated ORs did not materially change (Supplementary Table S3). Sensitivity analyses using different definitions of aggressive prostate cancer (models 2–4) showed similar results (Supplementary Table S4). However, results from model 3 showed a statistically significant association between the second quartile of AMH concentrations (2.65–4.21 ng/mL) and an increased risk of aggressive prostate cancer [odds ratio (OR), 1.55; 95% confidence intervals (CI), 1.02–2.37; $P_{trend} = 0.21$; Supplementary Table S5], relative to the first quartile. A similar association was observed in model 4 for the high-risk prostate cancer (OR, 1.72; 95% CI, 1.06–2.78; $P_{trend} = 0.74$; Supplementary Table S5).

Baseline AMH and PSA levels with respect to disease

Cases had a significantly higher median PSA concentration at baseline when compared with controls (3.31 ng/mL vs. 1.08 ng/mL, $P < 0.0001$). Of the four models, only model 1 found that patients diagnosed with nonaggressive prostate cancer and PSA levels < 4 ng/mL at baseline had significantly higher AMH concentrations ($OR_{Q4\ vs.\ Q1} = 1.42$; 95% CI, 1.01–1.99; $P_{trend} = 0.035$; Table 3; Supplementary Table S6).

Table 3. Age-adjusted ORs and 95% CIs for AMH quartiles and prostate cancer risk restricted to the subpopulation with PSA < 4.0 ng/mL at baseline

		Cases					
AMH quartiles (ng/mL)	Controls	Total		Aggressive[a]		Nonaggressive[b]	
Q1 (0.04–2.64)	232	142	1.00 (reference)	56	1.00 (reference)	79	1.00 (reference)
Q2 (2.65–4.21)	233	165	1.15 (0.86–1.54)	75	1.35 (0.91–1.99)	89	1.10 (0.77–1.57)
Q3 (4.22–6.74)	241	163	1.10 (0.82–1.46)	67	1.17 (0.78–1.74)	95	1.13 (0.79–1.60)
Q4 (6.75–25.0)	242	191	1.27 (0.96–1.69)	67	1.19 (0.79–1.77)	121	1.42 (1.01–1.99)
P_{trend}			0.135		0.713		0.035

NOTE: There were 12 prostate cancer cases that could not be classified to a subtype due to missing tumor characteristics.
[a]Aggressive prostate cancer: biopsy Gleason $\geq$ 7, or clinical stage $\geq$III, or fatal.
[b]Nonaggressive prostate cancer: biopsy Gleason $\leq$ 6, and clinical stage = I or II.

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Discussion

Prediagnostic circulating AMH concentrations were not associated with any form of prostate cancer in this well-powered case–control analysis nested within the PLCO Cancer Screening Trial, despite *in vitro* evidence implicating a role for AMH in prostate carcinogenesis (3, 6). The associations between aggressive, or D'Amico high-risk prostate cancer, and the second quartiles of AMH concentrations in sensitivity analyses were likely due to chance, given the number of comparisons conducted. The significantly higher AMH concentrations in men with baseline PSA levels <4 ng/mL who were subsequently diagnosed with nonaggressive prostate cancer are also likely due to chance because it was only observed in one of the four analytic models described.

In agreement with previous publications (15), AMH levels declined slightly with advancing age in our control population. In addition, we observed an inverse relationship between AMH levels and BMI which was also reported by a prior study and may suggest that obesity has effects on Sertoli cell function (16). Interestingly, previous studies reported that the influence of BMI on AMH is reversible, with observations of significant increases in AMH concentrations after weight loss (17). AMH concentrations were also inversely associated with cigarette smoking. To our knowledge, no prior study has reported on this association in men, although it has been reported for women, with evidence that the effect is reversible with smoking cessation (18, 19). Finally, we did not observe any association between circulating AMH concentrations and various circulating androgen concentrations in this adult male population, which is in agreement with a prior study of AMH and testosterone (20).

Strengths of our study include the large prospective design in a well-defined population with long-term follow-up. Limitations of this analysis include the fact that we assessed only a single circulating AMH concentration 1 to 15 years before prostate cancer diagnosis in men aged 55 years or older at baseline (median, 65 years). Childhood, adolescent, or early adulthood AMH concentrations during prostate development may be more etiologically relevant, while assessment of the actual diagnostic blood samples that had PSA concentrations >4 ng/mL would provide results with greater clinical relevance compared to the baseline, prediagnostic blood samples we have used for this etiologic study. We used a single serologic measurement of AMH, which may not accurately capture intraindividual AMH variation. Finally, we only measured circulating AMH concentrations, yet intratesticular levels, intraprostatic levels, or receptor expression (AR, AMHR2) could be more relevant for prostate carcinogenesis. This premise is exemplified by the ongoing debate of whether circulating sex steroid hormones reflect intraprostatic concentrations (10).

In conclusion, this analysis of prediagnostic serum AMH concentrations in adult men provides no evidence for an association with prostate cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Authors' Contributions

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