Research Article

Cancer Epidemiology, Biomarkers & Prevention

A Prospective Study of Intraprostatic Inflammation, Focal Atrophy, and Progression to Lethal Prostate Cancer

Yiwen Zhang[1], Cindy Ke Zhou[1], Emily M. Rencsok[1], Katja Fall[1,2], Tamara L. Lotan[3], Massimo Loda[4,5], Francesca Giunchi[6], Elizabeth A. Platz[7,8], Angelo M. De Marzo[8,9], Lorelei A. Mucci[1,10], Michelangelo Fiorentino[6], and Ericka M. Ebot[1]

Abstract

Background: Inflammation and focal atrophy are common features adjacent to prostate tumors. Limited evidence exists on whether these features have prognostic significance.

Methods: In the Health Professionals Follow-Up Study and Physicians' Health Study, we studied 1,035 men diagnosed with prostate cancer. A genitourinary pathologist centrally reviewed tumor and normal areas of hematoxylin and eosin slides from prostate cancer specimens for the presence of acute and chronic inflammation, and four subtypes of focal atrophy. Cox proportional hazards models adjusted for potential confounders were used to estimate HRs and 95% confidence intervals (CI) for the association of these features with lethal prostate cancer, defined as development of metastatic disease or death during follow-up.

Results: During a median of 12 years of follow-up, 153 men developed lethal prostate cancer. A total of 84% of men had histologic evidence of chronic inflammation and 30% had acute inflammation. Both chronic and acute inflammation were inversely associated with lethal prostate cancer in age- and lifestyle-adjusted models. Chronic inflammation remained inversely associated with lethal prostate cancer after additionally adjusting for prognostic clinical features (HR = 0.45; 95% CI, 0.30–0.69 for mild and HR = 0.51; 95% CI, 0.33–0.80 for moderate to severe). None of the atrophic lesions were associated with lethal prostate cancer.

Conclusions: Our data suggest that the presence of inflammation, particularly chronic inflammation, in prostate cancer tissue is associated with better prognosis among patients with prostate cancer.

Impact: This is the largest prospective cohort study to examine the association between inflammation, focal atrophy, and lethal prostate cancer.

Introduction

Acute and chronic inflammation are commonly found in both normal prostate and prostate cancer tissue. The inflammatory infiltrate of chronic inflammation has been hypothesized to be involved in prostate cancer initiation or progression through the induction of oxidative stress and generation of reactive oxygen species (1, 2). Along with their protumorigenic effects, tumor-infiltrating immune cells may also suppress tumor development and growth through tumor immune surveillance mechanisms, and current immunotherapeutic approaches are being developed to amplify the immune response against tumor cells (3, 4).

Focal atrophy of the prostate gland, which has been put forth previously as a potential precursor of prostate cancer, often occurs in close association with chronic inflammation (5). It is highly proliferative compared with matched normal-appearing epithelium and, together with inflammation, frequently occurs in the peripheral zone where prostate cancer most commonly develops (6–8). The term "proliferative inflammatory atrophy" (PIA) was proposed to designate foci of proliferative glandular epithelium with the morphologic appearance of simple atrophy or postatrophic hyperplasia, two forms of focal atrophy, occurring in association with inflammation (5).

Few studies have investigated the association of inflammation in prostate tumor tissue with prostate cancer outcomes (9–11). Only one study (11) to date has examined the relationship

[1]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [2]Department of Clinical Epidemiology and Biostatistics, School of Health and Medical Sciences, Orebro University Hospital, Orebro, Sweden. [3]Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland. [4]Department of Oncologic Pathology, Dana-Farber Cancer Institute, Boston, Massachusetts. [5]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, New York. [6]Department of Pathology, Addarii Institute of Oncology, S.Orsola-Malpighi Teaching Hospital, University of Bologna, Bologna, Italy. [7]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland. [8]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland. [9]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland. [10]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

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Y. Zhang and C.K. Zhou contributed equally as co-first authors for this article.

M. Fiorentino and E.M. Ebot contributed equally as co-senior authors for this article.

Corresponding Author: Ericka M. Ebot, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Kresge 9th Floor, Boston, MA 02115. Phone: 617-233-4870; E-mail: enoonan@hsph.harvard.edu

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between histologic measures of atrophy and inflammation and prostate cancer–specific mortality. In this population-based nested case–control study of men diagnosed with localized prostate cancer, a positive association was observed between chronic inflammation and lethal prostate cancer, although this finding was not statistically significant.

In this study, we characterized intraprostatic inflammation and focal atrophy in prostate tumor tissue among over 1,000 men diagnosed with prostate cancer from two prospective studies, the Physicians' Health Study (PHS) and the Health Professionals Follow-Up Study (HPFS), and investigated the associations between these histologic features and the development of lethal (metastatic or fatal) prostate cancer.

Materials and Methods

Study population

We included 1,035 men from the PHS ($n = 73$) or HPFS ($n = 962$) who were diagnosed with prostate cancer from 1983 to 2010, and had hematoxylin and eosin (H & E) stained slides available for pathologic review. H & E slides were primarily from prostatectomy specimens ($n = 926$, 89.5%). Other tissue specimens included transurethral resection of the prostate (TURP, $n = 69$, 6.7%), biopsy ($n = 37$, 3.6%), and benign prostate hyperplasia (BPH) adenomectomy ($n = 2$, 0.2%). The PHS was a randomized trial of aspirin and beta-carotene for the prevention of cardiovascular disease and cancer among 22,071 male physicians ages 40–84 years at enrollment. Information on lifestyle and medical history was ascertained at baseline and updated annually through questionnaires (12). The HPFS is an ongoing cohort study of 51,529 male health professionals ages 40–75 years at enrollment. Information on demographics, lifestyle, medical history, and diet was collected at baseline and updated biannually through questionnaires, except that diet information was updated every 4 years by a validated semiquantitative food frequency questionnaire (13).

Identification of prostate cancer cases and outcome ascertainment

In both PHS and HPFS, self-reported prostate cancer diagnoses on follow-up questionnaires were subsequently confirmed through medical record and pathology report review. Age and year of diagnosis, clinical and pathologic stage, PSA level at diagnosis, and prostate cancer progression (i.e., distant metastases and biochemical recurrence) after diagnosis were collected by medical records and questionnaires sent to prostate cancer survivors and their attending physicians. Details of the prostate cancer survivor cohort within these two studies are available elsewhere (14–16). In both PHS and HPFS, vital status was ascertained by reports from family members, autopsy reports, and searches of the National Death Index. The underlying cause of death was determined by the endpoint review committee, consisting of trained clinicians who have the credentials for outcome adjudication and were blinded to any exposure information, based on all available data including medical history, medical records, registry information, and death certificates. Lethal prostate cancer was defined as cancer that progressed to distant metastases or death from prostate cancer as the underlying cause during follow-up. Fatal prostate cancer was defined as death from prostate cancer as the underlying cause (i.e., prostate cancer–specific mortality).

Assessment of intraprostatic inflammation, focal atrophy, and other histologic features

For each patient all available H & E slides with prostate tumor foci were centrally reviewed by a single experienced genitourinary pathologist (M. Fiorentino) blinded to disease outcome and other clinical data to confirm cancer status; to determine Gleason patterns; to evaluate histologic features such as perineural invasion, acute and chronic inflammation, and classes of focal atrophy (17); and to identify areas of interest for tissue microarray (TMA) construction (at least three cores each). Both the tumor and adjacent normal areas were included when scoring inflammation. Acute inflammation was characterized by the presence of neutrophils and scored as absent versus present. Chronic inflammation was characterized by the presence of mononuclear cells, for example, lymphocytes and macrophages, and graded as absent, mild ($\leq$10% of the microscopically benign area), moderate (11%–19%), or severe ($\geq$20%).

Focal atrophy was characterized according to the classification scheme proposed in 2006 by the Working Group for Histologic Classification of Prostate Atrophy Lesions with the following subtypes: simple atrophy, simple atrophy with cyst formation (SACF), postatrophic hyperplasia, and partial atrophy (17). Figure 1 shows a typical pathologic view of normal prostate glands, inflammation, and postatrophic hyperplasia on H & E slides. Details of the major characteristics of the four classes of focal atrophy are described elsewhere (11, 17).

The presence of perineural invasion was defined as the existence of complete circumferential encirclement of nerve structures by malignant glands. Patients with noncircumferential perineural invasion or a single focus of perineural invasion among multiple tumor slides were deemed as perineural invasion absent (18).

PTEN gene loss and the *TMPRSS2:ERG* gene fusion (measured by ERG protein expression) were assessed by IHC on TMAs using validated antibodies. The markers were scored blinded to disease outcome and other clinical data. PTEN loss was considered if the intensity of cytoplasmic and nuclear staining was markedly decreased or entirely lost across all TMA cores compared with surrounding benign glands and/or stroma (19). We classified tumors as ERG fusion positive if at least one TMA core stained positive for ERG, and ERG fusion negative if all cores stained negative for ERG (20).

Statistical analyses

We used χ^2 tests and Fisher exact tests to examine the associations between measures of inflammation and focal atrophy. HRs and 95% confidence intervals (CI) of the associations of inflammation and focal atrophy with lethal prostate cancer were estimated using Cox proportional hazards regression models. Person-time for progression to lethal outcome was calculated from the date of cancer diagnosis to the earliest date among the following: development of distant metastases, deaths due to any cause, or the end of follow-up (June 2015 for PHS and January 2014 for HPFS). For analyses using lethal prostate cancer as the endpoint, prostate cancer cases with M1 stage at diagnosis were excluded. In the secondary analysis, we examined the associations of inflammation and focal atrophy with fatal prostate cancer.

To control for potential confounding (13), we considered three models: (i) adjusted for age at diagnosis (years and continuous); (ii) additionally adjusted for body mass index (BMI) at diagnosis (<25, 25–29, and $\geq$30 kg/m^2), regular aspirin use at diagnosis

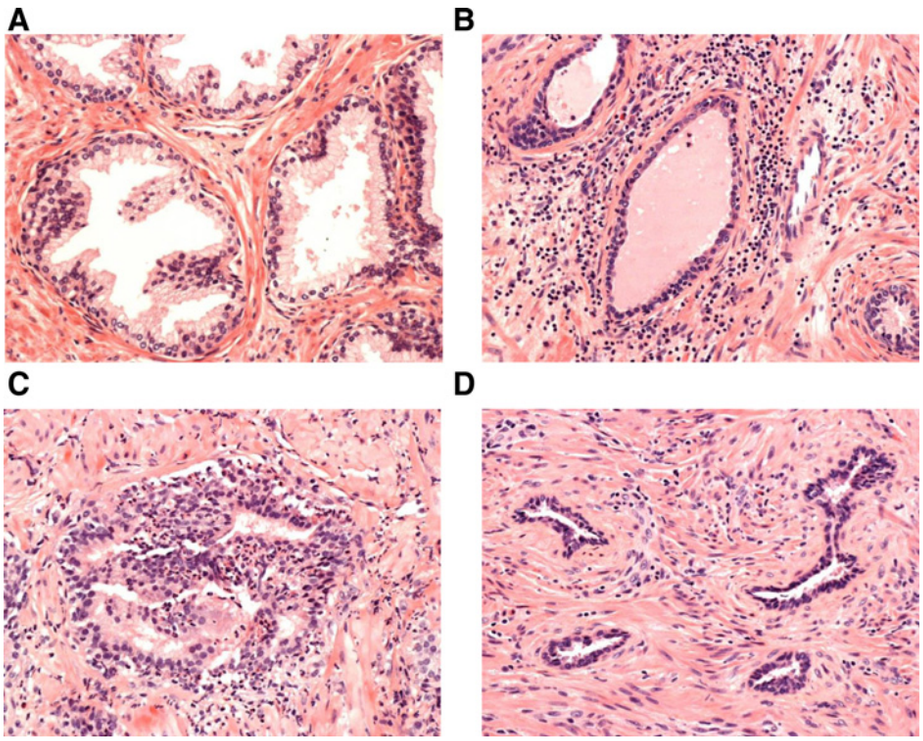

Figure 1.
Pathologic view of normal prostate glands, typical intraprostatic inflammation, and postatrophic hyperplasia on H & E slide. **A,** Normal prostate glands. **B,** Periglandular chronic inflammation. **C,** Intraglandular acute inflammation. **D,** Postatrophic hyperplasia.

(yes and no; defined as >twice per week in HPFS and >3 days per week in PHS), and history of diabetes at diagnosis (yes and no); and (iii) additionally adjusted for clinical or pathologic tumor stage (T1b–T3a and T3b/T4/N1/M1), Gleason score [≤6, 7(3+4), 7(4+3), 8(4+4), and 9–10], and PSA at diagnosis (<10, 10–20, and >20 ng/mL). For all models, the proportional hazards assumption was evaluated and satisfied by plotting Schoenfeld residuals of the exposure against follow-up time and found to be satisfied. We also explored which specific factors in Model 3 were responsible for the attenuation of the association of acute inflammation with lethal prostate cancer.

As chronic inflammation and focal atrophy often occur concurrently (5) and our primary analysis showed men with chronic inflammation were more likely to have simple atrophy and postatrophic hyperplasia compared with men who did not have chronic inflammation, we assessed whether the association between chronic inflammation and lethal prostate cancer varied according to the presence of simple atrophy and postatrophic hyperplasia. We also performed a stratification analysis within strata of Gleason score categories [≤7(3+4) vs. ≥7(4+3)] and tumor stage (T1b–T3a vs. T3b/T4/N1/M1) for the association between chronic inflammation and lethal prostate cancer. We further conducted two separate sensitivity analyses examining chronic inflammation and lethal prostate cancer, restricting to (i) cases with prostatectomy tissue type and (ii) cases diagnosed in the PSA era (i.e., 1993 onward).

Analyses were conducted using SAS version 9.4 (SAS Institute Inc.), and all statistical tests were two-sided, with *P* values below 0.05 considered statistically significant.

This research project was approved by the Institutional Review Board at the Harvard T.H. Chan School of Public Health (Boston, MA). Written informed consent was obtained from each study participant.

Results

Table 1 shows the frequency of individual pathologic features and their associations among the 1,035 study participants. More than 80% of the prostate cancer cases had chronic inflammation (mild 51% and moderate to severe 33%; Table 1). Thirty percent of the cases had acute inflammation (Table 1). Acute and chronic inflammations were positively associated ($P < 0.0001$). Among the four types of focal atrophy, simple atrophy was the most common (74%), followed by postatrophic hyperplasia (21%), SACF (19%), and partial atrophy (2%). Men with chronic or acute inflammation were more likely to have simple atrophy, postatrophic hyperplasia, and SACF than men without inflammation (Table 1).

The patient characteristics overall and with respect to the histologic features of inflammation are shown in Table 2. More than half of the patients were older than 65 years (61%), and were diagnosed during the PSA era (after 1993, 71%). Most men had localized cancer (stage T1b–T3a, 84%), and about half had low grade disease (Gleason score ≤7/3+4, 52%). Approximately 15% of tumors showed complete PTEN loss. Forty-eight percent of tumors were ERG positive.

A higher percentage of localized stage (T1b–T3a) disease was observed among cases with acute or chronic inflammation compared with cases without inflammation (Table 2). The prevalence of low grade (Gleason score ≤ 7/3+4) disease was slightly higher among tumors with acute or chronic inflammation compared with tumors without inflammation (Table 2). The majority of patients has a PSA at diagnosis <10 ng/mL, irrespective of inflammation status (Table 2). Perineural invasion, complete PTEN loss, and positive ERG expression were less often observed among tumors with acute inflammation compared with tumors without acute inflammation (Table 2). Similar relationships were generally observed for the four types of focal atrophy lesions with

Table 1. Associations between inflammation and focal atrophy among men diagnosed with prostate cancer between 1983 and 2010 in the HPFS and the PHS

		Men according to inflammation and atrophy lesions, *n* (%)[a]				
	All men, *N* (%)	**Acute inflammation**	**SA**	**PAH**	**SACF**	**Partial atrophy**
Acute inflammation						
Yes	299 (29.8)		266 (89.0)	93 (31.1)	79 (26.4)	8 (2.7)
No	703 (70.2)		473 (67.3)	120 (17.1)	107 (15.2)	15 (2.1)
			$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P = 0.59$
Chronic inflammation						
Moderate/severe	339 (33.3)	208 (61.7)	302 (89.4)	118 (34.9)	67 (19.8)	9 (2.7)
Mild	516 (50.6)	85 (16.7)	375 (73.8)	90 (17.8)	103 (20.3)	12 (2.4)
None	164 (16.1)	5 (3.3)	62 (40.3)	5 (3.3)	16 (10.4)	2 (1.3)
		$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P = 0.02$	$P = 0.71$[b]
SA						
Yes	740 (73.7)			187 (25.3)	176 (23.8)	21 (2.8)
No	264 (26.3)			27 (10.2)	10 (3.8)	2 (0.8)
				$P < 0.0001$	$P < 0.0001$	$P = 0.06$[b]
PAH						
Yes	214 (21.3)				49 (22.9)	10 (4.7)
No	789 (78.7)				137 (17.4)	13 (1.7)
					$P = 0.06$	$P = 0.008$
SACF						
Yes	186 (18.5)					5 (2.7)
No	818 (81.5)					18 (2.2)
						$P = 0.69$
Partial atrophy						
Yes	23 (2.3)					
No	980 (97.7)					

NOTE: Among 1,035 men diagnosed with prostate cancer, acute inflammation was missing for 33 men, chronic inflammation was missing for 16 men, simple atrophy was missing for 31 men, postatrophic hyperplasia was missing for 32 men, SACF was missing for 31 men, and partial atrophy was missing for 32 men.
Abbreviations: PAH, postatrophic hyperplasia; SA, simple atrophy; SACF, simple atrophy with cyst formation.
[a]Row percentage restricted to patients positive for features, including chronic inflammation, acute inflammation, simple atrophy, postatrophic hyperplasia, SACF, and partial atrophy.
[b]*P* values based on the Fisher exact test; all other *P* values based on the χ^2 test.

respect to the clinical and pathologic features described (Supplementary Table S1).

During a median follow-up of 12.0 years, 153 lethal prostate cancer events occurred. The associations between inflammation and focal atrophy features and lethal prostate cancer are shown in Table 3. Overall, we found that the presence of chronic inflammation was associated with a reduced risk of lethal prostate cancer after adjusting for age, BMI, diabetes, aspirin use, disease stage, tumor grade, and PSA (HR 0.45, 95% CI, 0.30–0.69 for mild; HR 0.51, 95% CI, 0.33–0.80 for moderate to severe inflammation), compared with cases without chronic inflammation. Presence of acute inflammation was associated with a reduced risk of lethal prostate cancer after adjusting for age, BMI, diabetes, and aspirin use (HR 0.66; 95% CI, 0.45–0.99). The association was attenuated and became not significant after additional adjustment for disease stage, tumor grade, and PSA (HR 0.91; 95% CI, 0.61–1.37). No statistically significant associations were observed between any of the four classes of focal atrophy and lethal prostate cancer (Table 3).

When restricting only to patients with prostatectomy specimens ($n = 926$), the association between chronic inflammation and lethal prostate cancer adjusted for clinical and lifestyle factors was similar to the full analysis (HR 0.45, 95% CI, 0.28–0.74 for mild; HR 0.50, 95% CI, 0.30–0.85 for moderate to severe inflammation, data not tabulated). When restricting to patients diagnosed in the PSA era ($n = 730$), the association between chronic inflammation and lethal prostate cancer adjusted for clinical and lifestyle factors was slightly attenuated but remained inverse (HR 0.49, 95% CI, 0.27–0.88 for mild; HR 0.63, 95% CI, 0.34–1.15 for moderate to severe inflammation, data not tabulated).

When using 151 fatal prostate cancer events accrued during a mean follow-up of 13 years, we found similar associations to what was observed using lethal prostate cancer as the outcome, except that the presence of simple atrophy became inversely associated with fatal prostate cancer (HR 0.68; 95% CI, 0.46–0.99, adjusting for age, BMI, diabetes, aspirin use, disease stage, tumor grade, and PSA; Supplementary Table S2).

The association between chronic inflammation and lethal prostate cancer did not statistically differ according to the presence of simple atrophy or postatrophic hyperplasia (Supplementary Table S3).When stratifying by stage at diagnosis, the inverse association between chronic inflammation and lethal prostate cancer appeared to be stronger among patients with localized tumor stage (T1b–T3a) compared with those with regional tumor stage (T3b/T4/N1). However, estimates for regional tumor stage were limited by small sample size rendering wide confidence intervals (Supplementary Table S4).

We also explored which specific factors in Model 3 (Table 3) were responsible for the attenuation of the association of acute inflammation with lethal prostate cancer. Gleason score and tumor stage at diagnosis were the predominant factors for the attenuation (Supplementary Table S5).

Discussion

In this large prospective study of lethal prostate cancer, we found the presence of chronic inflammation to be inversely associated with progression to lethal disease, independent of prognostic clinical and lifestyle factors. Acute inflammation was also inversely associated with lethal prostate cancer, but this

Table 2. Tumor, clinical, and lifestyle characteristics among men diagnosed with prostate cancer between 1983 and 2010 in the HPFS and the PHS overall and according to inflammation status

			Chronic inflammation, *n* (%)[a]	
	Overall, *n* (%) (*n* = 1,035)	**Acute inflammation, *n* (%)[a] (*n* = 299)**	**Mild (*n* = 516)**	**Moderate/severe (*n* = 339)**
Cohort				
HPFS	962 (93.0)	274 (91.6)	477 (92.4)	320 (94.4)
PHS	73 (7.0)	25 (8.4)	39 (7.6)	19 (5.6)
Age at diagnosis, years				
<65	401 (38.7)	120 (40.1)	208 (40.3)	126 (37.2)
65–69	345 (33.3)	101 (33.8)	168 (32.5)	120 (35.4)
70–74	212 (20.5)	55 (18.4)	104 (20.2)	67 (19.7)
≥75	77 (7.5)	23 (7.7)	36 (7.0)	26 (7.7)
Year of diagnosis				
Before 1990 (pre-PSA era)	68 (6.6)	15 (5.0)	29 (5.6)	21 (6.2)
1990–1993 (peri-PSA era)	237 (22.9)	59 (19.7)	125 (24.2)	75 (22.1)
After 1993 (PSA era)	730 (70.5)	225 (75.3)	362 (70.2)	243 (71.7)
Stage[b]				
T1b–T3a	873 (84.3)	268 (89.6)	451 (87.4)	288 (85.0)
T3b/T4/N1/M1	158 (15.3)	31 (10.4)	63 (12.2)	50 (14.7)
Unknown	4 (0.4)	0 (0.0)	2 (0.4)	1 (0.3)
Gleason score				
≤6	172 (16.6)	61 (20.4)	83 (16.1)	67 (19.8)
7 (3+4)	371 (35.9)	108 (36.1)	198 (38.4)	113 (33.3)
7 (4+3)	199 (19.2)	62 (20.8)	108 (20.9)	60 (17.7)
8	100 (9.6)	27 (9.0)	42 (8.1)	32 (9.4)
9–10	188 (18.2)	38 (12.7)	82 (15.9)	65 (19.2)
Unknown	5 (0.5)	3 (1.0)	3 (0.6)	2 (0.6)
PSA at diagnosis, ng/mL				
<10	668 (64.5)	200 (66.9)	350 (67.8)	205 (60.5)
10–20	151 (14.6)	49 (16.4)	71 (13.8)	59 (17.4)
>20	82 (7.9)	20 (6.7)	33 (6.4)	28 (8.2)
Unknown	134 (13.0)	30 (10.0)	62 (12.0)	47 (13.9)
Specimen type				
Prostatectomy	926 (89.5)	273 (91.3)	467 (90.5)	306 (90.5)
TURP	69 (6.7)	20 (6.7)	36 (7.0)	25 (7.4)
Biopsy or BPH adenomectomy	39 (3.8)	6 (2.0)	13 (2.5)	7 (2.1)
Perineural invasion				
Yes	470 (45.4)	123 (41.1)	235(45.5)	146 (43.1)
No	562 (54.3)	176 (58.9)	280 (54.3)	192 (56.6)
Unknown	3 (0.3)	0 (0.0)	1 (0.2)	1 (0.3)
Complete PTEN loss[c]				
Yes	102 (14.8)	17 (9.7)	52 (14.9)	31 (13.5)
No	587 (85.2)	158 (90.3)	296 (85.1)	198 (86.5)
ERG expression[d]				
Positive	399 (48.2)	90 (43.3)	202 (48.9)	127 (46.0)
Negative	429 (51.8)	118 (56.7)	211 (51.1)	149 (54.0)
BMI at diagnosis, kg/m^2				
<25	428 (41.3)	117 (39.1)	207 (40.1)	134 (39.5)
25–29	506 (48.9)	153 (51.2)	254 (49.2)	167 (49.3)
≥30	101 (9.8)	29 (9.7)	55 (10.7)	38 (11.2)
Smoking status at diagnosis[e]				
Never	438 (42.3)	120 (40.1)	229 (44.4)	138 (40.7)
Past	420 (40.6)	130 (43.5)	203 (39.3)	143 (42.2)
Current	65 (6.3)	12 (4.0)	26 (5.0)	25 (7.4)
Unknown	112 (10.8)	37 (12.4)	58 (11.3)	33 (9.7)
Regular aspirin use at diagnosis[e]				
Yes	462 (44.6)	138 (46.2)	221 (42.8)	164 (48.4)
No	567 (54.8)	158 (52.8)	291 (56.4)	175 (51.6)
Unknown	6 (0.6)	3 (1.0)	4 (0.8)	0 (0.0)
History of diabetes at diagnosis[e]				
Yes	52 (5.0)	14 (4.7)	27 (5.2)	16 (4.7)
No	983 (95.0)	285 (95.3)	489 (94.8)	323 (95.3)

[a]Column percentage restricted to patients who had acute or chronic inflammation.
[b]Pathologic stage as primary, clinical stage as secondary if pathologic stage is missing.
[c]PTEN status was missing for 346 men.
[d]ERG status was missing for 207 men.
[e]Smoking, aspirin use, and diabetes information was obtained from questionnaire at prostate cancer diagnosis or the most recent questionnaire prior to prostate cancer diagnosis.

Table 3. Associations of inflammation and focal atrophy with lethal prostate cancer among men diagnosed with prostate cancer in the HPFS and the PHS, 1983–2015

	Lethal prostate cancer (HR, 95% CI)				
	***N* lethal (*N* total)[a]**	**Person-years**	**Model 1[b]**	**Model 2[c]**	**Model 3[d]**
Inflammation					
Acute inflammation					
Absent	107 (679)	8,141.42	Reference	Reference	Reference
Present	31 (293)	3,601.92	0.66 (0.44–0.99)	0.66 (0.45–0.99)	0.91 (0.61–1.37)
Chronic inflammation					
Absent	39 (150)	1,620.58	Reference	Reference	Reference
Mild	61 (501)	6,283.25	0.41 (0.28–0.62)	0.42 (0.28–0.63)	0.45 (0.30–0.69)
Moderate to severe	46 (332)	3,959.58	0.49 (0.32–0.75)	0.49 (0.32–0.76)	0.51 (0.33–0.80)
Focal atrophy					
SA					
Absent	43 (242)	2,894.75	Reference	Reference	Reference
Present	96 (732)	8,862.00	0.73 (0.51–1.05)	0.74 (0.52–1.07)	0.75 (0.51–1.09)
PAH					
Absent	113 (761)	9,204.17	Reference	Reference	Reference
Present	26 (212)	2,541.25	0.88 (0.57–1.35)	0.89 (0.58–1.36)	1.12 (0.72–1.74)
SACF					
Absent	115 (790)	9,520.83	Reference	Reference	Reference
Present	24 (184)	2,235.92	0.84 (0.54–1.31)	0.83 (0.53–1.30)	0.94 (0.60–1.48)
Partial atrophy					
Absent	136 (950)	11,437.83	Reference	Reference	Reference
Present	3 (23)	298.08	0.95 (0.30–2.99)	0.98 (0.31–3.09)	1.75 (0.55–5.61)

NOTE: Among 153 lethal prostate cancer events, acute inflammation was missing for 15 men, chronic inflammation was missing for 7 men, simple atrophy was missing for 14 men, postatrophic hyperplasia was missing for 14 men, SACF was missing for 14 men, and partial atrophy was missing for 14 men.

Abbreviations: CI, confidence interval; HR, hazard ratio; PAH, postatrophic hyperplasia; SA, simple atrophy; SACF, simple atrophy with cyst formation.

[a]*N* = number of events

[b]Model 1: adjusted for age at diagnosis (years and continuous).

[c]Model 2: adjusted for age at diagnosis (years and continuous), BMI at diagnosis (<25, 25–29, and ≥30 kg/m^2), regular aspirin use at diagnosis (yes and no), and history of diabetes at diagnosis (yes and no).

[d]Model 3: adjusted for age at diagnosis (years and continuous), BMI at diagnosis (<25, 25–29, and ≥30 kg/m^2), regular aspirin use at diagnosis (yes and no), history of diabetes at diagnosis (yes and no), stage (T1b–T3a vs. T3b/T4/N1), Gleason score [≤6, 7(3+4), 7(4+3), 8(4+4), and 9–10], and PSA at diagnosis (<10, 10–20, and >20 ng/mL).

association was attenuated when adjusting for clinical factors. Our data showed none of the focal atrophy lesions were associated with lethal prostate cancer.

Relatively few studies have examined the association between intraprostatic inflammation and prostate cancer aggressiveness (9–11). Klink and colleagues (9) and Irani and colleagues (10) both reported that inflammation (not distinguishing chronic or acute) was positively associated with biochemical recurrence among men treated with radical prostatectomy, yet the association became nonsignificant after adjusting for pathologic features. In a case–control study among men diagnosed with stage T1a–b prostate cancer through TURP (11), neither acute nor chronic inflammation was found to be significantly associated with prostate cancer–specific death, but there was a suggestion of a positive association for chronic inflammation.

In this study, we found presence of acute and chronic inflammation to be inversely associated with progression to lethal prostate cancer. There are several potential reasons to explain the different findings in our study. We evaluated inflammation comprehensively in both tumor and adjacent normal tissue, whereas the positive association reported by Klink and colleagues (9) and Irani and colleagues (10) both restricted inflammation within the tumor. Moreover, our study used lethal prostate cancer as the endpoint compared with biochemical recurrences which was used by Klink and colleagues (9) and Irani and colleagues (10). While the study by Davidsson and colleagues (11) used the same inflammation evaluation and lethal endpoint as our study, the tumor specimens were from TURP arising primarily in the transitional zone, compared with the majority of RP tumor specimens in our study. The difference in study population may also play a role in the differences observed; the study by Davidsson and colleagues (11) only included T1a or T1b tumors from an active surveillance cohort, while our study included men with advanced stage tumors treated by radical prostatectomy. Interestingly, when restricting to cases with localized stage in our study, the inverse association between chronic inflammation and lethal prostate became even stronger.

Our findings provide supportive evidence that innate and adaptive immune cells may play an antitumorigenic role at some time point in the continuum of tumor development and progression. Biologically, it is plausible that a robust immune response in the tumor microenvironment may play a role in preventing prostate cancer growth. Previous research has suggested specific immune cells are important in the antitumorigenic immune response (21); further studies are needed to understand which immune cells are influencing our findings. In a recent study by Hempel and colleagues, the presence of intratumoral mast cells was found to be inversely associated with prostate cancer recurrence after prostatectomy taking into account prognostic factors (22).

Studies from the Finnish prostate cancer screening trial (23) and Reduction by Dutasteride of prostate cancer Events study (REDUCE; ref. 24) reported that men who were biopsy negative for prostate cancer had a lower prostate cancer risk if inflammation was present in their biopsy. However, Platz and colleagues (25) showed a positive association between benign tissue inflammation and prostate cancer risk in their prospective study

of men without biopsy indication (regardless of PSA level) and argued that the Finnish and REDUCE studies could be biased by detection as inflammation might lead to a higher PSA concentration. As both the Finnish and REDUCE studies required men to have had a negative biopsy following an elevated PSA, it is possible those men with elevated PSA leading to a negative biopsy may indeed be more likely to have a smaller risk for cancer on a follow-up biopsy if their initial biopsies showed inflammation because the main determinant of the PSA rise in these men was the inflammation and not cancer. Similarly, for prostate cancer progression, it is possible that men with more intraprostatic inflammation throughout their prostate would be more likely to be detected early due to a PSA rise resulting from the inflammation, and as such have longer survival. However, our study is not likely to be subject to such detection bias, as the association between chronic inflammation and lethal prostate cancer remained inverse after adjusted for PSA at diagnosis or restricting patients to those diagnosed in the PSA era when the majority of participants in HPFS and PHS were routinely screened.

Although it has been suggested that focal atrophy may give rise to prostate cancer both through or independently of high-grade prostatic intraepithelial neoplasia (hgPIN; refs. 6, 26), studies evaluating the relationship between focal atrophy and prostate cancer risk or aggressiveness have shown inconsistent findings. A morphologic transition from PIA to hgPIN and to prostate cancer has been observed histologically (26), yet other studies have not observed an association between focal atrophy and prostate cancer risk (27, 28). With respect to outcomes in men with prostate cancer, a cross-sectional study nested in the REDUCE cohort found that baseline focal atrophy is associated with lower Gleason score (29) and lower prostate cancer volumes (30). In our data, all four types of focal atrophy were more often detected in prostate cancer with localized stage disease or with a low PSA level at diagnosis. Neither Davidsson and colleagues (11) or our study observed an association between focal atrophy in prostate cancer specimens and progression to lethal prostate cancer. However, our data suggested an inverse relationship between simple atrophy and fatal prostate cancer.

ERG, PTEN, and perineural invasion are important biomarkers in prostate cancer. The ERG gene fusion is the most common somatic event in prostate cancer, and there is compelling evidence to suggest fusion may play a role in prostate cancer progression through its cooperation with other events or alterations (19, 20). In addition, both presence of perineural invasion and PTEN loss has been associated with worse prostate cancer outcomes (18, 19). Interestingly, in our samples we found presence of acute inflammation was inversely associated with complete PTEN loss, and previous animal study reported that loss of PTEN in tumor cells decreases T-cell trafficking into tumors (31). We did not observe any other associations between these molecular subtypes and inflammation or focal atrophy. This may be limited by statistical power, as PTEN or ERG information was only available for 689 and 828 men, respectively.

The strengths of this study include long-term follow-up, prospectively monitored and validated prostate cancer outcomes, and central pathologic review for all morphologic features, which reduces measurement error and interobserver variations. We also used distant metastases and prostate cancer–specific death to define outcomes, which are the most clinically relevant endpoints for prostate cancer. Moreover, using prostatectomy specimens provides a more comprehensive review of the tumor and therefore better accuracy in characterizing the tumor compared with biopsy or TURP specimens. However, our study has limitations to consider. First, although this is the largest study of inflammation and lethal prostate cancer to date, we had a modest number of lethal events despite long-term follow-up, limiting the statistical power to evaluate effect modifications. Second, our results may not be generalizable to other racial/ethnic groups, as white men primarily comprise the PHS and HPFS cohorts, and racial difference in inflammatory cell composition are evident (32). In particular, black men are more likely to have tumors arising in the transitional zone, which may have different types or causes of inflammation. Third, sampling bias is possible because not all slides were available for review. However, if an advanced tumor is more likely to be classified as having inflammation due to more slides reviewed, and subsequently more likely to develop lethal prostate cancer, we would expect a positive association between inflammation and lethal prostate cancer. We observed an inverse association between inflammation and lethal prostate cancer, therefore the sampling bias is likely to pull the true association toward the null. Fourth, as our pathologist was blinded to patients' information, nondifferential misclassification of inflammation or atrophy was possible, and it would also bias the association toward null. Also, as data for several potential confounders (e.g., family history) were not available, a possibility of residual confounding exists. Finally, we were only able to characterize inflammation on H & E slides according to the presence and percentage of overall lymphocytes. Future studies may want to classify inflammation with more detailed information, such as location and specific cell types present.

In summary, this study adds to evidence that the presence of inflammation, particularly chronic inflammation, in prostate cancer tissue may be associated with better prostate cancer–specific survival, while none of the atrophic lesions were associated with lethal prostate cancer. Our findings support the inclusion of chronic inflammation as a standardized component of pathologic review of prostate tissue specimens, and provide evidence for the use of these markers in prognostic prediction and treatment decisions if future studies with greater sample size confirm our results.

Disclosure of Potential Conflicts of Interest

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Authors' Contributions

Conception and design: Y. Zhang, C.K. Zhou, M. Loda, A.M. De Marzo, L.A. Mucci, E.M. Ebot

Development of methodology: Y. Zhang, C.K. Zhou, M. Loda

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.K. Zhou, T.L. Lotan, M. Loda, F. Giunchi, L.A. Mucci, M. Fiorentino

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Zhang, C.K. Zhou, E.M. Rencsok, M. Loda

Writing, review, and/or revision of the manuscript: Y. Zhang, C.K. Zhou, E.M. Rencsok, K. Fall, T.L. Lotan, M. Loda, E.A. Platz, A.M. De Marzo, L.A. Mucci, E.M. Ebot
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.K. Zhou, F. Giunchi
Study supervision: L.A. Mucci, E.M. Ebot

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