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ORIGINAL ARTICLE

# Prostate chronic inflammation type IV and prostate cancer risk in patients undergoing first biopsy set: Results of a large cohort study



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## KEYWORDS

Prostate;  
Prostate cancer;  
Prostate specific antigen;  
Prostate biopsy;  
Chronic inflammation;  
Prostate volume;  
Biopsy Gleason score

**Abstract** *Objective:* In prostate specimens, chronic inflammatory infiltrate (CII) type IV has been detected, but its association with prostate cancer (PCa) is controversial. The aim of the present study is to investigate on associations of CII with PCa detection in patients undergoing prostate first biopsy set.

*Methods:* Ultrasound transrectal-guided biopsies by the transperineal approach were retrospectively evaluated in 441 consecutive patients. The study excluded patients who were in active surveillance, prostate specific antigen (PSA)  $\geq 30$  ng/mL, re-biopsies, incidental PCa after transurethral resection of the prostate (TURP), less than 14 cores or metastatic. Analysis of population and subpopulations (with or without PCa) was performed by statistical methods which included Mann–Whitney (*U* test), Kruskal–Wallis test, Chi-squared statistic, logistic regression. Multivariate logistic regression models predicting mean probability of PCa detection were established.

*Results:* PCa detection rate was 46.03%. Age, PSA, prostate volume (PV), prostate intraepithelial neoplasia (PIN) and CII were the significant independent predictors of PCa detection. PV (OR = 0.934) and CII (OR = 0.192) were both negative independent predictors. CII was a significant negative independent predictor in multivariate logistic regression models predicting the mean probability of PCa detection by age, PSA and PV. The inverse association of CII with PCa does not necessary mean protection because of PSA confounding.

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*Conclusion:* In a population of patients undergoing prostate first biopsy set, CII was a strong negative independent predictor of PCa detection. CII type IV should be considered as an adjunctive parameter in re-biopsy or active surveillance protocols.

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## 1. Introduction

The concept of zonal anatomy is used to indicate origin and location of growing processes within the prostate [1]. The two major diseases affecting the human prostate are benign prostate hyperplasia (BPH) and prostate cancer (PCa), and the former predominantly develops within the transition zone while the latter in the peripheral part of the gland.

The prostate gland may also undergo chronic inflammatory processes. The prostate is considered an immunocompetent organ and its environment is populated by inflammatory cells including T and B lymphocytes, macrophages and mast cells [2,3]. The histology of proliferative inflammatory atrophy (PIA), which appears as simple atrophy or postatrophic hyperplasia, includes proliferative glandular epithelium and associates with inflammation [3]. It has been suggested that infiltrates and mediators of chronic inflammation might be involved in PCa carcinogenesis [4–12]. Basic science has shown that chronic inflammation plays an important role in human carcinogenesis [2,3]; indeed, development and progression of cancer might be related to reactive oxygen and nitrogen species developing in tissue microenvironment after related damage and regeneration [13–21]. Experimental and epidemiologic studies show that estrogens might also have an independent role in chronic inflammation and PCa carcinogenesis [22–26]. There are studies showing that chronic inflammation is the link between BPH and PCa [27,28]. Because of the association of chronic inflammation with oxidative stress which is mediated by the cyclo-oxygenase (COX) gene pathway, it has been proposed that aspirin, which is a nonsteroidal anti-inflammatory drug, might prevent PCa carcinogenesis by inhibiting COXs [29–31]. However, the inflammatory infiltrate includes cells of both the innate (e.g., monocytes and macrophages) and adaptive (B and T lymphocytes) immune system which is currently used for PCa immunotherapy strategies [5,32].

Clinically, the prostatitis syndromes have been classified in four categories by the National Institutes of Health (NIH) [33]. The last category is named type IV and is diagnosed in patients who have no history of genitourinary tract pain complaints, but undergo prostate biopsy for evaluation of possible PCa because of increased serum prostate specific antigen (PSA) level, abnormal digital rectal exam (DRE) or both. The presence of chronic inflammatory infiltrate (CII) has been detected in prostate specimens and might be involved in the growing processes involving both PCa and BPH [34–37]. However, the nature of the association of CII with PCa is a matter of controversy and still holds unsettled.

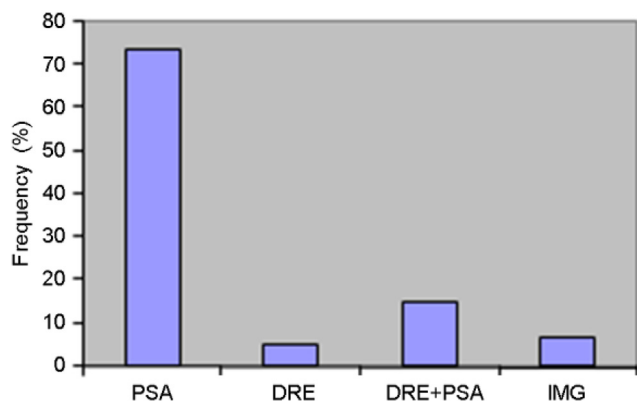
The aim of the present study was to investigate on associations, if any, of CII with PCa detection in a population of patients who were referred to our institution for a first set biopsy because of suspected PCa.

## 2. Materials and methods

We retrospectively reviewed the records of 1260 patients who underwent transrectal ultrasound biopsy (TRUSB) at our institution from September 2010 to September 2014. Excluding criteria were as follows: (i) prostate re-biopsy, (ii) patients in active surveillance, (iii) PSA  $\geq$  30 mg/dL, (iv) metastatic patients, (v) number of biopsy cores less than 14, (vi) incidental PCa after transurethral resection of the prostate (TURP) and (vii) painful rectal exam. After excluding criteria, indications of TRUSB included increased serum PSA levels, abnormal DRE with normal PSA, increased PSA and abnormal DRE (DRE + PSA), abnormal ultrasound imaging of the prostate with normal PSA. Abnormal DRE findings were as follows: diffusely hard prostate, discrete firm area, irregular contours or prominent lobe asymmetry. Family history of PCa (Fam PCa) and treatment with inhibitors of the enzyme 5- $\alpha$  reductase (5-ARI) were also investigated. Age (years) and body mass index (BMI, kg/m<sup>2</sup>) were calculated in each patient. PSA was measured by immuno-radiometric test (normal range: 2–4 mg/dL). The volume of the prostate (PV) was measured by TRUS before performing biopsies. PV was determined by using the formula for an ellipsoid when viewed 3-dimensionally and the formula was transformed into volume (mL). The density of PSA (PSAD) was also computed.

In each biopsy core, the dedicated pathologists systematically assessed the following issues: (i) length, (ii) detection and grade of PCa according to the Gleason score system (biopsy Gleason score: BGS), (iii) length of biopsy core involved by PCa, (iv) prostatic intraepithelial neoplasia (PIN), (v) chronic inflammatory infiltrate (CII), (vi) glandular atrophy (GA) and (vii) atypical small acinar cell proliferation (ASAP). Chronic inflammation criteria, which have already been reported [9,10], included inflammatory cell infiltrate composed predominantly of lymphocytes associated with admixed plasma cells showing a periglandular distribution pattern. Sheets of neutrophils around and within the glands as well as aspects granulomatous prostatitis were the histopathology criteria which excluded a diagnosis of CII of the prostate.

According to biopsy outcome, the patient population was clustered in subpopulations with or without PCa. Summary statistics of population and subpopulations (with or without PCa) were calculated, and included means (SD) for continuous variables as well as proportions (rates) for



**Figure 1** Prostate biopsy indications. PSA, increased serum prostate specific antigen values; DRE, abnormal digital rectal exam with normal PSA values; DRE+PSA, both DRE and increased PSA; IMG, abnormal prostate imaging with normal PSA values.

categorical variables. The tests of Mann–Whitney (*U* test) and Kruskal–Wallis were used to compare continuous variables. The Chi-squared statistic was computed to test categorical variables. Covariates associating with PCa detection were investigated by logistic regression. PCa mean probability logistic regression models were computed after assessing independent predictive variables. All tests were two-sided, with a significance level of 0.05.

### 3. Results

After excluding criteria, 441 patients were available for assessment. Prostate biopsy indications are depicted by Fig. 1. As depicted in Fig. 1, prostate biopsies were indicated because of increased serum PSA values (73.70%, 325/441), abnormal DRE with normal PSA values (4.76%, 21/441), both abnormal DRE and increased PSA (14.97%, 66/441), abnormal prostate imaging with normal PSA values (6.58%, 29/441).

As shown in Table 1, PCa was detected in 203 out of 441 patients (detection rate 46.03%). The PCa subpopulation,

**Table 1** Statistics of the population and subpopulations of patients (with or without PCa) undergoing prostate biopsy.

Variables	Population <i>n</i> = 441	PCa		<i>p</i> -Value
		No <i>n</i> = 238 (53.97)	Yes <i>n</i> = 203 (46.03)	
Age (year, mean ± SD)	65.9 ± 8.13	64.4 ± 7.9	67.70 ± 7.9	<0.0001
BMI (kg/m <sup>2</sup> , mean ± SD)	26.54 ± 3.4	26.58 ± 3.5	26.5 ± 3.3	0.86
PSA (ng/mL, mean ± SD)	6.91 ± 3.8	6.4 ± 3.1	7.5 ± 4.5	0.045
PV (mL, mean ± SD)	41.1 ± 19.5	47.6 ± 21.3	33.35 ± 13.5	<0.00001
PSAD (ng/mL <sup>2</sup> , mean ± SD)	0.19 ± 0.14	0.15 ± 0.09	0.25 ± 0.17	<0.0001
FAM PCa, <i>n</i> (%)				0.27
No	376 (85.3)	207 (46.9)	169 (38.3)	
Yes	65 (14.7)	31 (7.0)	34 (7.7)	
5-ARI, <i>n</i> (%)				0.41
No	421 (95.5)	229 (51.9)	192 (43.5)	
Yes	20 (4.5)	9 (2.0)	11 (2.5)	
SMK, <i>n</i> (%)				0.52
No	231 (52.4)	128 (29.0)	103 (23.4)	
Yes	210 (47.6)	110 (24.9)	100 (22.7)	
DRE, <i>n</i> (%)				0.23
No	420 (95.2)	224 (50.8)	196 (44.4)	
Yes	21 (4.8)	14 (3.2)	7 (1.6)	
GA, <i>n</i> (%)				0.01
No	411 (93.2)	215 (48.89)	196 (44.4)	
Yes	30 (6.8)	23 (5.2)	7 (1.6)	
ASAP, <i>n</i> (%)				0.72
No	384 (87.1)	206 (47.7)	178 (40.4)	
Yes	57 (12.9)	32 (7.3)	25 (5.7)	
PIN, <i>n</i> (%)				0.002
No	421 (95.5)	234 (53.1)	187 (42.4)	
Yes	20 (4.5)	4 (0.9)	16 (3.6)	
CII, <i>n</i> (%)				<0.0001
No	348 (78.9)	162 (36.7)	186 (42.2)	
Yes	93 (21.1)	76 (17.2)	17 (3.9)	

BMI, body mass index; PCa, prostate cancer; PSA, total prostate specific antigen; PV, prostate volume; PSAD, prostate specific antigen density; FAM PCa, family prostate cancer; 5-ARI, 5  $\alpha$ -reductase inhibitor; SMK, smoking; DRE, digital rectal exam; GA, glandular atrophy; ASAP, atypical small acinar proliferation; PIN, prostate intraepithelial neoplasia; CII, chronic inflammatory infiltrate.

when compared to the group without PCa, showed to be significantly older with higher mean values of PSA; however, PV was significantly smaller and the corresponding density higher. When considering the variables relating to histopathology, CII, GA and PIN significantly were associated with PCa; moreover, the association was inverse in the first two (CII and GA) and direct in the latter (PIN). BMI, Fam PCa, 5-ARI, abnormal DRE and ASAP did not show any significant association in the detection of PCa. Fig. 2 shows the negative association of CII and PCa.

Table 2 shows that the results of univariate and multivariate logistic regression analysis of variables associating with PCa detection. Age, PSA, PV, CII and PIN were the significant independent predictive variables associating with PCa detection in the final multivariate logistic regression model. Moreover, the association was positive with age (OR = 1.076), PSA (OR = 1.200) and PIN (OR = 3.875), and negative with CII (OR = 0.192) and PV (OR = 0.934).

Table 3 includes six multivariate logistic regression models which are all significant in predicting the mean probability of PCa detection. The models are stratified by the presence (+) or absence (−) of CII which might interact (models B, D, F) or not (models A, C, E) with the significant continuous variables including age (model A, B), PSA (models C, D) and PV (models E, F). Fig. 3 depicts the curves stratified by CII of the six models which are reported in Table 3. As shown, the probability curves of models A, C, E have different intercepts but same slopes, while the curves of models B, D, F have different slopes but same intercepts. Interestingly, models A, B, C, D show that the mean probability of detecting PCa is decreased by the presence of CII and models E, F give evidence that the inverse risk of

detecting PCa by PV is even more decreased when CII is present in the biopsy cores.

#### 4. Discussion

In the present study, CII inversely and independently associated with PCa detection. An inverse association between CII and PCa has been reported by previous and recent studies [35–44]; however, the subject has also been approached by other investigators who failed to detect any association at all [45–47]. Although our findings suggest that the presence of CII decreases the probability of detecting PCa, the negative association of CII with PCa does not necessary mean causation. Trying to explain the reason of such negative association of CII with PCa detection is a hard task, however, as a theory, CII might protect from the different steps involving PCa genesis. Indeed, it is interesting to realize that recently anticancer vaccines and immunotherapies focus on empowering the immune system to overcome the tumor [48–50]. Vaccine therapy or immunotherapies aim to stimulate the immune system and activate an appropriate immune-mediate response against malignant cells. The immune system consists of innate and adaptive components. The innate immune system encompasses phagocytic cells, natural killer cells, and cells that release inflammatory mediators. Macrophages and dendritic cells function as antigen presenting cells which serve as a bridge from innate to adaptive immunity. The adaptive arm of the immune system consists of B cells and T cells. The T cells are the most crucial component in mediating antitumor responses induced by cancer vaccines and immunotherapies. In the prostate microenvironment, CII might induce the liberation of tumor related antigens which stimulate the components of the immune system. Basic science studies are mandatory in order to assess the nature of the inflammatory infiltrate and its impact on the androgenic receptors gene in the prostate gland microenvironment. According to the improving evidence of PCa immunotherapy efficacy and the results of the present study, we propose, as illustrated in Fig. 4, a schematic mechanistic diagram showing the potential cellular exchange of signaling pathways towards inflammation in PCa. Indeed, in early stages of PCa carcinogenesis, high grade PIN associates with disruption of the basement membrane which allows the cancer cell to migrate into the prostate microenvironment where they are attached by inflammatory cells with delivery of tumor antigens. Moreover, macrophages and dendritic cells expose the antigens to both helper (CD4<sup>+</sup>) and cytotoxic (CD8<sup>+</sup>) T lymphocytes which trigger a cytotoxic response against the cancer cells structuring the focus of high grade PIN. As a consequence, PCa carcinogenesis progression might be interrupted and the risk of PCa is reduced because of the activated immune system.

In the current study, it was shown that PV inversely associated with PCa. This finding confirms what has already been reported [51,52]. Moreover, our study gives evidence how the mean probability of detecting PCa by PV may be decreased by the presence of CII. For example (see model E in Table 3 and Fig. 1), the probability of detecting PCa of PV of 40 mL decreases by 60%–20% by the presence of CII (OR = 0.113).

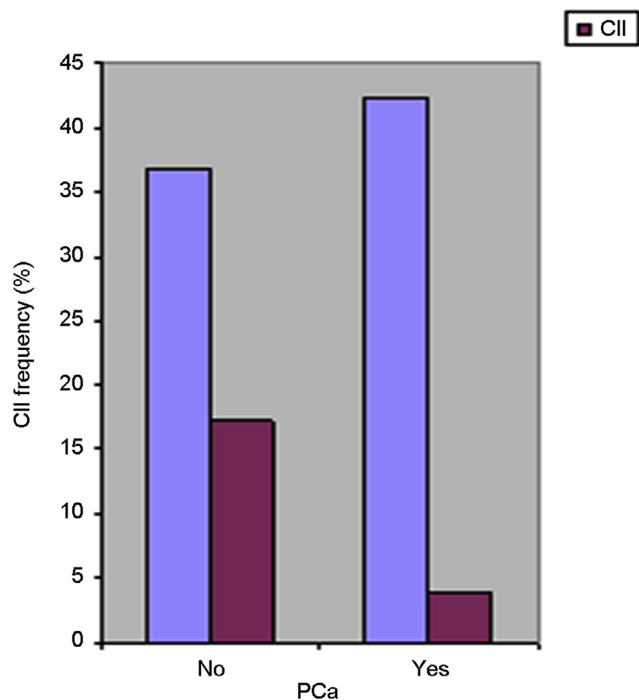


Figure 2 Associations of CII with PCa. CII, chronic inflammatory infiltrate; PCa, prostate cancer.

**Table 2** Logistic regression analysis of covariates associating with PCa detection (dependent variable) in patients who underwent TRUSB ( $n = 441$ ).

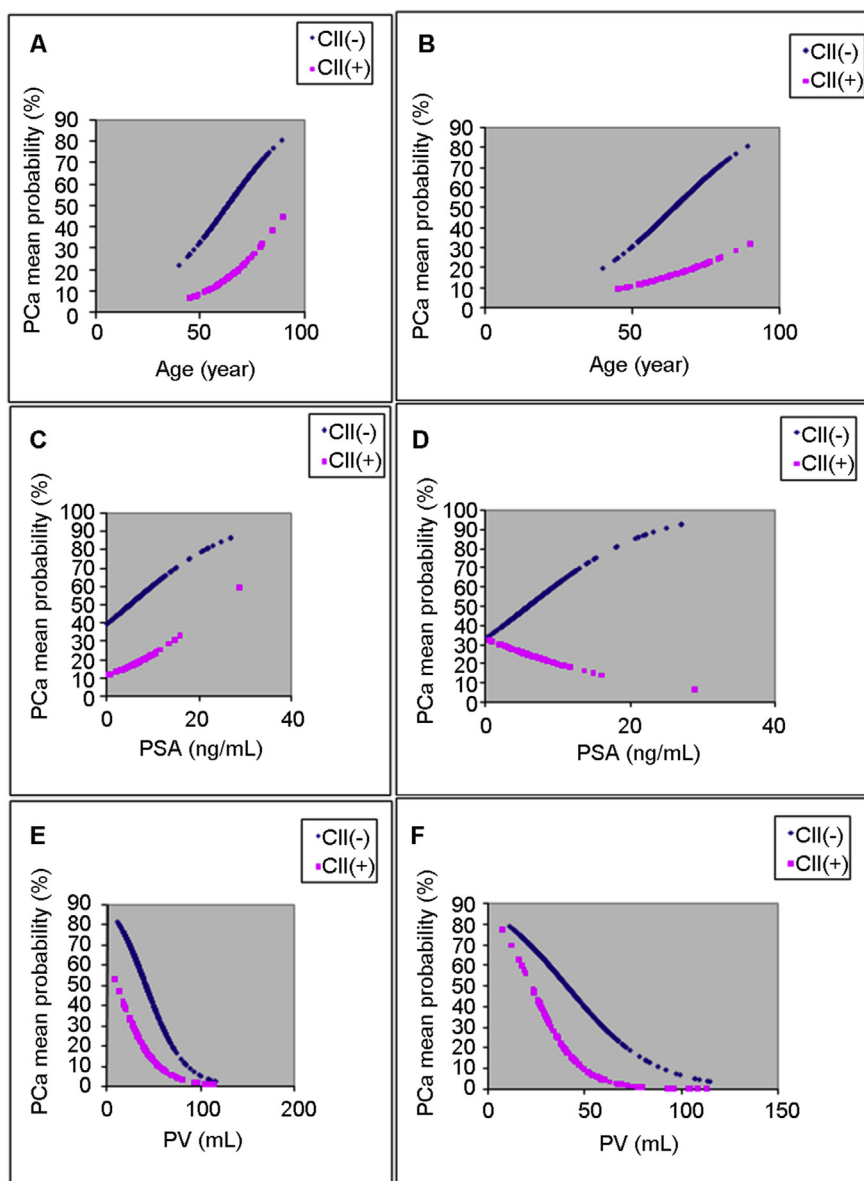
Covariates	B	SE	OR	95%CI of OR		p-Value
				INF	SUP	
<i>Univariate logistic regression analysis</i>						
Age	0.051	0.12	1.052	1.027	1.078	<0.001
PSA	0.008	0.027	1.083	1.027	1.143	0.003
PV	-0.050	0.007	0.951	0.938	0.964	<0.0001
PVD	8.421	1.223	4541.760	413.647	49867.577	<0.0001
CII	-1.636	0.289	0.195	0.111	0.343	<0.0001
GA	-1.097	0.443	0.334	0.140	0.795	0.013
PIN	1.011	0.568	5.005	1.646	15.224	0.005
<i>Multivariate logistic regression analysis</i>						
Age	0.072	0.015	1.075	1.043	1.107	<0.0001
PSA	0.162	0.080	1.176	1.006	1.375	0.042
PV	-0.065	0.015	0.937	0.937	0.909	<0.0001
PVD	0.452	2.538	1.571	0.011	227.302	0.859
CII	-1.657	0.338	0.191	0.098	0.370	<0.00001
GA	-0.788	0.516	0.455	0.165	1.1250	0.127
PIN	1.390	0.624	4.017	1.182	13.651	0.026
<i>Final multivariate logistic regression model predicting PCa</i>						
Age	0.073	0.015	1.076	1.044	1.109	<0.0001
PSA	0.183	0.040	1.200	1.109	1.299	<0.0001
PV	-0.068	0.009	0.934	0.918	0.950	<0.0001
CII	-1.653	0.336	0.192	0.099	0.370	<0.0001
PIN	1.354	0.616	3.875	1.158	12.966	0.028
Intercept	-3.299	0.982	0.037			0.001

B, regression coefficient; SE, standard error; OR, odds ratio; PCa, prostate cancer; PSA, prostate specific antigen; PV, prostate volume; PIN, prostate intraepithelial neoplasia; CII, chronic inflammatory infiltrate.

**Table 3** Multivariate logistic regression models predicting PCa in patients undergoing biopsy.

Model	Covariates	B	SE	OR	95%CI of OR		p-Value
					INF	SUP	
A	Age	0.055	0.013	1.056	1.030	1.084	<0.0001
	CII	-1.693	0.295	0.184	0.103	0.328	<0.0001
	Intercept	-3.478	0.867	0.031			<0.0001
B	Age	0.058	0.13	1.060	1.033	1.088	<0.0001
	CII $\times$ age	-0.025	0.04	0.975	0.967	0.984	<0.0001
	Intercept	-3.714	0.870	0.024			<0.0001
C	PSA	0.086	0.029	1.090	1.030	1.153	0.003
	CII	-1.666	0.293	0.189	0.106	0.336	<0.0001
	Intercept	-0.447	0.220	0.639			0.042
D	PSA	0.118	0.032	1.125	1.056	1.198	<0.0001
	CII $\times$ PSA	-0.188	0.038	0.829	0.769	0.893	<0.0001
	Intercept	-0.714	0.231	0.489			0.002
E	PV	-0.050	0.007	0.952	0.938	0.966	<0.0001
	CII	-1.581	0.305	0.206	0.113	0.374	<0.0001
	Intercept	2.068	0.302	7.913			<0.0001
F	PV	-0.045	0.007	0.956	0.943	0.970	<0.0001
	CII $\times$ PV	-0.037	0.008	0.964	0.948	0.980	<0.0001
	Intercept	1.839	0.293	6.285			<0.0001

PCa, prostate cancer; PSA, prostate specific antigen; PV, prostate volume; CII, chronic inflammatory infiltrate; B, regression coefficient; SE, standard error; OR, odds ratio.



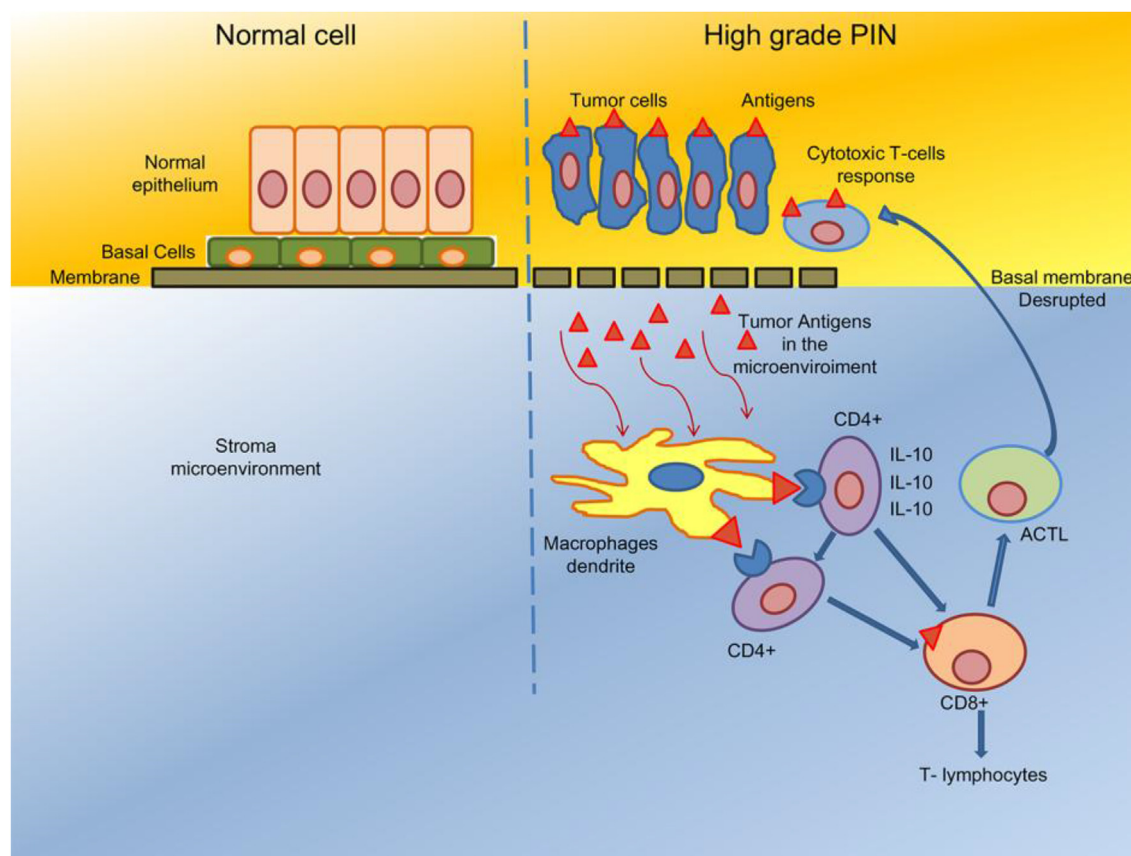
**Figure 3** Probability risk curves stratified by CII of the six models which are reported in Table 3. (A) CII associated with age; (B) CII interacting with age; (C) CII associated with PSA; (D) CII interacting with PSA; (E) CII associated with PV; (F) CII interacting with PV. CII, chronic inflammatory infiltrate; PCa, prostate cancer; PSA, total prostate specific antigen; PV, prostate volume.

PSA selection for prostate biopsy may pose a potential bias because its increments also associate with CII [53–55]. Interestingly, our investigation gives new evidence when dealing with this controversial subject. Indeed, as shown in Table 3 and Fig. 1 (model C and D), for a PSA of 10 ng/mL the mean probability of detecting PCa is decreased by 60%–20% by CII; moreover, when PSA interacts with CII (interaction, model D), two completely different probability curve risks of PCa are depicted. Indeed, the probability risk curve elevates (positive slope) as PSA increases when CII is absent; however, the curve declines (negative slope) when PSA interacts with CII.

There are limits in our study. First, it was single center, but the sample size was enough large. Second, we measured PV by means of TRUS and not by prostatectomy specimens; however, TRUS is widely used and is considered

and effective technique. Finally, the inverse association of chronic inflammation with PCa might be confounded by PSA. Indeed, PSA may elevate by both inflammation and cancer; hence, if biopsies are performed in cases with increased PSA, some patients will have cancer and others CII [53–55]. Patients with inflammation may undergo biopsy procedures more frequently than men without inflammation because of potential higher PSA levels. As a result, men with CII will automatically be less likely to have cancer and vice versa.

In a patient population undergoing first biopsy after prostate assessment, CII of the prostate type IV inversely and independently associated with a reduced risk of PCa. In multivariate logistic mean probability models, CII was an independent prognostic factor which lowered the risk of PCa detection. As a consequence, CII of the prostate



**Figure 4** Schematic mechanistic diagram showing the potential cellular exchange of signaling pathways towards inflammation in prostate cancer; prostatic intraepithelial neoplasia (PIN).

type IV might have drawbacks for approaching and managing prostate diseases. Furthermore, the role of chronic inflammation in PCa carcinogenesis remains a controversial issue which needs further clinical and basic research. In the future, it might be interesting to include in clinical practice other diagnostic elements such as new biomarkers (prostate health index, phi or PCa antigen 3, pca3) and/or multiparametric magnetic resonance imaging in order to investigate the possibility of differentiating the inflammatory infiltrates from high grade PIN or PCa.

CII type IV should be considered as an adjunctive parameter in re-biopsy or active surveillance protocols.

### Conflicts of interest

The authors declare no conflict of interest.

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