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Review Article

The Origin of BPH and Prostate Cancer in Different Prostate Zones and the Impact on the Incidence of Prostate Cancer: A Systematic Review and Update of the Literature for Urologists and Clinicians

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Abstract

Background and objectives: Numerous clinical studies over recent years have reported an inverse relationship between benign prostatic hyperplasia (BPH) size and the incidence of prostate cancer (PCa), leading to the clinical hypothesis that the expanding BPH zone damages the glandular tissue where PCa predominately develops. This systematic review aims to establish a historical basis and reference on the zonal origin of BPH and prostate cancer (PCa) within the prostate.

Methods: Using the PRISMA guidelines, an in-depth review was conducted of studies published in the PubMed database between January 1978 and November 2022. Due to clinical heterogeneity in type of study designs, meta-analysis was not possible, and a narrative review approach was adopted.

Results: Thirty-eight studies met the inclusion criteria, all of which showed that BPH predominantly develops within the transition zone (TZ) and that PCa predominantly develops in the peripheral zone (PZ) of the prostate respectively. This report provides a systemic overview of the historical evolution on the concept of zonal origin for BPH and PCa. The listed studies support the current clinical understanding that BPH mainly originates in the TZ and that the majority of PCa originates in the PZ of the prostate.

Conclusions: To our knowledge, this is the first systemic review on the zonal origin of BPH and PCa and is an important step in the context of evidence-based medicine. This review should encourage other clinicians and investigators to further study the dynamic interactions between the different prostate zones, in particular between the TZ and the PZ, and whether BPH size may be protective against development of PCa.

Introduction

Among elderly men with a prostate condition, 95–98% who have "primary organ disease" have been diagnosed with benign prostatic hyperplasia (BPH), prostate cancer (PCa), or both.[1] Other primary diagnoses of the prostate, such as sarcoma, lymphoma, or metastases from other organ malignancies, have also been reported but are extremely rare.[1] PCa is currently the most common non-skin cancer and second most common cause of cancer-related mortality affecting men in the United States, after lung cancers.[2] Most men older than 50 have histological findings of BPH,[3] and more than 80% of patients with PCa also have histo-anatomical findings of BPH.[3–5] Although BPH and PCa are both common and characterized by tissue growth, the interaction between the two disease states is not well understood.[6] Numerous clinical studies over recent years have reported an inverse relationship between prostate/BPH size and the incidence and aggressiveness of PCa, which supports the hypothesis that increasing prostate size may be protective against PCa.[6] Therefore, studies of the prostate zonal anatomy are critical for gaining a better understanding of the interaction between BPH and PCa.

Keywords: Prostate; Benign prostatic hyperplasia; Prostate cancer.
Abbreviations: BPH, benign prostatic hyperplasia; ER, estrogen receptor; PCa, prostate cancer; PZ, peripheral zone; TZ, transition zone.
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The prostate is separated into three main zones based on its unique embryologic origin and function: the transition zone (TZ), the peripheral zone (PZ), and the central zone.[7] While many clinicians consider the TZ as the main site for BPH development and the PZ as the zone of PCa development,[5] there has never been a systematic literature review confirming these hypotheses. Thus, the purpose of this systematic review is to confirm the basis of the zonal origin of BPH and PCa within the prostate.

Methods

A thorough literature search of the PubMed database was conducted according to the Preferred Reported Items for Systematic Reviews (PRISMA) guidelines.[8] The search terms "origin benign prostatic hyperplasia" OR "origin prostate cancer" AND "prostate zone" were used to identify studies recording the zonal origin of BPH and PCa, respectively. The inclusion criteria for the search were as follows: (1) articles in English, (2) published between the dates of January 1978 and November 2022, (3) cohort studies performed only in humans, (4) data provided a comparison of prostate zones, and (5) incidence of either BPH or PCa reported in the cohorts. The exclusion criteria were as follows: (1) data not specifying the zonal origin of either BPH or PCa, and (2) data not identifying the incidence of BPH or PCa in relation to their zonal origins. Due to clinical heterogeneity in type of study designs, meta-analysis was not possible, and a narrative review approach was adopted. Qualifying data were extracted and all studies that met the inclusion and exclusion criteria have been presented in the following manner: First author of study, journal, year of publication, sample size of patients in the reported cohort, and documented percentages of either BPH or PCa findings within the respective prostate zones. Percentage values are presented as they were published in the listed studies.

The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of the articles and the risk of bias. This scale is designed to evaluate the quality of retrospective cohort studies based on variables observed in the studies.[9] The maximum score possible for each study is nine points. Studies have been classified based on their scores as either low quality (0–3), moderate quality (4–6), or high quality (7–9) (Table 1).[10–47]

Results

Figure 1 shows the literature search strategy and outlines the PRISMA guidelines utilized for study selection in this review.[8] Two reviewers independently searched the literature in PubMed for all relevant studies and collected the data from each report independently. Thirty-eight articles met the inclusion criteria (34 studies for PCa and 4 studies for BPH, respectively). Figure 2 and Table 2 summarize the review results for PCa.[10–43] Table 3 summarizes the results for BPH.[44–47] No information was assumed regarding the zone of origin, and all included studies were retrospective studies.

The sample size of the 38 studies included in this review ranged from 4 to 2,494 patients or specimens, and some of these studies also included large multi-institutional cohorts. For instance, Iremashvili *et al.* investigated the clinicopathological origin of PCa in the PZ on radical prostatectomy specimens.[21] Of the 1,411 surgical specimens included in this review, PCa originated from the PZ in 1,141 (80.9%) cases and from the TZ in only 147 (10.4%) cases.[21] None of the studies included from the PRISMA-guided search revealed a larger percentage of PCa originating from the TZ (Table 2) or BPH originating from the PZ (Table 2).

There were 34 reports on the zonal origin of PCa that included a total of 12,708 prostatic specimens, of which 9,210 (72.5%) specimens originated within the peripheral zone.

Discussion

In our systematic review, 38 studies extracted from the literature showed overwhelming and significant evidence of the zonal origins for both BPH and PCa. For example, Kojima *et al.* found that in 101 (88%) of the 115 patients observed, the primary PCa tumor originated in the PZ while only 14 (12%) cases originated in the TZ.[25] Several additional studies supported this histo-pathological finding but could not be included in this review as they did not meet the inclusion criteria. For instance, Mikolajckyz *et al.* excluded transition zone cancers from their sample selection to focus on the peripheral zone as the prominent site of PCa. They found that pro-prostate-specific antigen levels were significantly higher in the PZ compared to the TZ, supporting their hypothesis that pro-prostate-specific antigen may be a more cancer-specific antigen, and thus a better diagnostic parameter for distinguishing PCa in the PZ from BPH in the TZ.[48]

In another interesting study, Wilson *et al.* analyzed dipeptidyl peptidase IV, a multifunctional type II plasma membrane glycoprotein secreted by the prostate, and found that this protein was increased in PCa.[49] The results showed more activity of dipeptidyl peptidase IV in the PZ compared to the TZ, and that protein expression was significantly higher in patients with PCa compared to their non-cancerous counterparts ($p < 0.0001$).[49] To note a third example, Konishi *et al.* studied transient amplifying cells, a subset of basal cell populations within the prostate from which cancers are thought to originate. Using flow cytometry, they found that the percentage of transient amplifying cell clones was the highest in the PZ in PCa specimens, which could be a possible explanation for why prostate cancer predominantly arises within the PZ.[50] These studies all support the hypothesis of the origin of PCa in the TZ as outlined in this systematic review.

We also found a number of studies confirming the TZ as the origin of BPH, but these studies were not included in this review due to not meeting the inclusion criteria. For example, Tsurusaki *et al.* studied the expression and cellular distribution of estrogen receptors (ERs), which have been implicated in the pathogenesis of BPH.[51] Using *in situ* hybridization and immunohistochemistry, they found that ER_a expression was restricted to the PZ and ER_b was mainly expressed in the TZ, suggesting that ER_b may play an important role in the pathogenesis of BPH in the TZ.[51] McNeal *et al.* published a study demonstrating that BPH predominately originates in the TZ.[46] This study has been cited by many clinical reports in recent years, and its results were confirmed by Fisher *et al.* and Roehrborn *et al.* revealing different gland structures and configurations that may lead to new zonal specific and targeted treatment options for BPH in the near future.[44,47]

The inverse relationship between prostate size and the incidence and aggressiveness of PCa has been well demonstrated in numerous recent clinical studies.[52–55] As prostate volume increases, the incidence of PCa decreases, and patients with larger prostates have also been shown to have a better prognosis.[56] These findings are not challenged in the recent literature, and no systematic reviews or meta-analyses have shown evidence to the contrary.[6,52,55,57–59] This inverse relationship supports the hypothesis that BPH size may be protective against PCa. One potential explanation for this phenomenon could involve dynamic zonal changes in a growing prostate. As a BPH prostate grows, the TZ expands and causes di-

Table 1. Risk of bias assessment using the Newcastle-Ottawa Quality Assessment Scale (NOS)

First Author	Selection (Out of 4)	Comparability (Out of 2)	Outcome (Out of 3)	NOS Score Total (Out of 9)	Quality Classification
Al-Ahmadie HA[10]	4	1	2	7	High
Alver KH[11]	3	1	2	6	Moderate
Barbissan F[12]	2	1	3	6	Moderate
Braun M[13]	4	2	3	9	High
Carroll PR[14]	3	1	2	6	Moderate
Chun FK[15]	3	1	2	6	Moderate
Cohen RJ[16]	4	2	3	9	High
Falzarano[17]	3	1	3	7	High
Garcia JJ[18]	3	1	2	6	Moderate
Gopalan A[19]	3	1	2	6	Moderate
Greene DR[20]	4	1	3	8	High
Iremashvili[21]	3	1	3	7	High
Kanao K[22]	3	1	2	6	Moderate
Kimura T[23]	3	1	3	7	High
King CR[24]	2	1	3	6	Moderate
Kojima M[25]	3	1	3	7	High
Lee F[26]	3	1	3	7	High
Li Y[27]	3	1	3	7	High
Mahjoub S[28]	4	1	3	8	High
McNeal JE[29]	3	1	1	5	Moderate
McNeal JE[30]	3	1	1	5	Moderate
Nevoux P[31]	4	1	3	8	High
O'Neil LM[32]	2	1	3	6	Moderate
Ohori M[33]	3	1	2	6	Moderate
Pepe P[34]	3	1	3	7	High
Reissigl A[35]	4	1	2	7	High
Sakai I[36]	4	2	3	9	High
Sakai I[37]	3	1	3	7	High
Sato S[38]	3	1	3	7	High
Sinnott M[39]	4	1	3	8	High
Stamatiou KN[40]	3	1	2	6	Moderate
Takamatsu[41]	4	1	3	8	High
Zhen L[42]	3	1	3	7	High
Zhou Y[43]	3	1	3	7	High
Fisher JD[44]	-	-	-		
Jones DR[45]	3	1	2	6	Moderate
McNeal J[46]	3	1	2	6	Moderate
Roehrborn CM[47]	-	-	-		

rect mechanical pressure on the outer PZ, which is trapped within the prostate capsule. As histological studies have shown, this growth-related mechanical pressure and stress can lead to fibrosis and glandular tissue atrophy within the PZ, where 80–85% of PCa originates.[60–63] This dynamic interaction between the prostate zones may explain the decreased incidence of PCa in patients with larger BPH prostates. However, the assumption that BPH predominantly originates in the TZ and PCa predominately originates in

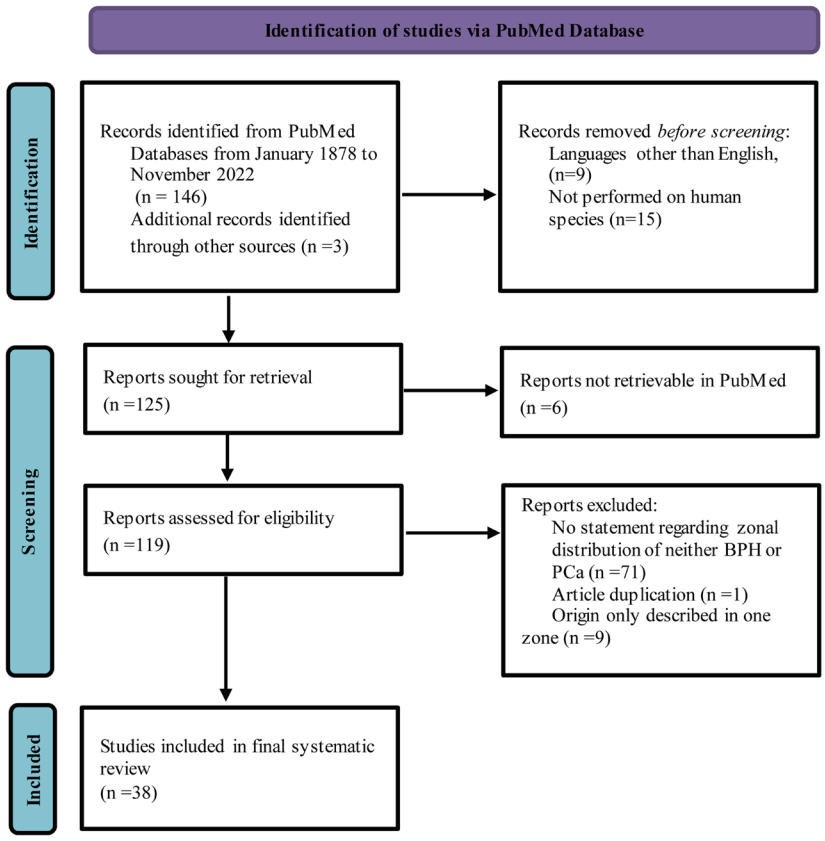

Fig. 1. PRISMA flowchart for literature search and study selection, modified according to Page *et al.*[8]

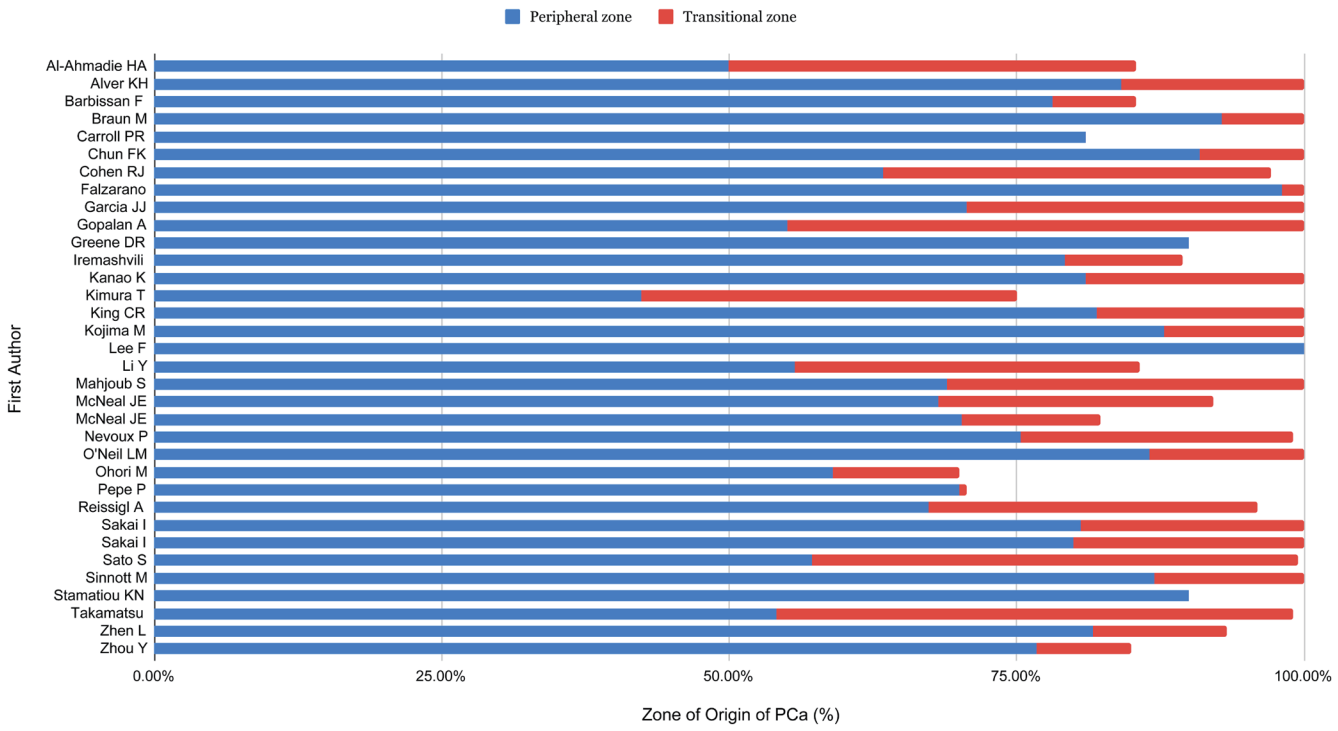

Fig. 2. Studies investigating the zonal origin of PCa. PCa, prostate cancer.

Table 2. Studies investigating the zonal origin of PCa

First Author	Journal	Year	N*	Number of prostatic tumor specimens with PZ origin (%)	Number of prostatic tumor specimens with TZ origin (%)	Does the study support that PCa originates primarily in the PZ?
Al-Ahmadie HA[10]	Am J Surg Pathol.	2008	197	97 (49.9%)	70 (35.5%)	Yes
Alver KH[11]	J Magn Reson Imaging.	2022	63	53 (84.1%)	10 (15.9%)	Yes
Barbissan F[12]	BJU Int.	2009	123	96 (78.1%)	9 (7.3%)	Yes
Braun M[13]	Histopathology	2011	156	145 (92.9%)	11 (7.1%)	Yes
Carroll PR[14]	J Urol	1992	17	14 (81%) **	0 (0%)	Yes
Chun FK[15]	Eur Urol	2007	1262	1147 (90.9%)	115 (9.1%)	Yes
Cohen RJ[16]	J Urol.	2008	2494	1589 (63.37%)	842 (33.8%)	Yes
Falzarano[17]	J Urol	2010	106	104 (98.1%)	2 (1.9%)	Yes
Garcia JJ[18]	Am J Surg Pathol	2008	215	152 (70.7%)	63 (29.3%)	Yes
Gopalan A[19]	Histopathology	2013	136	75 (55.1%)	61 (44.9%)	Yes
Greene DR[20]	Br J Urol	1991	96	86 (90%) **	-	Yes
Iremashvili[21]	Urology	2012	1441	1141 (79.2%)	147 (10.2%)	Yes
Kanao K[22]	BJU Int	2013	800	648 (81.0%)	152 (19.0%)	Yes
Kimura T[23]	Pathol Int	2012	92	39 (42.4%)	30 (32.6%)	Yes
King CR[24]	Urol Oncol	2008	494	405 (82.0%)	89 (18.0%)	Yes
Kojima M[25]	Urology	1998	115	101 (87.8%)	14 (12.2%)	Yes
Lee F[26]	Prostate	1985	4	4 (100%)	0 (0%)	Yes
Li Y[27]	BJU Int	2020	203	113 (55.7%)	61 (30%)	Yes
Mahjoub S[28]	Eur J Radiol	2020	309	213 (68.9%)	96 (31.1%)	Yes
McNeal JE[29]	Am J Surg Pathol	1988	88	60 (68.2%)	21 (23.9%)	Yes
McNeal JE[30]	Prostate	2001	571	401 (70.2%)	69 (12.1%)	Yes
Nevoux P[31]	BJU Int	2012	215	162 (75.3%)	53 (24.7%)	Yes
O'Neil LM[32]	BJU Int	2015	382	331 (86.6%)	51 (13.4%)	Yes
Ohori M[33]	Mod Pathol.	2004	1148	677 (59.0%) **	126 (11.0%) **	Yes
Pepe P[34]	Int Braz J Urol	2015	180	126 (70.0%)	1 (.6%)	Yes
Reissigl A[35]	Cancer	1997	98	66 (67.3%)	28 (28.6%)	Yes
Sakai I[36]	BJU Int	2005	124	100 (80.6%)	24 (19.4%)	Yes
Sakai I[37]	Int J Urol	2006	134	107 (79.9%)	27 (20.1%)	Yes
Sato S[38]	BJUI Compass	2020	201	115 (57.2%)	85 (42.3%)	Yes
Sinnott M[39]	Prostate	2012	54	47 (87.0%)	7 (13.0%)	Yes
Stamatiou KN[40]	Med Sci Monit.	2009	50	45 (90.0%)	-	Yes
Takamatsu[41]	Urol Oncol	2019	638	345 (54.1%)	293 (45.9%)	Yes
Zhen L[42]	Eur J Med Res	2022	429	350 (81.6%)	50 (11.7%)	Yes
Zhou Y[43]	Prostate	2021	73	56 (76.7%)	6 (8.2%)	Yes

*N = number of prostatic tumor specimens studied; ** Study reported percentages only, total number of specimens recalculated. PCa, prostate cancer; PZ, peripheral zone; TZ, transition zone.

the PZ is crucial for this outlined hypothesis. Although this assumption is a well-accepted clinical concept, to the best of our knowledge a systematic literature review on this important question has never been reported.

There are some limitations of this review. First, only a relatively small number of articles met the inclusion criteria. There was a significantly greater number of studies on the origin of PCa (34) than studies on the origin of BPH (4). This is likely due to the exceedingly clinical importance of PCa as the most common non-skin related cancer affecting men worldwide.[5] There could also be

Table 3. Studies investigating zonal origin of BPH

First Author	Journal	Year	N*	Number of benign hyperplastic lesions with PZ origin (%)	Number of benign hyperplastic lesions with TZ origin (%)	Does this support that BPH originates from the TZ?
Fisher JD[44]	Urology in service and board review	2013	–	–	–	Yes
Jones DR[45]	Br J Urol.	1990	71	54 (76%)	–	Yes
McNeal J[46]	Urology	1996	32	32 (100%)	0%	Yes
Roehrborn CM[47]	Campbell's Urology ed. 9	2007	NA		–	Yes

*N = number of specimens studied. BPH, benign prostatic hyperplasia; PZ, peripheral zone; TZ, transition zone.

a bias of excluding specimens from the less-accepted zonal origins of PCa and BPH, respectively. Several studies started with larger cohorts but excluded various specimens in order to appropriately differentiate the zone of origin. For example, Reissigl *et al.* initially began their study with 340 patients for prostate biopsy due to elevated prostate-specific antigen levels, then 98 of the 340 men had biopsy-proven prostate cancer and were included in their final study analysis.[35] Additionally, all of the studies included in this review were retrospective cohort studies. A broader variety of study types, such as prospective and multi-institutional studies, would increase statistical power and the validity of the presented conclusions. Our study was also limited to the PubMed database. Using other databases and search engines could provide a wider breadth of articles and more representative data. Also, in more advanced cases it is difficult for researchers to accurately identify the origin of PCa. For most studies the origin was assigned to the zone where more than 70% of the cancerous tissue was located.[37] However, the current literature lacks a definite approach in specifying the zonal origin.

Despite these limitations, this systematic literature review of the last 44 years provides an important and relevant update on the zonal origins of two clinically significant prostate diseases in elderly men. The presented data confirm that BPH growth predominantly occurs in the TZ, whereas the majority of PCa originates in the PZ of the prostate. As recent literature indicates that dynamic zonal interactions may play a role in the development or suppression of PCa, it is crucial that the literature provides a reliable historical basis for the zonal origin of these two urologic diseases.

Future directions

This review provides insight for clinicians and researchers to further investigate the zonal interactions related to BPH growth and its possible effect on PCa development. A better understanding of the relationship between BPH/prostate size and PCa development will greatly influence future diagnostics and treatment of both BPH and PCa.[64]

Conclusions

To our knowledge, no systematic review on the zonal origin of BPH and PCa has been published. This systematic review summarizes the etiologic literature as an important step in evidence-based medicine on this topic. This review supports the current clinical understanding that BPH predominantly originates in the TZ, whereas the majority of PCa arises from the PZ of the prostate. As BPH and PCa are very common and significant diseases in the elderly population, this review should encourage future studies on dynamic zonal interactions between BPH and PCa.

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Conflict of interest

None.

Author contributions

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