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Systematic Review Links the Prevalence of Intraductal Carcinoma of the Prostate to Prostate Cancer Risk Categories

Laura H. Porter [a,b,†], *Mitchell G. Lawrence* [a,b,†], *Dragan Ilic* [c], *David Clouston* [d], *Damien M. Bolton* [e,f], *Mark Frydenberg* [a,g], *Declan G. Murphy* [h,i,j,*], *Carmel Pezaro* [a,k,†], *Gail P. Risbridger* [a,b,†], *Renea A. Taylor* [a,b,l,†,**]

[a] *Department of Anatomy and Developmental Biology, Biomedicine Discovery Institute, Monash University, Melbourne, Australia;* [b] *Prostate Cancer Research Program, Cancer Research Division, Peter MacCallum Cancer Centre, Melbourne, Australia;* [c] *School of Public Health & Preventive Medicine, Monash University, Melbourne, Australia;* [d] *TissuPath, Mount Waverley, Australia;* [e] *Department of Urology, Austin Hospital, Melbourne, Australia;* [f] *Department of Surgery, University of Melbourne, Melbourne, Australia;* [g] *Department of Surgery, Monash University, Melbourne, Australia;* [h] *Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Australia;* [i] *Australian Prostate Cancer Research Centre, Epworth Healthcare, Richmond, Australia;* [j] *Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia;* [k] *Eastern Health Clinical School, Monash University, Melbourne, Australia;* [l] *Department of Physiology, Biomedicine Discovery Institute, Monash University, Melbourne, Australia*

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Abstract

Intraductal carcinoma of the prostate (IDC-P) is associated with poor prognosis. While it is often regarded as a rare pathology, the prevalence of IDC-P remains unclear, with variable reports from small and disparate patient populations. To determine how common IDC-P is across the spectrum of prostate cancer, we conducted a systematic review correlating IDC-P prevalence with prostate cancer risk. Electronic searches of the OVID Medline, PubMed, and Scopus literature databases identified 38 patient cohorts in 24 articles, which were divided between four prostate cancer risk categories (low, moderate, high, and recurrent or metastatic disease). This review, which included radical prostatectomy and prostate biopsy specimens from >7000 patients, revealed an unexpectedly high rate of IDC-P. The IDC-P prevalence increased from 2.1% in low-risk patient cohorts to 23.1%, 36.7%, and 56.0% in moderate-risk, high-risk, and metastatic or recurrent disease risk categories, respectively ($p < 0.0001$). IDC-P was also highly prevalent in tumours following androgen deprivation therapy or chemotherapy (60%). Contrary to common perceptions, this study demonstrates a strong association between IDC-P prevalence and aggressive prostate cancer, with a significantly higher frequency in high-risk disease. Greater recognition and systematic reporting of IDC-P may improve patient risk stratification.

Patient summary: Prostate cancer can grow within ducts of the prostate, as well as in prostate tissue. By reviewing all reports describing prostate cancer growing within ducts, we found that it occurs more commonly than many scientists and clinicians appreciate, especially in aggressive prostate cancers. We conclude that there should be more awareness of this pattern of prostate cancer.

† These authors contributed equally to this work.
* Corresponding author. Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Victoria 3000, Australia. Tel. +61 3 94216425; Fax: +61 3 85597379.
E-mail address: renea.taylor@monash.edu (R.A. Taylor).
** Co-corresponding author. Department of Physiology, Monash Biomedicine Discovery Institute, 26 Innovation Way, Clayton, Victoria 3800, Australia. Tel. +61 3 99029287; Fax: +61 3 9902 9223.
E-mail address: declan.murphy@petermac.org (D.G. Murphy).

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In prostate cancer, intraductal carcinoma of the prostate (IDC-P) is defined as growth of tumour cells within native prostatic ducts and acini [1]. IDC-P is usually juxtaposed with invasive adenocarcinoma, and a recent genomic study showed that both histopathologies arise from a common tumour clone [2]. Tumours with IDC-P are also enriched for copy number aberrations associated with poor prognosis [2]. This is consistent with the reporting of IDC-P in patients with adverse pathological and clinical features [1]. This includes men with germline *BRCA2* mutations, for which the presence of IDC-P is associated with worse survival outcomes [3]. Despite this, reporting of IDC-P is not widespread, and is predominantly confined to small patient cohorts. Thus, IDC-P is often considered a rare feature of prostate cancer and its potential therapeutic impacts have not been fully elucidated. To define the overall prevalence of IDC-P and its association with traditional features conferring cancer risk, we performed a systematic review investigating the prevalence of IDC-P across diverse prostate cancer cohorts.

The systematic review was undertaken in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [4]. The keywords "prostate cancer AND intraductal carcinoma" were used to search the OVID Medline, PubMed and Scopus literature databases in August 2016. This yielded 664 articles, which were screened by study title and abstract, excluding articles not in English, reviews, editorials, and letters. Two authors independently reviewed the resulting 59 articles against predetermined inclusion criteria. Studies were considered eligible if they reported the prevalence of IDC-P within patient cohort(s); and listed or cited histopathological criteria used to identify IDC-P. On the basis of these criteria, 24 articles were included (Fig. 1A). Eleven articles contained more than one distinct patient cohort that were recorded separately. Two patient cohorts were duplicated across articles and were recorded only once in the systematic review. Therefore, 38 data sets were included from the 24 articles (Fig. 1A; Supplementary Table 1).

To compare the prevalence of IDC-P between different patient populations, data sets were divided into four risk categories on the basis of histopathological and clinical features: low-risk, moderate-risk, high-risk, and metastatic or recurrent disease (defined in Table 1). Thirty-four data sets were assigned a category according to predicted risk features. The remaining four data sets comprised patients with known poor outcomes and were included in the recurrent/metastatic category. Study details and patient characteristics are listed in Supplementary Table 1.

In total, the 38 data sets involved 7279 patient specimens, of which 1523 (20.9%) were positive for IDC-P (Fig. 1B). IDC-P was present in 13.7% of biopsies and 31.1% of radical prostatectomies (Supplementary Fig. 1A,B). The average prevalence of IDC-P was 2.1% in the low-risk category, 23.1% in the moderate-risk category, 36.7% in the high-risk category, and 56.0% in the recurrent/metastatic disease risk category (Fig. 1B). Compared to the low-risk category, the prevalence of IDC-P was significantly greater in both the high-risk ($36.7 \pm 5.2\%$; $p < 0.01$) and the recurrent/metastatic disease categories ($56.0 \pm 9.9\%$; $p < 0.0001$). Findings were consistent across prostate biopsies and prostatectomy specimens (Fig. 1B; Supplementary Fig. 1A,B). This demonstrates that IDC-P is highly prevalent in patients at risk of poor outcomes, further supporting the association between IDC-P and high-grade prostate cancer.

The appropriate clinical management of patients diagnosed with IDC-P has not been established. However, six data sets evaluated the presence of IDC-P after patients received androgen deprivation therapy and/or chemotherapy (Supplementary Table 1). The average prevalence of IDC-P in these cohorts was 59.7% (Supplementary Fig. 2). The persistence of IDC-P following therapy has led to speculation that it may be inherently resistant to treatment [5]; however, this requires further investigation.

This study demonstrates that IDC-P is variably present in cohorts with diverse clinicopathological features. This may have contributed to the commonly held misconception that IDC-P is a rare pathology. Although it is true that IDC-P is infrequent in low-risk cohorts, IDC-P is significantly more frequent in patients with high-risk disease, rising to over 50% in patients who developed metastatic or recurrent disease. Thus, IDC-P should not be disregarded.

Despite the prevalence of IDC-P in high-risk disease and its association with poor clinical outcomes [1], it is currently unknown whether IDC-P is simply a marker of aggressiveness or a mediator of disease progression. Recent

Table 1 – Data sets reporting the incidence of intraductal carcinoma of the prostate (IDC-P) according to risk category

	Patient characteristics (one or more of the criteria listed)			
	Low risk	Moderate risk	High risk	Metastatic or recurrent PC
	No prior PC diagnosis GS 6	GS 7 Intermediate DARC Cohort with varying GS	GS ≥8 High DARC Germline *BRCA2* mutation or family history of cancer Locally advanced disease (SVI, LNI)	Distant metastases at diagnosis Biochemical recurrence (median time to progression <4 yr)
Data sets (*n*)	5	14	12	7[a]
Patients (*n*)	2255	3176	1214	634
Positive for IDC-P (%)	2.1	23.1	36.7	56.0[b]

DARC = D'Amico risk classification; GS = Gleason score; LNI = lymph node invasion; PC = prostate cancer; SVI = seminal vesicle invasion.
[a] For 4/7 data sets the outcome was known.
[b] The percentage of cases positive for IDC-P in the primary tumour.

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