Cancer Management and Research

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Chromogranin A is a predictor of prognosis in patients with prostate cancer: a systematic review and meta-analysis

This article was published in the following Dove Press journal:
Cancer Management and Research

Zhenlang Guo[1]
Yuliang Wang[2]
Songtao Xiang[3]
Shusheng Wang[3]
Franky Leung Chan[2]

[1]The Second Clinical College, Guangzhou University of Chinese Medicine, Guangzhou, People's Republic of China; [2]School of Biomedical Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong, People's Republic of China; [3]Department of Urology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, People's Republic of China

Background: The prognostic value of chromogranin-A (CHGA) as a biomarker of prostate cancer (PCa) has been evaluated extensively. However, to date the results still remain controversial. This study aims to perform a meta-analysis on previous studies in order to determine whether CHGA would be a biomarker for survival in PCa patients.

Methods: MEDLINE, Embase, Web of Science, and Cochrane Library databases were searched to identify eligible studies published before September 2018, regarding the association of *CHGA* gene expression with survival outcomes in patients with PCa. Multivariate adjusted HRs and associated 95% CIs were calculated using random effects models.

Results: Ten cohort studies involving 3,172 patients were finally included. According to the included studies, circulating CHGA levels were tested in serum, plasma, and tissues. The results showed an association between high CHGA expression and worse overall survival (OS) (HR=1.24, 95% CI: 1.07–1.44; P=0.004; I^2=77.6%) in PCa patients. However, no significant association was observed between increasing *CHGA* expression and shorter progression-free survival (HR=1.73, 95% CI: 0.92–3.28; P=0.090; I^2=73.9%). The results of sensitivity analysis validated the rationality and reliability of our analysis.

Conclusion: Current evidence indicates that high CHGA expression is a potential marker for poor OS in PCa. Future studies are needed to explore tailored treatments that directly target *CHGA* for the improvement of survival in men with PCa.

Keywords: prostate cancer, chromogranin-A, prognosis, survival, meta-analysis

Background

Prostate cancer (PCa) is the second leading cause of cancer death in men with a worldwide annual mortality of over 200,000.[1–3] The first symptom occurs mostly during the progression of PCa when it cannot be treatable anymore. Therefore, early detection of PCa in asymptomatic men is the key to reducing mortality. Prostate-specific antigen (PSA)-based screening detects substantial clinically insignificant patients with PCa.[4,5] However, most of these asymptomatic patients are treated unnecessarily and subject to side effects of treatment. Therefore, population-based PSA screening is not recommended by current guidelines.[6] In order to distinguish between indolent and high-risk PCa, reliable biomarkers are needed for the better prognostication of PCa.

Chromogranin-A (CHGA) is a common glycoprotein expressed in neuroendocrine cells. Neuroendocrine activity can also be detected in other tumors except for neuroendocrine tumors, such as prostate and breast tumors.[7–10] One study

Correspondence: Shusheng Wang
Department of Urology, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Dade Road No. 111, Yuexiu District, Guangzhou, Guangzhou 510120, People's Republic of China
Email shushengwanggzy@163.com

Franky Leung Chan
Lo Kwee-Seong Integrated Biomedical Sciences Building, School of Biomedical Sciences, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong, People's Republic of China
Tel +8 523 943 6841
Fax +8 522 603 5031
Email franky-chan@cuhk.edu.hk

demonstrated that CHGA levels are significantly elevated in patients with castration-resistant prostate cancer (CRPC) in immunohistochemical studies.[11] As tumors develop in neuroendocrine tissues, they become the main source of circulating CHGA which can be detected in blood and tissues.[12,13] Moreover, elevated circulating CHGA levels have been confirmed to be a helpful biomarker for the diagnosis of different types of neuroendocrine tumors.[14–17] Some researches have shown that high serum CHGA levels are associated with advanced stage disease and poor prognosis,[18,19] but its practicability and prognostic value in clinically localized PCa is still debatable.

Several studies have suggested that the high mRNA expression of CHGA is related to worse survival, but other studies did not reach these conclusions.[20–23] We thus performed a meta-analysis to reveal the prognostic significance of *CHGA* expression for overall survival (OS) and progression-free survival (PFS) in patients with PCa.

Materials and methods

This study was performed in accordance with the Cochrane Collaboration criterion.[24] For reporting, we followed the PRISMA statement guidelines.[25] Thus, no ethical approval and patient consent are required.

Literature search

To identify eligible studies, we performed a comprehensive literature search in the electronic databases of MEDLINE, Embase, Web of Science, and Cochrane Library databases for eligible studies regarding the association of *CHGA* expression with survival outcomes in PCa from database inception up to September 2018. Each database was searched without restrictions to languages, publication types, or regions using the following combination of Medical Subject Headings (MeSH) and non-MeSH search terms: ("chromogranin A" OR "parathyroid secretory protein" OR "*CHGA*") AND ("prostate cancer" OR "prostatic cancer" OR "prostate neoplasm" OR "prostatic neoplasm"). The main search was completed by the senior author (ZLG). Any discrepancy was resolved through consultation of an investigator (SSW) not involved in the initial procedure (as shown in Supplementary Material).

Inclusion and exclusion criteria

Two independent investigators (ZG and YW) selected eligible studies regarding the association of *CHGA* expression with survival outcomes in PCa without publication status or language restrictions in accordance with the following inclusion criteria: 1) diagnoses were confirmed as PCa by pathology; 2) original trials regarding the association of CHGA expression with survival outcomes (eg, OS, PFS, etc.) in PCa; and 3) studies reporting sufficient data of risk estimates with corresponding 95% CIs or enough data to calculate them directly were eligible for inclusion. If more than one study was identified from the duplicated database, we retained only the most recent or largest study to avoid duplication of information. The exclusion criteria were as follows: 1) reviews, letters, conference papers, case reports, case series, and expert opinion articles were not eligible for inclusion; 2) absence of detailed results; and 3) animal studies. Any disagreement was resolved through adjudication of senior authors.

Data extraction and methodological quality assessment

Two reviewers (ZG and SX) extracted the data independently using a predefined data extraction form, and discrepancies were settled through a consensus discussion. The following data were extracted into a standardized evidence table: first author, year of publication, country, study design, baseline population characteristics (ie, mean age and sample size), duration, adjusted factors, and HRs with corresponding 95% CIs for survival in each comparisons. We also checked these data for accuracy. Moreover, we contacted, if possible, the primary authors of studies with insufficient information to acquire and verify the data.

The quality and risk of bias of the included cohort studies were evaluated by two independent reviewers (FLC and SW) separately according to the Newcastle-Ottawa Scale (NOS).2[6] Disagreements were also settled through discussion among authors. The standards consist of 10 items that assess the representativeness of the included studies. Each item was evaluated as "yes," "no," or "unclear" corresponding, respectively, to "1," "0," or "0" according to the information provided by the studies. The total score ranged from 0 to 10 with the overall score categorized as follows: 7 to 10: "high quality," 4 to 6: "moderate quality," and 0 to 3: "low quality."

Statistical analyses

For meta-analysis, the total risk estimate of extracted data was pooled using HRs with associated 95% CIs through the STATA statistical package (version 14.0; serial number: 10699393; StataCorp Wyb) to determine the association of *CHGA* expression with survival outcomes in PCa.

For consistent definitions, HRs with corresponding 95% CIs were used as a common measure in the included studies because *CHGA* expression in PCa was considered as a rare event. We could generally ignore the distinctions among the various measures of risk estimates. Thus, the ORs values in the observational studies were considered as approximations of HRs.[27] The aggregated results and 95% CIs for effect size were calculated using inverse-variance weighted meta-analysis. The I-square (I^2) test was performed to assess the effect of study heterogeneity on the meta-analysis results, with I^2 values of 0%, 25%, 50%, and 75% representing no, low, moderate, and high heterogeneity, respectively. Based on the Cochrane review guidelines,[24] a severe heterogeneity of $I^2 \geq 50\%$ warrants the use of random-effects models. Otherwise, a fixed-effects model is utilized. Statistical significance was set at $P<0.05$. Subgroup analyses were performed in accordance with different countries, study designs, and chromogranin-A level measurements. Sensitivity analysis was conducted by deleting each study individually to evaluate the quality and consistency of the results. A meta-regression analysis was conducted to investigate possible sources of heterogeneity on certain variable. The restricted maximum likelihood method was used for analysis. Finally, Egger's and Begg's tests were performed to assess publication bias, and the funnel plot symmetry was examined.[28,29]

Results

Study selection process

A flow chart depicts the search process and study selection (as shown in Figure 1). A total of 665 studies were identified through our comprehensive search of several electronic databases. Only 594 studies were retrieved after removal of duplicates. After screen the titles and abstracts, only 28 studies remained. Finally, a total of 18 full-text articles were discarded for the following reasons:

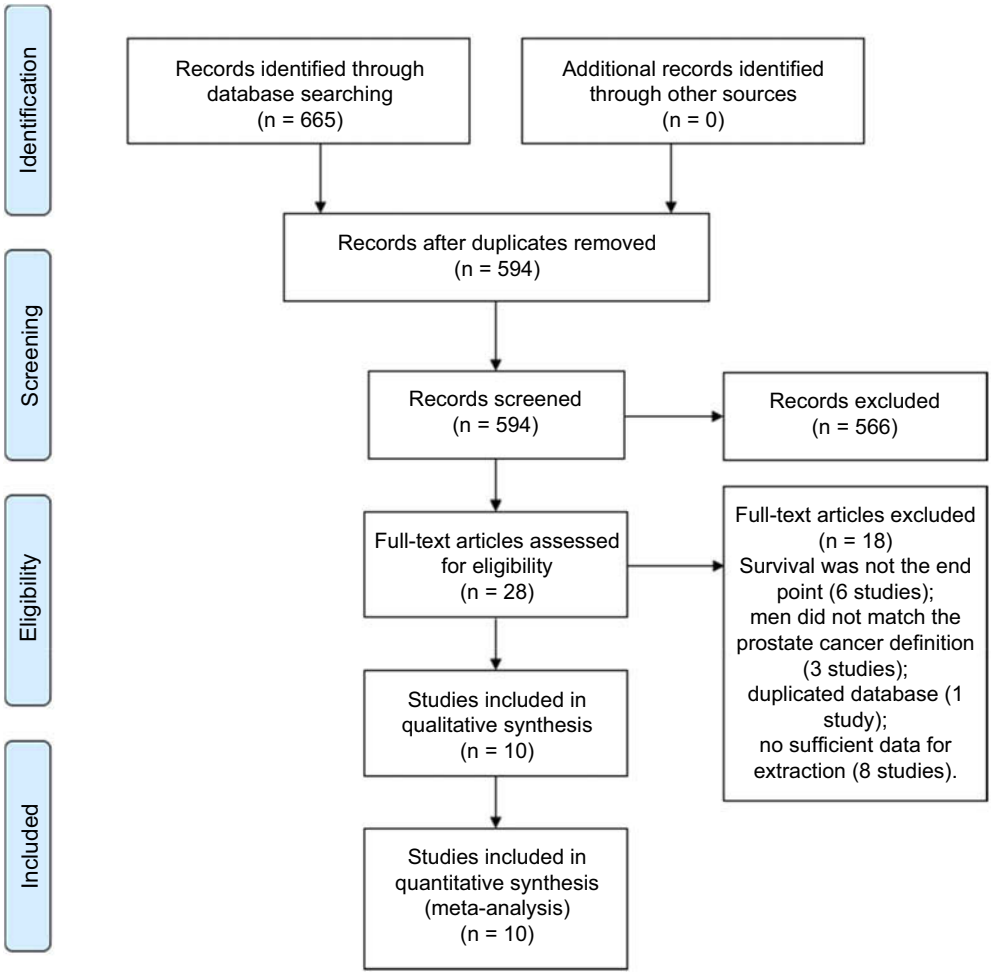

Figure 1 Flow diagram of literature searches according to the preferred reporting items for systematic reviews and meta-analyses statement.

survival was not the end point (6 studies), men did not match the PCa definition (3 studies), duplicated database (1 studies), and no sufficient data for extraction (8 studies). Therefore, 10 cohort studies[20–23,30–35] comprising 3,172 participants were included in our meta-analysis in compliance with the inclusion criteria.

Study characteristics and methodological quality

The basic characteristics of the included studies[20–23,30–35] are described in Table 1. These studies (7 retrospective cohort studies[20,21,23,30–33] and 3 prospective cohort studies[22,34,35]) were published between 2005 and 2018 and involved 3,172 participants. In total, 10 eligible cohorts with 3,172 patients were analyzed for OS outcomes,[20–23,30–35] and 3 qualified studies with 139 patients were analyzed for PFS outcomes.[21,31,35] The sample sizes varied from 39 to 1,018. Among the included studies, five were conducted in Italy,[20–22,30,31] two in Germany,[33,35] two in USA,[32,34] and one in UK.[23] Furthermore, serum CHGA levels were measured in six studies,[21–23,31,32] tissue CHGA levels were measured in one study[20] and plasma CHGA levels were measured in three studies,[30,33,34] respectively. All studies were published in English,[20–23,30–35] and nine studies[20,21,23,30–35] provided adjusted HRs and one[22] reported ORs for survival, accounting for confounding factors. Moreover, the

Table 1 Characteristics of the included studies

First author, year	Study design (duration)	Country	Study characteristics	Adjustments	CHGA levels measurements	Diseases stage
Berruti et al, 2005[30]	Retrospective cohort (1998–2003)	Italy	108 males, 74 (58–86) y	PSA, serum ALP, Hb, Gleason score, serum ALB, and serum LDH	Plasma	CRPC
Berruti et al, 2010[20]	Retrospective cohort (1996–2003)	Italy	414 males, 69 (43–91) y	Gleason score, serum PSA, disease stage, and local treatments	Tissue	PC
Burgio et al, 2014[31]	Retrospective cohort (2011–2012)	Italy	48 males, 73 (57–90) y	Gleason score, serum PSA, and age	Serum	CRPC treated with abiraterone
Conteduca et al, 2014[36]	Retrospective cohort (NA)	Italy	39 males, 75 (43–91) y	Gleason score, serum PSA, and age	Serum	CRPC treated with enzalutamide
De Nunzio et al, 2014[22]	Prospective cohort (2006–2012)	Italy	1,018 males, 68 (62–74) y	Age, PSA, DRE, and prostate volume	Serum	PC
Giridhar et al, 2018[32]	Retrospective cohort (2002–2009)	USA	256 males, 72 (65–77) y	Age, Gleason score, serum PSA, disease stage, and local treatments	Serum	CRPC treated with abiraterone
Jeetle et al, 2012[23]	Retrospective cohort (1990–1996)	UK	806 males, >76 y	Gleason score and serum PSA	Tissue	PC
Niedworok et al, 2017[33]	Retrospective cohort (2003–2004)	Germany	110 males, 66 (49–86) y	Gleason score, serum PSA, disease stage and, local treatments	Plasma	PC
Taplin et al, 2005[34]	Prospective cohort (1996–1998)	USA	321 males, 70 (65–75) y	Demographics, metastases, Gleason score, performance status, disease assessment, prior therapy, suramin dose	Plasma	CRPC
von Hardenberg et al 2017[35]	Prospective cohort (2013–2015)	Germany	52 males, 71.3±7.2 y	Gleason score, Charlson comorbidity index, age, and local treatments	Serum	CRPC treated with docetaxel

Abbreviations: ALB, albumin; ALP, alkane phosphatase; *CHGA*, chromogranin-A gene; CRPC, castration-resistant prostate cancer; DRE, digital rectal examination; Hb, hemoglobin; LDH, lactate dehydrogenase; OS, overall survival; PC, prostate cancer; PFS, progression-free survival; PSA, prostate-specific antigen; NA, not available; y, years.

duration and the mean age of patients were also detailed in Table 1.

In addition, the methodological quality was evaluated in accordance with NOS.[23] It was found that eight studies[20,23,31–35] got 8 points, respectively, one study22 got 6 points, and one study21 obtained 5 points. In all, the methodological quality of eight studies was considered of high quality,[20,23,31–35] and two studies were evaluated as moderate quality.[21,22] The main deficiency was the selection bias related to the insufficient adjustment of clinical tumor stage and initial treatment modality among the included studies.

CHGA expression and OS in PCa

Ten cohort studies involving 3,172 patients provided the data on OS in PCa.[20–23,30–35] The results showed an association between high *CHGA* expression and worse OS (HR=1.24, 95% CI: 1.07–1.44; P=0.004) in PCa. Significant heterogeneity was observed among studies (I^2=77.6%, P<0.001), and a random effects model was used for pooled analysis (Figure 2). Sensitivity analysis indicated that none of the individual studies influenced the summary statistic by omitting single study from the pooled estimate substantially (Table 2). As summarized in Table 3, we conducted subgroup analyses regarding different study designs, showing that the summary HR was statistically significant in the retrospective cohort studies (HR=1.51, 95% CI: 1.14–1.99; P=0.004; I^2=72.4%) rather than prospective cohort studies (HR=1.08, 95% CI: 0.95–1.23; P=0.257; I^2=69.1%). Additionally, as for subgroup analyses of the different countries and CHGA levels measurements, the results were inconsistent with overall analysis except for the plasma CHGA level measurement, USA, and Germany on account of the limited number of studies evaluated. Literature reports of potential impact on tissue CHGA levels in PCa are scarce and also with contrary results. Thus future studies regarding tissue CHGA levels in PCa would verify our results. Notably, when stratified by clinical tumor stage, the results showed that the summary HR was statistically significant in patients with CRPC (HR=1.29, 95% CI: 1.07–1.55; P=0.008; I^2=57.9%) compared with patients with PCa (HR=1.23,

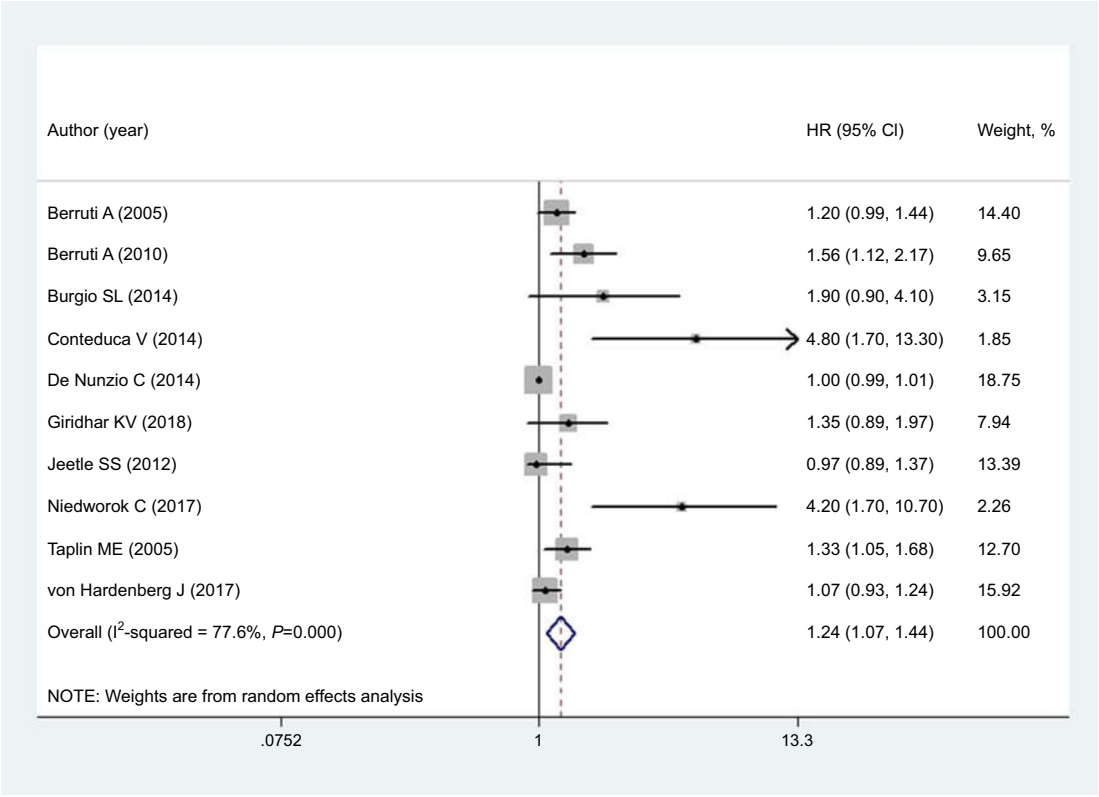

Figure 2 *CHGA* expression and OS in PCa. Individual studies are represented by black squares and horizontal lines that correspond to the point estimate and 95% CI of the OR. The size of the black square reflects the weight of the study in the meta-analysis. The solid vertical line corresponds to "no effect" of treatment – an HR of 1. The diamond at the bottom and the dotted line represent the combined or pooled HR of all 10 trials with their 95% CI.
Abbreviations: *CHGA*, chromogranin-A gene; OS, overall survival; PCa, prostate cancer.

Table 2 Results of sensitivity analyses

Study omitted	HR	95% CI	
Berruti et al, 2005[30]	1.26	1.07	1.49
Berruti et al, 2010[20]	1.20	1.04	1.39
Burgio et al, 2014[31]	1.22	1.06	1.42
Conteduca et al, 2014[36]	1.20	1.05	1.37
De Nunzio et al 2014[22]	1.33	1.11	1.60
Giridhar et al 2018[32]	1.23	1.06	1.44
Jeetle et al 2012[23]	1.31	1.11	1.55
Niedworok et al 2017[33]	1.19	1.04	1.36
Taplin et al 2005[34]	1.23	1.05	1.44
von Hardenberg et al 2017[35]	1.32	1.09	1.59
Combined	1.24	1.07	1.44

95% CI: 0.93–1.63; P=0.148; I^2=81.7%). However, the subgroups could not find the potential factors that may substantially affect the heterogeneity. Meta-regression analysis results shown that none of the covariates (country, P=0.826; study design, P=0.295; CHGA levels measurements, P=0.415; clinical tumor stage, P=0.762) resulted in heterogeneity among the included studies. Therefore, the adjusted R-squared of −57.20% to −27.62% what expresses is that the regressors are contributing little to the explanation of the response variables (Table 4). Finally, potential publication bias might exist because of the small number of studies evaluated (Egger's test, P=0.001; Begg's test, P=0.020) (Figure 4).

CHGA expression and PFS in PCa

Three cohort studies involving 139 patients provided data on PFS in PCa.[22,34,35] The combined analysis of three studies suggested that high *CHGA* expression was not significantly associated with shorter PFS (Figure 3), with

Table 3 Results of subgroup analyses

Overall survival	Studies, N	Participants, N	HR (95% CI)	*P*-value	*P* of heterogeneity	I^2 (%)
	10	**3,172**	**1.24 (1.07–1.44)**	**0.004**	**<0.001**	**77.6**
Country						
Italy	5	1,627	1.36 (1.03–1.79)	0.029	<0.001	82
UK	1	806	0.97 (0.78–1.20)	0.782	NA	NA
USA	2	577	1.34 (1.09–1.63)	0.005	0.949	0
Germany	2	162	1.96 (0.52–7.42)	0.322	0.004	87.9
Study design						
Retrospective cohort	7	1,781	1.51 (1.14–1.99)	0.004	0.001	72.4
Prospective cohort	3	1,391	1.08 (0.95–1.23)	0.257	0.039	69.1
CHGA levels measurements						
Tissue	2	1,220	1.21 (0.76–1.92)	0.423	0.018	82.0
Serum	5	1,413	1.17 (0.96–1.43)	0.113	0.005	72.8
Plasma	3	539	1.43 (1.03–2.01)	0.035	0.031	71.3
Clinical tumor stage						
CRPC	6	824	1.29 (1.07–1.55)	0.008	0.036	57.9
PC	4	2,348	1.23 (0.93–1.63)	0.148	0.001	81.7

Abbreviations: CHGA, chromogranin-A protein; CRPC, castration-resistant prostate cancer; NA, not available; PC, prostate cancer.

Table 4 Results of meta-regression

Covariates	The exponent of b	Standard error	t	P>|t|	95% CI		R-squared
Country	0.9739739	0.1127419	−0.23	0.826	0.457975	1.271961	−57.20%
Study design	0.764022	0.1834384	−1.12	0.295	0.4391912	1.329101	−29.22%
CHGA levels measurements	0.9011292	0.1091306	−0.86	0.415	0.6815581	1.191437	−27.62%
Clinical tumor stage	0.9203951	0.2434193	−0.31	0.762	0.5001601	1.693712	−49.17%

Notes: Country (1=Italy, 2=USA, 3=UK, 4=Germany); study design (1=retrospective cohort, 2=prospective cohort); CHGA levels measurements (1=plasma, 2=tissue, 3=serum); and clinical tumor stage (1=CRPC, 2=prostate cancer).
Abbreviations: CHGA, chromogranin-A protein; CRPC, castration-resistant prostate cancer.

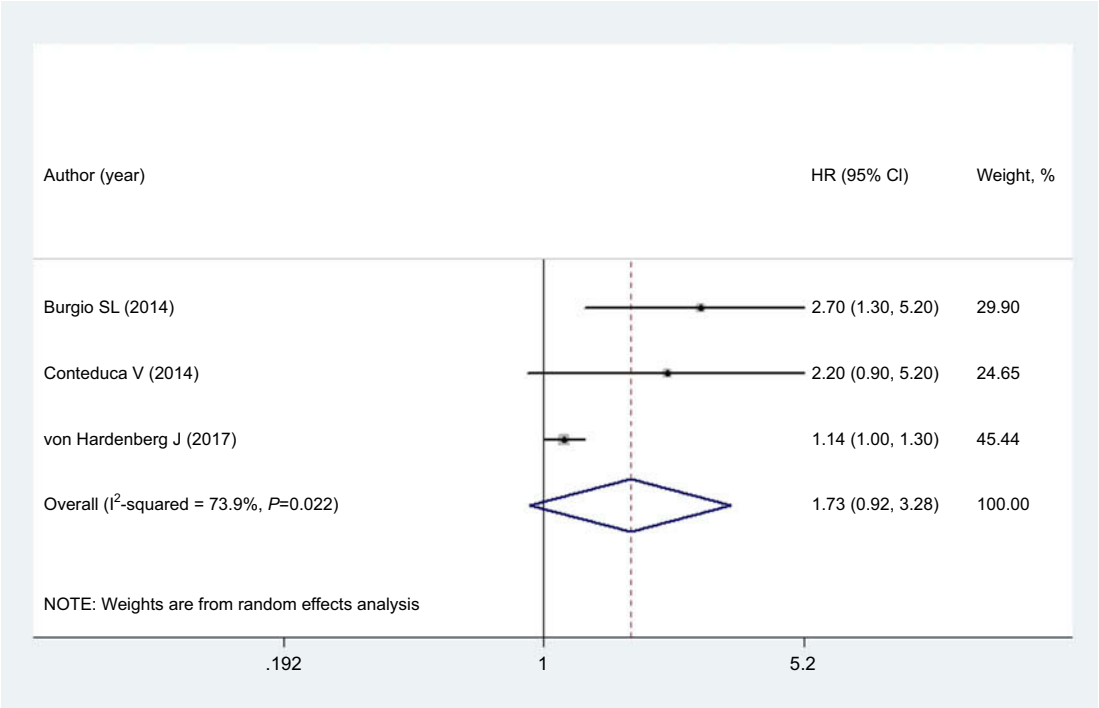

Figure 3 *CHGA* expression and PFS in PCa. Individual studies are represented by black squares and horizontal lines, which correspond to the point estimate and 95% CI of the odds ratio. The size of the black square reflects the weight of the study in the meta-analysis. The solid vertical line corresponds to "no effect" of treatment - an HR of 1. The diamond at the bottom and the dotted line represent the combined or pooled HR of all 3 trials with its 95% CI.
Abbreviations: *CHGA*, chromogranin-A gene; PCa, prostate cancer; PFS, progression-free survival.

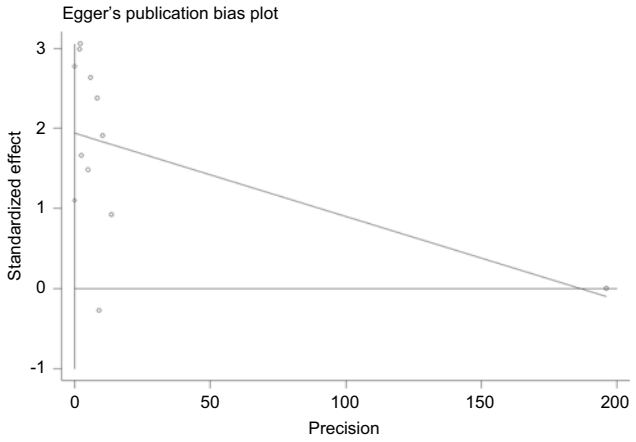

Figure 4 Funnel plot of the HR of *CHGA* expression and overall survival in prostate cancer. The Egger regression asymmetry plot shows the standardized effect estimates versus precision, the variance-weighted regression line, and the CI for the intercept. Individual studies are represented by white circles. Failure of this CI to include zero indicates asymmetry in the funnel plot and may give evidence of publication bias. Guidelines at x=0 and y=0 are plotted to assist in visually determining if zero is in the CI.
Abbreviation: *CHGA*, chromogranin-A gene.

HR of 1.73 (95% CI: 0.92–3.28; P=0.090; I^2=73.9%). However, the use of subgroup analysis and sensitivity analysis were limited because of the small number of studies evaluated.

Discussion

Main findings

In this study, we analyzed the associations between *CHGA* expression and survival in patients with PCa using a meta-analysis of the 10 included studies.[20–23,30–35] Overall, our results indicated a significant association of high *CHGA* expression with poor OS in PCa, although statistically significant difference was not observed in the PFS group. Also, it should be noted that significant heterogeneity was observed in the overall analysis. The meta-regression and subgroup analyses could not find the potential factors that may substantially affect the heterogeneity. The results of sensitivity analysis validated the rationality and reliability of our analysis.

Five studies suggested a significant association between high *CHGA* expression with poor OS in PCa,[20,21,30,33,34] whereas five studies reported conflicting results.[22,23,31,32,35] The retrospective cohort conducted by Burgio et al[31] reported that in the multivariate analysis, high *CHGA* expression was a predictor of PFS (HR=2.70, 95% CI: 1.30–5.20; P=0.0047), while CHGA levels remained of borderline significance of OS (HR=1.90, 95% CI: 0.90–4.10; P=0.0919). Moreover, De Nunzio et al[22] focused on poorly differentiated PCa, their study

indicated that high *CHGA* expression was not a significant predictor of OS on univariate (OR=1.00, 95% CI: 0.99–1,01; *P*=0.66). Similarly, Giridhar et al[32] Jeetle et al[23] and von Hardenberg et al[35] demonstrated that *CHGA* expression was not an independent predictor of survival (HR=1.35, 95% CI: 0.89–1.97; *P*=0.154; HR=0.97, 95% CI: 0.89–1.37, *P*=0.87; HR=1.07, 95% CI: 0.93–1.24, *P*=0.0919, respectively). When we excluded this study from the meta-analysis, the stability of the results showed no significant changes, validating the rationality and reliability of our analysis.

Implications for clinical practice

CHGA is considered to be a useful predictor in PCa patients with lower PSA levels.[36,37] However, Our results suggest that the lack of correlation between the low PSA levels and high CHGA value, which may be the expression of patients with advanced CRPC with neuroendocrine differentiation in the context of a heterogeneous tumor volume. Moreover, elevated serum CHGA levels are usually associated with neuroendocrine differentiation of CRPC, suggesting that patients with CRPC have a poor prognosis and may be related to the increasing degrees of differentiation.[34,38] In recent years, several studies have suggested that serum levels of CHGA are significantly higher in metastatic PCa as compared to non-metastatic and primary PCas.[39,40] Nevertheless, despite this interest in neuroendocrine serum markers, little is known about their sources in different growth patterns and PCa metastasis. Previous studies indicated that CHGA values were not substantially affected by either endocrine therapy or chemotherapy.[30,41] Since preoperative treatment decisions based on the prognosis may be active surveillance rather than surgery, our results may have direct clinical relevance. In addition, our results show that those who are eligible for active surveillance may also benefit from the analysis of CHGA, as this may improve the accuracy of disease surveillance.

Latest classification of neuroendocrine prostate tumors suggests that variants of neuroendocrine prostate cancer (NEPC) contain a mixed form between conventional adenocarcinoma and NEPC, which was often characterized by androgen receptor independence.[42] However, neuroendocrine markers and androgen receptor are dually expressed in the mixed tumor cells due to clinical and pathological heterogeneity among patients.[42] Moreover, a large proportion of the treatment-related recurrent prostate tumors have strong neuroendocrine characteristics, which was caused by pre-existing prostate adenocarcinoma.[43] Several studies indicated that neuroendocrine differentiation cells are potentially derived from the common pluripotent stem cell populations, which play a crucial role in CRPC and might contribute to hormone therapy and chemoresistance.[44,45] Notably, NEPC cells express high levels of chromogranin and synaptophysin.[46] Hence, the overlapping clinical entities require more accurate clinical and molecular classification, and further research is needed to determine their prognostic impact.[47]

Strengths and limitations

In general, our meta-analysis exhibited several crucial strengths. First, the meta-analysis was the first to assess the association between *CHGA* expression and survival in patients with PCa through thorough systematic search and rigorous analytical approaches. Second, multivariable-adjusted risk estimates were applied to minimize the confounding factors that might influence the whole results. Third, the rationality and reliability of our meta-analysis was observably improved because the overall combined estimates were based on a large sample size. Furthermore, sufficient subgroup analyses and sensitivity analyses were also performed to ensure the reliability of this study.

This study has several limitations, which may affect the interpretation of some of our results. Firstly, there was the problem of heterogeneity in the overall analysis, although we could not find the potential factors that may substantially affect the heterogeneity through the meta-regression and subgroup analyses. Moreover, clinical tumor stage and initial treatment modality should also be accounted for potential considerable factors, which possibly contribute to heterogeneity. However, our understanding of the effects of clinical tumor stage and initial treatment modality among the included studies on the overall results remains insufficient, although these factors have been investigated, albeit inadequately, in other studies. Further research is needed to verify the findings of this meta-analysis with regard to the factors affecting extensive consequences and common objectives as mentioned above. Second, *CHGA* expression has been associated with other molecular biomarkers for PCa prognosis. Inadequate adjustment for these biomarkers in several included studies might have resulted in spurious associations. Finally, potential publication bias might exist because of the small number of studies evaluated and the small effect size estimated.

Conclusion

In summary, current evidence supported the viewpoint that high *CHGA* expression is significantly associated with poor OS in PCa. Future studies with large sample sizes and stratified analyses according to clinicopathological characteristics are needed to explore tailored treatments that directly target *CHGA* for the improvement of survival in men with PCa.

Acknowledgments

This study was supported by grants from the National Natural Science Foundation of China (Grant No. 61301294). The supporting institution had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893–2917. doi:10.1002/ijc.25499
2. Buja A, Lange JH, Perissinotto E, et al. Cancer incidence among male military and civil pilots and flight attendants: an analysis on published data. *Toxicol Ind Health*. 2005;21(10):273–282. doi:10.1191/0748233705th238oa
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7–30. doi:10.3322/caac.21442
4. Scherr D, Swindle PW, Scardino PT. National Comprehensive Cancer Network. National Comprehensive Cancer Network guidelines for the management of prostate cancer. *Urology*. 2003;61(2 suppl 1):14–24.
5. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*. 2009;360(13):1320–1328.
6. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet*. 2014;384(9959):2027–2035.
7. Sun Y, Niu J, Huang J. Neuroendocrine differentiation in prostate cancer. *Am J Transl Res*. 2009;1(2):148–162.
8. Nesland JM, Holm R, Johannessen JV, et al. Neuroendocrine differentiation in breast lesions. *Pathol Res Pract*. 1988;183(2):214–221.
9. Puca L, Vlachostergios PJ, Beltran H, et al. Neuroendocrine differentiation in prostate cancer: emerging biology, models, and therapies. *Cold Spring Harb Perspect Med*. 2019;9(2): pii: a030593.
10. Adams RW, Dyson P, Barthelmes L. Neuroendocrine breast tumours: breast cancer or neuroendocrine cancer presenting in the breast? *Breast*. 2014;23(2):120–127. doi:10.1016/j.breast.2013.11.005
11. Hirano D, Okada Y, Minei S, Takimoto Y, Nemoto N. Neuroendocrine differentiation in hormone refractory prostate cancer following androgen deprivation therapy. *Eur Urol*. 2004;45(5):586–589. doi:10.1016/j.eururo.2003.11.032
12. Campana D, Nori F, Piscitelli L, et al. Chromogranin A: is it a useful marker of neuroendocrine tumors? *J Clin Oncol*. 2007;25(15):1967–1973. doi:10.1200/JCO.2006.10.1535
13. O'Connor DT, Deftos LJ. Secretion of chromogranin A by peptide-producing endocrine neoplasms. *N Engl J Med*. 1986;314(18):1145–1151. doi:10.1056/NEJM198605153142021
14. Nobels FR, Kwekkeboom DJ, Coopmans W, et al. Chromogranin A as serum marker for neuroendocrine neoplasia: comparison with neuron-specific enolase and the alpha-subunit of glycoprotein hormones. *J Clin Endocrinol Metab*. 1997;82(8):2622–2628.
15. Baudin E, Gigliotti A, Ducreux M, et al. Neuron-specific enolase and chromogranin A as markers of neuroendocrine tumours. *Br J Cancer*. 1998;78(8):1102–1107. doi:10.1038/bjc.1998.635
16. Nobels FR, Kwekkeboom DJ, Bouillon R, et al. Chromogranin A: its clinical value as marker of neuroendocrine tumours. *Eur J Clin Invest*. 1998;28(6):431–440. doi:10.1046/j.1365-2362.1998.00305.x
17. Guignat L, Bidart JM, Nocera M, Comoy E, Schlumberger M, Baudin E. Chromogranin A and the alpha-subunit of glycoprotein hormones in medullary thyroid carcinoma and phaeochromocytoma. *Br J Cancer*. 2001;84(6):808–812. doi:10.1054/bjoc.2000.1677
18. Hirano D, Minei S, Sugimoto S, et al. Implications of circulating chromogranin A in prostate cancer. *Scand J Urol Nephrol*. 2007;41(4):297–301. doi:10.1080/00365590701303934
19. Matei DV, Renne G, Pimentel M, et al. Neuroendocrine differentiation in castration-resistant prostate cancer: a systematic diagnostic attempt. *Clin Genitourin Cancer*. 2012;10(3):164–173. doi:10.1016/j.clgc.2011.12.004
20. Berruti A, Bollito E, Cracco CM, et al. The prognostic role of immunohistochemical chromogranin A expression in prostate cancer patients is significantly modified by androgen-deprivation therapy. *Prostate*. 2010;70(7):718–726.
21. Conteduca V, Burgio SL, Menna C, et al. Chromogranin A is a potential prognostic marker in prostate cancer patients treated with enzalutamide. *The Prostate*. 2014;74(16):1691–1696. doi:10.1002/pros.22890
22. De Nunzio C, Albisinni S, Presicce F, Lombardo R, Cancrini F, Tubaro A. Serum levels of chromogranin A are not predictive of high-grade, poorly differentiated prostate cancer: results from an Italian biopsy cohort. *Urol Oncol*. 2014;32(2):80–84. doi:10.1016/j.urolonc.2012.07.012
23. Jeetle SS, Fisher G, Yang ZH, et al. Neuroendocrine differentiation does not have independent prognostic value in conservatively treated prostate cancer. *Virchows Arch*. 2012;461(2):103–107. doi:10.1007/s00428-012-1259-2
24. Higgins JPT, Green S Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. *The Cochrane Collaboration*. 2011.
25. Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264–269. doi:10.7326/0003-4819-151-4-200908180-00135

26. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Ottawa Hospital Research Institute website. 2014. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
27. Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev*. 1987;9:1–30. doi:10.1093/oxfordjournals.epirev.a036298
28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634. doi:10.1136/bmj.315.7109.629
29. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088–1101. doi:10.2307/2533446
30. Berruti A, Mosca A, Tucci M, et al. Independent prognostic role of circulating chromogranin A in prostate cancer patients with hormone-refractory disease. *Endocr Relat Cancer*. 2005;12(1):109–117. doi:10.1677/erc.1.00876
31. Burgio SL, Conteduca V, Menna C, et al. Chromogranin A predicts outcome in prostate cancer patients treated with abiraterone. *Endocr Relat Cancer*. 2014;21(3):487–493. doi:10.1530/ERC-14-0071
32. Giridhar KV, Sanhueza C, Hillman DW, et al. Serum chromogranin-A-based prognosis in metastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis*. 2018;21(3):431–437. doi:10.1038/s41391-018-0046-9
33. Niedworok C, Tschirdewahn S, Reis H, et al. Serum chromogranin A as a complementary marker for the prediction of prostate cancer-specific survival. *Pathol Oncol Res*. 2017;23(3):643–650. doi:10.1007/s12253-016-0171-5
34. Taplin ME, George DJ, Halabi S, et al. Prognostic significance of plasma chromogranin A levels in patients with hormone-refractory prostate cancer treated in Cancer and Leukemia Group B 9480 study. *Urology*. 2005;66(2):386–391. doi:10.1016/j.urology.2005.03.040
35. von Hardenberg J, Schwartz M, Werner T, et al. Prospective evaluation of neuromediator dynamics in castration-resistant prostate cancer patients during docetaxel. *Anticancer Res*. 2017;37(9):5117–5124.
36. Conteduca V, Aieta M, Amadori D, et al. Neuroendocrine differentiation in prostate cancer: current and emerging therapy strategies. *Crit Rev Oncol Hematol*. 2014;92(1):11–24. doi:10.1016/j.critrevonc.2014.05.008
37. Isshiki S, Akakura K, Komiya A, et al. Chromogranin A concentration as a serum marker to predict prognosis after endocrine therapy for prostate cancer. *J Urol*. 2002;167(2 Pt 1):512–515. doi:10.1016/S0022-5347(01)69075-X
38. Angelsen A, Syversen U, Haugen OA, et al. Neuroendocrine differentiation in carcinomas of the prostate: do neuroendocrine serum markers reflect immunohistochemical findings? *Prostate*. 1997;30(1):1–6.
39. Sciarra A, Di Silverio F, Autran AM, et al. Distribution of high chromogranin A serum levels in patients with nonmetastatic and metastatic prostate adenocarcinoma. *Urol Int*. 2009;82(2):147–151.
40. Genitsch V, Zlobec I, Seiler R, et al. Neuroendocrine differentiation in metastatic conventional prostate cancer is significantly increased in lymph node metastases compared to the primary tumors. *Int J Mol Sci*. 2017;18(8):E1640.
41. Kalkner KM, Acosta S, Thorsson O, et al. Octreotide scintigraphy and chromogranin A do not predict clinical response in patients with octreotide acetate-treated hormone-refractory prostate cancer. *Prostate Cancer Prostatic Dis*. 2006;9(1):92–98.
42. Epstein JI, Amin MB, Beltran H, et al. Proposed morphologic classification of prostate cancer with neuroendocrine differentiation. *Am J Surg Pathol*. 2014;38(6):756–767.
43. Wang HT, Yao YH, Li BG, et al. Neuroendocrine Prostate Cancer (NEPC) progressing from conventional prostatic adenocarcinoma: factors associated with time to development of NEPC and survival from NEPC diagnosis-a systematic review and pooled analysis. *J Clin Oncol*. 2014;32(30):3383–3390.
44. Germann M, Wetterwald A, Guzmán-Ramirez N, et al. Stem-like cells with luminal progenitor phenotype survive castration in human prostate cancer. *Stem Cells*. 2012;30(6):1076–1086.
45. Bae KM, Su Z, Frye C, et al. Expression of pluripotent stem cell reprogramming factors by prostate tumor initiating cells. *J Urol*. 2010;183(5):2045–2053.
46. Berman-Booty LD, Knudsen KE. Models of neuroendocrine prostate cancer. *Endocr Relat Cancer*. 2015;22(1):33–49.
47. Beltran H, Tomlins S, Aparicio A, et al. Aggressive variants of castration-resistant prostate cancer. *Clin Cancer Res*. 2014;20(11):2846–2850.

Supplementary material

Appendix 1: Detailed search strategy

1. MEDLINE (via PubMed) search strategy

Search ID#	Search Terms
#29	Search #20 AND #28
#28	Search #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#27	Search "CHGA"[Text Word]
#26	Search "Secretory Protein I, Parathyroid Gland"[Text Word]
#25	Search "Secretory Protein I, Parathyroid Gland"[Text Word]
#24	Search "CHGA Protein"[Text Word]
#23	Search "Secretory Protein, Parathyroid"[Text Word]
#22	Search "Parathyroid Secretory Protein"[Text Word]
#21	Search "Chromogranin A"[Mesh]
#20	Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#19	Search Cancer of Prostate[Text Word]
#18	Search Prostatic Cancers[Text Word]
#17	Search "Cancers, Prostatic"[Text Word]
#16	Search "Cancer, Prostatic"[Text Word]
#15	Search Prostatic Cancer[Text Word]
#14	Search Cancer of the Prostate[Text Word]
#13	Search Prostate Cancers[Text Word]
#12	Search "Cancers, Prostate"[Text Word]
#11	Search "Cancer, Prostate"[Text Word]
#10	Search Prostate Cancer[Text Word]
#9	Search Prostatic Neoplasm[Text Word]
#8	Search "Neoplasm, Prostatic"[Text Word]
#7	Search "Neoplasms, Prostatic"[Text Word]
#6	Search Prostate Neoplasm[Text Word]
#5	Search "Neoplasm, Prostate"[Text Word]
#4	Search "Neoplasms, Prostate"[Text Word]
#3	Search Prostate Neoplasms[Text Word]
#2	Search Prostatic Neoplasms[Text Word]
#1	Search "Prostatic Neoplasms"[Mesh]

2. Embase search strategy

Search ID#	Search Terms
#29	#20 AND #28
#28	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#27	"CHGA":tw
#26	"Secretory Protein I, Parathyroid Gland":tw
#25	"Secretory Protein I, Parathyroid Gland":tw
#24	"CHGA Protein":tw
#23	"Secretory Protein, Parathyroid":tw
#22	"Parathyroid Secretory Protein":tw
#21	"Chromogranin A"/exp
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#19	"prostatic neoplasms":tw
#18	"cancer of prostate":tw
#17	"prostatic cancers":tw
#16	"cancers, prostatic":tw
#15	"cancer, prostatic":tw
#14	"prostatic cancer":tw
#13	"cancer of the prostate":tw
#12	"prostate cancers":tw
#11	"cancers, prostate":tw
#10	"cancer, prostate":tw
#9	"prostatic neoplasm":tw
#8	"neoplasm, prostatic":tw
#7	"neoplasms, prostatic":tw
#6	"prostate neoplasm":tw
#5	"neoplasm, prostate":tw
#4	"neoplasms, prostate":tw
#3	"prostate neoplasms":tw
#2	"prostate cancer":tw
#1	"prostate cancer"/exp

3. Cochrane Library search strategy

Search ID#	Search Terms
#29	#20 and #28
#28	#21 or #22 or #23 or #24 or #25 or #26 or #27
#27	"CHGA":ti,ab,kw
#26	"Secretory Protein I, Parathyroid Gland":ti,ab,kw
#25	"Secretory Protein I, Parathyroid Gland":ti,ab,kw
#24	"CHGA Protein":ti,ab,kw
#23	"Secretory Protein, Parathyroid":ti,ab,kw
#22	"Parathyroid Secretory Protein":ti,ab,kw
#21	MeSH descriptor: [Chromogranin A] explode all trees
#20	#1 or #2 or #3 or#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#19	"prostatic neoplasms":ti,ab,kw
#18	"cancer of prostate":ti,ab,kw
#17	"prostatic cancers":ti,ab,kw
#16	"cancers, prostatic":ti,ab,kw
#15	"cancer, prostatic":ti,ab,kw
#14	"prostatic cancer":ti,ab,kw
#13	"cancer of the prostate":ti,ab,kw
#12	"prostate cancers":ti,ab,kw
#11	"cancers, prostate":ti,ab,kw
#10	"cancer, prostate":ti,ab,kw
#9	"prostatic neoplasm":ti,ab,kw
#8	"neoplasm, prostatic":ti,ab,kw
#7	"neoplasms, prostatic":ti,ab,kw
#6	"prostate neoplasm":ti,ab,kw
#5	"neoplasm, prostate":ti,ab,kw
#4	"neoplasms, prostate":ti,ab,kw
#3	"prostate neoplasms":ti,ab,kw
#2	"prostate cancer":ti,ab,kw
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees

4. Web of Science search strategy

Search ID#	Search Terms
#29	#20 AND #28
#28	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#27	Topic=(CHGA)
#26	Topic=(Secretory Protein I, Parathyroid Gland)
#25	Topic=(Secretory Protein I, Parathyroid Gland)
#24	Topic=(CHGA Protein)
#23	Topic=(Secretory Protein, Parathyroid)
#22	Topic=(Parathyroid Secretory Protein)
#21	Topic=(Chromogranin A)
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#19	Topic=(prostatic neoplasms)
#18	Topic=(cancer of prostate)
#17	Topic=(prostatic cancers)
#16	Topic=(cancers, prostatic)
#15	Topic=(cancer, prostatic)
#14	Topic=(prostatic cancer)
#13	Topic=(cancer of the prostate)
#12	Topic=(prostate cancers)
#11	Topic=(cancers, prostate)
#10	Topic=(cancer, prostate)
#9	Topic=(prostatic neoplasm)
#8	Topic=(neoplasm, prostatic)
#7	Topic=(neoplasms, prostatic)
#6	Topic=(prostate neoplasm)
#5	Topic=(neoplasm, prostate)
#4	Topic=(neoplasms, prostate)
#3	Topic=(prostate neoplasms)
#2	Topic=(prostate cancer)
#1	Topic=(prostate cancer)