

VEGF and prostatic cancer: a systematic review

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Elevated vascular endothelial growth factor (VEGF) blood concentration reflects its prostatic production, making this a potentially interesting tumour marker to support the decision of submitting a patient for prostatic biopsy. The objective was to review systematically the evidence on the role of VEGF blood concentration in prostate cancer detection. Published studies addressing the relation between serum or plasma VEGF levels and prostate cancer were identified by searching Pubmed, ISI Web of Knowledge, SCOPUS and LILACS up to January 2010, and reviewed following a standardized protocol. Three studies reported higher plasma VEGF (pg/ml) in patients with localized prostate cancer than in healthy controls (7.0 vs. 0.0, 9.9 vs. 2.2, and 210 vs. 26.5, $P < 0.01$), and two showed higher serum VEGF (pg/ml) in prostate cancer patients than in patients with benign prostate hypertrophy (518.9 vs. 267.9, $P < 0.001$; no specific values, $P < 0.05$). In one study, serum VEGF was significantly lower in healthy controls than in patients with benign prostate hypertrophy, localized or metastatic prostate cancer. The three studies that used controls with previous suspicion of prostatic cancer but a negative biopsy reported non-statistically significant difference in VEGF serum levels

(pg/ml) between controls and localized prostate cancer patients (241 vs. 206; 69.5 vs. 55; 215.2 vs. 266.4). Higher VEGF plasma levels are observed in prostatic cancer patients compared with healthy controls, but serum levels do not appear to be useful in differentiating benign from malignant prostatic disease using, as controls, individuals with high risk of prostate cancer and negative biopsy.

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Introduction

Prostate cancer is the most frequently diagnosed noncutaneous cancer in men (Jemal *et al.*, 2008). Its incidence increased dramatically after the introduction of the prostate-specific antigen (PSA) test but the lack of sensitivity and specificity of PSA as a diagnostic test is of great concern in clinical practice (Hammerer *et al.*, 2006; Pepe *et al.*, 2006; Thompson and Ankerst, 2007). The need for better detection and optimal staging of prostate cancer underlies the need for new biological markers that could help to avoid unnecessary prostate biopsies, allowing the detection of prostatic cancers with low PSA levels (Schenk-Braat and Bangma, 2006; Margreiter *et al.*, 2008).

The growth of prostate cancers, as many other solid tumors, depends on angiogenesis (Nicholson and Theodorescu, 2004). Vascular endothelial growth factor (VEGF) is the most prominent cytokine responsible for endothelial cell differentiation, migration, proliferation, tube formation, and vessel assembly (Fong *et al.*, 1995).

Prostate is a significant source of systemic VEGF in prostate cancer patients (George *et al.*, 2004), as it is synthesized either by adenocarcinoma cells and tumour-infiltrating lymphocytes (Freeman *et al.*, 1995; Ferrer *et al.*, 1997). Elevated blood VEGF levels could reflect prostatic VEGF production, making VEGF a potentially interesting tumour marker to support the decision of submitting

a patient for prostatic biopsy. However, earlier reports on this topic provide conflicting evidence.

This study aims to systematically review the published studies assessing the role of serum or plasma VEGF levels in prostate cancer detection.

Methods

Published studies addressing the relation between VEGF plasma or serum levels and prostate cancer were identified in Pubmed, ISI Web of Knowledge, SCOPUS and LILACS, from inception to January 2010. For Pubmed, ISI Web of Knowledge and SCOPUS the search expression was: (VEGF OR VEGF-A OR Vascular Permeability Factor) AND (Prostate OR Prostatic) AND (Cancer OR Neoplasm). For LILACS the search terms were: VEGF OR VEGF-A OR Vascular Permeability Factor. Two investigators screened the reference lists to identify potentially relevant studies. Papers reporting original research published in English, Spanish, French, Portuguese and Italian were eligible. Papers written in other languages were also considered for the systematic review when the English abstracts provided the necessary information. In addition, we also included in the systematic review an article from our own group recently accepted for publication (Botelho *et al.*, 2010).

Two articles written in Russian (Trapeznikova *et al.*, 2004, 2005) were included in the systematic review, but only the information provided in the English abstract was considered after several unsuccessful attempts to contact the investigators.

We excluded from the review the studies not conducted in humans, those that did not evaluate VEGF-A [the classical VEGF and the most important form in tumour tissues (Nicholson and Theodorescu, 2004)], those that evaluated VEGF levels in biological products other than plasma or serum, in which VEGF was not assessed as a potential diagnosis tool for prostate cancer (e.g. measurements done more than 1 year before diagnosis) or when the control group included cancer patients. The reference lists provided by the identified papers were screened following the same criteria. The systematic review flowchart is presented as Fig. 1.

Data extraction was independently conducted by two reviewers after a previously defined data collection protocol. The following information was obtained from each study: year of publication and country of origin, patient selection/study design (consecutive patients, case-control), number of participants diagnosed with the different prostatic pathologies (healthy controls, benign pathology, localized prostatic cancer or metastatic prostatic cancer), biological product used for VEGF evaluation (serum or plasma), method of VEGF measurement (quantifying all the five VEGF-A isoforms or only VEGF-A 121 and 165), VEGF levels in the different prostatic pathologies and corresponding *P* values, measure of association and

respective precision estimate for the relation between VEGF and PSA levels, biopsy or the specimen Gleason score and clinical or pathological staging. Any discrepancies between the two reviewers were resolved by consensus, or involving a third researcher.

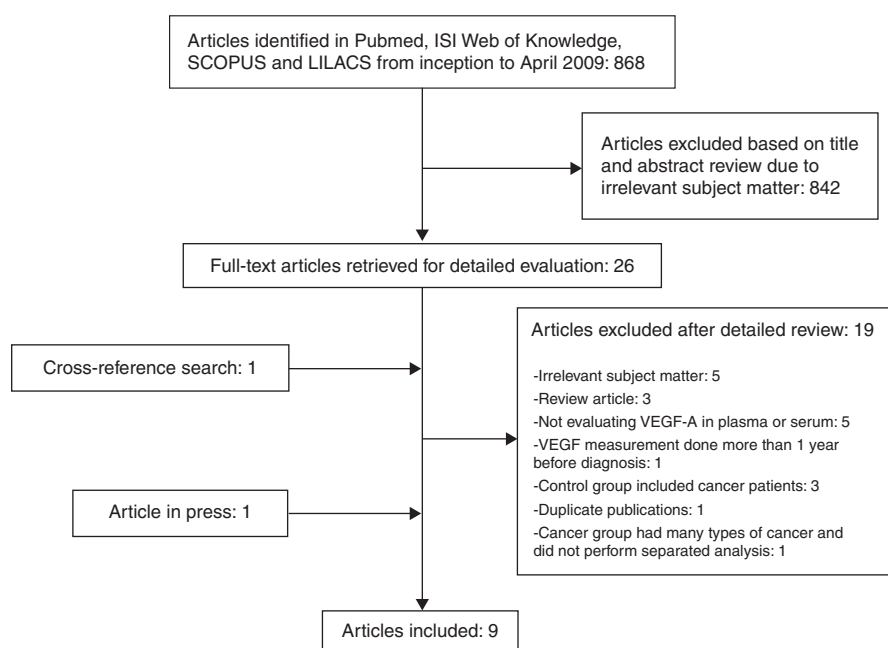
No information was available on the method used for patient selection and type of controls from two reports (Trapeznikova *et al.*, 2004, 2005), and no description of the method used to measure VEGF and its levels in the different prostatic pathologies could be obtained from one (Trapeznikova *et al.*, 2005).

Owing to the limited information provided in the original reports regarding the precision of the estimates, and the small number of studies with similar characteristics regarding the control group selection and methods used to quantify VEGF, both potentially responsible for heterogeneity in the observed VEGF levels across studies, no meta-analysis was conducted.

Results

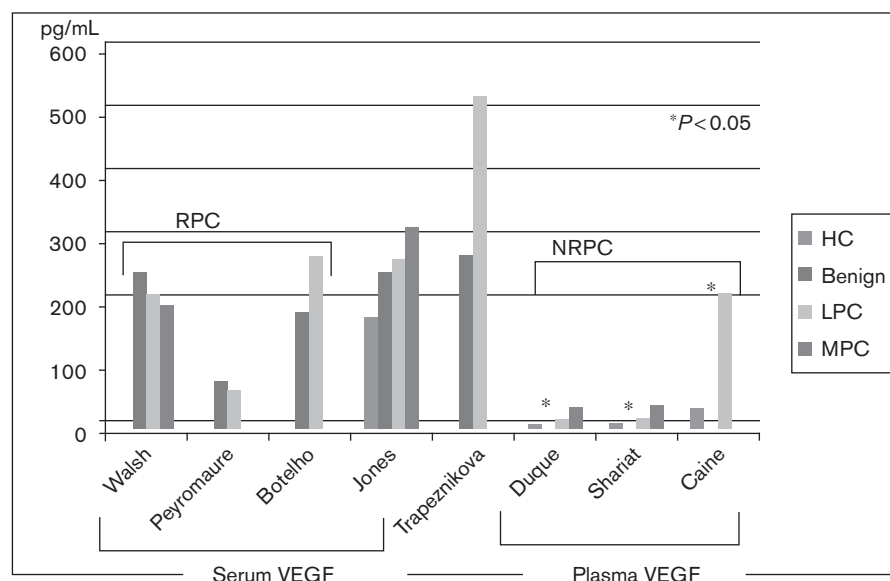
The nine studies considered for systematic review (Duque *et al.*, 1999; Walsh *et al.*, 1999; Jones *et al.*, 2000; Shariat *et al.*, 2004; Caine *et al.*, 2004a; Trapeznikova *et al.*, 2004, 2005; Peyromaure *et al.*, 2005; Botelho *et al.*, 2010) are summarized in Fig. 2 and Table 1. Five studies were conducted in Western European countries [three in the United Kingdom (Walsh *et al.*, 1999; Jones *et al.*, 2000; Caine *et al.*, 2004a), one in Portugal (Botelho *et al.*, 2010) and one in France (Peyromaure *et al.*, 2005)], two in the United

Fig. 1



Systematic review flowchart.

Fig. 2



Vascular endothelial growth factor (VEGF) levels according to prostatic pathology. Benign, patients with benign prostatic pathology or no prostatic pathology; HC, healthy controls; LPC, localized prostatic cancer, as defined by authors; MPC, metastatic prostatic cancer, as defined by authors; NRPC, controls with negligible risk of prostate cancer; RPC, controls with high risk of prostatic cancer but the prostate biopsy was negative for malignancy. Notes: one article from Trapeznikova *et al.* (2005) included in the systematic review is not presented in this figure as it does not describe VEGF levels in the different prostatic pathologies [just reports that mean VEGF was significantly higher ($P < 0.05$) in LPC than in patients with benign prostatic hyperplasia] the abstract from Trapeznikova *et al.* (2004) did not provide information about the type of controls used and Jones *et al.* (2000) evaluated healthy controls and controls with benign prostatic hyperplasia whose risk of prostatic cancer is not reported.

States of America (Duque *et al.*, 1999; Shariat *et al.*, 2004) and the other two in Russia (Trapeznikova *et al.*, 2004, 2005). The median sample size was 106 participants, ranging from 47 to 264.

In four studies (Duque *et al.*, 1999; Jones *et al.*, 2000; Shariat *et al.*, 2004; Caine *et al.*, 2004a) prostatic cancer cases and controls were selected separately [this study design has been called case-control with two-gate design using healthy controls (Rutjes *et al.*, 2005)], two selected a consecutive series of patients undergoing prostatic biopsy (Peyromaure *et al.*, 2005; Botelho *et al.*, 2010), and the others used a non-consecutive series of patients with suspected prostatic cancer because of elevated PSA (not further specified) in which the investigators choose some patients with benign prostatic hyperplasia (BPH), localized prostatic cancer and metastatic prostatic cancer (Walsh *et al.*, 1999).

In three reports, controls were men with negligible risk of prostate cancer based on digital rectal examination and PSA levels (Duque *et al.*, 1999; Shariat *et al.*, 2004; Caine *et al.*, 2004a). In three other studies (Walsh *et al.*, 1999; Peyromaure *et al.*, 2005; Botelho *et al.*, 2010) controls were men with high risk of prostate cancer who had a negative prostate biopsy, and in the remaining studies the type of controls selected is not clear (Trapeznikova *et al.*, 2004, 2005) or both healthy individuals and BPH patients were evaluated (Jones *et al.*, 2000).

All studies measured VEGF levels using enzyme linked immunoabsorbent assay (ELISA) methods. Five studies assessed serum (Walsh *et al.*, 1999; Jones *et al.*, 2000; Trapeznikova *et al.*, 2004; Peyromaure *et al.*, 2005; Botelho *et al.*, 2010) and three assessed plasma VEGF (Duque *et al.*, 1999; Shariat *et al.*, 2004; Caine *et al.*, 2004a), with the latter reporting lower median VEGF levels. Peyromaure *et al.* (2005) used an ELISA kit with a polyclonal antibody designed to measure all the five VEGF-A isoforms but in the other studies (Walsh *et al.*, 1999; Jones *et al.*, 2000; Shariat *et al.*, 2004; Trapeznikova *et al.*, 2004; Caine *et al.*, 2004a; Peyromaure *et al.*, 2005; Botelho *et al.*, 2010) an immunoassay technique designed to measure only the two active isoforms of VEGF-A (VEGF 121 and VEGF 165) was used.

The comparison of VEGF levels between controls and different prostatic pathology groups is presented in Fig. 2.

Five (Duque *et al.*, 1999; Shariat *et al.*, 2004; Caine *et al.*, 2004a; Trapeznikova *et al.*, 2004, 2005) of the nine studies report statistically significantly higher VEGF levels in patients with prostatic adenocarcinoma compared with controls. Three of these reports (Duque *et al.*, 1999; Shariat *et al.*, 2004; Caine *et al.*, 2004a) referred to studies that measured VEGF in the plasma and whose controls had negligible risk of prostatic cancer, although such diagnosis was not excluded by prostatic biopsy. The other

Table 1 Summary of the studies of vascular endothelial growth factor and prostatic cancer included in the systematic review

| First author, publication year country | Participants | Biological product/ method for VEGF measurement | VEGF pg/ml | Notes/other results |
|---|--|---|--|---|
| Walsh <i>et al.</i> (1999) UK | 40 BPH ^c 26 LPC 40 MPC | Serum ELISA-1 | Median (interquartile range) BPH: 241 (169–324); LPC: 206 (126–954); MPC: 190 (104–285) NS (not further specified) | |
| Duque <i>et al.</i> (1999) USA | 26 HC 54 LPC 26 MPC | Plasma ELISA-1 | Median (interquartile range) HC: 0 (0–24); LPC: 7.0 (0–26.5); MPC: 28.5 (19.3–57.0) $P<0.001$ | Controls were 17.5 years younger, on average VEGF vs. PSA ^a : $r=0.14$ ($P=0.22$) VEGF by Gleason ^b : ≤ 6 : 5.5; ≥ 7 : 11.5; ≥ 8 : 23.5 ($P=0.18$) VEGF levels stratified by clinical stage in LPC: T1c: 4.0; T2: 8.5; T3: 4.5 ($P=0.54$) |
| Jones <i>et al.</i> (2000) UK | 21 HC 9 BPH ^c 16 LPC 32 MPC (including 9 HRMPC) | Serum ELISA-1 | Mean HC: 170.7; BPH: 241.7; LPC: 263.9; MPC: 313.5 HRMPC: 535.0 $P>0.05$ | Controls were 42 years younger, on average VEGF vs. PSA ^a : $r=0.35$ ($P=0.02$) VEGF levels in HC and HRMPC were different from the others ($P<0.01$) but no differences between BPH, LPC or MPC ($P>0.05$) |
| Shariat <i>et al.</i> (2004) USA | 40 HC 215 LPC 9 MPC | Plasma ELISA-1 | Median (range) HC: 2.24 (1.61–2.99); LPC: 9.91 (1.99–166.9); MPC: 31.30 (15.3–227.1) $P<0.001$ | VEGF vs. PSA ^a : $r=0.119$; $P=0.081$ VEGF by Gleason ^b : ≤ 6 : 9.6; ≥ 7 : 13.2; $P=0.036$ VEGF levels by pathological stage: \leq T2: 9.6; \geq T3: 12.4; ($P=0.047$); NO: 9.6; N+: 29.8 ($P<0.001$) |
| Caine <i>et al.</i> (2004a) UK | 30 HC 30 LPC | Plasma ELISA-1 | Median (interquartile range) HC: 26.5 (25–50); LPC: 210 (166–360) $P=0.0001$ | |
| Trapeznikova <i>et al.</i> (2004) Russia | 80 BPH 38 PC | Serum ELISA-1 | Mean BPH: 267.9; PC: 518.9 $P<0.001$ | VEGF (cut-off: 151.5 pg/ml) Sensitivity, 76.2% Specificity, 57.6% |
| Peyromaure <i>et al.</i> (2005) France | 20 BPH ^c 27 PC | Serum ELISA-2 | Median (interquartile range) Benign: 69.5 (34.5–145.5); PC: 55 (25–113) $P=0.55$ | VEGF vs. PSA ^a : $r=-0.003$ ($P=0.98$) VEGF by Gleason ^b : 6: 47; 3+4: 39; 4+3: 49; ≥ 8 : 159 ($P=0.12$) VEGF levels by clinical stage: \leq T2: 48; T3: 66; N+ or M+: 104 ($P=0.62$) |
| Trapeznikova <i>et al.</i> (2005) Russia | 36 BPH 25 PC | Serum NSA | Mean VEGF was significantly higher ($P<0.05$) than in patients with BPH, not further specified | VEGF vs. PSA ^b : $r=0.72$ ($P<0.05$) in PC patients No association between VEGF and stage or Gleason score (not further specified) |
| Botelho <i>et al.</i> (2010) Portugal | 51 BPH ^c 30 Pathological Prostatitis ^c 99 PC | Serum ELISA-1 | Median (interquartile range) BPH: 178.2 (134.0–279.0); Prostatitis: 261.3 (180.7–570.9); PC: 266.4 (144.7–408.5) $P=0.029$ | Benign vs. malignant pathology: 215.2 vs. 266.4; $P=0.551$ OR of the association between VEGF (< and >266.4) and malignant disease, adjusted for age and PSA: 1.22 (95% CI: 0.62–2.40) VEGF vs. PSA ^a : $r=0.18$; $P=0.013$ VEGF by Gleason ^b : 6: 258.8; 7: 272.5; ≥ 8 : 234.9; $P=0.716$ AUC=0.53 (95% CI: 0.44–0.61); Cut-off value for which a higher proportion of patients was correctly classified (57.0%) was 266.4 |

BPH, benign prostatic hyperplasia; ELISA-1, ELISA kit (Quantikine, R&D Systems, MN, Minneapolis; also distributed by Abingdon, UK) that measures VEGF-A 121 and 165; ELISA-2, ELISA kit (Bender MedSystems, Vienna, Austria) that measures all the five VEGF-A isoforms; HC, healthy controls with negligible risk of prostatic cancer; HRMPC, hormone-refractory metastasized prostatic cancer; LPC, localized prostatic cancer; MPC, metastasized prostatic cancer; NS, not significant; NSA, not specified in the abstract; PSA, total prostatic-specific antigen.

^aCorrelation between VEGF levels and total prostatic-specific antigen.

^bVEGF levels stratified by Gleason score in the biopsy.

^cControls with high risk of prostatic cancer based on PSA levels or digital rectal examination but with a negative prostate biopsy; All the VEGF levels are in pg/ml.

two studies evaluated serum VEGF levels (Trapeznikova *et al.*, 2004, 2005) and also reported higher levels of VEGF in prostatic cancer patients, but the controls' risk of prostatic cancer was not made clear.

In two studies (Walsh *et al.*, 1999; Peyromaure *et al.*, 2005) that used only controls with risk of prostatic cancer and that measured VEGF in serum, the VEGF levels were higher in patients with benign prostatic disease compared with cancer patients but the results were not statistically significant. Jones *et al.* (2000) used controls with and without high risk of prostatic cancer and measured serum VEGF. Controls with negligible risk of cancer had lower

VEGF levels and hormone-refractory prostatic cancer patients higher VEGF levels than benign prostatic hyperplasia and hormone-sensitive prostatic cancer, although there were no statistical differences when comparing all the groups.

Botelho *et al.* (2010) used controls with risk of prostate cancer whose pathological result in the prostate biopsy was stratified as no pathology or benign prostatic hyperplasia and prostatitis. Cancer patients had significantly higher VEGF levels than controls with no evidence of pathology in the biopsy or only benign prostatic hyperplasia, but similar VEGF levels to those observed in

prostatitis patients, with no overall significant differences between subjects with benign and malignant pathology (Fig. 2).

Three studies (Duque *et al.*, 1999; Shariat *et al.*, 2004; Peyromaure *et al.*, 2005) showed no statistically significant correlation between VEGF and PSA (one reported a negative and two a positive correlation), but positive [$r = 0.35$, $P = 0.02$, (Jones *et al.*, 2000); $r = 0.18$, $P = 0.013$, (Botelho *et al.*, 2010)] and negative [$(r = -0.72$; $P < 0.05$) (Trapeznikova *et al.*, 2005)] significant correlations were also observed. Only one study (Botelho *et al.*, 2010) evaluated the role of VEGF as an indicator of prostatic cancer independently from PSA levels and no meaningful association was observed (odds ratio = 1.22; 95% confidence interval: 0.62–2.40).

Five studies (Duque *et al.*, 1999; Shariat *et al.*, 2004; Peyromaure *et al.*, 2005; Trapeznikova *et al.*, 2005; Botelho *et al.*, 2010) evaluated the relationship between VEGF levels and biopsy Gleason score, with only one (Shariat *et al.*, 2004) showing a significant positive association ($G \leq 6$ vs. $G \geq 7$: 9.6 vs. 13.2, $P = 0.036$) and two (Duque *et al.*, 1999; Peyromaure *et al.*, 2005) reporting a non-significant positive relation.

Regarding the differences in VEGF according to the tumour clinical stage, four studies (Duque *et al.*, 1999; Jones *et al.*, 2000; Shariat *et al.*, 2004; Peyromaure *et al.*, 2005) reported higher VEGF levels in metastatic than in localized prostate cancer but the differences were statistically significant only in two (Duque *et al.*, 1999; Shariat *et al.*, 2004). Peyromaure *et al.* (2005) also reported higher levels of VEGF in locally advanced tumours ($cT \leq 2$: 48 pg/ml; $cT3$: 66 pg/ml; $P = 0.62$), but the results were not statistically significant. Duque *et al.* (1999) reported no significant relation between clinical stage and VEGF levels ($cT1c$: 4.0 pg/ml; $cT2$: 8.5 pg/ml; $cT3$: 4.5 pg/ml; $P = 0.54$).

Shariat *et al.* (2004) have also shown differences according to pathological stages. In addition they report higher levels of VEGF in patients with adenocarcinoma with extraprostatic extension ($pT \leq 2$ vs. $pT \geq 3$: 9.6 vs. 12.4, $P = 0.047$) and with lymph node metastasis ($pN0$ vs. $pN+$: 9.6 vs. 29.8, $P < 0.001$) in the prostatectomy specimens, but no other study investigated this association. Trapeznikova *et al.* (2005) reported no association between VEGF serum levels and stage, but no further information is provided in the abstract.

Discussion

Plasma VEGF levels are higher in prostate cancer patients than in controls with negligible risk of prostate cancer, as confirmed by all the studies that evaluated this association. This difference was not verified when controls at risk of prostatic cancer but with negative prostate biopsy were used. Serum VEGF levels were not consistently different across groups of prostate cancer patients with diverse clinical characteristics.

In this review we systematically evaluated the best available evidence assessing the role of VEGF serum or plasma levels in prostate cancer diagnosis. Our conclusions, however, are limited by the small number of studies identified, despite comprehensive electronic database and cross-reference searches, and by the heterogeneous methodology and presentation of results, in addition to the intrinsic limitations of the primary studies.

Publication bias is a potential source of error in literature reviews, which we tried to overcome in this study. On the one hand, we conducted a comprehensive search and included in the review two articles written in Russian from which information could be obtained only in the English abstract, and one article in press. On the other hand, VEGF is an investigational marker, not measured by routine, which expectedly increases the probability of publication regardless of the existence of positive findings. Our review includes small studies with non-significant results, which also argues against publication bias.

The articles included in the review used two different ELISA kits, one that measured all five VEGF-A isoforms and the other designed to measure only the two active isoforms of VEGF-A (VEGF 121 and VEGF 165). The results obtained with this kit correlate well with total VEGF, as reported by the manufacturer, and have very good reproducibility (Walsh *et al.*, 1999; Shariat *et al.*, 2004; Caine *et al.*, 2004a). Therefore, we do not expect these technical differences to be responsible for the heterogeneous results across studies.

The VEGF concentrations observed were much higher in studies evaluating serum (Walsh *et al.*, 1999; Jones *et al.*, 2000; Trapeznikova *et al.*, 2004; Peyromaure *et al.*, 2005; Botelho *et al.*, 2010) than in those assessing plasma levels (Duque *et al.*, 1999; Shariat *et al.*, 2004; Caine *et al.*, 2004a), which reflects the fact that serum VEGF includes VEGF stored in the platelet α -granules and released during blood clotting, in addition to plasma VEGF. Cancer patients have a higher platelet load compared with healthy individuals (Salgado *et al.*, 2001) and platelets from patients with breast or prostate cancer contain more VEGF than platelets from age-matched and sex-matched controls (Caine *et al.*, 2004b). Plasma and serum VEGF levels, however, are strongly correlated and at the moment there is no consensus regarding the more appropriate biological product for assessment of VEGF levels (Banks *et al.*, 1998; George *et al.*, 2000; Salgado *et al.*, 2000; Jacobsen *et al.*, 2002; Bachelot *et al.*, 2003).

The selection of controls is essential to ensure the validity of the conclusions from studies addressing diagnostic accuracy. The diagnostic tests must be evaluated in clinically relevant populations, preferably in consecutive series of individuals in whom the target condition is suspected (Rutjes *et al.*, 2005). Studies using healthy controls, not representing the whole spectrum of potential diagnostic

alternatives to prostate cancer, suffer from limited-challenge bias (Rutjes *et al.*, 2005, 2006) and produce inflated estimates of diagnostic accuracy (Lijmer *et al.*, 1999).

The three studies that measured VEGF in plasma were the same that used controls with negligible risk of prostatic cancer, and found statistically higher levels of VEGF in prostatic cancer patients. Conversely, three studies using subjects with some criteria for suspicion of prostate cancer but negative biopsy as controls measured VEGF in serum and found no such difference. Although it is not possible to disentangle the effect of both biological specimen for VEGF measurement and type of controls, Jones *et al.* (2000) evaluated serum levels and controls with and without risk of prostatic cancer and found no statistically significant differences among all groups, but did report some differences when comparing the extreme groups with all the others (healthy controls and hormone-refractory prostate cancer patients had lower and higher VEGF levels than the remaining participants, respectively). Botelho *et al.* (2010), also assessed VEGF serum levels and found no statistically significant differences between patients with benign and malignant disease, despite the lower VEGF levels in patients with no prostatic disease or only BPH than in prostatitis or prostate cancer patients. These results support the hypothesis of limited-challenge bias being responsible for biased positive associations between VEGF levels and prostate cancer as studies using healthy controls, not representing the whole spectrum of potential diagnostic alternatives to prostate cancer which are able to generate false-positive results, namely prostatitis, can produce inflated estimates of diagnostic accuracy.

The characteristics of the control group are especially important when assessing the role of VEGF in prostate cancer diagnosis as it is expected to be used as an add-on. Its purpose is not to replace PSA testing or to be used as a screening tool, but to contribute to identify false-positive or false-negative results of the PSA test. Unfortunately, the studies included in this review showing significant differences between prostate cancer patients and controls used control groups including individuals likely to have low PSA levels that would never been considered for VEGF testing in a clinical setting.

Despite tissue expression of VEGF being associated with the tumor Gleason sum in studies using immunohistochemical staining (Kuniyasu *et al.*, 2000) and rapid colorimetric in situ hybridization (Kuniyasu *et al.*, 2000), such association was not shown in most of the articles that assessed blood VEGF levels. The results are also inconsistent for the association between total PSA levels and serum or plasma VEGF.

VEGF levels appear to be higher in patients with metastatic prostatic cancer, especially those in hormone-refractory status, compared to localized prostatic cancer, but evidence is inconclusive regarding differences according to clinical local staging.

We did not identify any article specifically addressing the role of VEGF in prostate cancer prevention, in addition to its use as a tumour marker to support the decision of submitting subjects suspected of having prostate cancer, namely those identified in secondary prevention actions, for prostatic biopsy. One study (Shariat *et al.*, 2004) (also included in the systematic review) also evaluated the association of VEGF with prognosis after radical prostatectomy. VEGF plasma levels were significantly associated with biochemical progression in the preoperative multivariate model [hazard ratio: 1.009; $P = 0.014$] adjusted for clinical stage, preoperative VEGF, preoperative sVCAM-1, preoperative PSA and the biopsy Gleason sum and in the postoperative multivariate model (hazard ratio: 1.007; $P = 0.019$) adjusted for preoperative sVCAM-1, preoperative PSA, the biopsy Gleason sum, extracapsular extension, seminal vesicle invasion, surgical margin status and the final Gleason sum. These results have the potential of altering the follow-up of prostate cancer patients, if confirmed by other studies.

VEGF levels have also been compared between healthy individuals and patients with other types of tumours. Serum VEGF in patients with cervical (Gadducci *et al.*, 2008), bladder (Nakanishi *et al.*, 2009), papillary thyroid (Yu *et al.*, 2008), kidney (Schips *et al.*, 2007), pancreas (Chang *et al.*, 2008), gastric or colorectal cancers (Yamamoto *et al.*, 1996; Kumar *et al.*, 1998; Al-Moundhri *et al.*, 2008), lymphoma (Poreba *et al.*, 2005), multiple myeloma (Shen *et al.*, 2005), melanoma (Tas *et al.*, 2008), cholangiocarcinoma (Alvaro *et al.*, 2007), pediatric solid tumors (El-Houseini *et al.*, 2004) and advanced lung cancer (Jin *et al.*, 2009) has been reported as significantly higher than in healthy individuals, but not in the case of localized breast (Duranyildiz *et al.*, 2009), localized nasopharyngeal (Li *et al.*, 2004), hepatocellular (Tseng *et al.*, 2004) or medullary thyroid carcinoma (Joao Bugalho *et al.*, 2008) or leukemia (Poreba *et al.*, 2005) and results were conflicting for ovarian cancer (Dvorak, 2002; Jain *et al.*, 2009). VEGF levels have been correlated with poor prognosis in breast, kidney, brain, cervical and colon carcinomas (Dvorak, 2002).

One area of recent developments is the discovery that single nucleotide polymorphisms in VEGF alters VEGF protein concentrations, influence the process of angiogenesis, and relates to interindividual variation in the risk and progression of breast, lung, colon and prostate cancers (Jain *et al.*, 2009). In the future it might even be associated with resistance to specific treatments and drive the choice of treatment for a particular patient. So far none of these associations have changed clinical practice, but they might as studies unravel new uses of VEGF and gene polymorphisms influencing its levels for the diagnosis, prognosis and treatment options in oncology.

The conclusion that plasma VEGF levels are higher in patients with prostate cancer compared to healthy controls is unlikely to be of any clinical benefit. PSA level is

certainly a better indicator of disease (Schroder, 2009) and no study proved that VEGF was an independent predictor of cancer in those with prostate pathology associated with elevated PSA levels.

Serum VEGF levels do not seem clinically useful for selection of patients to be submitted to prostate biopsy. Despite we cannot exclude that serum VEGF levels are not as useful as plasma levels, the exclusion of patients with pathological prostatitis from the control groups is a likely explanation for the heterogeneous results in previous studies.

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