# Cancer pathology: panel of diagnostic markers for cancer

**Anuj Kumar Gupta* and Prashant Khadke**

Shri Jagdishprasad Jhabarmal Tibrewala University, Vidyanagari 333 001, India

**Cancer is the second known lethal disorder after coronary heart disease, characterized by the loss of control of cell growth leading to excessive proliferation and spread of cells. Different diagnostic tools and different protein or glycoprotein markers are available for diagnostic utility and prognosis of cancer in patients. Of these, some diagnostic markers are promising but some still need to be validated for their utility. In this study, we demonstrate the pathogenesis of different types of cancer, such as cancer of breast tissue, pancreatic tissue, ovary, prostate, lung tissue and colorectal tract and the utility of a panel of diagnostic markers for them.**

**Keywords:** Diagnostic marker, glycoprotein, pathogenesis, protein.

TUMOURS are usually acknowledged by cells having abnormal growth, with the loss of controlled growth mechanism[1]. Tumours are classified into benign, *in situ* and malignant tumours. Malignant tumours have abnormal genetic expression and this expression depends on age, degree of cell differentiation, growth, invasion and metastatic potential as well as therapy responses[2]. In different cancer conditions, tumour cells produce a range of proteins that stimulate the growth of blood vessels into the tumour, thus allowing continuous growth to occur and may be responsible for invasive behaviour. Different carcinogens, proved to be responsible for carcinogenesis, do not cause tumours directly. There are a series of events that include initiation of transformation of cell (preneoplastic). After initial transformation, different factors (promoting agents) cause changes in genetic material (DNA) leading to development of neoplastic malignant tumour[3].

Apoptosis is one of the most extensively studied phenomena to understand the programmed cell death process in cancer conditions as it gives a clear vision into disease pathogenesis. Cancer is characterized by loss of equilibrium between cell division and apoptosis. *p53* is a tumour suppressor gene which itself down-regulates in cancer and hence, reduced apoptosis of cancer cells[4]. Different tools for diagnosis of cancers are imaging procedures, including CT scan, nuclear scan, MRI, PET, ultrasound, X-ray and biopsy. However, due to affordability, screening of diagnostic makers has higher potential. For diagnosis of different types of cancer, there are several diagnostic biomarkers available. Of these, some are well established and some still need to be validated. In this study, we describe a panel of diagnostic markers for different types of cancer.

## Head and neck carcinoma

There are several ways to classify the biomarker of head and neck cancer but few have shown positive results. In most cases, head and neck tumours can be distinguished when the disease shows symptoms. Epidermal growth factor receptor (EGFR), a member of the ErbB family of receptors, is an important therapeutic target, but a poor prognostic marker of head and neck squamous cell carcinoma (HNSCC). A comparative study was done using specific monoclonal antibodies, which recognized EGFR extracellular domain molecule, to know the impact of EGFR expression in HNSCCs patients' status. They carried out quantitative EGFR immunohistochemical analysis to get mean absorbance (MOD), staining index (SI), and quick score (QS). They reported that HNSCCs had a wide discrepancy in expression of EGFR (MOD, 0.2 to 66.0; SI, 0.3 to 97.0; QS, 0.01 to 69.9) with a comparatively strong, but nonlinear, relationship between MOD and SI ($r = 0.79$)[5]. Despite extensive studies on squamous cell carcinoma of head and neck (SCCHN), EGFR remains the only non-chemotherapeutic molecular target used by clinicians for clinical benefit[6].

## Brain cancer

Brain cancer begins with the transformation of normal brain cells to cancerous cells. Glioma is reported as a very common subgroup of brain tumours arising from glial cells. Apart from mechanical tools including CT scan, MRI, angiogram, X-ray, spinal tap and biopsy, some biomarkers are also reported for diagnosis of glioma that includes EGFR, which was found to be highly expressed or mutated in malignant condition. Activation of EGFR was also reported to block the development of new neurons and was linked with a remarkable increase in chemotaxis process in the presence of EGF[7]. YKL-40

*For correspondence. (e-mail: rtr.anujgupta@gmail.com)

is an important biomarker to check the response of radiation therapy and for prognosis in glioblastoma multiforme. YKL-40 was reported to be an independent marker of survival in glioblastoma patients, after considering several factors such as age of patients, performance status of brain and degree of re-section[8]. It was also suggested that it could be carcinogenic in brain cancer[8]. The expression of protein marker, glial fibrillary acidic protein (GFAP), was studied in serum of patients with brain tumour. It was found that the concentration of GFAP was directly proportional to the degree of glioblastoma and degree of tumour necrosis imaged using MRI[9]. It is reported that inactive Ephrin type-A receptor 2 (EphA2) is responsible for the spread of cancerous cell in glioblastoma multiforme, but its active form inhibits abnormal cell growth and division[10]. Huntingtin interacting protein 1 (HIP1) is also reported in high level in brain cancer and is also correlated with the expression of EGFR[11]. The expression of HIP1 was found considerably elevated in tissue of primary brain tumour as compared to that in normal cortical brain tissue (63% versus 28%; $P < 0.001$)[11].

## Thyroid cancer

Thyroid cancer is one for which well-established diagnostic markers are not available[12]. Calcitonin is an anti-hypercalcemic hormone containing 32-amino acids, primarily produced by parafollicular cells of thyroid and is reported as a serum biomarker of medullary thyroid cancer (MTC). However, higher concentration of calcitonin is also reported in ageing, in C-cell hyperplasia, heavy weight, milk feeding, smoking, and small cell carcinoma of the lung with low incidence[13–15]. Serum thyroglobulin is reported as a biomarker for detecting thyroid cancer of follicular cell origin because it is not significantly detected after a total thyroidectomy[16,17]. Galectin-3 could be another biomarker as it is overexpressed in thyroid carcinoma of follicular cell origin, whereas it is not significantly detected in normal thyroid tissues, goiters and follicular adenoma[18].

## Breast cancer

Breast cancer is one of the most predominant malignancies among female population in developed and developing countries. Breast cancer susceptible genes, *BRCA1/2*, play an important role in development of breast carcinoma. *BRCA1* and *BRCA2* are reported as tumour suppressor genes and mutation of these genes causes the development of premature truncated form, which was reported in malignant tumours[19]. For breast cancer, CA 15-3 and CEA are the most common diagnostic markers, but the sensitivity and specificity of CA15-3 and CEA is an issue with no correlation of concentrations of CA15-3 and CEA protein to disease progression[20,21]. MUC1 gene product, MUC1/Y, has also been reported as a potential breast cancer marker and monoclonal antibody developed against MUC1/Y shows specific signals in breast cancer tissue[22]. ST3Gal-1 is a sialyl-transferase, responsible for sialylation of T antigen to Sialyl-T antigen. Antibodies against ST3Gal-1 show prominent and specific signals in sections of breast cancer tissue but not in fibroadenoma sections[23]. It is reported that p53 gene product is required for the integrity of non-tumourogenic phenotype of cells and tumour suppressor functions. MUC1 down-regulates p53 in breast cancer, which suggests its potential in breast cancer diagnosis[24]. Mammaglobin is another suggested biomarker for breast cancer with 76% sensitivity and 90% specificity[25].

There are several other biomarkers detected in breast cancer tissues. These include galectin-3, which was found to be correlated with disease progression[26], survivin[27], EGFR, ER and PR[28], cytokeratin 19, cytokeratin 20, urokinase plasminogen activator (uPA), plasminogen activator inhibitor-1 (PAI-1) and small breast epithelial mucin (SBEM)[29,30]. Maspin is reported as an inhibitor of serine proteases, having tumour suppressive activity in breast carcinoma and its expression decreases with tumour progression[31]. Human epidermal growth factor receptor 2 (HER2) is a protein found on the surface of normal breast cells. It is reported that some breast cancer cells have high expression of HER2, in such cases breast cancer is termed as HER2 positive breast cancer. Almost 15–25% of women are usually reported to have HER2 positive breast cancer[32,33]. The identification of a new biomarker for breast cancer is still going on.

## Lung cancer

Lung (bronchogenic) carcinoma is one of the most frequent cancers with a high mortality rate because of lack of early detection and thus, low cure rates. It is reported that only 1/7th of the patients is usually detected at an early stage with lung cancer[34]. It is also found that smoking is the main cause of lung cancer with smokers having a 10-fold greater risk to develop lung cancer than non-smokers[35]. Small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are two broad categories of lung cancer and of these, NSCLC accounts for more than 85% of lung cancer. NSCLC has further histological subtypes as adeno-carcinoma, squamous cell lung carcinoma and large cell carcinoma[36]. Several biomarkers have been studied and some show satisfactory results with each other rather than a single biomarker. Neuron-specific enolase (NSE), CYFRA 21-1, CEA and CA-125 are the most popular lung cancer biomarkers[35–37].

Neuron specific enolase (NSE) is an isomer of the glycolytic enzyme, enolase which is responsible for the development of phosphoenol pyruvate from phosphoglycerate.

It is present in neuroendocrine cells of brain tissue and neuroendocrine tumours. The concentration of NSE is frequently increased in SCLC patients as compared to NSCLC patients, thus being used to monitor the disease progression and management of SCLC[38]. Cytokeratin 19 fragment (CYFRA 21-1) is generally associated with SCLC type. The level of CYFRA 21-1 is generally linked with prognosis and disease response with sensitivity ranges between 23% and 70%, but it is also found in other respiratory diseases[39,40]. CEA is oncofetal protein not expressed in normal condition in adults and it is involved in cell adhesion and cell signalling. De-repression of CEA gene causes large production of CEA in lung cancers[36].

## Esophageal cancer

Esophageal carcinoma is reported with recurrence at high rate with very poor prognosis due to late diagnosis and non-availability of a defined biomarker. CEA and squamous cell carcinoma antigen (SCCAg) are biomarkers generally used for esophageal carcinoma with CT scan biopsy. High level of SCCAg was linked with a reduced response to treatment and an increased possibility of recurrence of disease and death. Nonetheless, sensitivity and specificity in esophageal cancer still need satisfactory validation because of the presence of these markers in other cancer conditions[41,42].

## Liver cancer

Hepatocellular carcinoma (HCC) is the fifth most common malignant condition and the third leading cause of cancer mortality[43]. High level of alpha-fetoprotein (AFP) is reported in HCC but increased levels are also reported in pregnancy and gastrointestinal cancers[44,45]. It is reported that AFP concentrations in serum do not correlate with progression of HCC. Three different glycoforms of AFP are reported, i.e. AFP-L1, AFP-L2 and AFP-L3, on the basis of its binding capacity to lectin, lens culinaris agglutinin (LCA). It is reported that a high proportion of AFP-L3 is associated with poor differentiation, carcinogenic characteristics and malfunction of liver[46,47].

Glypican-3 (GPC3), protein and its mRNA, is upregulated significantly in tumour tissues of HCC, confirmed by western blot, ELISA and immunohistochemical analysis. GPC3 is a membrane anchored heparin sulphate proteoglycan, which interacts with several growth factors and modulates their activities[48]. SCCAg is a serine protease inhibitor, which is produced at high level in the early stages of HCC[49]. Tumour associated glycoprotein 72 (TAG-72) and transforming growth factor-$\beta$1 (TGF-$\beta$1) are not only overproduced in HCC, but also produced significantly in other carcinomas. Their increased production is directly proportional to poor survival of patients with HCC. TAG-72 and TGF-$\beta$1 could be potential prognostic markers for HCC[50,51].

## Pancreatic cancer

Although pancreatic cancer accounts for only 3–4% of all types of cancers, the survival rate of patients is low[52]. The most common and validated marker for pancreatic cancer is CA19-9 with specificity of 70–98% and sensitivity of 70–90%. But the expression of CA19-9 is also significantly high in other types of digestive tract cancer[53]. The cancer antigen, CA-50, is defined by MAb of CA-50, which was developed against the COLO205 colorectal cancer cell line[54]. The sensitivity and specificity of CA-50 in serum is comparable to CA19-9 (ref 55). Recently, glypican-1, a cell surface proteoglycan, is reported as a potential biomarker for diagnosis of cancer in pancreatic tissue at an early stage with high specificity and sensitivity, allowing to distinguishing the patients with early stage and late stage of pancreatic cancer from healthy subjects and benign tumour[56].

## Prostate cancer

The prostate specific antigen (PSA) is a kallikrein-like serine protease, the most studied biomarker for prostate cancer during the past two decades. PSA is secreted from prostate epithelial cells and responsible for liquefying human semen through its enzymatic action[57]. It is established that the serum level of PSA is a useful marker for prostate cancer along with rectal examination. Apart from prostate cancer, the amount of serum PSA is higher in other conditions, such as benign prostatic hypertrophy (BPH) and prostatitis, hence leading to false positive results[58].

Kattan *et al.*[59] studied more than 700 prostatectomy cases from a single institute and found that pretreatment plasma levels of interleukin-6 soluble receptor (IL6SR) and TGF-$\beta$1 can be useful markers for predicting prostate cancer disease progression. They analysed more than 700 patients with stage cT1c to cT3a prostate cancer without any therapy for plasma concentration of TGF-$\beta$1 and IL6SR. With the help of nomogram, they found that plasma concentration of TGF-$\beta$1 and IL6SR improved the ability to predict biochemical progression by a prognostically considerable sideline[59]. Several other markers for prostate cancer are prostate specific membrane antigen, $\alpha$-methylacyl-coenzyme A racemase, hepsin, telomerase, d-catenin, a serine protease, TMPRSS2 and a prostate-specific non-coding RNA, PCA3. The potential of these markers alone or in combination with serum PSA is under study and needs to be validated for their utility as diagnostic or prognostic markers for prostate cancer[60–73].

CCL11 is a cytokine of CC chemokine family with 97 amino acid residues containing 23 amino acid signal

peptide. CCL11 is reported for inducing chemotaxis and hence allergic responses. Multiplex ELISA assays were done to quantify protein concentration of various CCLs and IL-6 in the serum samples of males having <10 μg/l of serum PSA. It was found that CCL11 serum concentration was elevated in prostate cancer patients. So, CCL11 could be a new biomarker for prostate cancer along with PSA[64]. Beta-micro-semino protein (MSMB) is also known as prostate secretory protein 94 (PSP94) encoded by *MSMB* gene in human and expressed in benign and malignant prostatic epithelium. Several reports suggested that expression level of MSMB was significantly high in tissue of prostate cancer patients and dropped significantly after radical prostatectomy. Further study is needed to validate MSMB as a diagnostic or prognostic biomarker for prostate cancer[65,66]. Prostate cancer patients expressing high levels of MSMB which expressively reduced the risk for recurrence of disease after radical prostatectomy. They have demonstrated that MSMB is a prominent independent factor in prostate cancer, evaluating favourable outcome after radical prostatectomy[66].

## Colorectal cancer

Colorectal cancer is also known as rectal cancer, bowel cancer or colon cancer based on their origin. CEA is the most widely accepted tumour marker used for the diagnosis of colorectal cancer and the concentration of CEA is proportional to the progression of disease. About 53% of patients with involvement of regional lymph nodes have shown higher CEA concentration which decreased after radical surgery[67]. Along with CEA, CA19-9 is also reported in significant amount but both CEA and CA19-9 are also associated with other cancer conditions as pancreatic, gastric cancer and bladder cancer[68]. Cancer antigen, CA 72-4, is also reported as one of the promising markers for gastric cancer along with CEA and CA19-9 with an overall specificity of 95%, approximately 50% specificity in ovarian cancer and 40% specificity in colorectal and gastric cancer[69].

Midkine (MK or MDK), a nonglycosylated small protein, is a heparin-binding growth factor having two domains joint by S–S bridges. It is reported that MDK enhances the angiogenesis and proliferation of tumour cells. The increased expression of mRNA and protein of MDK have been found in various cancer types including colorectal, glioblastoma, thyroid carcinomas, liver, ovary, lung, esophageal, stomach, breast, prostate and bladder cancers[70,71].

## Bladder cancer

There are several biomarkers described and others are under study for bladder cancer diagnosis. The bladder tumour antigen (BTA) assay is easy and one-step immunochromatographic assay for the detection of bladder tumour associated antigen in urine with 66% specificity[72]. FDA has approved bladder tumour antigen and nuclear matrix protein 22 (NMP22) assays for diagnosis and prognosis of bladder cancer. However, BTA is not very efficient to replace urine cytology in detecting tumours in bladder because of false-positive results[73]. Other biomarkers are survivin, BLCA-4, CYFRA 21-1 and DD23 but need validation for diagnostic potential in bladder cancer[74].

## Ovarian cancer

Cancer antigen 125 (CA-125) is the most extensively studied protein marker for screening of ovarian cancer. It has been proved to identify malignancy in ovarian tissue before the beginning of clinical symptoms. However, higher levels of CA-125 are also observed in patients with other gynecological disorders (e.g. polycystic ovarian disorder), other cancer conditions and in healthy women during menstruation (>300 KU/L) which gives high false-positive results[75,76]. Elevated concentration of antibodies against Her2/neu at early and late stage and antibodies against p53 at late stage have been reported in ovarian cancer patients. Hence, these antibodies may provide a more consistent serum marker for ovarian cancer[77,78].

Several biomarkers for ovarian cancer at the early stage are osteopontin, HE4, B7-H4, prostasin, vascular endothelial growth factor, mesothelin, interleukin-6, interleukin-8, eosinophil-derived neurotoxin and COOH-osteopontin fragments, OVX1, lysophosphatidic acid (LPA), apo-lipoprotein A1 (APOA1), transthyretin, BRCA1, RASSF1A, insulin like growth factor binding protein 3 (IGFBP-3). Biomarkers for ovarian cancer at late stage are haptoglobin, osteopontin, mesothelin, B7-H4, HE4, prostasin, macrophage colony stimulating factor (M-CSF), vascular endothelial growth factor (VEGF), LPA, BRCA1, Sat2-Chr1, Sat$\alpha$, RASSF1A, IGFBP-3 (ref. 79). Since the last decade, there have been several promising biomarkers evaluated for ovarian cancer. These have been evaluated either alone or in combination with each other for sensitivity and specificity. The study demonstrated that HE4 has highest sensitivity at 72.9% with 95% specificity. Evaluation results suggest that CA-125 and HE4 together have a greater sensitivity (76.4%) with 95% specificity[80].

## Melanoma

Melanoma is reported as the most aggressive form of skin carcinoma which begins in the melanin-forming cells of skin. Tumour-associated antigen 90 (TA-90) was first reported in the serum and urine of metastatic melanoma

patients. At early stages, TA-90 is abundant as circulating immune complexes (ICs), which can be quantified by ELISA. Several studies demonstrate that TA90-IC is a sensitive and specific marker of re-appearance of malignant melanoma in patients and it is also associated with poor survival[81]. Kelley *et al.*[82] demonstrated that TA-90 is the first biomarker that predicts subclinical metastatic disease (in 76% of reported patients) and survival for patients at early stage of melanoma with 77% and 76% sensitivity and specificity respectively. S-100$\beta$ protein, member of S100 family, has been reported as a promising serological biomarker and prognostic marker of melanoma metastases by immunohistochemistry and is currently being used as a routine biomarker for detection of melanoma[83–85]. By luminometric immunoassay analysis, it was found that 79% of patients have shown elevated S-100$\beta$ whereas NSE was significantly elevated in 42% patients[85].

A mature melanoma-inhibitory activity factor (MIA), a 107 amino acid protein, is also reported as one of the promising biomarkers for metastatic melanoma at late stage with higher sensitivity and specificity and it is not reported in melanocytes and normal skin. Melanoma-inhibitory activity was identified in the supernatant fraction of culture of metastatic melanoma cell line, which functions as inhibitory factor of a melanoma progression. It is found that high serum concentration of MIA protein and its mRNA expression is directly proportional to the degree of metastasis in melanoma patient[86,87].

## Lymphoma

Lymphoma is a common term used for cancer of lymphocytes. The WHO categorizes lymphoid neoplasms into 3 groups – B-cell, T/NK cell neoplasms and Hodgkin's lymphoma[88]. The most significant biomarkers for lymphoma are beta-2-microglobulin (B2M) and lactate dehydrogenase (LDH). It is reported that B2M increases with increased production and destruction of cells. On the basis of several findings it is assumed that increased serum concentration of B2M is directly linked with advancement of disease stage, higher lactate, LDH and greater tumour burden[89]. LDH is another biomarker reported in patients with non-Hodgkin's lymphoma. It is generally present in almost all cells of the body and released after cell damage. LDH is generally used for monitoring of patients with advanced lymphoma but the presence of LDH is non-specific[90].

## Leukemia

Leukemia, also called blood cancer, is a heterogeneous disease starting from bone marrow. Leukemia can be classified into acute and chronic myeloid leukemia. Acute myeloid leukemia (AML) is a condition in which bone marrow makes huge numbers of abnormal immature WBC (blast) derived from a myeloid stem cell[91]. Different studies demonstrate that RAS (Renin-angiotensin system) component, renin, is expressed in the microenvironment of bone marrow as well as in hematopoietic cells. Bone marrow blast cells of some types of AML produce renin in high amount while no expression was found in bone marrow of normal person[92–94]. The concentration of renin and angiotensin converting enzyme (ACE) was analysed in bone marrow (BM) aspirates along with blood samples. It was found that the concentration of ACE ($38 \pm 6.2$ U/l) in BM is ominously higher than blood samples ($29.5 \pm 5.3$ U/l) whereas concentration of renin in BM is slightly lower ($18.6 \pm 6.2$ U/l) than blood sample ($21.3 \pm 8.3$ U/l). In control samples the values were significantly lower[92]. Other reported potential biomarkers are core binding factor (CBF), retinoic acid receptor $\alpha$ (RAR$\alpha$), and c-KIT for diagnosis of leukemia[95]. Still diagnosis of leukemia is based on detection of mutations, deletion or alteration of some genes, like *IKZF1*, *CRLF2*, *JAK1/2*, *CREBBP*, *p53*, *PHF6*, *PTEN*, *N/K-RAS*, *NOTCH1*, *FBXW7* and *NT5C2* (ref. 96).

## Conclusion

There are several factors in the development of various types of cancer. So, along with mechanical tools, a combination of diagnostic markers could be a useful platform to understand the disease progression and patient prognosis. Few markers are found very specific, such as PSA for prostate cancer, CA15-3 for breast cancer, HE4 for ovarian cancer, etc. But most of the tumour markers involved in several cancers includes CEA, NSE, galectin-3, midkine, B2M, CA125, CA72-4, CA19-9, CRP, AFP, etc. Although PSA is routinely used for the profiling of prostate cancer patient, its sensitivity and specificity is always a concern. CA15-3 is used for the diagnosis of breast cancer, but in some cases, clinicians have failed to correlate the expression level and aberrant glycosylation with disease progression. HE4 is one for the new emerging biomarker for ovarian cancer, but still needs to be validated with disease progression. Serum diagnostic markers may help for accurate cancer diagnosis and prognosis. However, there is still a need to exploit the potential of these markers.

*Conflicts of interest:* The authors declare that they have no conflicts of interest.

1. Radic, S., Stanojevic, Z. and Dindic, B., The pathogenesis of neoplasia. *Arch. Oncol.*, 2004, **12**, 1–3.
2. Bhatt, A. N., Mathur, R., Farooque, A., Verma, A. and Dwarakanath, B. S., Cancer biomarkers – current perspectives. *Indian J. Med. Res.*, 2010, **132**, 129–149.
3. Yuspa, S. H., The pathogenesis of squamous cell cancer, lessons learned from studies of skin carcinogenesis. *Cancer Res.*, 1994, **54**, 1178–1189.

4. Bauer, J. H. and Hefand, S. L., New tricks of an old molecule, lifespan regulation by p53. *Aging Cell*, 2006, **5**, 437–440.
5. Smilek, P. *et al.*, Epidermal growth factor receptor (EGFR) expression and mutations in the EGFR signalling pathway in correlation with anti-EGFR therapy in head and neck squamous cell carcinomas. *Neoplasma*, 2012, **59**, 508–515.
6. Ang, K. K. *et al.*, Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer Res.*, 2002, **62**, 7350–7356.
7. Ayuso-Sacido, A. *et al.*, Activated EGFR signaling increases proliferation, survival, and migration and blocks neuronal differentiation in post-natal neural stem cells. *J. Neurooncol.*, 2009, **97**, 323–337.
8. Pelloski, C. *et al.*, YKL-40 expression is associated with poorer response to radiation and shorter overall survival in glioblastoma. *Clin. Cancer Res.*, 2005, **11**, 3326–3334.
9. Jung, C. *et al.*, Serum GFAP is a diagnostic marker for glioblastoma multiforme. *Brain*, 2007, **130**, 3336–3341.
10. Levin, V. A., Leibel, S. A. and Gutin, P. H., Neoplasms of the central nervous system. In *Cancer, Principles and Practice of Oncology* (eds DeVita, V. T., Hellman, S. and Rosenberg, S. A.), Lippincott Williams & Wilkins, Philadelphia (PA), 2091–2100, 6th edn, p. 200.
11. Bradley, S. V., Holland, E. C., Liu, G. Y., Thomas, D., Hyun, T. S. and Ross, T. S., Huntingtin interacting protein 1 is a novel brain tumour marker that associates with epidermal growth factor receptor. *Cancer Res.*, 2007, **67**, 3609–3615.
12. Gharib, H. and Papini, E., Thyroid nodules: clinical importance, assessment and treatment. *Endocrinol. Metab. Clin. North Am.*, 2007, **36**, 707–735.
13. Holyoke, E. D. *et al.*, Biologic markers in cancer diagnosis and treatment. *Curr. Probl. Cancer*, 1981, **6**, 1–68.
14. d'Herbomez, M. *et al.*, Reference range of serum calcitonin levels in humans, influence of calcitonin assays, sex, age, and cigarette smoking. *Eur. J. Endocrinol.*, 2007, **157**, 749–755.
15. van Veelen, W. *et al.*, Medullary thyroid carcinoma and biomarkers, past, present and future. *J. Intern. Med.*, 2009, **266**, 126–140.
16. Whitley, R. J. and Ain, K. B., Thyroglobulin, a specific serum marker for the management of thyroid carcinoma. *Clin. Lab. Med.*, 2004, **24**, 29–47.
17. Gupta, M. and Chia, S. Y., Circulating thyroid cancer markers. *Curr. Opin. Endocrinol. Diabetes Obes.*, 2007, **14**, 383–388.
18. Inohara, H. *et al.*, Expression of galectin-3 in fine-needle aspirates as a diagnostic marker differentiating benign from malignant thyroid neoplasms. *Cancer*, 1999, **85**, 2475–2484.
19. Szabo, C. I. and King, M. C., Inherited breast and ovarian cancer. *Hum. Mol. Genet.*, 1995, **4**, 1811–1817.
20. Duffy, M. J., Serum tumour markers in breast cancer, are they of clinical value? *Clin. Chem.*, 2006, **52**, 345–351.
21. Maric, P., Ozretic, P., Levanat, S., Oreskovic, S., Antunac, K. and Beketic-Oreskovic, L., Tumour markers in breast cancer-evaluation of their clinical usefulness. *Coll. Antropol.*, 2011, **35**, 241–247.
22. Gupta, A. K. *et al.*, Development of monoclonal antibodies against MUC1/Y recombinant protein expressed in *E. coli*. *Int. J. Pharm. Biol. Sci.*, 2015, **6**, 37–46.
23. Gupta, A. K., Kaur, P., Patil, H., Kadam, P., Bhanushali, P. B. and Chugh, M., Development of monoclonal antibodies against CMP-N-acetylneuraminate-beta-galactosamide-alpha-2,3-sialyltransferase 1 (ST3GAL1) recombinant protein expressed in *E. coli*. *Biochem. Res. Int.*, 2015, **2015**, 1–7.
24. Gupta, A. K. and Khadke, P., Co-expression and Regulation of p53 and MUC1 in human carcinomas. *Int. J. Curr. Res.*, 2015, **7**, 21127–21132.
25. Wang, Z. *et al.*, Mammaglobin, a valuable diagnostic marker for metastatic breast carcinoma. *Int. J. Clin. Exp. Pathol.*, 2009, **2**, 384–389.
26. Gupta, A. K., Kaur, P., Bhanushali, P. B. and Khadke, P., Multifunctional diagnostic exploitation of human Galectin-3. *Int. J. Pharm. Sci. Rev. Res.*, 2015, **32**, 26–37.
27. Al-Joudi, F. S., *et al.*, Expression of survivin and its clinicpathological correlations in invasive ductal carcinoma of the breast. *Singapore Med. J.*, 2007, **48**, 607–614.
28. Jarvinen, T. A., Pelto-Huikko, M., Holli, K. and Isola, J., Estrogen receptor beta is coexpressed with ER alpha and PR and associated with nodal status, grade, and proliferation rate in breast cancer. *Am. J. Pathol.*, 2000, **156**, 29–35.
29. Molina, R. *et al.*, Tumour markers in breast cancer – European group on tumour markers recommendations. *Tumour Biol.*, 2005, **26**, 281–293.
30. O'Brien, N. *et al.*, Use of a panel of novel genes for differentiating breast cancer from non-breast tissues. *Tumour Biol.*, 2007, **28**, 312–317.
31. Maass, N., Nagasaki, K., Ziebart, M., Mundhenke, C. and Jonat, W., Expression and regulation of tumour suppressor gene maspin in breast cancer. *Clin. Breast Cancer*, 2002, **3**, 281–287.
32. Incorvati, J. A., Shah, S., Mu, Y. and Lu, J., Targeted therapy for HER2 positive breast cancer. *J. Hematol. Oncol.*, 2013, **6**, 1–9.
33. Pinhel, S. *et al.*, ER and HER2 expression are positively correlated in HER2 non-overexpressing breast cancer. *Breast Cancer Res.*, 2012, **14**, 1–12.
34. Wingo, P. A., Tong, T. and Bolden, S., Cancer statistics. *CA Cancer J. Clin.*, 1995, **45**, 8–30.
35. Indovina, P., Marcelli, E., Pentimalli, F., Tanganelli, P., Tarro, G. and Giordano, A., Mass spectrometry-based proteomics, the road to lung cancer biomarker discovery. *Mass Spectrom. Rev.*, 2013, **32**, 129–142.
36. Ahn, J. M. and Cho, J. Y., Current serum lung cancer biomarkers. *J. Mol. Biomark. Diagn.*, 2013, **S4: 001**, 1–7.
37. Cho, W. C., Potentially useful biomarkers for the diagnosis, treatment and prognosis of lung cancer. *Biomed. Pharmac. Other.*, 2007, **61**, 515–519.
38. Ferrigno, D., Buccheri, G. and Giordano, C., Neuron-specific enolase is an effective tumour marker in non-small cell lung cancer (NSCLC). *Lung Cancer*, 2003, **41**, 311–320.
39. Schneider, J., Tumour markers in detection of lung cancer. *Adv. Clin. Chem.*, 2006, **42**, 1–41.
40. Kulpa, J., Wojcik, E., Reinfuss, M. and Kolodziejski, L., Carcinoembryonic antigen, squamous cell carcinoma antigen, CYFRA 21-1, and neuron-specific enolase in squamous cell lung cancer patients. *Clin. Chem.*, 2002, **48**, 1931–1937.
41. Tsavans, N. *et al.*, Carcinoembryonic antigen (CEA), alpha-fetoprotein, CA19-9 and CA125 in advanced colorectal cancer (ACC). *Int. J. Biol. Markers*, 1993, **8**, 88–93.
42. Munck-Wikland, E., Kuylenstierna, R., Wahren, B., Lindholm, J. and Haglund, S., Tumour markers carcinoembryonic antigen, CA 50, and CA 19-9 and squamous cell carcinoma of the esophagus. *Cancer (Phila.)*, 1988, **62**, 2281–2286.
43. Parkin, D. M., Bray, F., Ferlay, J. and Pisani, P., Global cancer statistics, 2002. *CA Cancer J. Clin.*, 2005, **55**, 74–108.
44. Doweck, I. *et al.*, Cyfra 21-1, A new potential tumour marker for squamous cell carcinoma of head and neck. *Arch. Otolaryngol. Head Neck Surg.*, 1995, **121**, 177–181.
45. Nakata, B. *et al.*, Clinical significance of serum CYFRA 21-1 in gastric cancer. *Br. J. Cancer*, 1996, **73**, 1529–1532.
46. Chen, D. S., Sung, J. L. and Sheu, J. C., Serum $\alpha$-fetoprotein in the early stage of human hepatocellular carcinoma. *Gastroenterology*, 1984, **86**, 1404–1409.
47. Khien, V. V. *et al.*, Clinical evaluation of lentil lectin-reactive alpha-fetoprotein-L3 in histology proven hepatocellular carcinoma. *Int. J. Biol. Markers.*, 2001, **16**, 105–111.
48. Nakatsura, T. *et al.*, Glypican-3, overexpressed specifically in human hepatocellular carcinoma, is a novel tumour marker. *Biochem. Biophys. Res. Commun.*, 2003, **306**, 16–25.

49. Guido, M. *et al*., Squamous cell carcinoma antigen in human liver carcinogenesis. *J. Clin. Pathol.*, 2008, **61**, 445–447.
50. Zhang, Y., Deng, Z. S., Liao, M. M., Wang, N., Zhang, X. Q. and Yu, H. Y., Tumour associated glycoprotein-72 is a novel marker for poor survival in hepatocellular carcinoma. *Pathol. Oncol. Res*., 2012, **18**, 911–916.
51. Zhou, L., Liu, J. and Luo, F., Serum tumour markers for detection of hepatocellular carcinoma. *World J. Gastroenterol*., 2006, **12**, 1175–1181.
52. Rosewicz, S. and Wiedenmann, B., Pancreatic carcinoma. *Lancet*, 1997, **349**, 485–489.
53. Chung, M. H., Gupta, R. K., Essner, R., Ye, W., Yee, R. and Morton, D. L., Serum TA90 immune complex assay can predict outcome after resection of thick (≥4 mm) primary melanoma and sentinel lymphadenectomy. *Ann. Surg. Oncol*., 2002, **9**, 120–126.
54. Podolsky, D. K., Serologic markers in the diagnosis and management of pancreatic carcinoma. *World J. Surg.*, 1984, **8**, 822–830.
55. Johansson, C., Nilsson, O., Baeckstrom, D., Jansson, E. L. and Lindholm, L., Novel epitopes on the CA50-carrying antigen, chemical and immunochemical studies. *Tumour Biol*., 1991, **12**, 159–170.
56. Melo, S. A. *et al.*, Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. *Nature*, 2015, **523**, 177–182.
57. Sardana, G., Jung, K., Stephan, C. and Diamandis, E. P., Proteomic analysis of conditioned media from the PC3, LNCaP, and 22Rv1 prostate cancer cell lines, discovery and validation of candidate prostate cancer biomarkers. *J. Proteome Res*., 2008, **7**, 3329–3338.
58. Cooner, W. H. *et al.*, Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. *J. Urol*., 1990, **143**, 1146–1154.
59. Kattan, M. W. *et al.*, The addition of interleukin-6 soluble receptor and transforming growth factor beta1 improves a preoperative nomogram for predicting biochemical progression in patients with clinically localized prostate cancer. *J. Clin. Oncol*., 2003, **21**, 3573–3579.
60. Netto, G. J. and Cheng, L., Emerging critical role of molecular testing in diagnostic genitourinary pathology. *Arch. Pathol. Lab. Med*., 2012, **136**, 372–390.
61. Cazares, L. H., Drake, R. R., Esquela-Kirscher, A., Lance, R. S., Semmes, O. J. and Troyer, D. A., Molecular pathology of prostate cancer. *Cancer Biomark*., 2010, **9**, 441–459.
62. Salami, S. S. *et al.*, Combining urinary detection of TMPRSS2, ERG and PCA3 with serum PSA to predict diagnosis of prostate cancer. *Urol. Oncol.*, 2013, **31**, 566–571.
63. Martin, N. E., Mucci, L. A., Loda, M. and Depinho, R. A., Prognostic determinants in prostate cancer. *Cancer J*., 2011, **17**, 429–437.
64. Agarwal, M., He, C., Siddiqui, J., Wei, J. and Macoska, J. A., CCL11 (Eotaxin-1), A new diagnostic serum marker for prostate cancer. *Prostate*, 2013, **73**, 573–581.
65. Abrahamsson, P. A., Lilja, H., Falkmer, S. and Wadstrom, L. B., Immunohistochemical distribution of the three predominant secretory proteins in the parenchyma of hyperplastic and neoplastic prostate glands. *Prostate*, 1988, **12**, 39–46.
66. Dahlman, A., Rexhepaj, E., Brennan, D. J., Gallagher, W. M., Gaber, A. and Lindgren, A., Evaluation of the prognostic significance of MSMB and CRISP3 in prostate cancer using automated image analysis. *Modern Pathol.*, 2011, **24**, 708–719.
67. Rieger, A. and Wahren, B., CEA levels at recurrence and metastases, importance for detecting secondary disease. *Scand. J. Gastroenterol*., 1975, **10**, 869–874.
68. Bhatnagar, J., Tewari, H., Bhatnagar, M. and Austin, G. E., Comparison of carcinoembryonic antigen in tissue and serum with grade and stage of colon cancer. *Anticancer Res*., 1999, **19**, 2181–2188.
69. Guadagni, F. *et al.*, CA 72-4 serum marker-a new tool in the management of carcinoma patients. *Cancer Invest.*, 1995, **13**, 227–238.
70. Kato, M., Maeta, H., Kato, S., Shinozawa, T. and Terada, T., Immunohistochemical and in situ hybridization analyses of midkine expression in thyroid papillary carcinoma. *Mod. Pathol.*, 2000, **13**, 1060–1065.
71. Ikematsu, S. *et al.*, Serum midkine levels are increased in patients with various types of carcinomas. *Br. J. Cancer*, 2000, **83**, 701–706.
72. Wald, M. *et al.*, Bladder tumour antigen stat test in non-urothelial malignant urologic conditions. *Isr. Med. Assoc. J.*, 2002, **4**, 174–175.
73. Murphy, W. M., Rivera-Ramirez, I., Medina, C. A., Wright, N. J. and Wajsman, Z., The bladder tumour antigen (BTA) test compared to voided urine cytology in the detection of bladder neoplasms. *J. Urol.*, 1997, **158**, 2102–2106.
74. Hajdinjak, T., UroVysion FISH test for detecting urothelial cancers, Meta-analysis of diagnostic accuracy and comparison with urinary cytology testing. *Urol. Oncol*., 2008, **26**, 646–651.
75. Zurawski Jr, V. R., Orjaseter, H., Andersen, A. and Jellum, E., Elevated serum CA 125 levels prior to diagnosis of ovarian neoplasia, relevance for early detection of ovarian cancer. *Int. J. Cancer*, 1988, **42**, 677–680.
76. Mastropaolo, W., Fernandez, Z. and Miller, E. L., Pronounced increases in the concentration of an ovarian tumour marker, CA-125, in serum of a healthy subject during menstruation. *Clin. Chem*., 1986, **32**, 2110–2111.
77. Disis, M. L., Pupa, S. M., Gralow, J. R., Dittadi, R., Menard, S. and Cheever, M. A., High-titer HER-2/neu protein-specific antibody can be detected in patients with early-stage breast cancer. *J. Clin .Oncol*., 1997, **15**, 3363–3367.
78. Gadducci, A. *et al.*, Assessment of the prognostic relevance of serum anti-p53 antibodies in epithelial ovarian cancer. *Gynecol. Oncol*., 1999, **72**, 76–81.
79. Rein, B. J. D., Gupta, S., Dada, R., Safi, J., Michener, C. and Agarwal, A., Potential markers for detection and monitoring of ovarian cancer. *J. Oncol.*, 2011, **475983**, 1–17.
80. Moore, R. G. *et al*., The use of multiple novel tumour biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. *Gynecologic Oncol*., 2008, **108**, 402–408.
81. Kelley, M. C., Gupta, R. K., Hsueh, E. C., Yee, R., Stern, S. and Morton, D. L., Tumour-associated antigen TA90 immune complex assay predicts recurrence and survival after surgical treatment of stage I-III melanoma. *J. Clin. Oncol*., 2001, **19**, 1176–1182.
82. Kelley, M. C. *et al*., Tumour-associated antigen TA-90 immune complex assay predicts subclinical metastasis and survival for patients with early stage melanoma. *Cancer*, 1998, **83**, 1355–1361.
83. Meral, R. *et al.*, Prognostic significance of melanoma inhibiting activity levels in malignant melanoma. *Melanoma Res.*, 2001, **11**, 627–632.
84. Cochran, A. J., Wen, D. R., Herschman, H. R. and Gaynor, R. B., Detection of S-100 protein as an aid to the identification of melanocytic tumours. *Int. J. Cancer*, 1982, **30**, 295–297.
85. Bonfrer, J. M., Korse, C. M., Nieweg, O. E. and Rankin, E. M., The luminescence immunoassay S-100, a sensitive test to measure circulating S-100B, its prognostic value in malignant melanoma. *Br. J. Cancer*, 1998, **77**, 2210–2214.
86. Bosserhoff, A. K., Dreau, D., Hein, R., Landthaler, M., Holder, W. D. and Buettner, R., Melanoma inhibitory activity (MIA), a serological marker of malignant melanoma. *Rec. Res. Can. Res*., 2001, **158**, 158–168.
87. Guba, M. *et al.*, Overexpression of melanoma inhibitory activity (MIA) enhances extravasation and metastasis of A-mel 3 melanoma cells *in vivo*. *Br. J. Cancer*, 2000, **83**, 1216–1222.
88. Chua, S. C., Rozalli, F. I. and O'Connor, S. R., Imaging features of primary extranodal lymphomas. *Clin. Radiol.*, 2009, **64**, 574–588.

89. Yoo, C., Yoon, D. H. and Suh, C., Serum beta-2 microglobulin in malignant lymphomas: an old but powerful prognostic factor. *Blood Res.*, 2014, **49**, 148–153.
90. Schneider, R. J. *et al.* Prognostic significance of serum lactate dehydrogenase in malignant lymphoma. *Cancer,* 1980, **46**, 139–143.
91. Romana, S. P. *et al.*, High frequency of t(12,21) in childhood B-lineage acute lymphoblastic leukemia. *Blood*, 1995, **86**, 4263–4269.
92. Abali, H. *et al.*, Circulating and local bone marrow renin-angiotensin system in leukemic hematopoiesis, preliminary evidences. *Hematology*, 2002, **7**, 75–82.
93. Wulf, G.G. *et al.*, Renin in acute myeloid leukaemia blasts. *Br. J. Haematol.*, 1998, **100**, 335–337.
94. Teresa Gomez Casares, M. *et al.*, Renin expression in hematological malignancies and its role in the regulation of hematopoiesis. *Leuk. Lymphoma*., 2002, **43**, 2377–2381.
95. Marella, S., Prognostic and predictive markers in early detection of different types of cancers for selected organ sites. *IOSR-JPBS*, 2013, **8**, 25–42.
96. Zhao, Y., Huang, H. and Wei, G., Novel agents and biomarkers for acute lymphoid leukemia. *J. Hematol. Oncol*., 2013, **6**, 1–11.

ACKNOWLEDGEMENTS. We thank authors of the primary studies included in this meta-analysis, and Parvinder Kaur, Department of Cell Culture, Yashraj Biotechnology Ltd., Navi Mumbai, for her review and valuable feedback on the manuscript.

Received 5 February 2016; revised accepted 18 November 2016

doi: 10.18520/cs/v112/i09/1831-1838