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High mobility group A protein-2 as a tumor cancer diagnostic and prognostic marker: a systematic review and meta-analysis

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Abstract

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Conflicts of interest

There are no conflicts of interest.

In summary, our systematic review included 42 studies that demonstrated that *HMGA2* was overexpressed (i.e. more than 64%) in all 15 types cancers and *HMGA2* overexpression was significantly associated with reduced survival. We also found a trend towards association between *HMGA2* expression and cancer recurrence, an indication of promising tumor marker for prognostic predictive value. Since prior effort has shown that using *HMGA2* in combination with other tumor marker would enhance test accuracy, we believe that *HMGA2* would be a promising tumor pronostic marker in the era of precision medicine.

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High mobility group A protein-2 (*HMGA2*) is an architectural transcription factor that binds to the A/T-rich DNA minor groove and is responsible for regulating transcriptional activity of multiple genes indirectly through chromatin change and assembling enhanceosome. *HMGA2* is overexpressed in multiple tumor types, suggesting its involvement in cancer initiation and progression, thus, making it an ideal candidate for cancer diagnostic and prognostic. We performed a systematic review to examine the role of *HMGA2* as a universal tumor cancer diagnostic and prognostic marker. We used Reporting Recommendations for Tumor Marker Prognostic Studies to systematically search OvidMedline, PubMed, and the Cochrane Library for English language studies, published between 1995 and June 2019. Meta-analysis provided pooled risk estimates and their 95% confidence intervals (CIs) for an association between overall survival and recurrence of cancers for studies with available estimates. We identified 42 eligible studies with a total of 5123 tumor samples in 15 types of cancer. The pooled percentage of *HMGA2* gene expression in tumor samples was 65.14%. Meta-analysis showed that cancer patients with *HMGA2* positive have significantly reduced survival, compared to patients without *HMGA2* gene [pooled-hazard ratio (HR) = 1.85, 95% CI 1.48–2.22]. There was a positive association between cancer patients with *HMGA2* overexpression and cancer recurrence though this association did not reach significance (pooled-HR = 1.44, 95% CI 0.80–2.07). Overexpression of *HMGA2* was found in 15 types of cancer. There was an association between HMGA2 overexpression with reduced survival of cancer patients.

Keywords

cancer diagnostic and prognostic; HMGA2; tumor marker

Introduction

Tumor markers are substances that are produced by cancer cells or by other cells of the body in response to cancer, that are found in body fluids (i.e. blood and urine) and tissue (Bigbee and Herberman, 2003). Two main types of tumor markers that can be used in clinical settings: (1) circulating tumor markers or tumor markers that are associated with tumor cells and (2) tumor tissue markers that are derived from tumor cells. In several cancer patients, they are mainly represented by protein macromolecules (Bigbee and Herberman, 2003). Tumor markers can be associated with a specific cancer site or with multiple cancers; however, up to date there is no marker that is specifically associated with a certain type of cancer.

Even though the National Cancer Institute does not have a guideline for the use of tumor markers in clinical practice, several organizations have such guidelines. Accordingly, the American Society for Clinical Oncology has published different clinical practice guidelines of tumor markers for breast cancer (Hammond et al., 2010; Ramakrishna et al., 2018), colorectal cancer (Locker et al., 2006; Sepulveda et al., 2017), lung cancer (Keedy et al., 2011), and others (Gilligan et al., 2010) while the National Academic of Clinical Biochemistry has also published the guideline entitled the ‘Use of Tumor Makers in Clinical Practice: Quality Requirements’, focusing on the appropriate use of tumor markers for specific cancers (Sturgeon and Diamandis, 2008). Currently, about 35 tumor markers have

been characterized and are being used in clinical practice, including *BRCA1* and *BRCA2* gene mutations, *CA19–9, CA-125*, carcinoembryonic antigen, *EGFR* gene mutation analysis or prostate-specific antigen, etc.

More than 30 years ago, the high mobility group A (*HMGA*) proteins were suggested potential tumor markers for cancer (Giancotti et al., 1987). The *HMGA* family includes *HMGA*1a, *HMGA*1b, *HMGA*1c, and *HMGA2* (formerly called *HMGI-C*). Since the first publication implicating high mobility group proteins in neoplastic transformation in 1987 (Giancotti et al., 1987) and identification of *HMGA2* (*HMGI-C*) in 1991 (Giancotti et al., 1991), the evidence of the involvement of *HMGA2* in cell cycle, neurogenesis, and carcinogenesis is steadily growing.

HMGA2 is an architectural transcription factor that binds to the A/T-rich DNA minor groove using so-called AT-hook sequences, changes its conformation and consequently facilitates binding of a group of transcription factors. It regulates transcriptional activity of multiple genes indirectly through chromatin change and assembling enhanceosome (Reeves, 2010). Accordingly, two mechanisms that have been identified involving in this process. The first mechanism related to the transcription of the *IFN-β* gene that is activated in virus infected cells where *HMGA* binds to and coordinates the formation of an enhanceosome on 'naked' promoter DNA. Noted that there are two positioned nucleosomes cause the flank of this 'naked' promoter DNA. The IFN-β enhancesome would then enroll chromatin modifying and remodeling complexes. The formation of remodeling complex induced sliding of the inhibitory nucleosome and introduced TATA box which then leading to the binding of TBP/TFIIB and initiating Poll transcription. The second mechanism is involved the activation of different promoters, including IL-2, IL-Rα, CRYAB, and the 5′ LTR of the HIV-1 virus prior to transcriptional activation. For each of the activation of the above promoters, a nucleosome is stably positioned on a regulatory DNA element, containing biding sites for transcriptional factors, including *HMGA*, Elf-1, or AP-1. One of the important hallmarks of these positioned nucleosomes is that there are one or more stretches of A/T-rich DNA position on the surface of the nucleosome and adjacent to one of its edges (Reeves, 2010).

While *HMGA2* is abundantly expressed during embryogenesis and re-expressed in pre-malignant or malignant tissues, the level of expression is very low or undetectable in adult tissues. However, *HMGA2* is overexpressed in multiple tumor types, suggesting its involvement in cancer initiation and progression (Pallante et al., 2015). This makes *HMGA2* unique, along with other embryonic biomarkers and an ideal candidate for cancer diagnostic and prognostic. Recently, we described a new prognostic biomarker of melanoma progression, transcription factor *HMGA2* (Raskin et al., 2013) associated with development of metastases and patient survival. Specifically, we used transcriptome profiling of 46 primary melanomas, 12 melanoma metastasized and 16 normal skin samples and replicated in an independent set of 330 melanomas using AQUA analysis of tissue microarray. We found that transcriptional factor *HMGA2* is significantly upregulated in primary melanomas and metastases ($P = 1.2 \times 10^{-7}$ and 9×10^{-5}, respectively), compared with normal samples. We also found that *HMGA2* overexpression is associated with *BRAF/NRAS* mutation ($P = 0.0002$) and that *HMGA2* is independently associated with disease-free survival (DFS) [hazard ratio (HR) = 6.3, 95% confidence interval (CI) 1.8–22.3] and overall survival (OS;

stratified log-rank $P = 0.008$) as well as distant metastases-free survival (DMFS) (HR = 6.4, 95% CI 1.4–29.7).

The oncogenic role of *HMGA2* has been well documented in almost all cancer types, where it can be overexpressed, amplified, or fused with other proteins (Fusco and Fedele, 2007). *HMGA2* can also become an excellent therapy target, since only tumor cells express this protein in adults. For example, inhibition of *HMGA2* has been demonstrated to reduce ovarian cancer growth both *in vitro* and *in vivo* (Malek et al., 2008).

Different mechanisms of *HMGA2* oncogenicity have been documented previously. For example, Fedele et al. (2006) found the activation of transcription factor E2F1 through binding *HMGA2* to pRB. Specifically, they reported that *HMGA2* interacts with pRB, leading to the induction of E2F1 activity in mouse pituitary adenomas by displacing HDAC1 from pRB/E2F1 complex, which later resulted in E2F1 acetylation. Other mechanisms include direct or indirect induction of cyclin A (Hammond et al., 2010) or negative regulation of nucleotide excision repair gene (Ramakrishna et al., 2018), the *ERCC1* gene, causing DNA bending.

In terms of prognostic value, it is also observed that the transcription of human telomerase reverse transcriptase is enhanced by *HMGA2* to upgrade carcinogenesis, a necessity for cancer cell development and self-renewal (Sepulveda et al., 2017). In addition, *HMGA2* plays an important role in the epithelial-to-mesenchymal transition by activating the TGFβ signaling pathway, leading to the invasion and metastasis of human epithelial cancers (Locker et al., 2006).

More than half of the publications on *HMGA2* in cancer have been published in the last 5 years, an indication of increasing interest to this oncogene. In addition to the research on *HMGA2* regulation in cancer, there is a growing number of studies demonstrating that expression of *HMGA2* in neoplasm is associated with metastatic phenotype and inferior patient survival. While the current understanding of *HMGA2* involvement in carcinogenesis and tumor invasiveness has been reviewed, to our knowledge, no effort has been made to systematically examine the role of *HMGA2* overexpression as a diagnostic and prognostic biomarker in multiple cancer types. We, therefore, performed this systematic review to address this gap and to present future perspectives of *HMGA2* in the era of precision medicine.

Methods

Search strategy

From January 2017 to June 2019, an experienced librarian (Allison M. Howard) and two investigators (Y.T.-H.P. and O.U.) conducted a systematic search to identify published studies on *HMGA2* from January 1995 to June 2019. Three main biomedical databases (i.e. OvidMedline, PubMed, and Cochrane Library) were searched using the following terms: (*HMGA2* protein) OR (‘high mobility group A2’ OR *HMGA2*) OR (HMGI-C OR HMGIC OR STQTL9) AND (humans OR not animals) AND (cancer) AND (limit to years = ‘1995–2019’).

Study screening and selection

Inclusion criteria for the present systematic review were English language reports of the studies that determined the association between gene or protein expression levels of *HMGA2* in tumor tissues/biospecimens and overall or progression-free survival (PFS) in any cancer types. All studies met Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) criteria during period 1995 to June 2019. The following exclusion criteria were applied: (1) no cancer outcomes; (2) not in English language; (3) not original research (i.e. review, commentary and editorial) or case report; (4) not using tumor tissues/biospecimens; and (5) unmet REMARK criteria (Altman et al., 2012). All extracted reports were reviewed independently by two investigators (i.e. Y.T.-H.P. and O.U.). We also requested additional information from corresponding authors of four articles (Sarhadi et al., 2006; Piscuoglio et al., 2012; Rizzi et al, 2013; Chang et al., 2015) that have reported *P* values without information on HRs or relative risks, and 95% CIs.

Data abstraction and coding

All eligible studies were abstracted independently by two reviewers (Y.T.-H.P. and O.U.) using coding system based on three guidelines: the REMARK criteria (Altman et al., 2012), the Strengthening the Reporting of Observational studies in Epidemiology-Molecular Epidemiology (Gallo et al., 2011), and the Standards for Reporting Diagnostic Accuracy (Bossuyt et al., 2003). Any discrepancies were resolved by discussion and consensus between the two investigators. The abstracted information for each study included: first author's name, year of publication, country of origin, study design (i.e. cross-sectional, case-control, cohort, and randomized controlled trial), and patient/biospecimen characteristics. We also extracted additional information regarding preservation methods [i.e. frozen or formalin-fixed paraffin embedded (FFPE)], quantification methods [i.e. immunohistochemistry (IHC) and real-time PCR (RT-PCR)], primary antibody and dilution for IHC and RNA-isolation for RT-PCR, *HMGA2* expression levels in tumor cells for diagnosis (i.e. proportion of cells expressing *HMGA2*) and survival estimates for prognosis (i.e. multivariable HR and respective 95% CI).

Systematic review and statistical analysis

Because of the study heterogeneity and limited data for each cancer type, except for thyroid cancer, we first reported the results of a systematic review of the expression of *HMGA2* as a biomarker for cancer diagnosis and prognosis. Then, we performed a pooled analysis of *HMGA2* expression in two types of estimates (percentage and fold change) and meta-analysis of OS/recurrence using the studies with available estimates as described below.

While *HMGA2* expression levels were reported in percentage format in 38 out of 42 identified articles, four articles (Jones et al., 2008; Arora et al., 2009; Klemke et al, 2014; Nagar et al., 2014) reported fold change as an estimate. We grouped these four articles to calculate pooled-adjusted fold change of *HMGA2* gene expression in cancers. Additionally, two articles (Miyazawa et al, 2004; Meyer et al., 2007) reported both types of estimate (i.e. percentage and fold change), we, therefore, included them in both analyses.

We also calculated the pooled-adjusted percentage of *HMGA2* gene expression as a weighted average of study-specific rates in which the weights were proportions of those study-specific sample sizes to the pooled-sample size, as described below:

$$Pooled - Precentage = \sum_{i=1}^{k}\left[\left(\frac{n}{N}\right)\times P\right]$$

Where i = individual study (from 1 to k);

n = sample size of individual study;

N = pooled-sample size;

P = percentage of *HMGA2* gene expression at individual study level.

We used the same formula to calculate pooled-fold change of *HMGA2* expression in six studies included in the current analysis.

In the meta-analysis, we calculated HRs and the corresponding 95% CIs for survival and recurrence in cohort studies. Overall pooled HR and its 95% CI was calculated based on the individual estimates from nine cohort studies (Motoyama et al., 2008; Wang et al., 2011; Wu et al., 2012; Zou et al., 2012; Raskin et al., 2013; Kong et al., 2014; Lee et al., 2014; Liu et al., 2015; Xia et al., 2015) for survival analysis and six cohort studies (Miyazawa et al., 2004; Yang et al., 2011; Raskin et al., 2013; Califano et al., 2014; Liu et al., 2015; Jun et al, 2015) for recurrence analysis. We included estimates from both training and validation sets in the study by Wang et al. (2011) for the meta-analysis of survival and recurrence. We also used estimates from training and validation sets from the study by Raskin et al. (2013) for meta-analysis of survival; however, only estimate from the training set was included in the meta-analysis of recurrence. In the meta-analysis, each study was given a weight based on the inverse of the effect variance. Random-effects models that included a study heterogeneity variance component were used in the meta-analysis (DerSimonian and Laird, 1986). To evaluate publication bias, both funnel plots for visualization and Egger's test for statistical significance were used (Egger et al, 1997). Meta-analysis was performed using the commands *metan* and *metafunnel* of the statistical software STATA 14.0 (College Station, Texas, USA). All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Among 42 eligible articles in the current review (Fig. 1) with a total of 5123 tumor samples, 11 studies were in thyroid cancer (Belge et al., 2008; Chiappetta et al., 2008; Prasad et al., 2008; Arora et al., 2009; Lappinga et al., 2010; Jin et al., 2011; Prasad et al., 2012; Klemke et al., 2014; Nagar et al., 2014; Jin et al., 2015; Jang et al., 2015), five studies in ovarian cancer (Mahajan et al., 2010; Hetland et al, 2012; Califano et al., 2014; Kim et al., 2015; Wu et al, 2015), four studies in gastric cancer (Motoyama et al., 2008; Kong et al., 2014; Jun et al., 2015; Lee et al., 2015), four studies in colorectal cancer (Huang et al., 2009; Wang et al., 2011; Helmke et al., 2012; Rizzi et al., 2013), three studies in liver cancer (Wu et al., 2012;

Lee et al., 2013, Lee et al., 2014), two studies in breast cancer (Rogalla et al., 1997; Jones et al., 2008), two studies in lung cancer (Sarhadi et al., 2006; Meyer et al., 2007), two studies in oral cancer (Miyazawa et al., 2004; Chang et al., 2015), two studies in nasopharyngeal cancer (Liu et al., 2015; Xia et al., 2015), one study in pancreatic cancer (Piscuoglio et al., 2012), one study in melanoma (Raskin et al., 2013), one study in bladder cancer (Yang et al., 2011), one study in bile duct carcinoma (Zakharov et al., 2013), one study in gallbladder cancer (Zou et al., 2012), one study in glioma (Liu et al., 2014), and one study in esophageal cancer (Liu et al., 2014).

The majority of studies were conducted in the USA (n = 12), followed by China (n = 7), Germany (n = 5), multi-countries (n = 5), South Korea (n = 4), Italy (n = 3), while each of the following countries – Finland, Japan, Norway, Switzerland, Taiwan, and UK – provided one study. Regarding to study design, 20 studies were cross-sectional studies, one was case-only study and 21 were cohort studies. Also, 20 studies were conducted for the purpose of diagnostic only, one study was for the purpose of prognostic only and 21 studies were for both purposes (Table 1 and Supplemental Table 1, Supplemental digital content 1, http://links.lww.com/EJCP/A297).

Sources of materials were both FFPE and fine-needle aspiration, except two studies (Motoyama et al., 2008; Raskin et al., 2013) in which *HMGA2* was also from frozen samples. The method to quantify *HMGA2* gene expression was either IHC or RT-PCR and expression microarray was also used additionally in two studies (Arora et al., 2009; Raskin et al., 2013) (Table 1 and Supplemental Table 1, Supplemental digital content 1, http://links.lww.com/EJCP/A297).

Thyroid cancer

Diagnostic—Between 2008 and 2019, eleven cross-sectional studies (Belge et al., 2008; Chiappetta et al., 2008; Prasad et al., 2008; Arora et al., 2009; Lappinga et al., 2010; Jin et al., 2011; Prasad et al., 2012; Klemke et al., 2014; Nagar et al., 2014; Jin et al., 2015; Jang et al., 2015) investigated the gene expression of *HMGA2* in thyroid cancer. The frequency of *HMGA2* expression in tumor samples varied from 30.8% in a study by Jin et al. (2015) (in a histologic diagnosis of Hürthle cell carcinoma) to 100% in a study by Belge et al. (2008). Additionally, two studies (Arora et al., 2009; Klemke et al, 2014) reported fold change of *HMGA2* in tumor sample in comparison with benign tumor. Accordingly, Arora et al. (2009) found that the expression level of *HMGA2* was 3.56-fold higher in thyroid tumor than that in benign tumor ($P = 0.02$). Also, using result of frequency of *HMGA2* gene expression (100% in thyroid tumor), Belge et al. (2008) found that the decision limit for the discrimination between benign and malignant tissues was 3.99 with a sensitivity of 95.9% and specificity of 93.9%; one of the best known single biomarker to distinguish between benign and malignant thyroid neoplasm.

Prognostic—In the current review, we did not find any such study for prognostic using *HMGA2* in thyroid cancer.

Ovarian cancer

Diagnostic—Between 2009 and 2019 there were one case-only study (Mahajan et al., 2010), one cross-sectional study (Wu et al., 2015) and three cohort studies (Hetland et al., 2012; Califano et al., 2014; Kim et al., 2015) which investigated the expression of *HMGA2* in ovarian cancer. The frequency of *HMGA2* expression was found to be lowest in a study of mucinous ovarian carcinoma (6.7%) by Mahajan et al. (2010) and highest in a study by Hetland et al. (2012) (96.0%).

Prognostic—Findings on the prognostic value of *HMGA2* to ovarian cancer is inconclusive. Accordingly, Hetland et al. (2012), in a study of 199 ovarian cancer patients, found null association between *HMGA2* expression and PFS or OS in effusions ($P = 0.5$ and $P = 0.9$, respectively), primary tumors ($P = 0.7$ and $P = 0.5$, respectively) or metastatic samples ($P = 0.1$ and $P = 0.5$, respectively). However, a study from Italy by Califano et al. (2014), found null association between *HMGA2* expression only and DFS (HR = 0.83, 95% CI 0.38–1.82); they did not find a significant association between combination/interaction between *HMGA2*-BMI (low vs. high score) and OS of ovarian cancer (HR = 3.17, 95% CI 1.25–8.03). Recently, Kim et al. (2015) reported that *HMGA2* expression was associated with distant metastasis ($P = 0.001$), FIGO stage ($P = 0.004$), and lymph node ($P = 0.008$). The expression of *HMGA2* was also correlated with OS of patients with high grade ovarian serous carcinomas (5-year OS rate: 78% vs. 35%, $P = 0.02$).

Gastric cancer

Diagnostic—From 2008 up to date, there are four cohort studies (Motoyama et al., 2008; Kong et al., 2014; Jun et al., 2015; Lee et al., 2015) investigating the association between expression of *HMGA2* and risk of gastric cancer. The lowest frequency of *HMGA2* gene expression was found in a study by Lee et al. (2015) of 170 FFPE samples (22.9%) and highest was in a study by Motoyama et al. (2008) of 110 frozen samples (75.4%)

Prognostic—Data from these four studies (Motoyama et al., 2008; Kong et al., 2014; Jun et al., 2015; Lee et al., 2015) showed consistently that *HMGA2* had poor survival for gastric cancer patients. Accordingly, in a study of 110 frozen samples in Japan, Motoyama et al. (2008) shown that *HMGA2* expression level was associated with reduced survival (OS HR = 2.00, 95% CI 1.32–3.15). In another study by Kong et al. (2014) of 158 gastric cancer and surrounding non-tumor tissues, they found that while there was no association between *HMGA2* or *Oct4* with poor survival of gastric cancer (HR = 0.99, 95% CI 0.34–2.33; and 1.00, 95% CI 0.41–2.86, respectively) the combination between these two proteins was a predictor of poor survival of gastric cancer (HR = 2.89, 95% CI 1.02–5.14). The other study by Lee et al. (2015) reported that patients with high-level expression have a significantly worse 5-year OS rate than those with low-level expression (43.6% vs. 54.2%; $P = 0.028$). Finally, Jun et al. (2015) found that high level of *HMGA2* expression in gastric cancer patients were significantly associated with recurrence-free survival (RFS) (HR = 3.20, 95% CI 1.50–6.79).

Colorectal cancer

Diagnostic—Between 2009 and 2019, four studies (Huang et al., 2009; Wang et al., 2011; Helmke et al., 2012; Rizzi et al., 2013) investigated the expression of *HMGA2* and colorectal cancer status of which two (Huang et al., 2009; Rizzi et al., 2013) were of cross-sectional study design and two (Wang et al., 2011; Helmke et al., 2012) were of cohort study design. The frequency of *HMGA2* expression in colorectal cancer was found from 36 (Wang et al., 2011) to 87.4% (Rizzi et al., 2013).

Prognostic—In a study of 280 FFPE samples, Wang et al. (2011) reported an association between *HMGA2* overexpression with poor survival (Training set: HR-OS/OS = 2.38, 95% CI 1.30–4.34; Validation set: HR-OS = 2.14, 95% CI 1.21–3.79). They also shown a significant association between *HMGA2* overexpression and distant metastasis (training set: OR = 3.53, 95% CI 1.37–9.70; validation set: OR = 6.38, 95% CI 1.47–43.95). In another study of 103 colorectal cancer cases in Italy, Rizzi et al. (2013) found that the increased *HMGA2* expression was strongly associated with an increase in tumor invasiveness, measured through both budding and vascular invasion ($P < 0.0001$).

Liver cancer

Diagnostic—From 2012 to date, we found three studies (Wu et al., 2012; Lee et al., 2013; Lee et al., 2014) that investigated the expression of *HMGA2* and liver cancer. The frequency of *HMGA2* expression in liver cancer was found to be as low as 33% in a study by Lee et al. (2013) and as high as 100% in a study by Lee et al. (2014). In the other study, Wu et al. (2012) also reported that *HMGA2* expression level was higher in tumor than non-tumor tissues (mean ± SD: 38.70 ± 10.41 vs. 8.41 ± 4.06, respectively; $P < 0.01$) and that *HMGA2* was expressed in 48% of liver cancer tumors.

Prognostic—*HMGA2* overexpression in liver cancer patients had consistently poor survival outcome. Accordingly, Wu et al. (2012) shown that *HMGA2* expression was associated with decreased OS (OS-HR = 1.97, 95% CI 1.17–3.33). Similarly, Lee et al. (2013), in a study of 15 hepatoblastoma, a rare but most common type of hepatocellular carcinoma-HCC in children with 71 other HCC types samples, reported that patients with *HMGA2* was 2.20 times higher risk of death than those without *HMGA2* (HR = 2.20, 95% CI 1.12–4.33).

Breast cancer

Diagnostic—Between 1998 and up to date, there are two cross-sectional studies (Rogalla et al., 1997; Jones et al., 2008) examining the relationship between *HMGA2* expression and breast cancer status. Accordingly, Rogalla et al. (1997) reported that *HMGA2* over-expressed in 45.45% of breast tumors while Jones et al. (2008) reported that *HMGA2* expression was 4.2-fold change in microarray test and six-fold change in RT-PCR test ($P = 0.003$).

Prognostic—We did not find any studies on prognosis for *HMGA2* in breast cancer in this review.

Lung cancer

Diagnostic—We found two studies, one cross-sectional study (Sarhadi et al., 2006) and one cohort study (Meyer et al., 2007) between 2006 and up to date, examining the expression of *HMGA2* and lung cancer status. The overexpression of *HMGA2* was particularly high in squamous cell carcinoma (SCC) sub-type (i.e. 96.8% in a study by Sarhadi et al. (2006) and 80% in a study by Meyer et al. (2007)). Also, Meyer et al. (2007) reported that the *HMGA2* expression levels were increased up to 911-fold (mean: 158.41, range: 1.02–911.02, $P < 0.0001$) for adenocarcinoma and up to 2504-fold for SCC (mean: 336.26, range: 4.34–2.503.68, $P < 0.0001$).

Prognostic—Only a study by Sarhadi et al. (2006) reported the survival data in which they shown that there was a significant association between *HMGA2* positive and poor survival in adenocarcinoma patients ($P = 0.05$).

Oral cancer

Diagnostic—From 2004 to date, we found two cohort studies (Miyazawa et al., 2004; Chang et al., 2015) that investigated the overexpression levels of *HMGA2* and oral cancer status. Accordingly, Miyazawa et al. (2004) reported that *HMGA2* was detected in 73.8% carcinomas but none in normal oral tissues. They also found that oral carcinoma tissues expressed the *HMGA2* gene at levels 84.4–315.2-fold greater than that of normal tissues (mean ± SD: 163.4 ± 90.4; $P < 0.05$). Similarly, Chang et al. (2015) reported that *HMGA2* levels was significantly expressed in oral SCC specimens compared with adjacent normal tissues (mean ± SD: 48 ± 75 vs. 1 ± 1.5 copy/10^5 GAPDH-glyceraldehyde 3-phosphate dehydronase copy, $P < 0.001$)

Prognostic—Both cohort studies shown that oral cancer patient with *HMGA2* had poorer survival than patient without *HMGA2* gene (Miyazawa et al., 2004; Chang et al., 2015). Accordingly, Miyazawa et al. (2004) reported that *HMGA2* was significantly associated with poor survival (DFS HR = 3.48, 95% CI 1.39–8.69) while Chang et al. (2015) indicated that the 5-year OS, disease-specific survival (DSS), and DFS rates for patient subgroups stratified by the absence or presence of *HMGA2* expression were 75.6% vs. 57.7% ($P = 0.007$), 78% vs. 59.1% ($P = 0.006$), and 72.7% vs. 53.1% ($P = 0.002$), respectively. In multivariable analysis (adjusted for age, sex, overall stage, perineural invasion), *HMGA2* expression is independent predictor of OS, DSS, and DFS ($P = 0.028$, 0.025, and 0.015, respectively) (Chang et al., 2015).

Nasopharyngeal cancer

Diagnostic—Recently, two cohort studies (Liu et al., 2015; Xia et al., 2015) have examined the relation between *HMGA2* expression and nasopharyngeal cancer status. The levels of *HMGA2* expression ranged from 43.5 (Liu et al., 2015) to 52.6% (Xia et al., 2015).

Prognostic—Both cohort studies (Liu et al., 2015; Xia et al., 2015) provided consistent evidence that *HMGA2* positive is a predictor of poor survival for patients with nasopharyngeal cancer. Accordingly, Liu et al. (2015), in a cohort study of 145 samples has shown that the OS HR for a patient of nasopharyngeal cancer with *HMGA2* positive was

1.72 (95% CI 1.02–2.91) compared with a patient without *HMGA2* gene. At the same time, Xia et al. (2015) found even higher estimate on the *HMGA2* expression in relation to with poor survival (OS-HR = 2.68, 95% CI 1.18–6.08).

Pancreatic cancer

Diagnostic—In a cohort study of 210 ductal pancreatic adenocarcinomas (PAD) in Switzerland, Piscuoglio et al. (2012) found that *HMGA2* was overexpressed in 94% of PAD tissues and 92% of pancreatic intraepithelial neoplasia-grade 3 (PanIN-3). They also reported that the mean ± SD for the percentage of cells showing *HMGA2* protein expression were found to 0.2 ± 0.9 in normal tissue, as compared with 16.3 ± 28.4 in carcinomas ($P < 0.001$). *HMGA2* protein expression were significantly higher in ductal PAD (mean ± SD: 16.3 ± 28.4) than in PanIN cases (2.7 ± 13.5) ($P < 0.001$). Similar observation was found between PanIN vs. normal tissue (2.7 ± 13.5 vs. 0.2 ± 0.9, $P < 0.001$).

Prognostic—In the same cohort study, Piscuoglio et al. (2012) did not find a difference in median survival between *HMGA2*positive vs. *HMGA2*-negative tissues ($P = 0.20$).

Melanoma

Diagnostic—In 2013, from a cohort study of 127 frozen samples (training set) and 330 FFPE samples (validation set), Raskin et al. (2013) showed that the frequency of *HMGA2* overexpression was 53.1 and 83.3% in primary melanoma and melanoma metastasis tissues, respectively. They also reported that *HMGA2* expression is significantly upregulated in primary melanoma and metastases ($P = 9 \times 10^{-5}$) compared with normal tissues.

Prognostic—In the same cohort study, Raskin et al. (2013) also reported that in the training set *HMGA2* is independently associated with DFS (HR = 6.3, 95% CI 1.8–22.3), OS (stratified log-rank $P = 0.008$), and DMFS (HR = 6.4, 95% CI 1.4–29.7) after adjusting for American Joint Committee on Cancer (AJCC) stage and age at. The validation set also confirmed that *HMGA2* overexpression was significantly associated with reduced OS of melanoma patients, after adjustment for AJCC stage and age at diagnosis (HR = 1.72, 95% CI 1.09–2.73).

Bladder cancer

Diagnostic—Yang et al. (2011), in a cohort study of 148 bladder cancer and 30 specimens of adjacent normal bladder tissues, reported that *HMGA2* was overexpressed in 52% of tumor samples and that the expression levels of *HMGA2* were significant higher in tumor tissues than adjacent normal tissues (mean ± SD: 121.84 ± 31.13 vs. 1.74 ± 0.42, respectively; $P < 0.001$).

Prognostic—Consistent with findings from other cancers, Yang et al. (2011) reported that *HMGA2* expression was associated with poor survival. The HR of RFS and PFS were 3.83 (95% CI 2.19–6.71) and 3.47 (95% CI 1.43–8.45), respectively.

Bile duct carcinoma

Diagnostic—In a cross-sectional study of 48 FFPE samples of bile duct carcinoma in the USA, Zakharov et al. (2013) reported that the frequency of *HMGA2* overexpression in tumor samples was 86%.

Prognostic—We found no study in the survival or recurrence of bile duct carcinoma in the current systematic review.

Gallbladder cancer

Diagnostic—In a cohort study of 204 FFPE samples, Zou et al. (2012) found that the percentage of *HMGA2* overexpression in gallbladder cancer was 59% compared with only 23% in cancer adjacent tissues ($P < 0.01$), 20% in polyps ($P < 0.01$) and 14% in chronic cholecystitis ($P < 0.01$)

Prognostic—In the same study (Zou et al., 2012), it was found that gallbladder cancer patients with *HMGA2* positive had poorer survival than patients without *HMGA2* (OS-HR = 3.02, 95% CI 1.58–5.78).

Glioblastoma

Diagnostic—In a recent cohort study of 85 FFPE samples of glioblastoma, Liu et al. (2014) found that 68% of cancer tumor tissues had *HMGA2* overexpression.

Prognostic—In this same cohort study, Liu et al. (2014) also found that patients with tumors expressing *HMGA2* at a higher level had a significantly shorter PFS time (11.2 months vs. 18.8 months; $P = 0.02$).

Esophageal cancer

Diagnostic—Liu et al. (2014), in a study of 123 esophageal SCC (OSCC) and 123 normal adjacent tissue (NAT), found that the expression of *HMGA2* was significantly more frequent in OSCC (98 of 113, 86.7%) than in NAT (50 of 113, 44.2%, $P < 0.0001$).

Prognostic—No data for prognostic purpose (i.e. survival) is currently available for review or further analysis.

Meta-analysis

To provide a better perspective on the frequency/levels of *HMGA2* gene expression in cancer tumor samples (for diagnostic purpose) and the survival and recurrence among *HMGA2* positive patients, compared with those without *HMGA2,* we performed a meta-analysis with articles that had relevant data and provided data after contacting to corresponding authors.

Overall, 37 over 42 articles had data on frequency (or percentage) of *HMGA2* overexpression in tumor samples. The pooled percentage of *HMGA2* gene expression in tumor samples was 65.14%. Six out of 42 articles had data on the levels of *HMGA2*

expression in tumor samples. The pooled levels of *HMGA2* Gene Expression in tumor samples was 113.08-fold changes (Table 2).

Nine studies had available data for OS meta-analysis. We found that cancer patients with *HMGA2* positive was significantly reduced survival in comparison with cancer patients without *HMGA2* gene (pooled-HR = 1.85, 95% CI 1.48–2.22) (Fig. 2a). There was a positive association between cancer patients with *HMGA2* positive with cancer recurrence (in six studies), though this association did not reach significant level (pooled-HR = 1.44, 95% CI 0.80–2.07) (Fig. 3a). There was no publication bias in both meta-analysis of OS and recurrence of cancer (Figs. 2b and 3b).

Discussion

In this review, we identified 42 studies published between 1998 and June 2019, with a total of 5123 tumor samples, that evaluated *HMGA2* expression in 15 cancer types, including thyroid cancer, ovarian cancer, gastric cancer, colorectal cancer, liver cancer, breast cancer, lung cancer, oral cancer, nasopharyngeal cancer, pancreatic cancer, melanoma, bladder cancer, bile duct carcinoma, gallbladder cancer, glioma and esophageal cancer. In our meta-analysis, we found that *HMGA2* was overexpressed in more than two-third of all 15 types of cancer and *HMGA2* overexpression was significantly associated with reduced survival. There was also a trend towards association between *HMGA2* expression and cancer recurrence, although not statistically significant.

The fact that the current systematic review demonstrated that *HMGA2* was overexpressed (i.e. more than two-third) of 15 cancer types in 42 included showed that *HMGA2* might be an important marker as an universal tumor marker for prognostic. To our knowledge, the current review is the most comprehensive systematic reviews on the role of *HMGA2* as tumor marker for diagnostic and prognostic in different types of cancer. A recent review by Pallante et al. (2015) found *HMGA2* overexpressed in seven types of cancer, including breast cancer (two studies), colorectal cancer (three studies), lung cancer (two studies), ovarian cancer (four studies), pancreatic cancer (one study), and testis cancer (one study).

The difference between our review and the review by Pallante et al. (2015) is that in addition to 13 studies that were already identified, we found 29 more studies in eight more cancer sites, a strong indication of emerging attention of the field on the role of *HMGA2* in diagnostic and prognostic of cancer. The other difference is that in our current review, not only did we identify articles associated with overexpression of HMGA2 for diagnostic purpose, we also found those for prognostic purpose. Indeed, we found nine studies that had available data for OS meta-analysis and that found that cancer patients with *HMGA2* positive was significantly reduced survival in comparison with cancer patients without *HMGA2* gene. This suggests the significant value of *HMGA2* as a universal tumor marker for both purposes (i.e. diagnostic and prognostic) in different types of cancer. With the number of cancer patients increasing (i.e. 1.8 million new cases in 2018 (American Cancer Society, 2018), that it is expected that 18 million Americans are living with a diagnosis of cancer by 2022 (Siegel et al., 2012), and a great attention to precision medicine as well as

the application of liquid biopsy, the role of *HMGA2* as a tumor marker in cancer cannot be overemphasized.

A recent meta-analysis Binabaj et al. (2019) on *HMGA2* and OS and correlation with clinicopathological parameters. The major difference between ours and the study by Binabaj et al. (2019) is that they did not evaluate the diagnostic value of *HMGA2*. In our study, we calculated pooled percentage of HMGA2 gene expression and levels of fold change in cancer specimens compared to benign tumor samples. Identifying the pooled level of *HMGA2* expression in tumors in addition to survival is of vital importance as since it is quite high, more than 64% among 15 cancer types, *HMGA2* may be a universal biomarker in diagnostic to determine severity and inform treatment plans as well as predict survival.

One interesting point is that while there are close to a dozen articles on thyroid cancer, studies on the role of *HMGA*s as tumor marker for diagnostic and prognostic and common and fatal cancers in the USA are few, including four studies in colorectal cancer (Mahajan et al., 2010; Wang et al., 2011; Helmke et al., 2012; Rizzi et al., 2013), two studies in lung cancer (Sarhadi et al., 2006; Meyer et al., 2007), two studies in breast cancer (Rogalla et al., 1997; Jones et al., 2008), five studies in ovarian cancer (Mahajan et al., 2010; Hetland et al., 2012; Califano et al., 2014; Kim et al., 2015; Wu et al., 2015) or one study in pancreatic cancer (Piscuoglio et al., 2012). Further studies on *HMGA*s and those cancers are thus warranted.

Several mechanisms may underlie the oncogenicity of *HMGA2*, including activation of transcription factor E2F1 by binding of *HMGA2* to pRB (Fedele et al., 2006), direct or indirect induction of cyclin A (Pagano et al., 1992), or negative regulation of nucleotide excision-repair genes (Borrmann et al., 2003). The chemokine *CXCL1* overexpressed in melanoma and involved in melanoma progression is also regulated by *HMGA2* (Nirodi et al. (2001)). TGF-beta mediates epithelial-mesenchymal transition by inducing *HMGA2* via the *SMAD* pathway and *HMGA2* also enhances the NF-kB complex formation (Noro et al., 2003). miRNA *let-7* family negatively regulates *HMGA2* expression (Peng et al., 2008) and loss of *let-7* expression upregulates *c-Myc*, *RAS*, *CDK4*, *integrin-β* (Bittner et al., 2000), and *HMGA2* (Johnson et al., 2005; Müller and Bosserhoff, 2008; Schultz et al., 2008). Activated MAPK pathway negatively regulates *let-7* by inducing *LIN28* expression through *Myc* transcription (Dangi-Garimella et al., 2009). It is worth noting that different miRNAs (i.e. let-7a, miR-15, miR-16, miR-26a, miR-34b, miR-196a2, miR-326, miR-432, miR-548c-3p, miR-570, and miR-603) have been identified to be associated with post-transitional repression of *HMGA* family, including *HMGA2* (D'Angelo et al., 2012; Palmieri et al., 2012). Therefore, more studies are warranted of both HMGA expression and microRNA levels in relation to diagnosis and OS.

The usage of HMGA2 with other markers to enhance their diagnostic values have been explored previously. For example, in a study to determine the diagnostic accuracy of different markers for follicular neoplasm, Jang et al. (2015) found that the sensitivity, specificity and diagnostic accuracy of *HMGA2* to follicular neoplasm were 49.0, 75.6, and 54.7%, respectively. However, when *HMGA2* was used in combination with either Hector

Battifora mesothelial 1 or *cyclin D1*, these values increased to 80.8, 75.6, and 79.7%, respectively (Jang et al, 2015).

One of the main challenges for the current review is that there are three main types of quantification methods for *HMGA2* expression (i.e. microarray, IHC, and RT-PCR), the source of antibody, concentration and evaluation methods used in selected studies are different. For this reason, a sub-group analysis for heterogeneity is not possible. Results from these testing methods, however, showed the presence or absence of HMGA2 in tumor tissues in comparison with normal tissues. In 23 of total 42 eligible studies, RT-PCR was performed first and their results were confirmed by IHC while 15 other used only IHC, three studies used RT-PCR only and one study used microarray for *HMGA2* quantification. For RT-PCR, the relative *HMGA2* expression between tumor tissue compared with normal tissue was calculated using $2^{-\Delta\Delta t}$ method (Keedy et al., 2011). We calculated OS and recurrence of cancers between HMGA2 positive vs. negative using data from studies used IHC only (Fig. 2a and b). In those studies (that used IHC method), standardized protocol was deployed (Gilligan et al., 2010) such that the staining (*HMGA2*) was considered positive when localized to the nucleus and the score of 4 was applied: 0 = no staining; 1 = 1–5%; 2 = 2–25%; 3 = 26–75%, and 4 = 76–100% stained tumor cells and that specimens should contain at least 100 tumor cells.

Additionally, there may be differences in cutoff thresholds for HMGA2 expression, using RT-PCR, for different studies; thus increasing heterogeneity of results. In studies using only IHC method that were used for meta-analysis of OS and recurrence of cancers, however, we did not find the publication bias (Figs. 2b and 3b). Also, since most studies in current review were from clinical settings, where clinicopathological variables were available, some important confounding factors (i.e. smoking, alcohol consumption, dietary, etc.) might not be available. For this reason, residual confounding in multivariable analysis models were unavoidable. The other limitations in our review are few prospective cohort studies and lack of comparison groups.

Despite these limitations, our work is one of the most comprehensive systematic reviews on the role of *HMGA2* as a universal tumor marker for diagnostic and prognostic across different types of cancer. When used in combination with other markers, its clinical accuracy might increase. We believe that when being used in clinical settings, this marker might help to monitor response to treatment regimens and to guide treatment decision in cancer patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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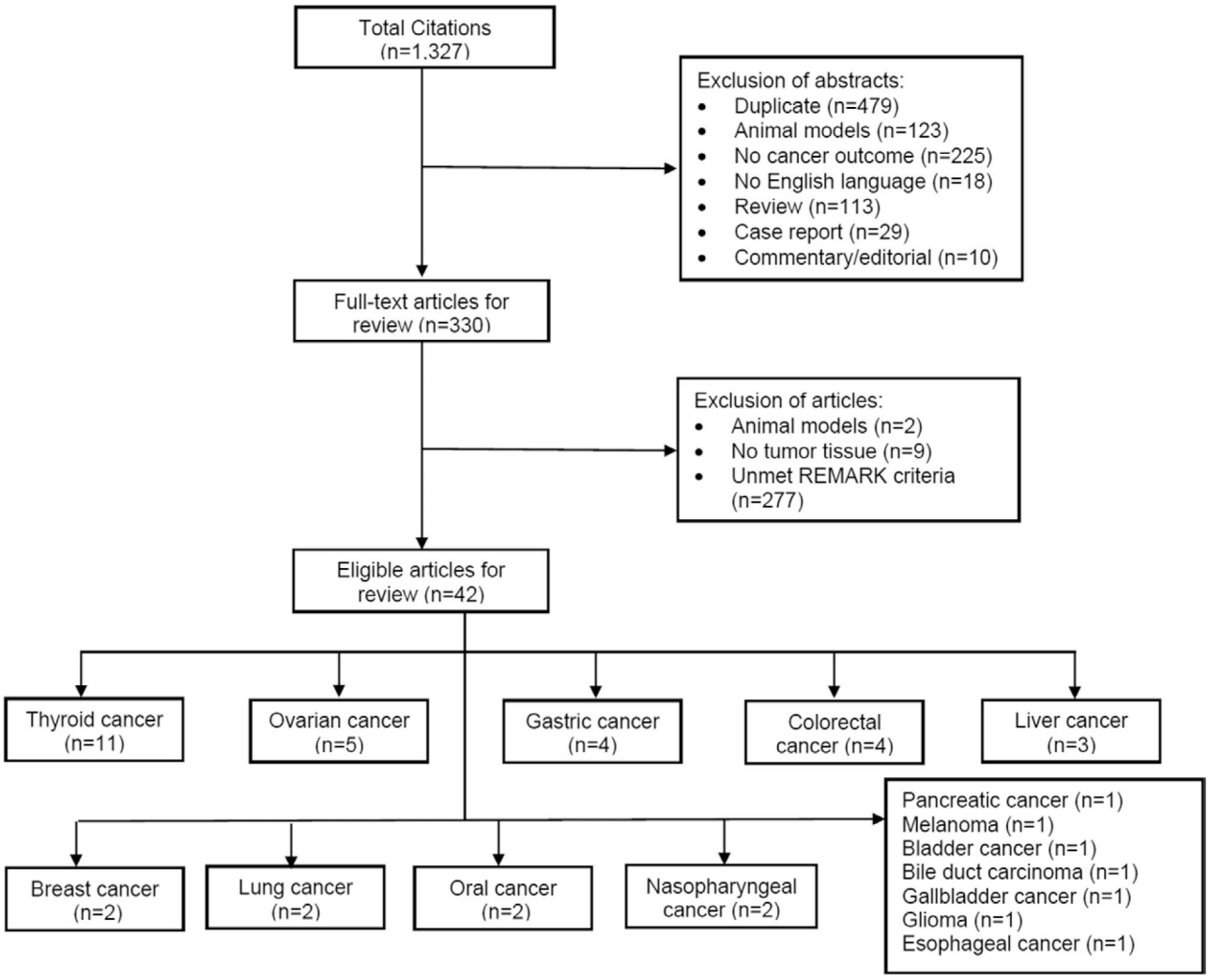

Fig. 1.

Search strategy and screening for eligibility for current systematic review. REMARK, Reporting Recommendations for Tumor Marker Prognostic Studies.

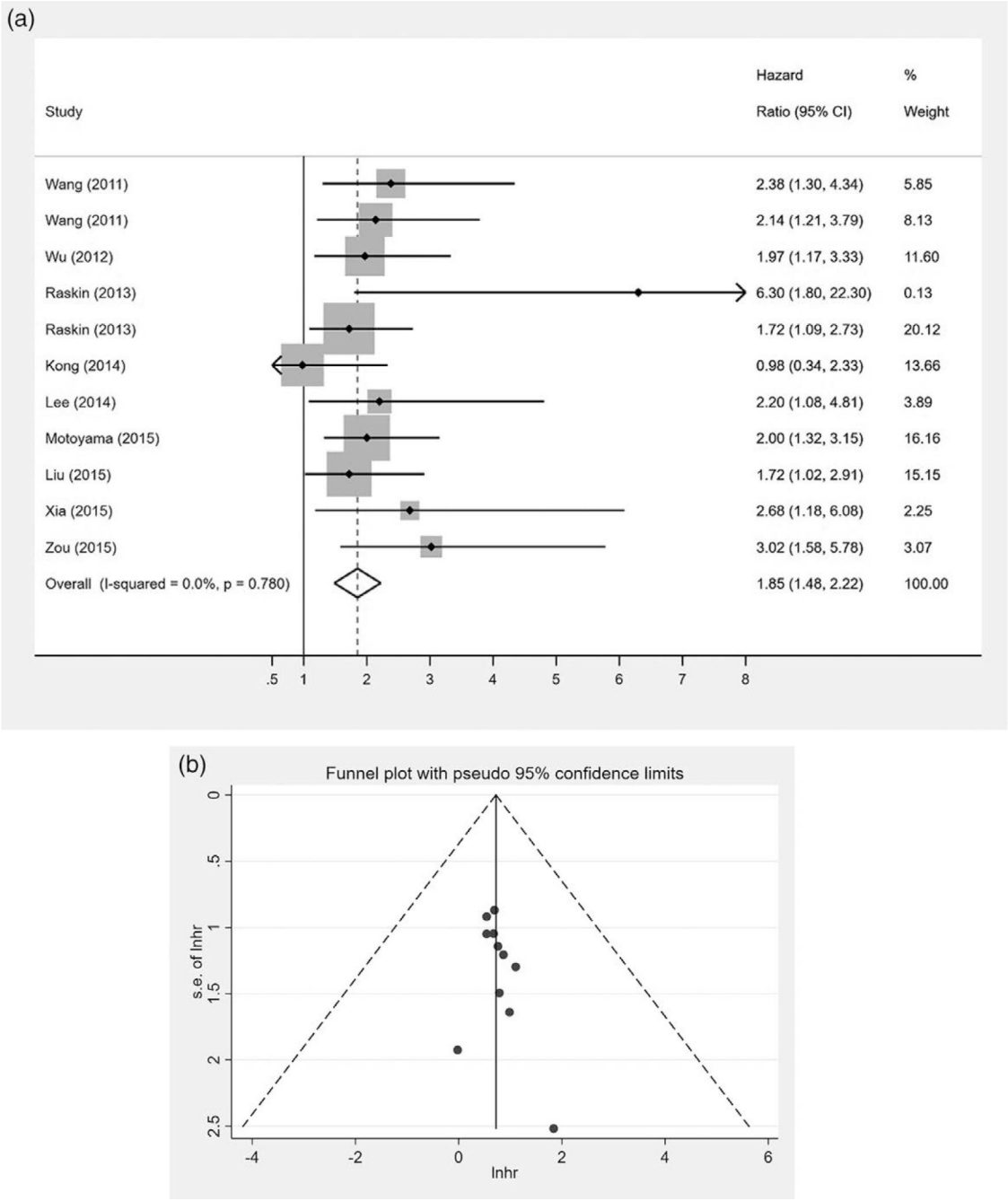

Fig. 2.

(a) Overall survival of cancers with *HMGA2* positive vs. *HMGA2* negative (using immunohistochemistry testing method only). (b) Funnel plots of publication bias in the overall survival of cancers with *HMGA2* positive vs. *HMGA2* negative.

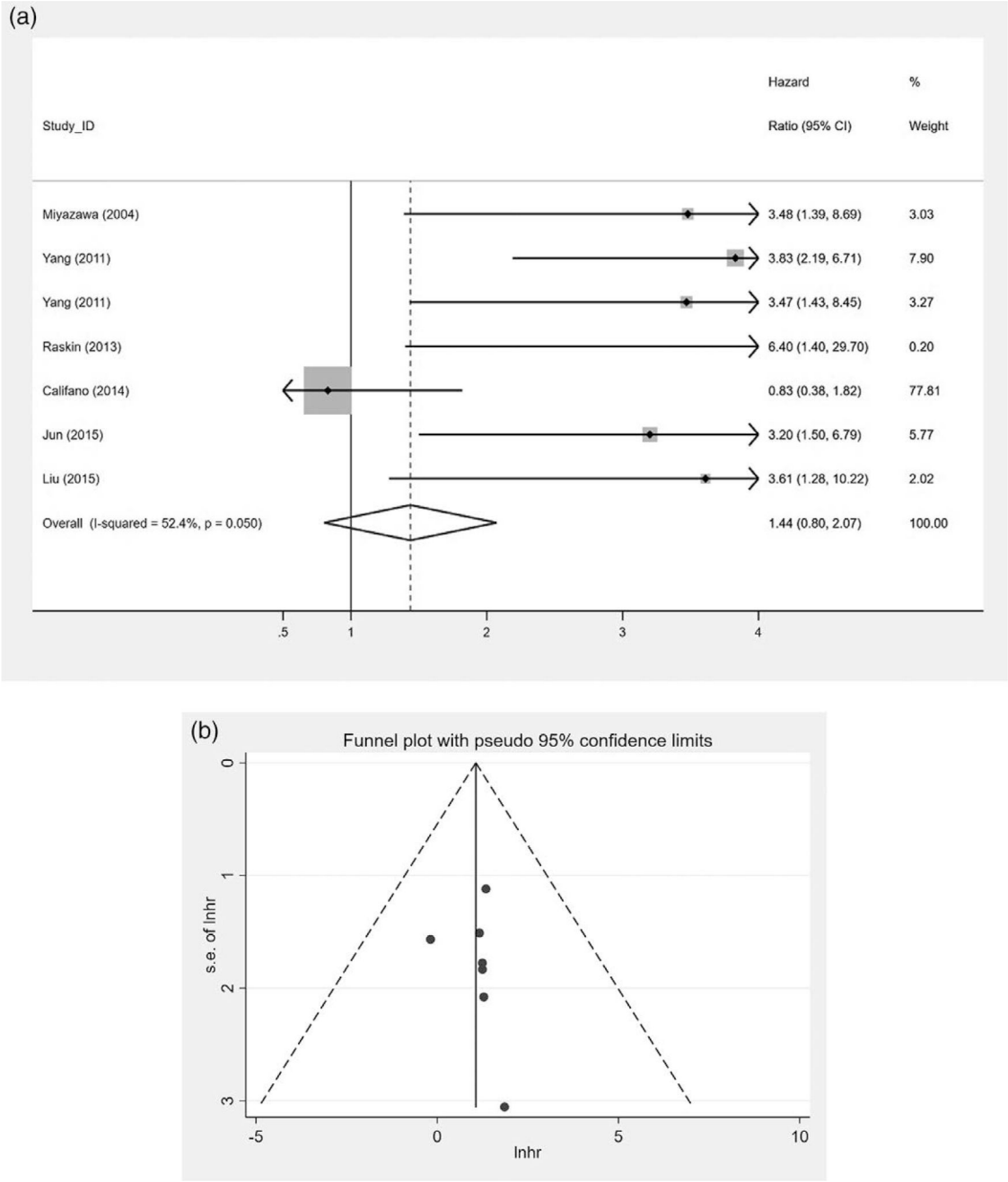

Fig. 3.

(a) Recurrence of Cancers with *HMGA2* positive vs. *HMGA2* negative (using immunohistochemistry testing method only). (b) Funnel plots of publication bias recurrence of cancers with *HMGA2* positive vs. *HMGA2* negative.

Table 1

Characteristics and summary of results of eligible studies for the current systematic review

Author, year (location)	Study design	Sample size and source	Patients	Quantification method	Detection/diagnostic results	Prognostic results
Thyroid cancer						
Belge et al. (2008) (Germany)	Cross-sectional	64 FFPE	19 adenomas; 28 PTC; 9 FTC; 3 ATC	IHC, RT-PCR	100%	
Chiappetta et al. (2008) (Italy)	Cross-sectional	128 FFPE	12 hyperplastic lesions; 31 adenomas; 21 FTC; 45 PTC; 12 ATC	IHC	PTC 30/45 = 75.5%; FTC 4/21 = 19.1%; ATC 11/12 = 91.6%	
				RT-PCR	Adenomas 1/7 = 14.3%; PTC 4/37 = 91.9%; FTC 13/16 = 81.2%; Anaplastic carcinoma 4/4 = 100%	
Prasad et al. (2008) (USA)	Cross-sectional	125 FFPE	70 benign (20 adenomatoid nodules; 20 adenomas; 17 HA; 13 lymphocytic nodules); 55 malignant (19 PTC; 16 FVPTC; 14 FTC; 6 HC)	IHC, RT-PCR	PTC 26/30 = 87%; FVPTC 13/16 = 81%; FTC 11/14 = 79%; very high in malignant tumor	
Arora et al. (2009) (USA)	Cross-sectional	90	16 PTC, 22 FVPTC, 15 hyperplastic nodules, 22 FA; 15 borderline	Expression microarray	In tumor 3.56-fold change (P = 0.02)	
Lappinga et al. (2010) (USA)	Cross-sectional	115	71 benign and 44 malignant (13 FTC, 22 PTC, 9 HC)	RT-PCR	FTC 11/13 = 85%; HC 3/9 = 33%; PTC 17/22 = 33%	
Jin et al. (2011) (USA)	Cross-sectional	170 FFPE, 226 FNA	34 FA, 10 HA, 6 hyperplastic nodules, 4 atypical adenomas, 44 PTC, 29 FVPTC, 23 FTC, 17 HC, 3 ATC	RT-PCR	Overall 71.6–79.8%; FNA 79.8–88.6%	
Prasad et al. (2012) (USA)	Cross-sectional	193 FFPE, 95 FNA	FFPE: 36 PTC; 20 FVPTC; 17 FTC; 30 FA; 18 Lymphocytic thyroid nodule; 18 adenomatoid nodule; 11 HA; 4 HC; 30 normal FNA: 67-benign; 28-malignant	IHC, RT-PCR	FTC 6/17 = 35%; FVPTC 12/20 = 60%; PTC 26/36 = 72%	
Klemke et al. (2014) (Germany)	Cross-sectional	37 FFPE	14-FA, 11-PTC, 4-FVPTC, 8 = FTC	RT-PCR	FVPTC 23.9–156.9; PTC 128.2–1207.5	
Nagar et al. (2014) (USA)	Cross-sectional	52 FNA	21-FA, 12-FTC, 19-FVPTC	RT-PCR	FVPTC 28-fold higher (P < 0.01)	
Jin et al. (2015) (USA)	Cross-sectional	80 FFPE, 120 FNA	FFPE: 48 benign and 32 carcinoma; 120 FNA (56 benign and 64 carcinoma)	RT-PCR	PTC 23/24 = 95.8%; FVPTC 8/10 = 80%; FC 15/17 = 88.2%; HC 4/13 = 30.8%	
Jang et al. (2015) (South Korea)	Cross-sectional	192 FFPE	41 goiter, 72 FA, 79 FTC	IHC	FA 30/72 = 41.7%; FTC 44/79 = 55.7% (P = 0.05)	
Ovarian cancer						

Author, year (location)	Study design	Sample size and source	Patients	Quantification method	Detection/diagnostic results	Prognostic results
Mahajan et al. (2010) (USA)	Case-only study	115 FFPE	30 HG-PSC; 10 SBT; 15 MMMT; 30 EOC; 15 MOC; 15 CCOC	IHC	HG-PSC 18/30 = 64.3%, MMMT 9/15 = 64.3%, SBT 1/10 = 10%, EOC 2/15 = 7.1%, MOC 1/15 = 6.7%, CCOC 3/15 = 23.1%	
Hetland et al. (2012) (Norway)	Retrospective cohort	199 FFPE	199-effusion samples; 50 Primary tumors; 50 solid metastasis	IHC	Effusion 188/199 = 94.5%, primary tumors 48/50 = 96%, solid metastasis 45/50 = 90%	No association between *HMGA2* expression and PFS or OS
Califano et al. (2014) (Italy)	Retrospective cohort	117 FFPE	117 primary advanced ovarian cancer	IHC	62/117 = 53.0%	DFS *HMGA2* only: HR = 0.83 (0.38–1.82); *HMGA2* + BMI: HR = 3.17 (1.25–8.03)
Kim et al. (2015) (South Korea)	Retrospective cohort	35 frozen, 39 FFPE	74 ovarian carcinomas treated with Paclitaxel and Cisplatin or Carboplatin	IHC, RT-PCR	30/74 = 40.5% in cancer	Significant association of *HMGA2*(+) expression with shorter OS 5-year OS rate: 78% vs. 35% ($P = 0.02$)
Wu et al. (2015) (US - China)	Cross-sectional	278 FFPE (Training), 150 FFPE (Validation)	Training: serous 80%, mucinous 20% Validation: serous 72%, mucinous 28%	IHC	Training ($P < 0.001$): serous 130/222 = 58.6%; mucinous 15/56 = 26.8% Validation ($P = 0.001$): serous 56/108 = 54.6%; mucinous 10/42 = 23.8%	
Gastric cancer						
Motoyama et al. (2008) (Japan)	Cohort	110 frozen, FFPE	110 gastric carcinoma	IHC, RT-PCR	83/110 = 75.4%	OS HR = 2.00 (1.32–3.15)
Kong et al. (2014) (China)	Cohort	212 FFPE	158 cancers, 30 peritumoral tissues, 24 normal gastric tissues	IHC, RT-PCR	68/1 18 = 43.0%	Multivariate OS: *HMGA2*(+) only HR = 0.98 (0.34–2.33); *HMGA2*(+)/Oct4(+) HR = 2.89 (1.02–5.14)
Lee et al. (2015) (South Korea)	Cohort	170 FFPE	170 gastric cancer	IHC, RT-PCR	39/170 = 22.9%	5-year OS rate: 54.2% vs. 43.6% ($P = 0.028$)
Jun et al. (2015) (South Korea)	Retrospective cohort	169 FFPE	110 gastric cancer; 29 adenoma; 30 non-cancerous gastric tissues	IHC	72/1 10 = 65.5%, ($P < 0.001$)	RFS HR = 3.20 (1.50–6.79)
Colorectal cancer						
Huang et al. (2009) (China)	Cross-sectional	62	6-A colorectal; 2-S colon; 3-D colon; 20 rectum	RT-PCR	47/62 = 76%	
Wang et al. (2011) (USA - China)	Cohort	280 FFPE	89 (training, USA), 191 (validation, China); 66/191 had adjuvant chemotherapy	IHC, RT-PCR	Training: 32/89 = 35.9; validation: 70/191 = 36.6%	OS stages I + II vs. III + IV in training: HR = 2.38 (1.30–4.34), validation: HR = 2.14 (1.21–3.79)

Author, year (location)	Study design	Sample size and source	Patients	Quantification method	Detection/diagnostic results	Prognostic results
Helmke et al. (2012) (Germany)	Cross-sectional	38 FFPE	38 colon cancer expressing HGMA2	IHC, RT-PCR	19/38 = 50%	
Rizzi et al. (2013) (Italy)	Retrospective cohort	103 FFPE	103 colorectal cancer	IHC	90/103 = 87.4%	No OS difference in *HMGA2*(+) vs. (−) (P = 0.59)
Liver cancer						
Wu et al. (2012) (China)	Cohort	23 pairs = 46 FFPE=107	23 HCC	IHC, RT-PCR	51/107 = 47.7%; HGMA2 high in tumor vs. normal (38.7 vs. 8.4, P < 0.01)	OS HR = 1.97 (1.17–3.33)
Lee et al. (2013) (USA-China)	Cross-sectional	86 FFPE	15 FL-HCC; 15 hepatoblastomas; 34 HCC; 22 hepatic adenomas	IHC	15/15 = 100%	
Lee et al. (2014) (USA)	Retrospective cohort	68 FFPE	14 - stage I; 21 - stage II; 7 - stage III; 11 - stage IV	IHC	18/55 = 33%	OS HR = 2.20 (1.12–4.33)
Breast cancer						
Rogalla et al. (1998) (Germany)	Cross-sectional	57	44 breast cancer, 13 normal adjacent tissue	RT-PCR	20/44 = 45.45%	
Jones et al. (2008) (UK)	Cross-sectional	23	12 benign phylloides tumors, 11 borderline malignant phylloides tumors	RT-PCR	Microarray: 4-fold change RT-PCR: 6-fold change	
Lung cancer						
Sarhadi et al. (2006) (Finland)	Cohort	152 FFPE	152 mainly small cell lung carcinoma	IHC, RT-PCR	Overall: 130/144 = 90% SCC: 60/62 = 96.8%; HGMA2 high in tumor vs. normal	Significant association of HGMA2 expression in AC with poor survival (P = 0.05)
Meyer et al. (2007) (Germany)	Cross-sectional	68 (34 pairs)	17 - AC, 17 - SCC	IHC, RT-PCR	10–50% AC; 80% SCC AC: mean 158.41-fold (1.02–911.02) SCC: mean 336.26-fold (4.34–2,503.68)	
Oral cancer						
Miyazawa et al. (2004) (USA-Japan)	Retrospective cohort	42 FFPE	42 primary oral squamous cell carcinomas	IHC, RT-PCR	31/42 = 73.8%; expression level: 163.4 ± 90.4 (P < 0.05)	DFS HR = 3.48 (1.40–8.69)
Chang et al. (2015) (Taiwan)	Cohort	215 FFPE	215 oral squamous cell carcinoma	IHC	HGMA2 high in tumor vs. normal (P < 0.001)	5-year OS: 75.6% vs. 57.7% (P = 0.007) 5-year DSS: 78.1% vs. 59.1% (P = 0.006) 5-year DFS: 72.7% vs. 53.1% (P = 0.002)
				RT-PCR	48 ± 75 vs. 1 ± 1.5 copy/10^5 GAPDH copy, P < 0.001	
Nasopharyngeal cancer						

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Author, year (location)	Study design	Sample size and source	Patients	Quantification method	Detection/diagnostic results	Prognostic results
Liu et al. (2015) (China)	Cohort	145 FFPE	116 NPC, 29 non-cancerous NP tissues	IHC	62/116 = 52.6%	OS HR = 1.72 (1.02–2.91)
Xia et al. (2015) (China)	Retrospective cohort	144 FFPE	124 NPC, 20 non-tumoral nasopharynx	IHC	54/124 = 43.55% ($P < 0.001$)	OS HR = 2.68 (1.18–6.08)
Pancreatic cancer						
Piscuoglio et al. (2012) (Switzerland)	Retrospective cohort	210 FFPE	210 PDAC, 40 PanIN-3; 40 Normal control	IHC	197/210 = 93.8% (PAD) 37/40 = 92.5% (PanIN-3)	OS was not significantly different between *HMGA2*(+) and (−)
Melanoma						
Raskin et al. (2013) (USA)	Retrospective cohort	127 frozen (training), 330 FFPE (validation)	67 primary melanoma, 20 melanoma metastases, 40 normal skin	Expression microarray, IHC, RT-PCR	Primary melanoma: 26/46 = 53.1%	Training: OS HR = 6.30 (1.80–22.30), DMFS HR = 6.40 (1.4–29.7)
					Melanoma metastasis: 10/12 = 83,3%	Validation: OS HR = 1.72 (1.09–2.73)
Bladder cancer						
Yang et al. (2011) (USA)	Retrospective cohort	148 FFPE	148 urothelial bladder cancer	IHC, RT-PCR	77/148 = 52%; HGMA2 expression: 121 ± 31.13 (cancer) vs. 1.74 ± 0.42 (normal), $P < 0.001$	RFS HR = 3.83 (2.19–6.71), PFS HR = 3.47 (1.43–8.45)
Bile duct carcinoma						
Zakharov et al. (2013) (USA)	Cross-sectional	48 FFPE	22 adenocarcinoma, 12 adenoma, 14 reactive atypia	IHC	41/48 = 86%	
Gallbladder cancer						
Zou et al. (2012) (China)	Retrospective cohort	204 FFPE	108 AC, 45 adjacent tissue, 15 polyps, 35 chronic cholecystitis	IHC	Adenocarcinoma: 64/108 = 59.3% ($P < 0.01$)	OS HR = 3.02 (1.58–5.78)
Glioma						
Liu et al. (2014) (China - Japan)	Retrospective cohort	85 FFPE	78 gliomas	IHC, RT-PCR	67.9% (53/78)	*HMGA2* at a higher level had a significantly shorter progression-free survival time (11.2 months vs. 18.8 months; $P = 0.02$)
Esophageal cancer						
Liu et al. (2014) (China)	Cross-sectional	226 FFPE	113 esophageal squamous cell carcinomas	IHC, RT-PCR	98/113 = 86.7%	

AC, adenocarcinoma; AFP, serum alpha-fetoprotein; AJCC, American Joint Committee on Cancer; ATC, anaplastic thyroid carcinoma; AUC, area-under-curve; CCOC, clear cell ovarian carcinoma; chemo, chemotherapy; DFS, disease-free survival; DMFS, distant metastases-free survival; DSS, disease-specific survival; EOC, endometroid ovarian carcinoma; FA, follicular adenoma; FFPE, formalin-fixed paraffin-embedded; FIGO, International Federation of Gynecology & Obstetrics; FL-HCC, fibrolamellar hepatocellular carcinoma; FNA, fine-needle aspiration; FTC, follicular carcinoma; FVPTC, follicular variant of papillary thyroid carcinomas; GAPDH, glyceraldehyde 3-phosphate dehydronase; GBM, glioblastoma multiforme; HA, Hürthle cell adenoma; HC, Hurthle cell carcinoma; HCC, hepatocellular carcinoma; HG-PSC, high-grade papillary serous carcinoma; *HMGA2,* high mobility group A2 protein; HR, hazard ratio; IHC, immunohistochemistry; MMMT, malignant mixed

Mullerian tumor; MOC, mucinous ovarian carcinoma; NPC, nasopharyngeal carcinoma; PAD, pancreatic adenocarcinoma; PanIN-3, pancreatic intraepithelial neoplasia, grade 3; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PTC, papillary thyroid carcinomas; radio, radiotherapy; RFS, recurrence-free survival; RT-PCR, real-time PCR; SBT, serous borderline tumor; SCC, squamous cell carcinoma; SCC, squamous cell carcinoma; Sen, sensitivity; Spe, specificity.

Table 2

Pooled percentage and levels of *HMGA2* gene expression (fold change) in cancer specimens

	Sample Size	%	Weight	Adjusted %
Belge et al. (2008)	64	100	0.012493	0.01249268
Chiappetta et al. (2008)	37	91.90	0.007222	0.006637322
	16	81.20	0.003123	0.002536014
	4	100.00	0.000781	0.000780793
	45	75.50	0.008784	0.006631856
	21	4.00	0.004099	0.000163966
	12	91.60	0.002342	0.002145618
Prasad et al. (2008)	30	87	0.005856	0.005094671
	16	81	0.003123	0.002529768
	14	79	0.002733	0.002158891
Lappinga et al. (2010)	13	85	0.002538	0.002156939
	9	33	0.001757	0.000579738
	22	77	0.004294	0.003306656
Jin et al. (2011)	170	71.6	0.033184	0.023759516
	170	79.8	0.033184	0.026480578
	226	79.8	0.044115	0.035203592
	226	88.6	0.044115	0.039085692
Prasad et al. (2012)	17	35.0	0.003318	0.001161429
	20	60.0	0.003904	0.002342378
	36	72.0	0.007027	0.005059535
Jin et al. (2015)	24	95.8	0.004685	0.004487995
	10	80.0	0.001952	0.001561585
	17	88.2	0.003318	0.002926801
	14	30.8	0.002733	0.000841694
Jang et al. (2015)	72	41.7	0.014054	0.005860629
	79	55.7	0.015421	0.008589303
Mahajan et al. (2010)	30	64.3	0.005856	0.003765372
	15	64.3	0.002928	0.001882686

	Sample Size	%	Weight	Adjusted %
	10	10.0	0.001952	0.000195198
	30	7.1	0.005856	0.000415772
	15	6.7	0.002928	0.000196174
	15	23.1	0.002928	0.000676362
Hetland et al. (2012)	199	94.5	0.038844	0.036707984
	50	96.0	0.00976	0.00936951
	50	90.0	0.00976	0.008783916
Califano et al. (2014)	117	53.0	0.022838	0.012104236
Kim et al. (2015)	74	40.5	0.014445	0.005850088
Wu et al. (2015)	222	58.6	0.043334	0.025393715
	56	26.8	0.010931	0.002929533
	108	54.6	0.021081	0.011510443
	42	23.8	0.008198	0.0019512
Motoyama et al. (2008)	110	75.4	0.021472	0.016189733
Kong et al. (2014)	158	43.0	0.030841	0.013261761
Lee et al. (2015)	170	22.9	0.033184	0.007599063
Jun et al. (2015)	110	65.50	0.021472	0.014064025
Huang et al. (2009)	62	76.0	0.012102	0.009197736
Wang et al. (2011)	89	35.9	0.017373	0.006236775
	191	36.6	0.037283	0.01364552
Helmke et al. (2012)	38	50.0	0.007418	0.003708764
Rizzi et al. (2013)	103	87.4	0.020105	0.017572126
Wu et al. (2012)	107	47.7	0.020886	0.009962717
Lee et al. (2013)	15	100.0	0.002928	0.002927972
Lee et al. (2014)	55	33.0	0.010736	0.003542846
Rogalla et al. (1998)	44	45.4	0.008589	0.003899278
Sarhadi et al. (2006)	144	90.3	0.028109	0.025382003
	62	96.8	0.012102	0.011715011
Meyer et al. (2007)	68	50.0	0.013273	0.006636736
	68	80.0	0.013273	0.010618778
Miyazawa et al. (2004)	42	73.8	0.008198	0.006050361

	Sample Size	%	Weight	Adjusted %
Liu et al. (2015)	116	52.6	0.022643	0.011910209
Xia et al. (2015)	144	43.5	0.028109	0.012227211
Piscuoglio et al. (2012)	210	93.8	0.040992	0.038450127
	40	92.5	0.007808	0.007222331
Raskin et al. (2013)	46	57.0	0.008979	0.005118095
	12	83.0	0.002342	0.001944173
Yang et al. (2011)	148	52.0	0.028889	0.015022448
Zakharov et al. (2013)	48	86.0	0.00937	0.008057779
Zou et al. (2012)	108	59.3	0.021081	0.012501269
Liu et al. (2014)	85	67.9	0.016592	0.01126586
Liu et al. (2014)	113	86.7	0.022057	0.019123756
Total	5123			0.651362288

	Sample size	Fold change	Weight	Adjusted fold change
Arora et al. (2009)	90	3.56	0.188679	0.671698113
Klemke et al. (2014)	37	23.9	0.077568	1.853878407
	37	156.9	0.077568	12.17044025
	37	128.2	0.077568	9.944234801
Jones et al. (2008)	23	4	0.048218	0.192872117
	23	6	0.048218	0.289308176
Nagar et al. (2014)	52	28	0.109015	3.052410901
Meyer et al. (2007)	68	158.41	0.142558	22.58255765
	68	336.26	0.142558	47.93643606
Myazawa et al. (2004)	42	163.4	0.08805	14.38742138
Total	477			113.0812579