High BANCR may manifest worse prognosis in human malignant carcinomas: An updated systematic review and meta-analysis

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Abstract

Background

BRAF-activated non-coding RNA (BANCR) was reported to be aberrantly expressed in various tumor tissues and has been confirmed to function as tumor suppressor or oncogene in many types of cancers. Considering the conflicting results and insufficient sampling, a meta-analysis was performed to explore the prognostic value of BANCR in various carcinomas.

Methods

A comprehensive literature search of PubMed, Web of Science, EMBASE, Cochrane Library and the China National Knowledge Infrastructure (CNKI) was conducted to collected relevant articles.

Results

Pooling results showed strong relevance of high BANCR expression and poor overall survival (OS) (HR=1.60, 95% confidence interval (CI): 1.19-2.15, P =0.002) and recurrence-free survival (RFS) (HR=1.53, 95%CI: 1.27-1.85, P <0.00001). In addition, high BANCR expression predicts advanced tumor stage (OR=2.39, 95%CI: 1.26-4.53, P =0.008), present lymph node metastasis (OR=2.03, 95%CI: 1.08-3.83, P =0.03), positive distant metastasis (OR=3.08, 95%CI: 1.92-4.96, P <0.00001) and bigger tumor size (OR: 1.63, 95%CI: 1.09-2.46, P =0.02).

Conclusions

The results showed that elevated BANCR expression was associated with unfavorable prognosis for most of cancer patients, and BANCR could be served as a promising therapeutic target and independent prognostic predictor for cancers.

1. Introduction
Currently, cancer remains one of the major public health concerns worldwide [1]. It’s reported that 1,762,450 new cancer cases and 606,880 cancer deaths are predicted to occur in the United States in 2019 [2]. Notably, due to the rapid advancement of cancer research, treatment and diagnostic methods, the cancer mortality continuously dropped by a total of 27% in the last two decades [3]. In spite of this, the 5-year relative survival rate of patients is still disappointing [4]. When the cancer is diagnosed, many patients are already in the middle and late stages of the disease, and there is still no ideal effective treatment. Therefore, it’s critical to explore specific and sensitive therapeutic target and promising prognostic biomarkers for effective treatment of cancer.

Increasing studies have suggested that long non-coding RNA (lncRNA), with longer than 200 nucleotides and without the ability to code proteins, plays a vital role in multifarious biological processes including cell differentiation, growth, apoptosis, cell cycle and metabolism [5]. Moreover, abnormal lncRNA expression has been observed in various tumor tissues and involved in the proliferation, invasion and metastasis of tumor cells [6, 7]. Growing number of publications uncovered the great application value of long non-coding RNA in target treatment and cancer prognosis [8]. For example, MALAT1 [9], CRNDE[10], ZEB1-AS1 [11] etc.

By using RNA-sequencing, Flockhart et al. originally found that BRAF-activated non-coding RNA (BANCR), a 693-bp lncRNA located in chromosome 9, was overexpressed in melanoma cell. Additionally, accumulating studies suggested that BANCR is correlated with metastasis and invasion of multiple tumor cells and could function as prognostic biomarker, such as gastric cancer [12, 13], hepatocellular carcinoma [14-17], renal cell carcinoma and non-small cell lung cancer [18, 19]. However, due to small sample size and discrepant conclusions among those studies, the association of BANCR expression with prognosis of patients is still undefined. Thus, a meta-analysis was performed to
investigate the prognostic value of BANCR in various cancers.

2. Materials And Methods

2.1. Literature search strategies

The literature search was conducted on electronic databases of PubMed, Cochrane Library, EMBASE, Web of science and Chinese National Knowledge Infrastructure (CNKI) by using (“BANCR” OR “Lnc RNA BANCR” OR “IncBANCR” OR “BRAF-activated non-coding RNA”) AND (“neoplasm” OR “carcinoma” OR “tumor” OR “cancer”). The latest literature search was up to July 25, 2019.

2.2. Inclusion and exclusion criteria

The selection of studies was completed by two independent researchers. The inclusion standards are as followed: (a) studies investigated the correlation of BANCR expression with survival outcome and clinical prognosis of cancer patients; (b) patients were classified into high expression group and low expression group in accordance with primary literature; (c) the expression level of BANCR was detected by validate techniques; (d) publications provide sufficient and usable data to calculate OR and HR; (e) studies in English or Chinese. The exclusion standards are: (a) publication explore the molecular biological mechanisms of BANCR but not investigate the relationship between the expression level of BANCR and the prognosis of cancer patients but; (b) reviews and meta-analysis, letters, animal studies, conference literature; (c) studies without enough data to perform prognostic analysis; (d) repetitive publication.

2.3. Data extraction and quality assessment

The data was extracted by two independent investigators (FSX and LZ), including first author’s name, publication date, cancer type, sample size, overall survival (OS), recurrence-free survival (RFS), disease free survival (DFS), (TNM) stage, tumor size,
distant metastasis (DM), histological grade, lymph node metastasis (LNM), depth of invasion, detection methods of BANC R and HR. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of included articles, and the high-quality studies are with NOS score more than 6 [20].

2.4. Statistical analysis

The meta-analysis was conducted to calculate the pooled ORs, HRs with corresponding 95% CI by using the Review Manager 5.3 software (Cochrane Collaboration, London, UK) and STATA 12.0 software (Stata, College Station, TX). Random-effect model was adopted when $I^2 > 50\%$, which demonstrating meaningful heterogeneity among enrolled studies, instead, fixed-effect model was applied. The latent publication bias was assessed by using Funnel plots and Begg’s test. When significant heterogeneity exists, the subgroup analysis was conducted to explore the source of heterogeneity. The sensitivity analysis was carried out for stability test of results. Specially, when survival data cannot be directly extracted and only Kaplan-Meier curves was provided by primary articles, the Enguage Digitizer tool (Version 4.1) was used to extract time-dependent survival rate from Kaplan-Meier curves, the HRs and 95%CI were calculated according to the method [21]. Statistically significance was deemed when $P < 0.05$.

3. Results

3.1 Study characteristics

386 studies were searched from the databases, among them, 174 duplicate studies were excluded and 158 studies were abandoned after reading abstract and full text. Furthermore, 16 publications did not investigate the association between BANC R expression and the prognosis of patients, 6 publications did not divided patients into high and low BANC R expression group, 12 publications lack usable data. Lastly, 20 eligible
studies were included for qualitative and quantitative synthesis (Figure 1). Of these 20 studies with 1997 patients, the 19 studies with 1847 patients were come from China, 1 study comprising 150 patients was from Iran [22]. Publication years range from 2014 to 2019, the expression level of BANCR were all detected by qRT-PCR, and included cancer type are: lung cancer [18], hepatocellular carcinoma, osteosarcoma [23], papillary thyroid cancer [24-28], gastrointestinal cancer [29, 30], bladder cancer [31], malignant melanoma [32], breast cancer [33, 34], clear cell renal cell carcinoma [19], esophageal squamous cell carcinoma [22, 35] and endometrial cancer (detail in Table 1) [36]. NOS scores were presented in Table 2.

3.2. The association of BANCR with OS

A total of 10 studies comprising 1151 patients were enrolled to inquiry the relationship between BANCR with OS. The random-effect model was applied for marked heterogeneity (I²=60%, p=0.008). Pooling result supported the conclusion that patients with high BANCR expression tended to undergo shorter overall survival (HR=1.60, 95%CI: 1.19-2.15, p=0.002, Figure 2A). Moreover, subgroup analysis was conducted to explore the sources of heterogeneity based on cancer types, the sources of HR (direct/indirect extraction), simple size (less/more than 100 patients) and NOS score (9 score/less than 9 score). A strong correlation was revealed between high BANCR expression and poor OS in digestive system (HR=1.94, 95%CI, 1.38-2.73; P=0.0001), HRs extracted directly from articles (HR=1.69, 95%CI, 1.44-1.99; P<0.00001), multivariate analysis (HR=1.71, 95%CI, 1.47-2.02; p<0.00001), cancer with less than 100 patients (HR=1.62, 95%CI, 1.11-2.35; P=0.05) or more than 100 patients (HR=1.57, 95%CI, 1.07-2.31; P=0.02) and the irrelevance between BANCR expression and OS with non-digestive system cancer (HR=1.35, 95%CI, 0.86-2.13; P=0.20), HR with univariate analysis (HR=0.84, 95%CI, 0.41-
1.75; p=0.65) or HRs extracted indirectly from articles (HR=1.15, 95%CI, 0.52-2.56; P=0.73) were also observed. Detail results were showed in Table 3. Bad prognosis of BANCR could also be identified by revealing the positive association between high BANCR expression and short DFS (HR=1.21, 95%CI: 0.33-4.41, P=0.77) and RFS (HR=1.53, 95%CI: 1.27-1.85, P=0.001) (Figure 2B).

3.3. The association of BANCR with TNM stage

14 studies of 1378 patients were enrolled to investigate the association of BANCR expression level with TNM stage. The random-effect model was adopted and subgroup was carried out due to significant heterogeneity (I^2=83.9%, p<0.001). Pooling OR manifested the strong connection of high BANCR expression with advanced tumor stage (HR=2.39, 95%CI: 1.26-4.53, P<0.001). In accordance with the result of subgroup analysis, a strong association of high BANCR expression and advanced TNM stage in digestive system cancers (HR=4.01, 95%CI: 2.45-6.57, P<0.00001) and Female reproductive system (HR=12.25, 95%CI: 1.27-118.37, P=0.03), negative association in non-small cell lung cancer (HR=0.26, 95%CI: 0.11-0.61, P=0.002) and irrelevance in other system cancers (HR=1.30, 95%CI: 0.40-4.27, P=0.15) could be observed. (Figure 3)

3.4. The association of BANCR with other clinic pathological parameters

Other prognostic parameters were also assessed, and obvious correlation between increasing BANCR expression and advanced lymph node metastasis (OR=2.03, 95%CI=1.08-3.83, p<0.05) (Figure 4), distant metastasis of tumor cells (OR=3.08, 95%CI: 1.92-4.96, P<0.001) (Figure 5A), advanced invasion depth (OR: 1.54, 95%CI: 1.06-2.24, P=0.02) (Figure 5B), worse histologic grade (OR: 1.54, 95%CI: 1.00-2.38, P=0.05) (Figure 5C), bigger tumor size (OR: 1.63, 95%CI: 1.09-2.46, P=0.02) (Figure 6) and more local tumor nodes (multiple/single) (OR: 1.78, 95%CI: 1.12-2.83, P=0.01) were uncovered.
However, irrelevant connection were also revealed in smoking (smoker vs. non-smoker) (OR: 1.01, 95%CI: 0.65-1.56, P=0.98), age (old vs. young) (OR: 0.88, 95%CI: 0.71-1.09, P=0.236) and gender (female vs. male) (OR: 0.91, 95%CI: 0.72-1.16, P=0.469) (Table 4).

3.5. Publication bias and sensibility analysis

Sensitivity analysis was performed to assess the outcome stability of OS among including studies, we found that removing each researches successively did not influence the total results significantly, means the results of each publications were almost consistent with combing result (Figure 7). Potential publication bias was estimated by the Begs test. As exhibited in Figure 8, small publication bias was uncovered among included studies in OS (Pr > |z| =0.245), TNM stage (Pr > |z| =0. 477), LNM (Pr > |z| =0. 493), DM (Pr > |z| =0. 042), histological grade (Pr > |z| = 0.245) and tumor size (Pr > |z| =0.497). Consequently, there was no significant publication bias in this meta-analysis.

4. Discussion

BRAF activated non-coding RNA (BANCR), was firstly found in melanoma cell by Flockhart RJ et al., was reported to involving in the occurrence and development of disease, such as coronary artery disease [37], diabetic retinopathy [38] and cancer [12]. After years of investigation, increasing researches reported that BANCR could serve as both oncogene and tumor suppressor gene in various cancers. In addition, growing literature reported that aberrant BANCR expression could be detected in breast cancer, gastric cancer, esophagus cancer, hepatocellular carcinoma, endometrial cancer, retinoblastoma and osteosarcoma, high BANCR expression predicts poor survival outcome, advanced TNM stage, positive lymph node metastasis, bad histological grade and earlier distant metastasis of tumor cells. However, there are several publications manifested that BANCR could act as favorable prognostic factor in non-small cell lung cancer and renal carcinoma.
Based on the controversial conclusions, some researchers tried to explore the potential molecular biological mechanisms of BANCR in the occurrence and development of cancer (Table 5 and Figure 8) [32], Flockhart et al. reported that knockdown BANCR may significantly down-regulates the expression of 86 genes, which closely related to the migration and proliferation of tumor cell [39]; Su et al detected high BANCR expression in retinoblastoma cells, and confirmed that elevated BANCR expression promotes the proliferation, migration and invasion of retinoblastoma cell [40]; Wang et al. manifested that high BANCR expression could be observed in HCC tissues, high BANCR may induce the proliferation and invasion of liver cancer cell via inhibiting E-cadherin expression and promote Vimentin expression [41]; Zhang et al. suggested down-regulated BANCR expression drives aggressiveness in papillary thyroid cancer through the MAPK and PI3K Pathways [42]; Lou et al. confirmed that knockdown BANCR expression could inhibit proliferation and induce apoptosis of breast cancer cell via promoting the Epithelial-mesenchymal Transition (EMT) Process [34]; Also, it's reported that the expression of BANCR increased in colorectal cancer (CRC), BANCR could strengthen the ability of migration and proliferation of CRC by inducing epithelial-mesenchymal transition (EMT) via activating the MEK/ERK signaling pathway [43, 44]. Inversely, Liao et al discovered that among papillary thyroid cancer (PTC) patients, the expression of BANCR was down-regulated, which partially suppress the proliferation, migration and invasion of PTC cells via ERK/MAPK signaling pathway[24]. Likewise, Sun et al implied that the decreased expression of BANCR could be observed in NSCLC cells, low BANCR expression may drive NSCLC cell invasion and metastasis by affecting EMT. In short, the expression level and role of BANCR varies from cancer to cancer, possibly due to inconsistency between tumors. A comprehensive analysis is therefore needed to accurately assess the prognostic value of BANCR in cancer.
In accordance with controversial conclusions mentioned above, 20 studies with 1997 patients and 11 types of cancers were finally enrolled to explore the relationship between BANCR expression level and the prognosis of cancer patients. Combining HR showed the marked association between high BANCR expression and worse OS. In view of underlying heterogeneity, an subgroup analysis according to cancer type, HR estimation method, NOS scores and sample size were conducted to investigate the sources of heterogeneity, and obvious association were uncovered in digestive system (HR=1.87, 95%CI, 1.40-2.50, \( P<0.0001 \)), HRs extracted directly from articles (HR=1.69, 95%CI, 1.44-1.99, \( P<0.0001 \)), multivariate analysis (HR=1.79, 95%CI, 1.47-2.18, \( P<0.0001 \)), cancer with less than 100 patients (HR=1.71, 95%CI, 1.01-2.90, \( P=0.01 \)) or more than 100 patients (HR=1.57, 95%CI, 1.07-2.31, \( P=0.01 \)). The unfavorable survival prognosis of BANCR in cancers can also be confirmed by RFS (HR=1.88, 95%CI: 1.09-3.25). However, the irrelevance between BANCR expression and OS with non-digestive system cancer (HR=1.35, 95%CI, 0.86-2.13; \( P=0.20 \)), HR with univariate analysis (HR=0.84, 95%CI, 0.41-1.75, \( P=0.78 \)) or HRs extracted indirectly from articles (HR=1.15, 95%CI, 0.52-2.56, \( P=0.69 \)) were also revealed. In addition, high BANCR expression was observed to be related with advanced clinical stage (OR=2.39, 95%CI: 1.26-4.53, \( P=0.008 \)), lymph node metastasis (OR=2.03, 95%CI: 1.08-3.83, \( P=0.03 \)), distant metastasis (OR=3.08, 95%CI: 1.92-4.96, \( P<0.00001 \)) more local tumor nodes (OR: 1.78, 95%CI: 1.12-2.83, \( P=0.01 \)) (Figure S1) and bigger tumor size (OR: 1.63, 95%CI: 1.09-2.46, \( P=0.02 \)), and unrelated with smoking (OR: 1.01, 95%CI: 0.65-1.56, \( P=0.98 \)) (Figure S2), age (OR: 0.88, 95%CI: 0.71-1.09, \( P=0.236 \)) (Figure S3) and gender (OR: 0.91, 95%CI: 0.72-1.16, \( P=0.469 \)) (Figure S4). In a word, in spite of serving as both oncogene and suppressor gene in different cancers, the pooling results still supported the conclusions most of primary researches provided that high BANCR expression indicating worse cancer prognosis. The results of sensitivity analysis in
OS showed that the total results would not be significantly affected by the arbitrary deletion of a certain study, which proved the stability of the results. In addition, small publication bias was observed in the included studies. Therefore, the expression level of BANCR could be used to evaluate the prognosis of tumor patients in most of cancers. Although the relationship between BANCR expression and clinical prognosis has been performed by Hu et al. and Fan et al. [45, 46], there are several differences between previous investigations and our research, first, pooling results uncovered the significant association between high BANCR expression and worse OS, RFS, advanced TNM stage and high risk of lymph node metastasis, which failed to be concluded by previous meta-analysis; second, larger sample size and more cancer type were included in this meta-analysis; thirdly, comprehensive subgroup analysis was performed and the connection between BANCR and tumor size, histologic grade, invasion depth, smoking, number of local tumor, age and gender were firstly explored in this study, which was not investigated in previous meta-analysis; finally, detail molecular biological mechanisms of BANCR in various cancers were discussed and summarized. Meanwhile, there exist some limitations in this meta-analysis: (a) most of the patients included in this study were came from China, which may limit the applicability of the results; (b) the sample size included is not large enough, which may affect the reliability of the results; (c) merely 11 types of cancers were enrolled to investigate the connection between BANCR and cancer prognosis, thus, the conclusions of this study could not represent all cancers; (d) HR value is partly extracted from the survival curve, may partly exist extraction bias.

5. Conclusion

In general, high expression of BANCR is significantly associated with shorter OS and poor clinical prognosis, BANCR may be treated as a biological indicator and therapeutic target for cancer. High quality, larger sample size and multi-center study was necessary to be
conducted to further confirm the reliability of this conclusion.

**Abbreviations**

NSCLC: non-small cell lung cancer; HCC: hepatocellular carcinoma; CRC: colorectal cancer; BL: bladder cancer; BC: breast cancer; ccRCC: clear cell renal cell carcinoma; GC: gastric cancer; LNM: lymphatic node metastasis; DM: distant metastasis; HTS: high tumor stage (III, IV); NA: not available; qRT-PCR: quantitative reverse transcription-polymerase chain reaction; ESCC: esophagus cancer; EC: Endometrial Cancer; SC: survival curve; directly: HR was extracted directly from article; PTC: thyroid Carcinoma; OS: overall survival; DFS: disease free survival; RFS: recurrence free survival; MMP2, The matrix metalloproteinases 2; MMP9, The matrix metalloproteinases 9; EMT, Epithelial-Mesenchymal Transition; ZEB1, zinc finger E-box binding homeobox 1; MAPK: Mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase; JNK: Jun N-terminal kinases; Random: random-effect model; TNM: TNM stage; Fixed: Fixed-effect model.

**Declarations**

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Not applicable.

**Founding**

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**Author contributions**

Project design: Gang Xu and Xixian Ke;

Searched databases and performed literature screen: Shixu Fang and Zhou Liu;

Data extraction and analysis: Yongxiang Song and Cheng Chen;

Evaluated the quality of included literature: Qiang Guo;
Manuscript writing: Shixu Fang, Gang Xu, XixianKe and Zhou Liu.

Final draft was approved by all the authors.

**Availability of data and materials**

All data analyzed during this study are available from the corresponding author on reasonable request.

**Conflicts of interest**

The authors proclaimed no underlying conflict of interest.

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Tables

Table 1. Basic features of the publications included in this meta-analysis (n=20)
| Study       | Year | Country | Cancer Type | No. of Patients | BANCR Expression | Detection Method |
|------------|------|---------|-------------|-----------------|------------------|------------------|
|            |      |         |             |                 | High             |                  |
|            |      |         |             |                 | No. of patients  |                  |
|            |      |         |             |                 | Low              |                  |
|            |      |         |             |                 | Total            |                  |
| Guo Q (43) | 2014 | China   | CRC         | 60              | 18               | 14              |
|            |      |         |             |                 | 16               | 42              | 13              | 16              | q               |
| He A (31)  | 2016 | China   | Bladder cancer | 54              | 19               | 1              |
|            |      |         |             |                 | 9                | 35              | 3               | 30              | q               |
| Jiang J (33)| 2018| China   | BC          | 216             | 125              | 63             |
|            |      |         |             |                 |                  |                  | 91              | 17              | q               |
| Li L (12)  | 2015 | China   | GC          | 184             | 92               | 60             |
|            |      |         |             |                 | 67               | 12              | 92              | 43              | 51              | 0               | q               |
| Liao T (24)| 2017 | China   | PTC         | 92              | 29               | 14             |
|            |      |         |             |                 | 4                | 63              | 30              | 22              | q               |
| Liu Z (35) | 2016 | China   | ESCC        | 142             | 71               | 57             |
|            |      |         |             |                 | 41               | 30              | 71              | 33              | 23              | 19              | q               |
| Lou K (34) | 2018 | China   | BC          | 65              | 34               | 24             |
|            |      |         |             |                 | 18              | 31              | 13              | 6               | q               |
| Shen X (30)| 2017 | China   | CRC         | 116             | 53               | 32             |
|            |      |         |             |                 |                  | 53              | 17              | q               |
| Sun M (18) | 2014 | China   | NSCLC       | 113             | 53               | 19             |
|            |      |         |             |                 | 11              | 60              | 40              | 30              | q               |
| Wang D (36)| 2016 | China   | EC          | 30              | 15               | 6              |
|            |      |         |             |                 | 7               | 15              | 1               | q               |
| Wang H (41)| 2016 | China   | HCC         | 108             | 43               | 29             |
|            |      |         |             |                 | 35              | 65              | 23              | 20              | q               |
| Jiang J (33)| 2018| China   | BC          | 216             | 125              | 63             |
|            |      |         |             |                 | 60              | 91              | 17              | 18              | q               |
| Zhang J (26)| 2018| China   | PTC         | 60              | 17               | 6              |
|            |      |         |             |                 |                  | 43              | 30              | q               |
| Sadeghpour (22)| 2018| Iran    | ESCC        | 150             | 75               | -              |
|            |      |         |             |                 | 38               | 41              | 75              | 17              | 10              | q               |
| Peng Z (23)| 2015 | China   | Osteosarcoma| 84              | 42               | -              |
|            |      |         |             |                 | 30              | 42              | 16              | 14              | q               |
| Zhao N (16)| 2018 | China   | HCC         | 46              | 23               | -              |
|            |      |         |             |                 | 7               | 23              | 4               | q               |
| Zhou T (17)| 2016 | China   | HCC         | 109             | 54               | -              |
|            |      |         |             |                 | 37              | 55              | 21              | q               |
| Su S (40)  | 2015 | China   | retinoblastoma| 60              | 30               | -              |
|            |      |         |             |                 |                  | 30              |                   | q               |
| Xue S (19) | 2018 | China   | ccRCC       | 62              | -                | -              |
|            |      |         |             |                 |                  | -               | -               | q               |
| Liu T (28) | 2018 | China   | PTC         | 30              | 17               | 4              |
|            |      |         |             |                 |                  | 13              | 6               | -               | q               |

Note. No.: number; Total: total patients in high expression group or low expression group; NSCLC: non-small cell lung cancer; HCC: hepatocellular carcinoma; CRC: colorectal cancer;
BL: bladder cancer; BC: breast cancer; ccRCC: clear cell renal cell carcinoma; GC: gastric cancer; LNM: lymphatic node metastasis; DM: distant metastasis; HTS: high tumor stage(III,IV); NA: not available; qRT-PCR: quantitative reverse transcription-polymerase chain reaction; ESCC: esophagus cancer; EC: Endometrial Cancer; SC: survival curve; directly: HR was extracted directly from article; PTC: thyroid Carcinoma; OS: overall survival; DFS: disease free survival; RFS: recurrence free survival

**TABLE 2** Quality assessment of eligible studies (Newcastle-Ottawa scale)

| Author       | Country | Selection          | Comparability       |
|--------------|---------|--------------------|---------------------|
|              |         | Adequate case definition | Representativeness of the cases | Selection of Controls | Definition of Controls | Comparability of cases and controls | Ascertainment of exposure |
| Guo Q (43)   | China   | *                   | *                   | *                     | *                    | **                                | *                        |
| He A (31)    | China   | *                   | *                   | *                     | *                    | *                                 | *                        |
| Jiang J (33) | China   | *                   | *                   | *                     | *                    | **                                | *                        |
| Li L (12)    | China   | *                   | *                   | *                     | *                    | **                                | *                        |
| Liao T (24)  | China   | *                   | *                   | *                     | *                    | **                                | *                        |
| Liu Z (35)   | China   | *                   | *                   | *                     | *                    | **                                | *                        |
| Lou K (34)   | China   | *                   | *                   | *                     | *                    | **                                | *                        |
| Shen X (30)  | China   | *                   | *                   | *                     | *                    | *                                 | *                        |
| Sun M (18)   | China   | *                   | *                   | *                     | *                    | *                                 | *                        |
| Wang D (36)  | China   | *                   | *                   | *                     | *                    | *                                 | *                        |
| Wang H (41)  | China   | *                   | *                   | *                     | *                    | *                                 | *                        |
| Jiang J (33) | China   | *                   | *                   | *                     | *                    | **                                | *                        |
| Zhang J (26) | China   | *                   | *                   | *                     | *                    | *                                 | *                        |
| Sadeghpour (22) | Iran | *                   | *                   | *                     | *                    | *                                 | *                        |
| Peng Z (23)  | China   | *                   | *                   | *                     | *                    | **                                | *                        |
| Zhao N (16)  | China   | *                   | *                   | *                     | *                    | **                                | *                        |
| Zhou T (17)  | China   | *                   | *                   | *                     | *                    | **                                | *                        |
| Su S (40)    | China   | *                   | *                   | *                     | *                    | **                                | *                        |
| Xue S (19)   | China   | *                   | *                   | *                     | *                    | **                                | *                        |
| Liu T (28)   | China   | NA                 | *                   | *                     | *                    | *                                 | *                        |

Note: NA: not available
TABLE 3 Subgroup analysis of the pooled HRs with BANCR expression in patients with cancer.
| Cancer type          | No. of studies | No. of patients | Pooled HR (95% CI) |
|---------------------|---------------|----------------|-------------------|
|                      |               |                | Fixed            | Random          |
| Overall survival    | 10            | 1151           | 1.56 (1.35-1.81) | 1.60 (1.19-2.15) |
| Digestive system    | 4             | 551            | 1.87 (1.40-2.50) | 1.94 (1.38-2.62) |
| GC                  | 1             | 184            | 1.51 (1.03-2.23) | 1.51 (1.03-2.23) |
| ESCC                | 1             | 142            | 2.24 (1.05-4.76) | 2.24 (1.05-4.76) |
| HCC                 | 1             | 109            | 4.24 (1.32-13.61)| 4.24 (1.32-13.61)|
| CRC                 | 1             | 116            | 2.24 (1.22-4.11) | 2.24 (1.22-4.11) |
| Non-digestive system| 6             | 600            | 1.47 (1.24-1.74) | 1.35 (0.86-2.05) |
| Respiratory system  | 1             | 113            | 0.5 (0.26-0.54)  | 0.5 (0.26-0.54)  |
| NSCLC               | 1             | 113            | 0.5 (0.26-0.54)  | 0.5 (0.26-0.54)  |
| Other system        | 5             | 487            | 1.59 (1.34-1.90) | 1.61 (1.25-2.07) |
| BC                  | 2             | 281            | 1.55 (1.29-1.87) | 1.55 (1.29-1.87) |
| Osteosarcoma        | 1             | 84             | 2.93 (1.12-7.67) | 2.93 (1.12-7.67) |
| Retinoblastoma      | 1             | 60             | 2.90 (1.05-8.03) | 2.90 (1.05-8.03) |
| ccRCC               | 1             | 62             | 0.77 (0.24-2.47) | 0.77 (0.24-2.47) |

| Analysis method      |               |                | Fixed            | Random          |
|---------------------|---------------|----------------|------------------|
| Univariate analysis | 3             | 238            | 0.95 (0.66-1.37) | 0.84 (0.41-1.73) |
| Multivariate analysis| 7            | 911            | 1.71 (1.47-2.02) | 1.79 (1.47-2.02) |

| HR estimation method|               |                | Fixed            | Random          |
|---------------------|---------------|----------------|------------------|
| Indirectly          | 4             | 349            | 1.07 (0.76-1.52) | 1.15 (0.52-2.23) |
| Directly            | 6             | 802            | 1.69 (1.44-1.99) | 1.69 (1.44-1.99) |

| number of patients   |               |                | Fixed            | Random          |
|---------------------|---------------|----------------|------------------|
| more than 100        | 6             | 880            | 1.56 (1.33-1.82) | 1.57 (1.07-2.19) |
| less than 100        | 4             | 271            | 1.62 (1.11-2.35) | 1.71 (1.01-2.85) |

| Quality scores       |               |                | Fixed            | Random          |
|----------------------|---------------|----------------|------------------|
| Score = 9            | 8             | 973            | 1.54 (1.32-1.80) | 1.61 (1.15-2.25) |
| Score < 9            | 2             | 178            | 1.78 (1.04-3.06) | 1.48 (0.53-3.42) |
| DFS                  | 3             | 320            | 1.29 (0.91-1.82) | 1.21 (0.33-4.31) |
| RFS                  | 1             | 216            | 1.53 (1.27-1.85) | 1.53 (1.27-1.85) |

Note: OS: overall survival; DFS: disease-free survival; PFS: progression-free survival;
Random: Random effects; Fixed: Fixed effects; directly: HR was extracted directly from the
primary articles; indirectly: HR was extracted indirectly from the primary articles; NSCLC: non-small cell lung cancer; HCC: hepatocellular carcinoma; CRC: colorectal cancer; BC: breast cancer; ccRCC: clear cell renal cell carcinoma; GC: gastric cancer; LNM: lymphatic node metastasis; DM: distant metastasis; HTS: high tumor stage(III,IV); NA: not available; ESCC: esophagus cancer; directly: HR was extracted directly from article; OS: overall survival; DFS: disease free survival; RFS: recurrence free survival.
### Table 4: Pool effects of Clinicopathologic characteristics in cancer patients with abnormal BANCR expression

| Clinicopathologic characteristics | No. of studies | No. of patients | Odds ratio (95% CI) Fixed | Random |
|-----------------------------------|----------------|----------------|----------------------------|--------|
| Age                               | 15             | 1469           | 0.88 (0.71,1.09)           | 0.88 (0.71-1.10) |
| gender                            | 13             | 1218           | 0.91 (0.72,1.16)           | 0.91 (0.70-1.18) |
| TNM (Ⅲ+IV vs. I+II)              | 14             | 1378           | 2.27 (1.82-2.84)           | 2.39 (1.26-4.53) |
| Digestive system                  | 7              | 724            | 3.69 (2.67-5.10)           | 4.01 (2.45-6.57) |
| Respiratory system                | 1              | 113            | 0.26 (0.11-0.60)           | 0.26 (0.11-0.61) |
| Female reproductive system        | 1              | 30             | 12.25 (12.7-118.36)        | 12.25 (12.7-118.37) |
| Other system malignancy           | 5              | 511            | 1.89 (1.30-2.73)           | 1.34 (0.38-4.79) |
| LNM (present vs. absent)          | 12             | 1226           | 2.09 (1.65-2.64)           | 2.03 (1.08-3.83) |
| Digestive system                  | 5              | 600            | 3.35 (2.38-4.72)           | 3.41 (2.32-5.00) |
| Respiratory system                | 1              | 113            | 0.28 (0.13-0.61)           | 0.28 (0.13-0.62) |
| Female reproductive system        | 1              | 30             | 9.33 (0.96-90.94)          | 9.33 (0.96-90.95) |
| Other system malignancy           | 5              | 483            | 1.92 (1.30-2.84)           | 1.30 (0.43-3.94) |
| Tumor size (big vs small)         | 14             | 1325           | 1.56 (1.25-1.95)           | 1.63 (1.09-2.46) |
| Digestive system                  | 6              | 571            | 1.45 (1.04-2.03)           | 1.45 (0.96-2.20) |
| Respiratory system                | 1              | 113            | 0.28 (0.13-0.60)           | 0.28 (0.13-0.60) |
| Other system malignancy           | 7              | 631            | 2.44 (1.74-3.41)           | 2.45 (1.74-3.45) |
| Histological grade                | 10             | 830            | 1.47 (1.10-1.97)           | 1.54 (1.00-2.38) |
| Digestive system                  | 6              | 646            | 1.28 (0.92-1.78)           | 1.25 (0.72-2.17) |
| Non-digestive system              | 4              | 174            | 2.45 (1.30-4.63)           | 2.43 (1.28-4.63) |
| DM (present vs. absent)           | 4              | 485            | 3.08 (1.92-4.96)           | 2.87 (1.58-5.21) |
| Invasion depth (T3+T4/T1+T2)      | 4              | 534            | 1.54 (1.06-2.24)           | 1.37 (0.66-2.83) |
| smoking (smoker vs. non-smoker)   | 3              | 330            | 1.01 (0.65, 1.56)          | 1.01 (0.56-1.82) |
| local tumors (multiple/total)     | 4              | 355            | 1.78 (1.12-2.83)           | 1.89 (0.95-3.74) |

Note: number; LNM: lymph node metastasis; Random: random-effect model; TNM: TNM stage; DM: distant metastasis; Fixed: Fixed effects model.

### Table 5: Regulation mechanism of BANCR involved in various cancers

| Cancer type                  | Expression | Micro-RNAs | Targets                  | Functions                              | References |
|------------------------------|------------|------------|--------------------------|----------------------------------------|------------|
| non-small cell lung cancer   | down-regulation | -          | MMP2; MMP9; N-cadherin; E-cadherin | epithelial-mesenchymal transition (EMT) | 19         |
| Tumor Type                     | Regulation | Factor(s)                      | Function(s)                                                                 | Gene(s) |
|-------------------------------|------------|--------------------------------|-----------------------------------------------------------------------------|---------|
| Hepatocellular carcinoma      | up-regulation | Vimentin; E-Cadherin         | migration, invasion                                                          | 17      |
|                               |            | Bcl-2; Bax; MEK; ERK; JNK; P38| cell invasion, proliferation and migration and apoptosis                    | 14      |
|                               |            |                                |                                                                             |         |
|                               | up-regulation |                                |                                                                             | 15      |
|                               |            |                                |                                                                             |         |
|                               | up-regulation |                                |                                                                             | 16      |
| Osteosarcoma                  | up-regulation | ZEB1                           | apoptosis                                                                    | 11      |
| Papillary thyroid cancer      | down-regulation | AKT; MEK; ERK; JNK; P38       | proliferation, migration and invasiveness                                   | 24      |
|                               |            | MAPK; PI3K-AKT                 | cell growth, cycle and apoptosis                                            | 25, 26  |
|                               | up-regulation | Raf; MEK; ERK                 | cell autophagy                                                              | 27      |
| Colorectal cancer             | up-regulation | Vimentin; E-Cadherin; MEK; ERK| epithelial-mesenchymal transition (EMT)                                     | 42      |
|                               |            | miR-203; CSE1L                 | proliferation and invasion; cell sensitivity to adriamycin (ADR)            | 43      |
| Bladder cancer                | down-regulation |                                | apoptosis and migration                                                      | 29      |
| Malignant Melanoma            | up-regulation | AKT; MEK; JNK                 | cell proliferation and migration                                             | 30      |
| Cancer Type                      | Regulation | Genes/Proteins                          | Functions                                      | Page |
|---------------------------------|------------|----------------------------------------|------------------------------------------------|------|
| Breast cancer                   | up-regulation | Bcl-2; Bax; PARP; Cleaved-caspase3     | cell proliferation and invasion                | 32   |
|                                 |            | Vimentin; E-Cadherin; MMP2; MMP9; MMP14 | cell migration and invasion                    | 31   |
| Clear cell renal cell carcinoma | up-regulation | caspase3; caspase9; CDK4; CDK6         | cell growth, cycle and apoptosis               | 18   |

**Note:** MMP2, The matrix metalloproteinases 2; MMP9, The matrix metalloproteinases 9; EMT, Epithelial-Mesenchymal Transition; ZEB1, zinc finger E-box binding homeobox 1; MAPK: Mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase; JNK: Jun N-terminal kinases; NA, Not Available.

**Supporting Information**

**Figure Supplement 1.** Forest plot about the relationship between BANCR expression and the number of local tumors (multiple/single)

**Figure Supplement 2.** Forest plot about the relationship between BANCR expression and smoking (smoker vs. non-smoker)

**Figure Supplement 3.** Forest plot about the relationship between BANCR expression and age (older vs. young)

**Figure Supplement 4.** Forest plot about the relationship between BANCR expression and gender (female vs. male)

**Figures**
Figure 1

The flow diagram of the eligible studies.
Figure 2

Forest plot showed the relationship between BANCR expression and overall survival (OS), disease free survival (DFS) and recurrence free survival (RFS) in cancers.
Figure 3

Forest plot about the relationship between BANCR expression and TNM stage
### Figure 4

Forest plot about the relationship between BANCR expression and Lymph node metastasis (LNM).
Figure 5

Forest plot about the relationship between BANCR expression and (A). Distant Metastasis (DM). (B). Depth of Invasion and (C). Histologic Grade
### 11.1.1 Digestive system malignancy

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total Weight | M-H. Random 95% CI | M-H. Random 95% CI |
|-------------------|---------------------|----------------|--------------|--------------|---------------------|---------------------|
| Guo QH 2014       | 13                  | 18             | 22           | 42           | 5.7%                | 2.36 [0.71, 7.82]   |
| Liu ZH 2016       | 39                  | 71             | 36           | 71           | 8.7%                | 1.18 [0.61, 2.29]   |
| Shen XG 2017      | 32                  | 53             | 29           | 53           | 8.0%                | 1.26 [0.58, 2.73]   |
| Wang LH 2016      | 20                  | 43             | 30           | 65           | 8.0%                | 1.01 [0.47, 2.20]   |
| Zhao NN 2018      | 10                  | 23             | 11           | 23           | 5.9%                | 0.84 [0.26, 2.68]   |
| Zhou T 2016       | 29                  | 54             | 14           | 55           | 7.8%                | 3.40 [1.51, 7.63]   |
| **Subtotal (95% CI)** | **262**             | **309**        | **44.2%**    | **309**      | **1.45 [0.96, 2.20]** |
| Total events      | 143                 | 142            |              |              |                     |                     |

Heterogeneity: Tau² = 0.08; Chi² = 7.06, df = 5 (P = 0.22); I² = 29%
Test for overall effect: Z = 1.77 (P = 0.08)

### 11.1.2 Respiratory system malignancy

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total Weight | M-H. Random 95% CI | M-H. Random 95% CI |
|-------------------|---------------------|----------------|--------------|--------------|---------------------|---------------------|
| Sun M 2014        | 18                  | 53             | 39           | 60           | 8.0%                | 0.28 [0.13, 0.60]   |
| **Subtotal (95% CI)** | **53**             | **60**         |              |              | **0.28 [0.13, 0.60]** |
| Total events      | 18                  | 39             |              |              |                     |                     |

Heterogeneity: Not applicable
Test for overall effect: Z = 3.24 (P = 0.001)

### 11.1.4 Other system malignancy

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total Weight | M-H. Random 95% CI | M-H. Random 95% CI |
|-------------------|---------------------|----------------|--------------|--------------|---------------------|---------------------|
| He AB 2016        | 11                  | 19             | 13           | 35           | 6.0%                | 2.33 [0.74, 7.28]   |
| Jiang J 2018      | 93                  | 125            | 52           | 91           | 9.2%                | 2.18 [1.22, 3.88]   |
| Liao T 2017       | 18                  | 29             | 25           | 63           | 7.3%                | 2.49 [1.01, 6.14]   |
| Lou KX 2018       | 22                  | 34             | 11           | 31           | 6.6%                | 3.33 [1.20, 9.22]   |
| Peng ZQ 2015      | 27                  | 42             | 14           | 42           | 7.3%                | 3.60 [1.46, 8.85]   |
| Su SZ 2015        | 23                  | 30             | 14           | 30           | 6.1%                | 3.76 [1.24, 11.38]  |
| Zhang JJ 2018     | 4                   | 17             | 13           | 43           | 5.3%                | 0.71 [0.19, 2.59]   |
| **Subtotal (95% CI)** | **296**             | **335**        | **47.8%**    | **335**      | **2.45 [1.74, 3.45]** |
| Total events      | 198                 | 142            |              |              |                     |                     |

Heterogeneity: Tau² = 0.00; Chi² = 5.30, df = 6 (P = 0.51); I² = 0%
Test for overall effect: Z = 5.16 (P < 0.00001)

Total (95% CI) | 611 | 704 | 100.0% | 1.63 [1.09, 2.46] |
Total events | 359 | 323 |                     |                     |

Heterogeneity: Tau² = 0.38; Chi² = 38.31, df = 13 (P = 0.0003); I² = 66%
Test for overall effect: Z = 2.36 (P = 0.02)
Test for subgroups differences: Chi² = 25.78, df = 2 (P < 0.000001). I² = 92.2%

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**Figure 6**

Forest plot about the relationship between BANCr expression and tumor size.
Sensitivity analysis for BANCR expression with overall survival (OS) in various cancers. HR: hazard ratio, CI: confidence interval.
Funnel plot for the correlation between BANCR expression level and different prognosis indicators. (A) Overall survive. (B) TNM stage. (C) Lymph node metastasis. (D) Distant metastasis. (E) Depth of invasion. (F) Tumor size.

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.
Figure S3.tif
