Prognostic significance of 8-hydroxy-2′-deoxyguanosine in solid tumors: a meta-analysis

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Abstract

Background: High level of reactive oxygen species (ROS) has been detected in almost all cancers, which make it become one of the best-characterized phenotypes in cancers. Though ROS plays an important role in tumors, the degree of oxidative stress can be better evaluated by assessing stable metabolites of oxidative reactions because of its high instability. 8-hydroxy-2′-deoxyguanosine (8-OHdG), a product of oxidative damage to 2′-deoxyguanosine, is known as a useful marker for assessing oxidative DNA damage and has been a feature of carcinogenesis in several researches. But the exact prognostic value of 8-OHdG expression in patients with cancer is still unclear.

Methods: A comprehensive search was performed in PubMed, Web of Science, EMBASE. Eligible studies were included based on defined exclusion and inclusion criteria to perform a meta-analysis. STATA 14.0 was used to estimate pooled hazard ratios (HRs) with 95% confidence interval (95% CI), the heterogeneity among studies and publication bias to judge the prognostic value.

Results: A total of 2121 patients from 21 eligible studies were included in the meta-analysis. A significant association was found between elevated 8-OHdG expression and poor OS (overall survival) in cancer patients (pooled HR 1.921, 95% CI: 1.437–2.570); In the subgroup analysis, race of sample, cancer types, detection method of 8-OHdG, sample classification, detection location of 8-OHdG and paper quality (score more or less than 7) did not alter the association between 8-OHdG expression and cancer prognosis. Furthermore, 8-OHdG expression was an independent prognostic marker for overall survival in patients with cancer (pooled HR 2.110, 95% CI: 1.482–3.005) using Cox multivariate analyses.

Conclusions: This meta-analysis found that highly expressed 8-OHdG in tumor tissues may be a predictor of prognosis in most solid tumors. However, especially in breast cancer, low 8-OHdG expression is associated with poor prognosis, which is partly because of the increased antioxidant mechanisms in breast cancer tissues. This study demonstrates for the first time that 8-OHdG expression is associated with the prognosis of cancer patients. In the future, whether the expression level of 8-OHdG can be used as a biomarker for the prognosis of all human cancers requires more research.

Keywords: 8-OHdG, Meta-analysis, Prognosis, Solid tumor, Reactive oxygen species, DNA oxidative damage
Background
Tumor cells constantly suffer various endogenous and environmental attacks, which make high level of reactive oxygen species (ROS) be detected in almost all cancers and become one of the best-characterized phenotypes [1–3]. The role of ROS in cancer is a “doubled edged sword”. ROS can serve as a carcinogenic factor through promoting tumorigenesis, development and spread of cancers by activating or regulating signaling pathways that affect tumor cell survival, proliferation and metastasis [4–6]. However, high levels of ROS can also play a role in tumor suppression by inhibiting cell proliferation and inducing cell death [7–9]. Many cancer treatments, such as radiotherapy and certain chemotherapy agents, act through oxidative stress pathways via the production of ROS to suppress tumor growth and progression [10]. In order to prevent cell death, cancer cells can scavenge reactive oxygen species to adapt high levels of ROS and activate pro-tumorigenic signaling pathways, by upregulating antioxidant pathways and regulatory factors [11–13].

Though ROS plays an important role in tumors, the degree of oxidative stress can be better evaluated by assessing stable metabolites of oxidative reactions because of its high instability. ROS can cause oxidative damage to double-stranded DNA directly, or to free bases in the cellular and mitochondrial deoxynucleoside triphosphate (dNTP) pool [14]. Among all the nucleobases, guanine is the most susceptible to oxidation by ROS [15]. Oxidative damage to 2′-deoxyguanosine produces 8-hydroxy-2′-deoxyguanosine (8-OHdG). The formation of 8-OHdG on DNA can cause G:C–T:A mispairing mutations, which are considered to have a close relationship with the development and progression of tumors, cell ageing and some degenerative diseases [16].

There is an increasing body of evidence indicating that 8-OHdG is a useful marker for assessing oxidative DNA damage and has been a feature of carcinogenesis in several researches [17, 18]. High levels of 8-OHdG in tumors, blood samples or urine have been found in various cancers and implicated as a promising marker for predicting the prognosis of cancers [19–40]. However, the association of oxidative damage to DNA with tumors still needs to be more extensively investigated and most studies reported so far are limited in discrete outcome and sample size. For these reasons we performed a quantitative meta-analysis and systematic review to gain better insight into the prognostic value of 8-OHdG expression in patients with cancer.

Methods
Search strategy
This analysis was conducted following the meta-analyses and systematic reviews guidelines for prognosis-related tumor marker researches [41, 42]. An electronic search of PubMed, Web of Science, EMBASE was performed independently by two authors (XQ and DS) prior to May 15, 2018. Search terms were used in all possible combinations as following: 7, 8-dihydro-8-oxodeoxyguanosine, 8-hydroxy-2′-deoxyguanosine, 8-hydroxy-2′-deoxyguanosine, 8-OHdG, 8OHG, 8-OH-dG, 8-OHG, 8-oxo-G, 8-oxo-dG, 8-hydroxydeoxyguanosine, 8-oxo-guanine, 8-hydroxyguanine, 8-hydroxyguanosine, 8-oxo-2-deoxy guanosine, 8-oxo-7,8-dihydro-2′-deoxyguanosine, 8-hydroxy-2-deoxyguanosine, 8-oxo-7,8-dihydro-2′-deoxyguanosine, tumor, cancer, sarcoma, carcinoma, neoplasm, malignancy, prognosis, mortality of metastasis, progression, development, outcome, survival, recurrence, clinical significance. Conflicts were solved through group discussion.

Inclusion and exclusion criteria
Studies included in the present meta-analysis were independently reviewed by two investigators (XQ and DS) and should meet the following criteria: (1) The prognostic data of 8-OHdG in any type of human solid tumors needed to be presented; (2) All cancer patients were diagnosed according to the gold standard for diagnosis, based on histopathological examinations; (3) 8-OHdG levels in tumors, blood samples or urine were estimated in each study; (4) The patients were divided into two groups according to the levels of 8-OHdG; (5) Sufficient data should be provided to obtain hazard ratios (HR) for survival rates and their 95% confidence intervals (95%CI). Studies were excluded from the present meta-analysis if one of the following criteria was met: (1) Case reports, reviews, meta-analysis, letters, editorials, comments, expert opinions or any other reviews that didn’t contain raw data; (2) Full text could not be obtained; (3) Researches on non-English writing; (4) Repetitive publications; (5) No survival data or data insufficient to be extracted and analyzed; (6) Survival data was acquired based on animal studies and no follow-up of patients. Detailed inclusion and exclusion criteria of each study are presented in Additional file 1: Table S1.

Data extraction and quality assessment
Data was extracted independently by the two researchers (XQ and DS), and final consensus was reached through discussion. Data were retrieved from each study including: author; year of publication; country of the population enrolled; ethnicity; tumor stage; sample size; study design; follow-up data; survival data; survival analysis methodology; expression levels, location and laboratory methods of 8-OHdG; cut-off values; HR values and their 95% confidence intervals. Quality assessment of cohort studies in this meta-analysis was performed using the Newcastle-Ottawa scale (NOS) as recommended by the Cochrane Non-Randomized Studies Methods Working Group. Studies with score ≥ 7 were considered high quality according to the NOS. Detailed NOS scores of all included studies were shown in Table 1.
| Author            | Region    | Cancer Type          | Sample size | Tumor stage | Follow-up (month) | Outcome measure | Expression associates with poor prognosis | Assay      | Cut-off value | Location of 8-oxo-dG | Survival analysis | NOS score | Method*            |
|-------------------|-----------|----------------------|-------------|-------------|-------------------|----------------|------------------------------------------|------------|---------------|---------------------|-------------------|-----------|-------------------|
| Li et al. 2012    | China     | Hepatocellular carcinoma | 103         | I-IV        | 36                | OS             | High                                     | IHC        | percentage of positive tumor cells     | Nuclei              | multivariate       | 6       | 1                 |
| Karihtala et al. 2009 | Finland | Ovarian cancer       | 68          | I-IV        | 41                | OS             | High                                     | IHC        | median                                   | Nuclei              | multivariate       | 6       | 1                 |
| Ma-on et al. 2017 | Thailand  | Hepatocellular carcinoma | 53          | NA          | 80                | OS             | High                                     | IHC        | IHC score 12                            | Nuclei              | NA                 | 5       | 2                 |
| Xu et al. 2013    | China     | Ovarian cancer       | 72          | I-IV        | Over 120          | OS, PFS        | High                                     | ELISA      | Fold change                             | NA                  | univariate, multivariate | 8       | 1,2               |
| He et al. 2014    | China     | Esophageal cancer    | 144         | I-IV        | 60                | OS             | High                                     | IHC        | percentage of positive tumor cells      | Nuclei              | multivariate       | 8       | 1,2               |
| Shen et al. 2007  | USA       | Nonsmall-Cell Lung cancer | 99          | I-IV        | 82                | OS             | High                                     | ELISA      | median                                   | NA                  | multivariate       | 7       | 1                 |
| Soini et al. 2011 | Finland   | Bladder carcinoma    | 252         | I-IV        | 300               | OS             | High                                     | IHC        | positive > 5%                            | Nuclei              | NA                 | 6       | 2                 |
| Dziaman et al. 2014 | Poland | Colorectal cancer | 79          | I-IV        | 100               | OS             | High                                     | LCEC       | median                                   | NA                  | NA                 | 6       | 2                 |
| Jakovecic et al. 2015 | Croatia | Breast cancer       | 145         | I-IV        | 112               | OS, DFS        | Low                                      | IHC        | percentage of positive tumor cells      | Nuclei              | univariate, multivariate | 6       | 1                 |
| Pylväs et al. 2011 | Finland | Ovarian cancer       | 84          | I-IV        | Over 125          | OS             | High                                     | IHC, ELISA | percentage of positive tumor cells for IHC, 140 pg/mL for ELISA | NA                  | univariate, multivariate | 6       | 2                 |
| Aman et al. 2017  | Japan     | Ovarian cancer       | 95          | I-IV        | 208               | OS             | High                                     | IHC        | percentage of positive tumor cells      | Nuclei              | univariate         | 6       | 1                 |
| Matosevic et al. 2015 | Croatia | Colorectal cancer    | 138         | I-IV        | 169               | OS             | High                                     | IHC        | percentage of positive tumor cells      | Cytoplasm           | multivariate       | 7       | 1                 |
| Matsumoto et al. 2003 | Japan | Hepatocellular carcinoma | 73          | NA          | Over 60           | CSS, RFS      | High                                     | IHC        | percentage of positive tumor cells      | NA                  | univariate, multivariate | 8       | 1,2               |
| Hintsala et al. 2016 | Finland | Melanoma             | 121         | NA          | Over 150          | CSS            | Low                                      | IHC        | NA                                       | Nuclei              | multivariate       | 6       | 1                 |
| Murtas et al. 2010 | Italy     | Melanoma             | 46          | III         | 60                | OS             | High                                     | IHC        | percentage of positive tumor cells      | Nuclei              | univariate         | 8       | 1                 |
| Sheridan et al. 2009 | Ireland | Colorectal cancer    | 113         | I-IV        | 80                | OS             | High                                     | IHC        | NA                                       | Nuclei              | multivariate       | 6       | 1                 |
| Karihtala et al. 2011 | Finland | Breast cancer       | 79          | I-III       | 60                | CSS            | Low                                      | IHC        | NA                                       | Nuclei              | univariate         | 6       | 2                 |
| Maki et al. 2007  | USA       | Hepatocellular carcinoma | 30          | III         | NA                | DFS            | High                                     | IHC        | percentage of positive tumor cells      | NA                  | multivariate       | 6       | 1                 |
| Pylväs-Eerola et al. 2015 | Finland | Ovarian cancer       | 105         | I-IV        | NA                | OS, DFS        | High                                     | ELISA      | median                                   | NA                  | multivariate       | 6       | 1,2               |
| Miyake et al. 2004 | Japan     | Renal cell carcinoma | 72          | I-IV        | NA                | CSS            | High                                     | ELISA      | mean plus one standard deviation        | NA                  | multivariate       | 6       | 1                 |
| Author               | Region     | Cancer Type   | Sample size | Tumor stage | Follow-up (month) | Outcome measure | Expression associates with poor prognosis | Assay | Cut-off value | Location of 8-oxo-dG | Survival analysis | NOS score | Method* |
|---------------------|------------|---------------|-------------|-------------|-------------------|----------------|-------------------------------------------|-------|--------------|----------------------|------------------|-----------|---------|
| Sova et al. 2010    | Finland    | Breast cancer | 150         | I-IV        | NA                | CSS            | Low                                       | IHC    | percentage of positive tumor cells       | Nuclei             | multivariate      | 6       | 1       |

OS overall survival, DFS disease free survival, PFS progression free survival, RFS recurrence free survival, CSS cancer specific survival, NOS Newcastle-Ottawa Scale, IHC Immunohistochemistry, ELISA Enzyme-linked immunosorbent assay, LCEC Liquid chromatography electrochemistry, NA not available

*1 denoted as obtaining HRs directly from publications; 2 denoted as HRs were extracted and calculated from Kaplan-Meier curves
Statistical analysis

The meta-analysis was performed as previously described [43]. In the present study, statistical analysis and graphical representation were performed using Stata version 14.0 (Stata Corporation, College Station, TX, USA). Pooled HRs and ORs with 95% CIs were used to evaluate the association between 8-OHdG expression and prognosis. HRs or ORs with 95% CIs can be directly obtained from most included studies or estimated from the existing data using methods as previously described [41]. An HR > 1 indicates a worse outcome of patient with high 8-OHdG expression, while an HR < 1 implied a worse survival for patients with decreased 8-OHdG expression. The test for heterogeneity of combined HRs was carried out using a $\chi^2$ based Cochran Q test and Higgins I$^2$ statistic. I$^2$ values > 50% indicated heterogeneity among studies. If there existed heterogeneity, a random-effect model, subgroup analysis and meta regression by factors contributing to heterogeneity would be carried out. Influence analyses was performed to examine the effect of each study on the overall pooled results. The presence of publication bias was evaluated by using funnel plots, Begg’s test and Egger’s test. P values < 0.05 were considered statistically significant.

Results

Included studies and characteristics

Based on our searching strategy, a total of 3537 articles were identified from PubMed ($n = 915$), Web of Science ($n = 1319$) and EMBASE ($n = 1303$). After removing duplicates, 1665 articles were left. Furthermore, 1607 of the remaining articles were excluded according to the titles and abstracts. Finally, a total of 21 relevant articles were included in this meta-analysis after a more careful full-text reading. The detailed screening process is shown in Fig. 1.

Among the 21 studies, a total of 2121 patients were included, with mean sample size of 101 patients (range 30 to 252). The period of these studies ranged from 2003 to 2017. The regions represented in the studies include various countries around Europe, Asia and America, of which the race contains both Caucasoid and Mongoloid. Eight different types of cancer were evaluated. Most studies analyzed the expression level of 8-OHdG by IHC or ELISA, while there was one study unitizing liquid chromatography electrochemistry. Overall survival (OS), cancer-specific survival (CSS), recurrence-free survival (RFS), disease-free survival (DFS) and progression-free survival (PFS) were estimated as survival outcomes in the studies. RFS, DFS and PFS were merged into the event-free survival (EFS) group for analysis. Cox multivariable analyses were performed in 17 studies. Further detailed characteristics of each study are presented in Table 1.

Overall survival (OS) based on different 8-OHdG expression levels was reported in 8 types of solid tumors from 15 of the 21 included studies with a total of 1596 patients. Elevated 8-OHdG was significantly associated with poor OS in these patients (pooled HR 1.921, 95% CI: 1.437 – 2.570) (Fig. 2a), while significant heterogeneity was found in these studies ($\chi^2 = 53.52$, df = 16, $p < 0.0001$; I$^2 = 70.1\%$). Since obvious heterogeneity was observed, subgroups analysis was performed by factors of the race of sample, cancer types, detection method of 8-OHdG, detection location of 8-OHdG, sample classification and research quality (Fig. 3). Detailed results of subgroup analysis were demonstrated in Table 2. Despite the subgroup of hepatocellular carcinoma (Cancer Types) and the subgroup of cytoplasm (Detection location of 8-OHdG), the significant association between 8-OHdG expression and poor OS could

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Fig. 1 The flow diagram of the meta analysis
Fig. 2 Meta-analysis of the pooled HRs of OS with elevated 8-OHdG expression in cancer patients. 

**A** All studies included. 

| Study ID          | HR (95% CI)   | Weight |
|-------------------|---------------|--------|
| Li et al. (2012)  | 6.58 (2.19, 19.60) | 4.06   |
| Karhila et al. (2009) | 2.69 (1.35, 5.35) | 6.31   |
| Ma–on et al. (2017) | 1.49 (1.03, 2.16) | 8.92   |
| Xu et al. (2013)  | 1.18 (1.01, 2.07) | 9.01   |
| He et al. (2014)  | 3.40 (2.05, 5.61) | 7.81   |
| Shen et al. (2006) | 3.33 (1.59, 6.99) | 5.93   |
| Sonni et al. (2011) | 3.13 (1.30, 7.56) | 5.01   |
| Dzieman et al. (2011) | 2.51 (1.02, 6.18) | 4.88   |
| Jakovcevic et al. (2015) | 0.10 (0.02, 0.68) | 2.12   |
| Pylyvis et al. (2011) | 2.53 (1.03, 6.20) | 5.01   |
| *Pylyvis et al. (2011) | 3.47 (1.07, 11.22) | 3.74   |
| Aman et al. (2015) | 1.02 (0.57, 1.86) | 6.85   |
| Matosevic et al. (2015) | 0.76 (0.45, 1.27) | 7.38   |
| Murta et al. (2009) | 1.47 (1.09, 2.27) | 8.32   |
| Sheridan et al. (2009) | 1.70 (0.80, 3.40) | 6.02   |
| *Sheridan et al. (2009) | 2.70 (1.30, 5.50) | 6.03   |
| Pylyvis–Eerola et al. (2015) | 3.58 (1.22, 10.50) | 4.14   |
| Overall (I²-squared = 70.1%, p = 0.000) | 1.92 (1.44, 2.57) | 100.00 |

**B** Study of Jakovcevic et al. excluded.

| Study ID          | HR (95% CI)   | Weight |
|-------------------|---------------|--------|
| Li et al. (2012)  | 6.58 (2.19, 19.60) | 3.87   |
| Karhila et al. (2009) | 2.69 (1.35, 5.35) | 6.31   |
| Ma–on et al. (2017) | 1.49 (1.03, 2.16) | 8.92   |
| Xu et al. (2013)  | 1.18 (1.01, 2.07) | 9.01   |
| He et al. (2014)  | 3.40 (2.05, 5.61) | 7.81   |
| Shen et al. (2006) | 3.33 (1.59, 6.99) | 5.93   |
| Sonni et al. (2011) | 3.13 (1.30, 7.56) | 5.01   |
| Dzieman et al. (2011) | 2.51 (1.03, 6.18) | 4.88   |
| Pylyvis et al. (2011) | 2.53 (1.03, 6.20) | 4.90   |
| *Pylyvis et al. (2011) | 3.47 (1.07, 11.22) | 3.54   |
| Aman et al. (2015) | 1.02 (0.57, 1.86) | 7.06   |
| Matosevic et al. (2015) | 0.76 (0.45, 1.27) | 7.73   |
| Murta et al. (2009) | 1.47 (1.09, 2.27) | 8.95   |
| Sheridan et al. (2009) | 1.70 (0.80, 3.40) | 6.05   |
| *Sheridan et al. (2009) | 2.70 (1.30, 5.50) | 6.07   |
| Pylyvis–Eerola et al. (2015) | 3.58 (1.22, 10.50) | 3.96   |
| Overall (I²-squared = 65.6%, p = 0.000) | 2.02 (1.54, 2.64) | 100.00 |
be observed in each subgroup. We further performed meta-regression with the covariates including above factors to explore the source of heterogeneity. From the result we found that p<0.05 was only observed in the subgroup of breast cancer (Cancer types) covariate, which implied that the subgroup of breast cancer may be the major source of heterogeneity. The study of Jakovcevic et al. enrolled patients with breast cancer and drew a conclusion that negative 8-OHdG expression was a poor prognostic biomarker, which was contrary to the other researches. It could be a consequence caused by cancer specificity. We discussed this point in the discussion part below.

Base on the above result of meta-regression, we excluded the study of Jakovcevic et al. and still found significant association between elevated 8-OHdG expression and poor OS in cancer patients (pooled HR 2.022, 95% CI: 1.540–2.641) with reduced heterogeneity (I² = 65.5%) (Fig. 2b). Furthermore, as shown in Fig. 4, influence analysis was carried out for purpose of ensuring the stability of the result. No obvious change of the pooled HR and 95% CIs could be observed after excluding any study from the whole studies. In aspect of the publication bias, Begg’s test and Egger’s linear regression test were performed. The Begg’s tests proved that there was no evidence of publication bias (p = 0.053) while the Egger’s test showed there was significant publication bias (p = 0.007) (Fig. 5a and Fig. 5b). Thus “Trim and fill” analysis was conducted and the result estimated that 8 studies evaluating the association between expression of 8-OHdG and overall survival of cancer patients were remaining unpublished. The result of filled meta-analysis was pooled HR 1.545, 95% CI: 1.179–2.026, which exhibited that the significant association between elevated 8-OHdG expression and poor OS in cancer patients maintained unchanged (Fig. 6a).

Among the 21 included studies, four studies reported event-free survival (EFS) in 489 patients. A close relationship was observed between elevated 8-OHdG expression and EFS (pooled HR 1.612, 95% CI: 1.121–2.310, I² = 78.7%) (Fig. 7a). However, due to the limited number of included studies, appraisal of publication bias was not performed.

There were 5 studies reported the association between 8-OHdG expression and cancer-specific survival (CSS), corresponding to hepatocellular carcinoma, melanoma, renal cell carcinoma and breast cancer, including a total of 495 patients. After summarizing the results, we found
there was no significant association between 8-OHdG expression and CSS (pooled HR 0.793, 95%CI: 0.344–1.828, I² = 81.0%) (Fig. 7b). We need to point out that this result is contrasted to the other results above. A total of 11 studies including 1243 patients used Cox multivariate analysis to assess whether 8-OHdG expression could be an independent prognostic factor for OS of cancer patients. Elevated 8-OHdG as an independent factor for poor prognosis was found alone in nine of them. The results of Cox multivariate analyses in these 11 studies showed that 8-OHdG expression was an independent prognostic factor for overall survival (pooled HR 2.110, 95% CI:1.482–3.005), and heterogeneity was still observed among studies (Tau² = 0.2339; χ² = 35.73, df = 10, p < 0.0001; I² = 72.0%). (Fig. 8).

As for the publication bias, the Begg’s test (p = 0.276) and Egger’s test (p = 0.031) showed opposite conclusion. (Fig. 5c and Fig. 5d) Thus we applied the “Trim and fill” analysis to confirm our result. There were 3 studies evaluating whether 8-OHdG expression could be an independent prognostic factor for OS remaining unpublished. The result of filled meta-analysis was pooled HR 1.793, 95% CI: 1.242–2.436, which confirmed that elevated 8-OHdG could be an independent factor for poor prognosis of overall survival after the “Trim and fill” analysis. (Fig. 6b).

**Discussion**

Cancer is a major public health problem worldwide and is the second leading cause of death in the United States [44]. The 5-year survival of many cancers is still quite low. For most types of cancers, the pathological staging is a gold standard to predict its prognosis. However, patients with the same tumor stage often exhibit quite different clinical outcomes, which suggests that this conventional method is unable to precisely predict the prognosis of cancer patients. Therefore, new potential

**Table 2** Subgroup analysis of pooled HR of OS by various factors with elevated 8-OHdG expression

| Subgroup analysis                   | No. of studies | No. of patients | Pooled HR (95%CI) | Meta regression (p -value) | Heterogeneity |
|-------------------------------------|----------------|-----------------|-------------------|-----------------------------|---------------|
|                                     |                |                 |                   |                             |               |
| **Race**                            |                |                 |                   |                             |               |
| Caucasian                           | 12             | 1129            | 1.962 [1.341–2.870] | 0.907                       | 66.6%         | 0.001         |
| Mongoloid                           | 5              | 467             | 1.862 [1.117–3.104] | –                           | 80.2%         | < 0.001       |
| **Cancer types**                    |                |                 |                   |                             |               |
| Hepatocellular carcinoma            | 2              | 156             | 2.853 [0.673–12.089] | 0.727                       | 84.2%         | 0.012         |
| Ovarian carcinoma                   | 6              | 424             | 1.867 [1.190–2.930] | 0.464                       | 58.0%         | 0.036         |
| Colorectal cancer                   | 4              | 330             | 1.637 [0.850–3.153] | 0.352                       | 71.5%         | 0.014         |
| Esophageal cancer                   | 1              | 144             | 3.400 [2.055–5.624] | 0.982                       | –             | –             |
| Nonsmall-Cell Lung cancer           | 1              | 99              | 3.330 [1.588–6.982] | –                           | –             | –             |
| Melanoma                            | 1              | 46              | 1.470 [1.019–2.121] | 0.367                       | –             | –             |
| Breast cancer                       | 1              | 145             | 0.100 [0.017–0.583] | 0.019                       | –             | –             |
| Bladder cancer                      | 1              | 252             | 3.130 [1.298–7.548] | 0.950                       | –             | –             |
| **Detection method of 8-OHdG**      |                |                 |                   |                             |               |
| IHC                                 | 12             | 1157            | 1.787 [1.246–2.563] | 0.646                       | 74.1%         | < 0.001       |
| ELISA                               | 4              | 360             | 2.386 [1.167–4.881] | 0.947                       | 71.0%         | 0.016         |
| LCEC                                | 1              | 79              | 2.510 [1.018–6.187] | –                           | –             | –             |
| **Sample classification**           |                |                 |                   |                             |               |
| Tissue                              | 14             | 1412            | 1.792 [1.307–2.458] | –                           | 73.6%         | < 0.001       |
| Plasma or urine                     | 3              | 268             | 3.042 [1.676–5.519] | 0.006                       | 0.0%          | 0.856         |
| **Detection location of 8-OHdG**    |                |                 |                   |                             |               |
| Nuclei                              | 10             | 1019            | 1.927 [1.321–2.810] | 0.596                       | 71.5%         | < 0.001       |
| Cytoplasm                           | 1              | 138             | 0.759 [0.454–1.268] | 0.118                       | –             | –             |
| Not mentioned                       | 6              | 439             | 2.345 [1.429–3.848] | –                           | 57.6%         | 0.038         |
| **research quality**                |                |                 |                   |                             |               |
| NOS score ≥ 7                       | 5              | 499             | 1.658 [1.002–2.743] | 0.526                       | 82.7%         | < 0.001       |
| NOS score < 7                       | 12             | 1097            | 2.104 [1.456–3.040] | –                           | 60.6%         | 0.003         |
Fig. 4 Influence analysis of the included studies for OS. No obvious change of the pooled HRs and 95% confidence intervals was observed after excluding any included study.

Fig. 5 Plot of publication bias analysis. a Begg’s test and (b) Egger’s test for analysis of the association between 8-OHdG expression and OS. c Begg’s test and (d) Egger’s test graph for analysis of the independent role of 8-OHdG expression for OS.
biomarkers for prognosis and diagnosis are urgently needed to improve the prognosis of cancer patients.

From the important role of oxidative stress in cancer treatment, progression and metastasis, we infer that it may also be particularly important in cancer prognosis. However, ROS is so instable that it's not easy to be precisely detected and the degree of oxidative stress can be better assessed by detecting its stable metabolites. 8-OHdG, a typical biomarker of oxidative stress, can originate from 8-oxo-dGTP in the nucleotide pool, or by direct oxidation of guanine base in DNA. MTH1 (MutT Homolog 1) with 8-oxo-dGTP hydrolyzing activity, OGG1 (8-oxoguanine DNA glycosylase) with 8-OHdG DNA glycosylase activity and MUTYH (MutY homolog) with adenine DNA glycosylase activity, all play roles in minimizing 8-oxoG accumulation in cellular DNAs [45]. Thus, the levels of 8-OHdG measured in tumor tissues may be representative of the DNA oxidative damage-repair ability of the cell and an intermediate biomarker of the extent of accumulated intratumoral oxidative DNA damage [26]. High levels of 8-OHdG in tumors, blood samples or urine have been found in various cancers and implicated as a promising marker for predicting the prognosis of cancers [19–40]. Nevertheless, the exact relationship between DNA oxidative damages and tumors is still unknown. To the best of our knowledge, this is the first meta-analysis performed to obtain a comprehensive insight into the prognostic value of 8-OHdG in solid tumors.

In our meta-analysis, we examined 21 independent studies enrolling a total of 2121 cancer patients. After systematic review of these studies, we discovered that 8-OHdG was highly expressed in various types of tumors except a few specific tumors such as breast cancer. By
combining the survival data obtained from these studies, we found that high 8-OHdG expression was a biomarker for poor prognosis for overall survival in most solid cancer patients.

Because obvious heterogeneity was observed among studies, we performed a subgroup analysis, meta regression analysis and influence analysis to examine the source of heterogeneity and the stability of the pooled
result. In subgroup analysis, we still found that high 8-OHdG expression was associated with poor overall survival in most subgroups. The factors such as race of sample, cancer types, detection method of 8-OHdG, detection location of 8-OHdG, sample classification and research quality would not influence the pooled result. Meta regression analysis found that the subgroup of breast cancer would be the major source of heterogeneity. After excluding the corresponding study, we could still find significant association between elevated 8-OHdG expression and poor OS in cancer patients with reduced heterogeneity. In addition, influence analysis was performed and confirmed the stability of our pooled result. Furthermore, through summarizing the data from studies using Cox multivariate analysis, we found that 8-OHdG could be an independent prognostic risk factor for overall survival. Besides, by collecting the survival data of cancer recurrence or progression, we found that elevated 8-OHdG expression was associated with event-free survival of cancer patients. However, the number of these studies was relatively limited, which made the conclusion not so convincing as above. It should be noted that there were three studies reporting the association between 8-OHdG expression and prognosis of breast cancer patients. One was analyzed with overall survival data and the other two were cancer specific survival data. All of the three studies reported that negative or weak 8-OHdG expression was associated with poor survival of breast cancer patients. These results were contrasted with the other studies and the pooled result.

There are several potential mechanisms behind the different association of 8-OHdG levels and tumor prognosis in breast cancer. To deal with the threats posed by high ROS production, tumor cells evolve lots of antioxidant mechanisms, which would prevent ROS from interacting with DNA or directly eliminate 8-OHdG, thus decreasing the expression level of 8-OHdG in tumor tissues. For example, transcription factor NF-E2-related factor 2 (Nrf2), the main inductor of multiple antioxidant enzymes, has been revealed to be highly expressed in various cancer cells [33, 46–49]. Nrf2 up-regulation and consequent antioxidant enzyme induction may lead to low expression level of 8-OHdG in tumor tissues. For example, transcription factor NF-E2-related factor 2 (Nrf2), the main inductor of multiple antioxidant enzymes, has been revealed to be highly expressed in various cancer cells [33, 46–49]. Nrf2 up-regulation and consequent antioxidant enzyme induction may lead to low expression level of 8-OHdG in tumor tissues. For example, transcription factor NF-E2-related factor 2 (Nrf2), the main inductor of multiple antioxidant enzymes, has been revealed to be highly expressed in various cancer cells [33, 46–49]. Nrf2 up-regulation and consequent antioxidant enzyme induction may lead to low expression level of 8-OHdG in tumor tissues. For example, transcription factor NF-E2-related factor 2 (Nrf2), the main inductor of multiple antioxidant enzymes, has been revealed to be highly expressed in various cancer cells [33, 46–49]. Nrf2 up-regulation and consequent antioxidant enzyme induction may lead to low expression level of 8-OHdG in tumor tissues.
expression were different among studies. Most were set to be the median, while some of them were set by different standards. Second, as for the race of included patients, there were only Caucasoid and Mongoloid, the representativeness of our results could be limited. Third, several HRs could not be directly obtained from the publications. Data extracted and calculated through survival curves might not be precise enough. Fourth, the association between 8-OHdG expression and clinicopathological characteristics could not be analyzed due to the insufficient data. Therefore, larger-scale, multicenter, and high-quality studies are highly necessary to further confirm our findings. Fifth, although we have confirmed that all the antibodies used in involved studies were mouse original and commercial antibodies, it’s definite that different clones may target different parts of the interest protein, which may possibly be a source of heterogeneity. Furthermore, it is necessary to discuss those different samples with various detecting laboratory methods to evaluate 8-OHdG. Because there hasn’t been a golden standard technique for detecting 8-OHdG, different samples (shown in Table 1) were used in the included studies. Although high-pressure liquid chromatography measurements are preferred by some investigators, it is a technically difficult method, takes a long time, and has some limitations (further 8-OHdG lesions can be artificially produced during DNA extraction and sample preparation) [50]. Excretion of 8-OHdG with urine represents the average rate of oxidative stress/DNA damage in the whole body. High urinary levels of oxidized DNA-derived metabolites have been reported in several pathological conditions [51], which indicate that it can not precisely represent the exact levels of 8-OHdG and DNA oxidative damages in tumor tissues. These might represent a potential source of heterogeneity. However, subgroup analysis and meta-regression using different laboratory methods with different biological samples (cancerous tissues, plasma or urine) for the measurement of 8-OHdG showed they were not the major source of heterogeneity. Another potential reason why obvious heterogeneity was observed in the current meta-analysis may be partially due to the different locations of 8-OHdG detected in the included studies. 8-OHdG is a major product of ROS damages to DNA and mainly located in nuclei. In order to localize the 8-OHdG, most included studies analyzed the expression levels of 8-OHdG using immunohistochemical method. However, there are also some limitations in immunohistochemistry, such as it can be only used as a method of semi-quantitative analysis and results in different studies are evaluated according to different standards and cutoff values. Nevertheless, in consistent with different biological samples, subgroup analysis and meta-regression in different locations of 8-OHdG (nuclei, cytoplasm or not mentioned) for the measurement of 8-OHdG showed they were also not the major source of heterogeneity. Given the above, further studies with uniform standards of detection assay and analysis method to evaluate the expression levels of 8-OHdG are required to elucidate the role of 8-OHdG in human cancers.

**Conclusion**

This meta-analysis found that highly expressed 8-OHdG in tumor tissues may be a predictor of prognosis in most solid tumors. However, especially in breast cancer, low 8-OHdG expression is associated with poor prognosis, which is partly because of the increased antioxidant mechanisms in breast cancer tissues. This study demonstrates for the first time that 8-OHdG expression is associated with the prognosis of cancer patients. In the future, whether the expression level of 8-OHdG can be used as a biomarker for the prognosis of all human cancers requires more research.

**Supplementary information**

**Abbreviations**

8-OHdG: 8-hydroxy-2′-deoxyguanosine; 95% CI: 95% confidence interval; CSS: Cancer-specific survival; DFS: Disease-free survival; dNTP: deoxynucleoside triphosphate; EFS: Event-free survival; ELISA: Enzyme-linked immunosorbent assay; HRs: Hazard ratios; IHC: Immunohistochemistry; LC/EC: Liquid chromatography electrochemistry; MTH1: MutT Homolog 1; MUTYH: MutY homolog; NA: Not available; NOS: Newcastle-Ottawa Scale; Nrf2: NF-E2-related factor 2; OGG1: 8-oxoguanine DNA glycosylase; OS: Overall survival; PFS: Progression-free survival; RFS: Recurrence-free survival; ROS: Reactive oxygen species

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**Authors’ contributions**

XQ and DS made equal contributions to research design, the acquisition, analysis or interpretation of data and to drafting the paper or revising it critically. XL made contributions to analysis or interpretation of data and to drafting the paper or revising it critically; ZS, the co-corresponding author, made contributions to research design, revising the paper and approval of the submitted and final versions. All of other authors took part in the research design, BW and SC made contributions to the acquisition, analysis of data. All authors have read and approved the final submitted manuscript.

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**Availability of data and materials**

The datasets supporting the conclusions of this article are included within the article.
Ethics approval and consent to participate
This work did not require any written patient consent. The ethics committee of the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology approved this work.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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