Tumor-associated Tissue Eosinophilia Predicts Favorable Clinical Outcome in Solid Tumors: A Meta-analysis

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Abstract
Background: Activated eosinophils have been deemed to affect carcinogenesis and tumor progression via various mechanisms in tumor microenvironment. However, the prognostic role of tumor-associated tissue eosinophilia (TATE) in human cancers still remains controversial. Therefore, we performed the meta-analysis to better understand the role of TATE in prognosis prediction for cancer patients. Methods: We searched PubMed and EBSCO to identify the studies evaluating the association of TATE and overall survival (OS) and/or disease-free survival (DFS) in cancer patients, then computed extracted data into hazard ratios (HRs) for OS, DFS and clinicopathological features such as lymph node metastasis etc with STATA 12.0. Results: A total of 6125 patients from 25 published studies were incorporated into this meta-analysis. We found that the presence of TATE significantly improved OS and 5-year DFS in all types of cancers. In stratified analyses based on cancer types, pooled results indicated that eosinophils infiltrating into tumor tissue was significantly associated with better OS in oral cancer, esophageal carcinoma and colorectal cancer. In addition, TATE was significantly inversely correlated with lymph node metastasis, tumor stage and lymphatic invasion of cancer. Conclusion: TATE leads to a favorable clinical outcome in cancer patients, implicating that it is a valuable biomarker for prognostic prediction for human cancers and clinical application of biological response modifiers or agonists promoting TATE may be the novel therapeutic strategy for patients.

Background
Tumor microenvironment (TME) linked closely with the initiation, promotion, and progression of cancer.[1] Innate and adaptive immunocytes such as mast cells, macrophages and memory T lymphocytes etc are the vital components of TME.[2] Multitudinous studies have demonstrated that these immune cells were significantly associated with survival in solid tumors.[3, 4] However, it is essential to distinguish among different types of immune cells as they may play differential roles in the TME. Eosinophils, as the important component of innate immune cells, have proven to play significant roles in a number of human solid tumors. Eosinophils are granulocytic leukocytes that are associated with multitudinous pathologic conditions including allergic reactions, parasitic and bacterial infections etc.[5] These cells secrete massive
proteins and cytokines upon activation and are involved in a variety of other functions including inducing tissue remodeling and promoting antigen presentation. [6] In the last decade, activated eosinophils have been deemed to affect carcinogenesis and tumor progression via various mechanisms including modulating innate and adaptive immune responses in TME. [7] Eosinophils infiltrating into tumor is also called tumor-associated tissue eosinophilia (TATE).[8] Recent studies of human solid tumors have investigated the role of TATE in tumor progression and survival, but their results were controversial.[9] Thus, it needs in-depth assessment. Furthermore, the potential of these cells as a prognostic biomarker and therapeutic strategy is necessary to be explored.

We performed this meta-analysis to clarify the association between TATE and clinical outcomes such as overall survival (OS) and disease-free survival (DFS) in patients with solid tumor.

Methods

Search strategy

PubMed and EBSCO were searched for studies to assess TATE and survival in cancer patients from 1980 to March 31th 2019. The keywords used for search were: (eosinophil [Title/Abstract] OR eosinophilia [Title/Abstract]) AND (neoplasms [Title/Abstract] OR tumor [Title/Abstract] OR cancer [Title/Abstract] OR carcinoma [Title/Abstract]).

Inclusion and exclusion criteria

In this meta-analysis, the inclusion criteria were: studies must have (1) been published as original articles; (2) assessed human subjects; (3) detected eosinophils in primary tumor specimens; (4) provided hazard ratios (HRs) with 95% confidence interval (CI), or Kaplan – Meier curves of eosinophil infiltration with OS, and/or DFS; (5) been published in English.

The exclusion criteria were: studies (1) were not published as research articles or full texts including commentary, case report, letters to editors and conference abstracts; (2) didn’t provide sufficient data to estimate HRs; (3) detected eosinophils in metastases or not in tumor tissues.

Endpoints

In this meta-analysis, we recorded OS and DFS as the primary and second endpoint respectively.

Data extraction
GM.H. and SM.W. independently reviewed and extracted data including first author’s name, publication year, number of patients, median age, method used to quantify eosinophils, cut-off value to define TATE as well as time of follow-up. OS, DFS and clinicopathological data such as tumor, node, metastasis (TNM) stage, lymphatic invasion and vascular invasion were extracted from the text, tables, or Kaplan – Meier curves.

**Quality assessment**

Two independent authors evaluated the quality of included cohort studies with Newcastle–Ottawa Scale (NOS),[10] and achieved consensus for each item under the help of third author. A total score of 6 or more points was considered high quality.

**Statistical Analysis**

We combined extracted data into meta-analyses using STATA 12.0 analysis software (Stata Corporation, College Station, TX, USA). Statistical heterogeneity was assessed with the chi-squared based Q-test or $I^2$[11] Data were combined based on the random-effect model in the presence of heterogeneity,[12] otherwise, the fixed-effect model was applied.[13] In addition, sensitivity analysis, Begg’s funnel plot and Egger’s test[14] were applied to probe the influence of each study on the pooled result and potential publication bias respectively. All $P$ values were two-sided and less than 0.05 are considered statistically significant.

**Results**

**Search results and description of studies**

9149 records were retrieved and the results were exhibited in Fig. 1. We ultimately identified 25 studies including 6125 patients for the assessment of TATE,[15-39] and then evaluated all these studies by the Newcastle–Ottawa Scale (NOS). Characteristics of included studies being in accordance with the inclusion criteria and suitable for data consolidation were shown in Table 1 and Table S1.

**Meta-analyses**

**Overall survival (OS)**

In this meta-analysis, the pooled result indicated that the presence of TATE was significantly associated with improved OS (HR = 0.77, 95% CI 0.64 to 0.92, $P = 0.004$) in human solid tumors, with
no significant heterogeneity detected ($I^2 = 44.1\%, P = 0.014$). (Fig. 2)

In stratified analyses by tumor types, as shown in Fig. 3, pooled results showed that TATE was significantly associated with better OS in esophageal carcinoma (EC) (HR = 0.35, 95% CI 0.14 to 0.88, $P = 0.026$). Similar results were observed between TATE and OS in oral cancer (OC) (HR = 0.66, 95% CI 0.51 to 0.87, $P = 0.003$) and colorectal cancer (CRC) (HR = 0.70, 95% CI 0.58 to 0.84, $P = 0.000$), with no heterogeneity detected respectively ($I^2 = 0\%, P = 0.665; I^2 = 0\%, P = 0.449$); Whereas there was no significant association between eosinophil infiltration and OS in laryngeal carcinoma (HR = 0.87, 95% CI 0.51 to 1.48, $P = 0.599$), Hodgkin’s lymphoma (HR = 0.90, 95% CI 0.48 to 1.69, $P = 0.741$) or cervical cancer (HR = 2.14, 95% CI 0.38 to 12.24, $P = 0.391$).

**Disease-free survival (DFS)**

The meta-analysis showed that there was no significant association between eosinophil infiltration and DFS (HR = 1.06, 95% CI 0.64 to 1.76, $P = 0.830$) in solid tumors. (Fig. 4) In the stratified analyses, the pooled results showed that TATE was significantly associated with better 5-year DFS (OR = 2.17, 95% CI 1.13 to 4.14, $P = 0.019$), but not with 1-year (OR = 1.91, 95% CI 0.97 to 3.77, $P = 0.063$) or 3-year DFS (OR = 1.62, 95% CI 0.90 to 2.90, $P = 0.107$) in cancer patients. (Fig. 5)

As exhibited in Fig. S1, the stratified analyses revealed that TATE was not significantly associated with improved DFS in oral cancer (HR = 2.00, 95% CI 0.22 to 17.98, $P = 0.535$), nasopharyngeal carcinoma (HR = 0.50, 95% CI 0.23 to 1.08, $P = 0.079$) or Hodgkin’s lymphoma (HR = 0.73, 95% CI 0.18 to 2.98, $P = 0.657$).

In addition, we found that TATE was significantly inversely associated with lymph node metastasis (OR = 0.59, 95% CI 0.40 to 0.87, $P = 0.007$), TNM stage (OR = 1.70, 95% CI 1.12 to 2.58, $P = 0.013$) and lymphatic invasion (OR = 0.58, 95% CI 0.36 to 0.91, $P = 0.018$), but not with vascular invasion (OR = 0.79, 95% CI 0.50 to 1.25, $P = 0.308$) of patients. (Fig. S2)

**Sensitivity analysis**

Sensitivity analysis indicated that each included study had no influence on the overall HR for OS or DFS. (Fig. S3)
**Publication bias**

There was no publication bias between TATE and OS ($P = 0.102$) or DFS ($P = 0.858$) in patients by Funnel plot and Egger’s test.

**Discussion**

Eosinophilia is commonly associated with allergies, helminth infections and several inflammatory states. In the past decades, it has also been found in human solid tumors. Although many studies have correlated TATE and prognosis of patients with solid tumor, their results were not consistent even controversial. In the present meta-analysis, we found that TATE had a positive prognostic effect associated with survival in human solid tumors, especially in OC, EC and CRC. In addition, TATE was significantly inversely correlated with lymph node metastasis, TNM stage and lymphatic invasion of tumor. Thus, we think these findings provide meaningful statistical evidence to exhibit the positive prognostic role of these cells in patients with solid tumor.

The close association between TATE and improved survival especially in OC, EC and CRC identified in this study possibly attribute to the following reasons: eosinophils in the TME can express same receptors and mediators such as garnzyme A etc as cytotoxic T lymphocytes (CTLs) and be directly involved in anti-tumor response, [40] and they can also secret several chemokines including CCL5, CXCL9 to promote anti-tumor immunity through attracting CD8$^+$ T cells to the tumor site. [41] In addition, eosinophils are capable of regulating immunity, for example, they can release major basic protein (MBP), a highly cationic protein to stimulate maturation of dendritic cells by increasing cell surface activation markers including MHC-Ⅱ, CD80 and CD86, [42] which has the potential to overcome immune tolerance and induce anti-tumor immunity with the powerful antigen-presentation ability.[43] Furthermore, they are able to induce cell death of various cell lines such as colo-205 cell line with some selectivity in their tumoricidal properties, which are dependent on the CD11a/CD18-mediated stable contacts with target cells. [44] Thus, it is reasonable to speculate that the TATE is able to regulate tissue homeostasis of the TME and inhibit tumor growth and spread thereby improving survival. However, in other tumor types, TATE as a prognostic marker for survival has been a controversial issue. This may be because of differences in methods of counting TATE as well as
heterogeneity of material.

Previous studies have demonstrated that cytokines such as IL-2, IL-4 could recruit eosinophils and lead to eosinophilia and enhanced eosinophil activation, thereby exert potent anti-tumor immune responses.[40, 45] Thus, based on our present result that TATE improving survival in human solid tumors identified in this study and the function of IL-2 and IL-4 stated above, we think that clinical application of biological response modifiers (BRM) such as carrier-assisted recombinant human IL-2 /or IL-4 may have the possibility to treat human solid tumors.

There were several limitations in this study. First, morphometric analyses for TATE used in included studies were not exactly consistent. In addition, studies with negative results may not be published, which may cause potential publication bias.

Conclusions
TATE leads to a favorable clinical outcome in human solid tumors especially in OC, EC and CRC, implicating that it is a valuable biomarker for prognostic prediction and clinical application of biological response modifiers or agonists promoting TATE may be a novel therapeutic strategy for patients.

Abbreviations
TATE: tumor-associated tissue eosinophilia; OS: overall survival; DFS: disease-free survival; HR: hazard ratio; OR: odds ratio; CI: confidence interval; TNM: tumor, node, metastasis; OC: oral cancer; CRC: colorectal cancer; EC: esophageal carcinoma; NR: not reported; TME: tumor microenvironment; BRM: biological response modifier.

Declarations

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Availability of data and materials
The datasets supporting the conclusions of this article are included within the article.

Authors’ contributions
GM.H. conceived of the study, participated in its design, extracted data, performed the statistical analysis and drafted the manuscript. SM.W. participated in data extraction; W.C. participated in statistical analysis. LM.H. participated in its design. All authors read and approved the final manuscript.

Competing interests
The authors have declared that no competing interests exist.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Ethical approval is not required for this article.

References
1. Motz GT, Coukos G: The parallel lives of angiogenesis and immunosuppression: cancer and other tales. Nat Rev Immunol 2011, 11(10):702-711.
2. Gajewski TF, Schreiber H, Fu YX: Innate and adaptive immune cells in the tumor microenvironment. Nat Immunol 2013, 14(10):1014-1022.
3. Hu G, Wang S, Cheng P: Tumor-infiltrating tryptase(+) mast cells predict unfavorable clinical outcome in solid tumors. Int J Cancer 2018, 142(4):813-821.
4. Hu G, Wang S: Tumor-infiltrating CD45RO+ Memory T Lymphocytes Predict Favorable Clinical Outcome in Solid Tumors. Scientific Reports 2017, 7(1).
5. Hogan SP, Rosenberg HF, Moqbel R, Phipps S, Foster PS, Lacy P, Kay AB, Rothenberg ME: Eosinophils: biological properties and role in health and disease. Clin Exp Allergy 2008, 38(5):709-750.
6. Akuthota P, Wang HB, Spencer LA, Weller PF: Immunoregulatory roles of eosinophils: a new look at a familiar cell. Clinical & Experimental Allergy 2008,
7. Kita H: **Eosinophils: multifaceted biological properties and roles in health and disease.** *Immunol Rev* 2011, **242**(1):161-177.

8. Jain M, Kasetty S, Sudheendra US, Tijare M, Khan S, Desai A: **Assessment of tissue eosinophilia as a prognosticator in oral epithelial dysplasia and oral squamous cell carcinoma-an image analysis study.** *Patholog Res Int* 2014, **2014**:507512.

9. Marichal T, Tsai M, Galli SJ: **Mast cells: potential positive and negative roles in tumor biology.** *Cancer Immunol Res* 2013, **1**(5):269-279.

10. Stang A: **Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses.** *Eur J Epidemiol* 2010, **25**(9):603-605.

11. Higgins JP, Thompson SG, Deeks JJ, Altman DG: **Measuring inconsistency in meta-analyses.** *BMJ* 2003, **327**(7414):557-560.

12. Kuritz SJ, Landis JR, Koch GG: **A general overview of Mantel-Haenszel methods: applications and recent developments.** *Annu Rev Public Health* 1988, **9**:123-160.

13. DerSimonian R, Kacker R: **Random-effects model for meta-analysis of clinical trials: an update.** *Contemp Clin Trials* 2007, **28**(2):105-114.

14. Egger M, Davey Smith G, Schneider M, Minder C: **Bias in meta-analysis detected by a simple, graphical test.** *BMJ* 1997, **315**(7109):629-634.

15. Peurala E, Tuominen M, Loyttyniemi E, Syrjanen S, Rautava J: **Eosinophilia is a favorable prognostic marker for oral cavity and lip squamous cell carcinoma.** *APMIS* 2018, **126**(3):201-207.

16. Oliveira DT, Biassi TP, Faustino SE, Carvalho AL, Landman G, Kowalski LP: **Eosinophils may predict occult lymph node metastasis in early oral cancer.**
Clin Oral Investig 2012, 16(6):1523-1528.

17. Dorta RG, Landman G, Kowalski LP, Lauris JR, Latorre MR, Oliveira DT: Tumour-associated tissue eosinophilia as a prognostic factor in oral squamous cell carcinomas. Histopathology 2002, 41(2):152-157.

18. Alrawi SJ, Tan D, Stoler DL, Dayton M, Anderson GR, Mojica P, Douglas W, Hicks W, Jr., Rigual N, Loree T: Tissue eosinophilic infiltration: a useful marker for assessing stromal invasion, survival and locoregional recurrence in head and neck squamous neoplasia. Cancer J 2005, 11(3):217-225.

19. Tostes Oliveira D, Tjioe KC, Assao A, Sita Faustino SE, Lopes Carvalho A, Landman G, Kowalski LP: Tissue eosinophilia and its association with tumoral invasion of oral cancer. Int J Surg Pathol 2009, 17(3):244-249.

20. Ercan I, Cakir B, Basak T, Ozdemir T, Sayin I, Turgut S: Prognostic significance of stromal eosinophilic infiltration in cancer of the larynx. Otolaryngol Head Neck Surg 2005, 132(6):869-873.

21. Sassler AM, McClatchey KD, Wolf GT, Fisher SG: Eosinophilic infiltration in advanced laryngeal squamous cell carcinoma. Veterans Administration Laryngeal Cooperative Study Group. Laryngoscope 1995, 105(4 Pt 1):413-416.

22. Thompson AC, Bradley PJ, Griffin NR: Tumor-associated tissue eosinophilia and long-term prognosis for carcinoma of the larynx. Am J Surg 1994, 168(5):469-471.

23. Fujii M, Yamashita T, Ishiguro R, Tashiro M, Kameyama K: Significance of epidermal growth factor receptor and tumor associated tissue eosinophilia in the prognosis of patients with nasopharyngeal carcinoma. Auris Nasus Larynx 2002, 29(2):175-181.

24. Leighton SE, Teo JG, Leung SF, Cheung AY, Lee JC, van Hasselt CA: Prevalence and
prognostic significance of tumor-associated tissue eosinophilia in nasopharyngeal carcinoma. Cancer 1996, 77(3):436-440.

25. Harbaum L, Pollheimer MJ, Kornprat P, Lindtner RA, Bokemeyer C, Langner C: Peritumoral eosinophils predict recurrence in colorectal cancer. Mod Pathol 2015, 28(3):403-413.

26. Fernandez-Acenero MJ, Galindo-Gallego M, Sanz J, Aljama A: Prognostic influence of tumor-associated eosinophilic infiltrate in colorectal carcinoma. Cancer 2000, 88(7):1544-1548.

27. Nielsen HJ, Hansen U, Christensen IJ, Reimert CM, Brunner N, Moesgaard F: Independent prognostic value of eosinophil and mast cell infiltration in colorectal cancer tissue. J Pathol 1999, 189(4):487-495.

28. Prizment AE, Vierkant RA, Smyrk TC, Tillmans LS, Lee JJ, Sriramarao P, Nelson HH, Lynch CF, Thibodeau SN, Church TR, Cerhan JR, Anderson KE, Limburg PJ: Tumor eosinophil infiltration and improved survival of colorectal cancer patients: Iowa Women's Health Study. Mod Pathol 2016, 29(5):516-527.

29. Zhang Y, Ren H, Wang L, Ning Z, Zhuang Y, Gan J, Chen S, Zhou D, Zhu H, Tan D, Zhang H: Clinical impact of tumor-infiltrating inflammatory cells in primary small cell esophageal carcinoma. Int J Mol Sci 2014, 15(6):9718-9734.

30. Ishibashi S, Ohashi Y, Suzuki T, Miyazaki S, Moriya T, Satomi S, Sasano H: Tumor-associated tissue eosinophilia in human esophageal squamous cell carcinoma. Anticancer Res 2006, 26(2B):1419-1424.

31. Hollander P, Rostgaard K, Smedby KE, Molin D, Loskog A, de Nully Brown P, Enblad G, Amini RM, Hjalgrim H, Glimelius I: An anergic immune signature in the tumor microenvironment of classical Hodgkin lymphoma is associated with inferior outcome. Eur J Haematol 2018, 100(1):88-97.
32. Keresztes K, Szollosi Z, Simon Z, Tarkanyi I, Nemes Z, Illes A: Retrospective analysis of the prognostic role of tissue eosinophil and mast cells in Hodgkin's lymphoma. Pathol Oncol Res 2007, 13(3):237-242.

33. von Wasielewski R, Seth S, Franklin J, Fischer R, Hubner K, Hansmann ML, Diehl V, Georgii A: Tissue eosinophilia correlates strongly with poor prognosis in nodular sclerosing Hodgkin's disease, allowing for known prognostic factors. Blood 2000, 95(4):1207-1213.

34. Enblad G, Sundstrom C, Glimelius B: Infiltration of eosinophils in Hodgkin's disease involved lymph nodes predicts prognosis. Hematol Oncol 1993, 11(4):187-193.

35. van Driel WJ, Hogendoorn PC, Jansen FW, Zwinderman AH, Trimbos JB, Fleuren GJ: Tumor-associated eosinophilic infiltrate of cervical cancer is indicative for a less effective immune response. Hum Pathol 1996, 27(9):904-911.

36. Bethwaite PB, Holloway LJ, Yeong ML, Thornton A: Effect of tumour associated tissue eosinophilia on survival of women with stage IB carcinoma of the uterine cervix. J Clin Pathol 1993, 46(11):1016-1020.

37. Flamm J: Tumor-associated tissue inflammatory reaction and eosinophilia in primary superficial bladder cancer. Urology 1992, 40(2):180-185.

38. Iwasaki K, Torisu M, Fujimura T: Malignant tumor and eosinophils. I. Prognostic significance in gastric cancer. Cancer 1986, 58(6):1321-1327.

39. Ono Y, Ozawa M, Tamura Y, Suzuki T, Suzuki K, Kurokawa K, Fukabori Y, Yamanaka H: Tumor-associated tissue eosinophilia of penile cancer. Int J Urol 2002, 9(2):82-87.

40. Gatault S, Legrand F, Delbeke M, Loiseau S, Capron M: Involvement of eosinophils in the anti-tumor response. Cancer Immunol Immunother 2012, 61(9):1527-1534.
41. Carretero R, Sektionlu IM, Garbi N, Salgado OC, Beckhove P, Hammerling GJ: *Eosinophils orchestrate cancer rejection by normalizing tumor vessels and enhancing infiltration of CD8(+) T cells*. Nat Immunol 2015, 16(6):609-617.

42. Lotfi R, Lotze MT: *Eosinophils induce DC maturation, regulating immunity*. J Leukoc Biol 2008, 83(3):456-460.

43. Sheng KC, Pietersz GA, Wright MD, Apostolopoulos V: *Dendritic cells: activation and maturation--applications for cancer immunotherapy*. Curr Med Chem 2005, 12(15):1783-1800.

44. Legrand F, Driss V, Delbeke M, Loiseau S, Hermann E, Dombrowicz D, Capron M: *Human eosinophils exert TNF-alpha and granzyme A-mediated tumoricidal activity toward colon carcinoma cells*. J Immunol 2010, 185(12):7443-7451.

45. Sosman JA, Bartemes K, Offord KP, Kita H, Fisher SG, Kefer C, Ellis TA, Fisher RI, Higgins TJ, Gleich GJ: *Evidence for eosinophil activation in cancer patients receiving recombinant interleukin-4: effects of interleukin-4 alone and following interleukin-2 administration*. Clin Cancer Res 1995, 1(8):805-812.

**Tables**

Table 1. Main characteristics of the included studies.

| Study                  | Year | Tumor type      | No. of Patients | Male/Female | Median age (range) (year) |
|------------------------|------|-----------------|-----------------|-------------|--------------------------|
| Peurala, E. et al [15] | 2018 | Oral cancer     | 99              | 55/44       | 65.3                     |
| Oliveira, D. T. et al [16] | 2012 | Oral cancer     | 71              | 55/16       | 59 (35, 77)              |
| Tostes Oliveira, D. et al [19] | 2009 | Oral cancer     | 43              | 27/16       | 55.79 (28, 8)            |
| Dorta, R. G. et al [17] | 2002 | Oral cancer     | 125             | 105/20      | 58 (30, 95)              |
| Alrawi, S. J. et al [18] | 2005 | Head and neck carcinoma | 87              | NR          | (41, 76)                 |
| Author(s) | Year | Study Type | Site                | Number | Relapse | 5-Year Survival |
|----------|------|------------|---------------------|--------|---------|-----------------|
| Ercan, I. et al [20] | 2005 | Laryngeal carcinoma | 78  | 78/0   | 55.9 (35, 80) |
| Sassler, A. M. et al [21] | 1995 | Laryngeal carcinoma | 248 | NR     | NR            |
| Thompson, A. C. et al [22] | 1994 | Laryngeal carcinoma | 104 | 85/19  | 64.6 (39, 91) |
| Fujii, M. et al [23] | 2002 | Nasopharyngeal carcinoma | 53   | 40/13  | 49.4 (15, 81) |
| Leighton, S. E. et al [24] | 1996 | Nasopharyngeal carcinoma | 96   | 68/28  | NR            |
| Harbaum, L. et al [25] | 2015 | Colorectal cancer | 381 | 166/215 | 68.5          |
| Fernandez-Acenero, M. J. et al [26] | 2000 | Colorectal cancer | 126 | 70/56  | 67.35 (32, 8) |
| Nielsen, H.J. et al [27] | 1999 | Colorectal cancer | 584 | 240/344 | 61 (49, 75)   |
| Prizment, A.E et al [28] | 2016 | Colorectal cancer | 441 | 0/441  | (55, 69)      |
| Zhang, Y. et al [29] | 2014 | Esophageal carcinoma | 36   | 25/11  | 59 (45, 77)   |
| Ishibashi, S. et al [30] | 2006 | Esophageal carcinoma | 97   | 82/15  | 62.7 ± 8.9   |
| Hollander, P. et al [31] | 2018 | Hodgkin's lymphoma | 459 | 242/217 | <45: 68%; ≥45: 32% |
| Kereszres, K. et al [32] | 2007 | Hodgkin's lymphoma | 104 | 54/50  | 33 (12, 72)   |
| von Wasielewski, R. et al [33] | 2000 | Hodgkin's lymphoma | 1511 | 745/766 | (15, 75)     |
| Enblad, G. et al [34] | 1993 | Hodgkin's lymphoma | 140 | NR     | 45 (11, 94)   |
| van Driel, W.J. et al [35] | 1996 | Cervical cancer | 83  | 0/83   | 42.1          |
| Bethwaite, P. B. et al [36] | 1993 | Cervical cancer | 67  | 0/67   | 43.7 (25, 76) |
| Flamm, J. et al [37] | 1992 | Bladder cancer | 428 | 289/139 | 70.2 (29, 91) |
| Reference                  | Year | Type          | Cases | Positive/Total | (Sensitivity, Specificity) |
|---------------------------|------|---------------|-------|----------------|---------------------------|
| Iwasaki, K. et al [38]    | 1986 | Gastric cancer| 647   | 364/283        | (22, 84)                  |
| Ono, Y. et al [39]        | 2002 | Penile cancer | 17    | 17/0           | 68 (36, 84)              |

H&E: haematoxilyn and eosin; EPX: eosinophil peroxide; NR: not reported.

Figures
Figure 1

Flow chart diagram of study selection.

1957 and 7192 potentially relevant studies identified in PubMed and EBSCO respectively.

4981 Records screened

4168 Duplicate studies were excluded

3352 were excluded:
1591 Non-human studies
674 Non English
611 Non full-text articles
476 Non research articles

1629 Studies assessed for eligibility

1604 were excluded:
1489 Not correlate eosinophils with cancer
63 Not contain survival data
23 Eosinophils detected not in tissue
11 Eosinophils detected in metastatic sites
18 Unavailable data

25 Full-length articles included
Forest plots describing HR of the association between TATE and OS in human solid tumors.
Figure 3

Stratified analyses describing HRs of the association between TATE and OS.
Figure 4

Forest plots describing HR of the association between TATE and DFS in human solid tumors.
Figure 5

Forest plots describing ORs of the association between TATE and DFS at 1-year, 3-year and 5-year of patients.

Supplementary Files

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