Prognostic value of Ki67 in phyllodes tumor of the breast: A systematic review and meta-analysis

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Abstract. Numerous clinicopathological features have been examined as predictive factors for adverse outcomes in patients with phyllodes tumor (PT) of the breast, but there are still no definitive predictive markers to guide management, despite the persistent risk of recurrence, even in benign disease. Whether Ki67 has prognostic value in PT remains uncertain. Therefore, a systematic review and meta-analysis were performed to examine whether Ki67 is associated with adverse clinical outcomes, particularly recurrence, in patients with PT. The PubMed/MEDLINE, Web of Science, Scopus, Embase and Cochrane Library databases were searched from inception to July 2024. Study characteristics and outcomes (recurrence and overall survival) according to Ki67 status were extracted from each eligible study, and pooled log odds ratios (OR) with 95% CI were derived using a random-effects model. A total of five studies comprising 280 cases were eligible for inclusion. The adverse outcome rate for the $Ki67^{high}$ (Ki67 >10 or >11.2%) population was 28.7% (95% CI, 20.1-38.6%), while the adverse outcome rate for the $Ki67^{low}$ population was 9.4% (95% CI, 5.4-13.5%). $Ki67^{high}$ was associated with an increased odds of an adverse outcome [log OR, 1.26 (95% CI, 0.38-2.15; P=0.005)] compared with a $Ki67^{low}$ status. All five studies scored 8 points on the Newcastle-Ottawa Scale, equivalent to 'good' quality according to Agency for Healthcare Research and Quality standards, and no significant publication bias was noted. This was the first meta-analysis of the predictive value of Ki67 in PT of the breast. A relatively high Ki67 index (>10%) is associated with recurrence. It is timely to re-evaluate the prognostic value of Ki67 in large retrospective cohorts with long follow-up to firmly establish whether it could contribute to identifying patients at risk of recurrence, particularly those with histologically benign disease. Doing so could impact clinical practice by refining follow-up recommendations based on quality evidence.

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Introduction

Phyllodes tumors (PTs) are rare (0.3-1% of all primary breast tumors) fibroepithelial breast neoplasms that carry a risk of recurrence and metastasis (1,2). PTs are classified into benign, borderline and malignant-grade disease according to histopathological criteria of stromal cellularity and atypia, mitotic count, stromal overgrowth and the nature of the tumor border (3,4). Histopathological grading is important for prognostication and management: Recurrence rates increase with higher tumor grades [10-17, 14-25 and 23-30% for benign, borderline and malignant PTs, respectively (3,4)]; benign tumors only very rarely metastasize (3); and malignant tumors may benefit from adjuvant therapy such as postoperative radiotherapy, although the optimal management remains uncertain (5). Metastasis of PTs heralds a usually dismal prognosis and death from the disease (6), but in almost all cases, metastasis only occurs when the primary tumor is graded as malignant (3,6).

Although complete excision is the gold standard treatment for PT and complete excision with an adequate margin reduces the subsequent recurrence risk, it is still being debated what constitutes an adequate margin to reduce the risk of recurrence (5). Other clinicopathological features, such as cellular atypia, mitotic rate and stromal overgrowth, have similarly been examined as predictive factors for recurrence, with conflicting results (3,5). Other protein biomarkers such as matrix metalloproteinase (MMP)-14, Six-1, PAX3, FoxC2, TWIST, C-X-C chemokine receptor 4, vascular endothelial growth factor, stromal Yes-associated protein, cellular E-cadherin and CD10 have been associated with recurrent PT, while others have not [e.g., epidermal growth factor receptor (EGFR), human EGFR 2, membranous E-cadherin; MMP-1, -2, -7, -9, -11 and -13; and tissue inhibitor of metalloproteinase (TIMP)-1, -2 and -3] (7). There are still no definitive markers of recurrence or other outcomes such as survival to guide management, despite the persistent risk of recurrence, even in patients with benign disease. Although benign disease does not usually result in clinically serious sequelae, it would still be helpful to identify all individuals at risk of recurrence, even those with benign disease, to tailor surveillance strategies (8).

Ki67 is a nuclear antigen that is expressed in all phases of the cell cycle (G1, S, G2), and it is a reliable and widely used immunohistochemical biomarker of proliferation in routine histopathological practice, including in breast cancer (9). Although practice varies, Ki67 is routinely used as a prognostic biomarker in invasive ductal carcinoma, and the Italian Association of Medical Oncology, European Group on Tumor Markers, European Society for Medical Oncology and the National Institute for Health and Care Excellence either recommend or advise considering Ki67 measurement for prognostication in patients with breast cancer (10). Furthermore, the European Society for Medical Oncology supports the use of Ki-67 expression as a predictive biomarker of response to neoadjuvant chemotherapy (10). Similarly, Ki67 is prognostic and used routinely in patients with other tumors, such as in pancreatic neuroendocrine neoplasia, where it predicts both recurrence and metastasis (11-13). While the mitotic index only reflects cells in the M-phase, Ki67 detects other cells at different stages of proliferation (or arrest) and therefore provides different information about proliferation in the histopathological snapshot of tumor biology captured in a tumor section (9). In PT, stromal expression of Ki67 has been reported to be 5-25% in benign tumors and 15-100% in malignant tumors, and this association with the grade has been reported in several studies (14). However, whether Ki67 has prognostic significance in PT remains uncertain.

Therefore, in the present study, a systematic review and meta-analysis were performed to examine whether Ki67 is associated with adverse clinical outcomes, particularly recurrence, in patients with PT.

Methods

This meta-analysis is reported according to the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (15).

Eligibility criteria. The Population, Intervention, Comparison, Outcomes and Study (PICOS) criteria for inclusion and exclusion were as follows: P (participants): Studies of uni- or bilateral PTs of the breast; I and C (intervention and control): Studies in which Ki67/MIB1 was measured in PTs by immunohistochemistry, where MIB1 describes the commonly used monoclonal antibody clone targeting the Ki67 antigen; O (outcome): Studies that included the local recurrence rate or overall survival (OS) rate were included; S (study type): Research articles published prior to July 11, 2024 were included. Any review papers, conference abstracts, meta-analyses, editorial/comment papers and case reports were excluded from the study.

Information sources and search strategy. The PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov), Web of Science (available via https://clarivate.com), Scopus (https://www.scopus.com/), Embase (https://www.embase.com) and Cochrane Library databases (https://www.cochranelibrary.com) were searched for reports meeting the inclusion criteria published before July 11, 2024. The following search strategies were used for each database: PubMed/MEDLINE: (phyllodes) AND (breast) AND ((Ki67) OR (proliferation)) AND ((survival) OR (recurrence) OR (outcome)); Web of Science: (phyllodes) AND (breast) AND ((Ki67) OR (proliferation)) AND (outcome); Scopus: TITLE-ABS-KEY (phyllodes) AND TITLE-ABS-KEY (breast) AND (TITLE-ABS-KEY (outcome) OR TITLE-ABS-KEY (survival) OR TITLE-ABS-KEY (recurrence)) AND (TITLE-ABS-KEY (Ki67) OR TITLE-ABS-KEY (proliferation)); Cochrane: Phyllodes tumor; Embase (1974 to 2024 July 11): (phyllodes and breast and (Ki67 or proliferation) and (survival or recurrence or outcome)).mp. (mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word).

Selection, data collection and data items. A total of two reviewers worked independently to screen the titles and abstracts of all literature retrieved from the database searches. After screening, two reviewers independently collected data from each report and input the data items (study country, outcome types, follow-up period, number of recurrences according to Ki67 status, clinicopathological characteristics and total number of cases) into a data entry sheet. These sheets were then compared and combined.

Risk of bias assessment. The Newcastle-Ottawa scale (NOS) (16) was used to assess the quality of prognostic/predictive value of studies with scores converted to Agency for Healthcare Research and Quality (AHRQ) standards, i.e., good quality: 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; fair quality: 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; and poor quality: 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 stars in the outcome/exposure domain.

Statistical analysis. Analyses were performed in JASP v0.19 for Apple Silicon (17). The log odds ratio (OR) with 95% confidence intervals (CI) was used to compare dichotomous variables, i.e., proportions of local and distant recurrences/deaths in patients with PTs with a Ki67 index >10 or >11.2%. Thresholds of 10 and 11.2% were selected, as these were the thresholds used in the selected studies and were deemed sufficiently close to not unduly affect the analysis. Homogeneity of effect sizes was assessed with the test of residual heterogeneity (Cochran's Q) test and I^2 calculations. Despite the effect sizes being homogeneous (test of residual heterogeneity Q-test P=0.18), a random-effects (DerSimonian-Laird) model was most appropriate for meta-analysis to account for the inevitable heterogeneity for intervention effects among multiple studies from different groups and geographical regions. Publication bias was assessed using a funnel plot and Egger's test. $P<0.05$ was considered to indicate statistical significance.

Results

Study selection. The flow chart of the study selection process is shown in Fig. 1. Of 287 records identified in five databases,

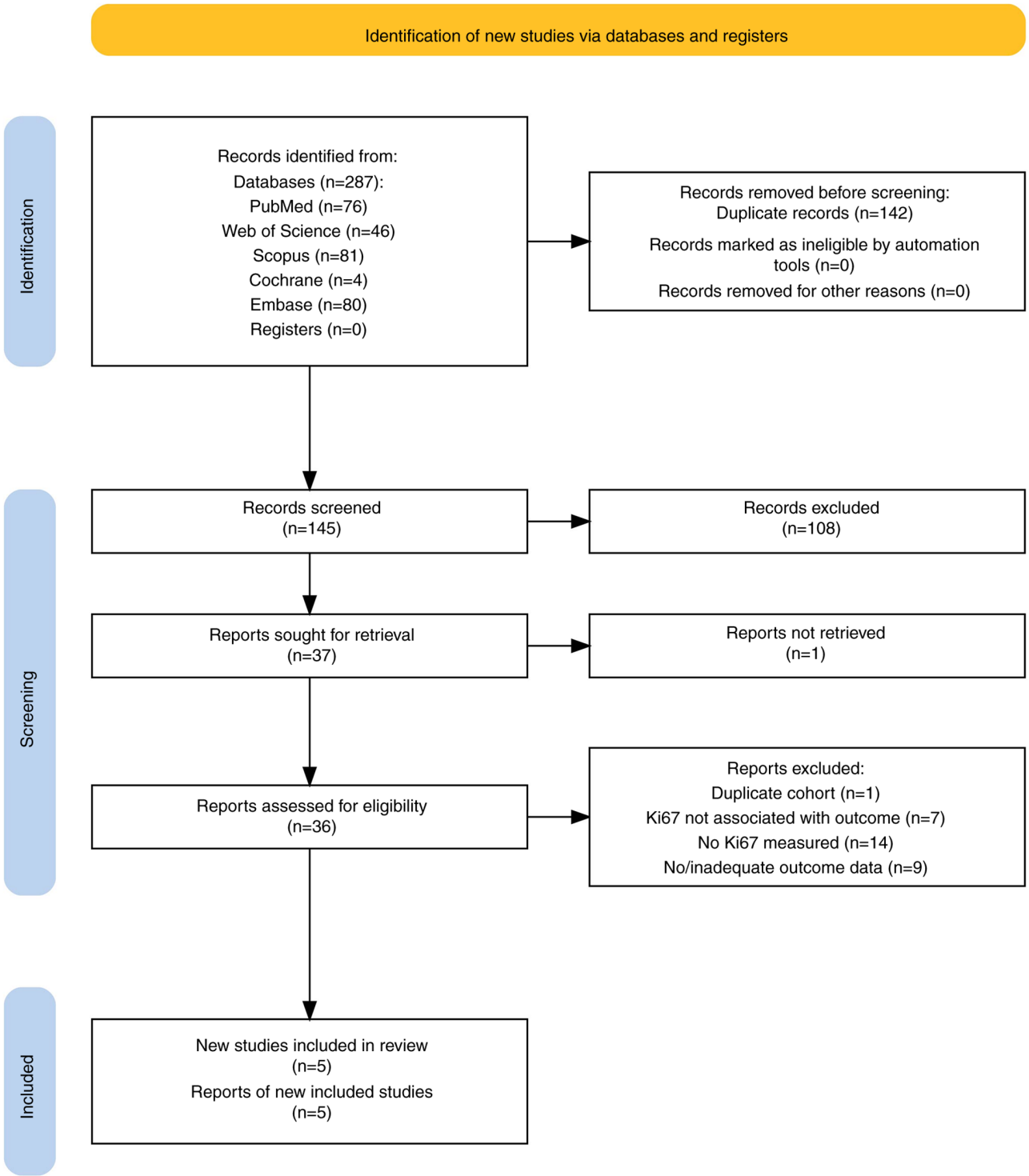

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flow chart of the study selection process.

145 were screened after removal of duplicates. Of these, 108 were excluded for not meeting the inclusion criteria. One report could not be retrieved from a source in China. Of 36 full reports assessed for eligibility, markers of proliferation (but not Ki67) were recorded, and in seven papers, Ki67 was not associated with the outcome of interest. Furthermore, nine papers did not record outcome data. Two studies (18,19) were authored by the same research team and published in the same year and, on closer examination of the cohorts, they were found to be nearly identical apart from a few more benign PTs in one of the cohorts. Therefore, the study with the larger cohort was selected for inclusion (18). After review, five reports were included in the final analysis (18,20-23).

Study characteristics and risk of bias/quality assessment. The characteristics of the included studies are shown in Table I. All five studies were retrospective observational studies and all five scored eight points on the NOS, equivalent to 'good' quality by AHRQ standards. Although follow-up varied, it was long enough to capture the most common period of recurrence

Table I. Characteristics of the included studies. $Ki67^{high}$ was defined as >10% for (18,20,22) and >11.2% for (21,23), as stated in the respective manuscripts, while an adverse outcome was either a recurrence [in four studies (18,20,22,23)] or death from the disease [in one study (21)].

Author, year	Country	Total cases	PT types	Age, years	Outcome type(s)	Follow-up period (range)	Adverse outcome, n/total $Ki67^{high}$	$Ki67^{low}$	Log OR	NOS (SE)	Quality (AHRQ scale)	(Refs.)
Chan, 2004	Taiwan	63	i) Benign (n=50); ii) malignant (n=13)	i) 42.4±14.3; ii) 44.3±9.9	Recurrence	Mean, 3 (range, 1-15) years	4/19	3/44	1.29 (0.67)	8	Good	(20)
Kuijper, 2005	Netherlands	40 (37 with follow-up)	i) Benign (n=21); ii) borderline (n=8); iii) malignant (n=11)	i) 45.5±16.8; ii) 57.9±12.8; iii) 54.3±12.9	Recurrence	93 (4-215) months	6/14	4/23	1.27 (0.77)	8	Good	(18)
Niezabitowski, 2001	Poland	117	i) Benign (n=52); ii) borderline (n=24); iii) malignant (n=42)	49 (16-87)	Overall survival	NS	10/31	3/86	2.58 (0.70)	8	Good	(21)
Shpitz, 2002	Israel	23 (22 with follow-up)	i) Benign (n=16); ii) borderline (n=4); iii) malignant (n=3)	41 (17-69)	Recurrence	52 (27-102) months	1/8	3/14	-0.65 (1.25)	8	Good	(22)
Yonemori, 2006	Japan	41	i) Benign (n=20); ii) borderline (n=5); iii) malignant (n=16)	47 (22-65)	Recurrence	42 (1-90) months	6/22	3/19	0.69 (0.79)	8	Good	(23)

Values are expressed as the mean standard deviation, median (range), n/total or n (%) unless otherwise specified. NS, not specified; OR, odds ratio; SE, standard error; NOS, Newcastle-Ottawa scale; PT, phyllodes tumor; AHRQ, Agency for Healthcare Research and Quality.

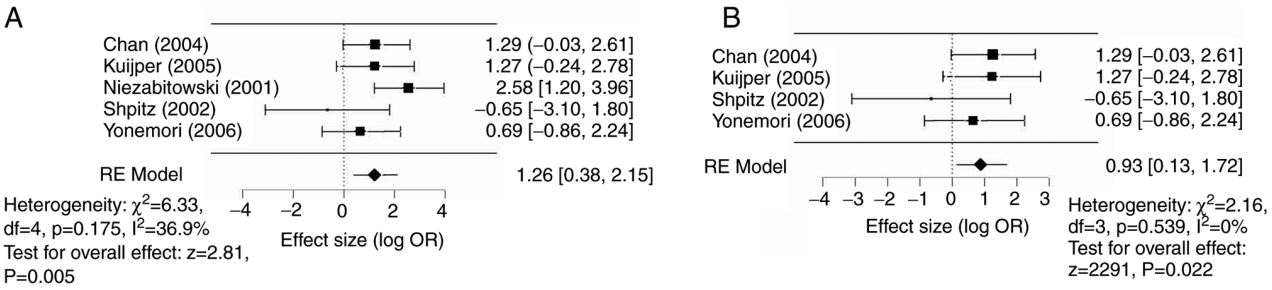

Figure 2. Forest plot showing the results of the meta-analysis of the relationship between Ki67 status and (A) any adverse outcome (local recurrence or death) and (B) local recurrence alone. The effect size is expressed as the log OR. OR, odds ratio; RE, random effects.

in all studies (average, 13.8 months) (24). While all five studies reported recurrence (local and/or distant) data and two studies reported OS data (21,23), one study only reported on the association of Ki67 with the OS (and not recurrence) outcome (21). A total of three studies (18,20,22) applied a Ki67 threshold of >10%, while two studies (21,23) applied a Ki67 threshold of 11.2%.

Results of individual studies. The pooled data consisted of five studies comprising 280 cases. The overall adverse outcome rate was 15.4% (95% CI, 11.6-20.1%). The adverse outcome rate for the $Ki67^{high}$ population was 28.7% (95% CI, 20.1-38.6%), while the adverse outcome rate for the $Ki67^{low}$ population was 9.4% (95% CI, 5.4-13.5%). The effect sizes of $Ki67^{high}$ scoring with an adverse outcome, expressed as the log OR together with their standard errors, are shown in Table I and ranged from -0.65±1.25 to 2.58±0.70.

Results of meta-analysis. A random-effects (DerSimonian-Laird) model was used for meta-analysis. $Ki67^{high}$ was associated with an increased odds of an adverse outcome [log OR, 1.26 (95% CI 0.38-2.15), P=0.005] compared with a $Ki67^{low}$ status (Fig. 2A). Similarly, when examining associations with recurrences alone [excluding (21), with an OS endpoint], $Ki67^{high}$ status was still associated with an increased odds of local recurrence [log OR 0.93 (95% CI 0.13-1.72), P<0.02] compared with a $Ki67^{low}$ status (Fig. 2B).

Publication bias. No significant publication bias with respect to adverse outcomes was noted in the funnel plot (Egger's test P=0.06; Fig. 3).

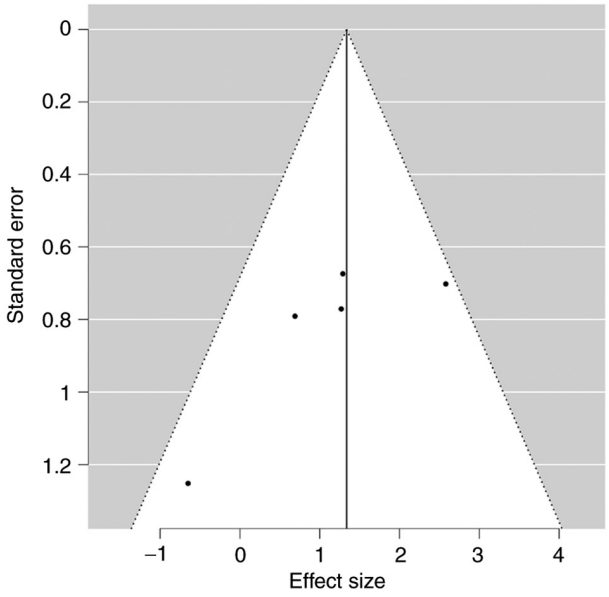

Figure 3. Funnel plot to examine publication bias with respect to adverse outcomes.

Discussion

As PT is a rare tumor, there are no large, prospective studies on PTs available. However, previous retrospective studies have reported that various clinicopathological factors, including adequacy of resection, histopathological features and tumor protein expression, are associated with clinical outcomes in patients with PT (7,8). Although PTs that clearly lie at the extreme ends of the diagnostic spectrum, such as those that are difficult to differentiate from fibroadenomas or those with overt features of malignancy, allow straightforward clinicopathological correlation and management planning, the disease still poses pathological and clinical challenges in practice. The absence of clear prognostic factors means that there are still no evidence-based guidelines for the follow-up of patients with PT, and accordingly, certain patients with benign lesions are subjected to unnecessary routine follow-up imaging, which may not be required (8). Any indicator of an adverse prognostic course, particularly in patients with clinically benign lesions, would be useful to tailor follow-up and spare the costs and resources associated with surveillance imaging or, conversely, to divert resources to those at greatest risk of future recurrence.

This situation inspired the present systematic review and meta-analysis of the prognostic significance of the Ki67 proliferation marker in patients with PT. Although only five studies that specifically examined the prognostic value of Ki67 in patients with PT were identified, the present analysis indicates that patients with PT with high expression of Ki67, here defined as >10 or >11.2% expression in tumor stroma cells, have a significantly increased risk of an adverse outcome, particularly recurrence. Although the small sizes of the included studies and a lack of relevant data precluded formal subgroup analysis of the prognostic significance of Ki67 in patients with benign and borderline disease alone, the available data appear to suggest that the association between high Ki67 and recurrence is not

limited to malignant disease. Indeed, all seven recurrences reported by Chan *et al* (20) occurred after the resection of benign primary lesions, four of which had Ki67 indices >10%. In the other included reports, even though some initially benign primary lesions went on to recur, their Ki67 status was unclear. The present analysis suggests that a Ki67 index >10% may be an indicator of the need for extra vigilance during follow-up, regardless of other clinical or histopathological features. Even though locally recurrent PT often presents clinically and not through imaging (8,25), establishing Ki67 as an adverse prognostic indicator could be helpful for identifying the subset of patients who may benefit from focused radiological follow-up.

There have been previous attempts to devise predictive models of the clinical behavior of PT. For instance, Tan *et al* (6) developed a nomogram that included atypia, mitoses, stromal overgrowth and surgical margin status that predicted recurrence-free survival up to 10 years, which was subsequently validated in several independent cohorts from around the world (26-28). Of note, stromal mitotic activity was usually associated with recurrence even when the other included parameters were not (26,27). Given the present findings and that proliferation as measured by mitosis counts are likely to be critical factors related to recurrence in PT, there is a need to re-evaluate the relationship between Ki67 indices and clinical outcomes to establish whether this simple and cost-effective ancillary diagnostic test should be integrated into clinical nomograms, particularly with regard to predicting responses in benign and borderline tumors.

This meta-analysis has several limitations. As noted above, only five studies were available for analysis, all of which were retrospective, and thus, selection bias cannot be excluded. The sample size in the meta-analysis was relatively small, limiting the level of evidence. Due to the limited number of available studies, it was required to combine results for similar but slightly different Ki67 thresholds (10 and 11.2%), which may have introduced a certain imprecision into the results. As the different Ki67 cut-off points were not considered, the optimal threshold for prognostication remains uncertain. Although the results of the meta-analysis remained the same when the study reporting OS outcomes was excluded, it was necessary to combine outcomes to fully evaluate the small number of available studies. Likewise, it was not possible to separate local from distant recurrences to evaluate the impact of the Ki67 index on the risk of distant recurrence/metastasis. Finally, Ki67 measurements were not standardized across laboratories, which may have influenced the results.

In conclusion, the present study was the first meta-analysis of the predictive value of Ki67 in PT of the breast and the results clearly show that a relatively high Ki67 index (>10%) is associated with recurrence. Given that Ki67 is widely used in clinical practice, it seems timely to re-evaluate the prognostic value of the marker in large retrospective cohorts with long follow-up to firmly establish whether it could contribute to identifying patients at risk of recurrence, particularly those with histologically benign disease. Doing so could impact clinical practice by refining follow-up recommendations based on quality evidence and sparing low-risk individuals from unnecessary imaging.

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Availability of data

The data generated in the present study may be requested from the corresponding author.

Author's contributions

FR was responsible for the conception and design of the study, data collection, analysis and interpretation of the data, drafting and revising the manuscript, and approval of the final version for publication. FR also checked and confirms the authenticity of the raw data for the pooled analysis.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that he has no competing interests.

References

1. Lissidini G, Mule A, Santoro A, Papa G, Nicosia L, Cassano E, Ashoor AA, Veronesi P, Pantanowitz L, Hornick JL and Rossi ED: Malignant phyllodes tumor of the breast: A systematic review. Pathologica 114: 111-120, 2022.
2. Rakha EA and Ellis IO: Phyllodes Tumor of the Breast. In: Textbook of Uncommon Cancer. Raghavan D, Blanke CD, Johnson DH, Moots PL, Reaman GH, Rose PG and Sekeres MA (eds). Wiley-Blackwell, Hoboken, NJ, p. 243-56, 2012.
3. Tan BY, Acs G, Apple SK, Badve S, Bleiweiss IJ, Brogi E, Calvo JP, Dabbs DJ, Ellis IO, Eusebi V, *et al*: Phyllodes tumours of the breast: A consensus review. Histopathology 68: 5-21, 2016.
4. Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, Lazar AJ, Morris EA, Sahin A, Salgado R, *et al*: The 2019 World Health Organization classification of tumours of the breast. Histopathology 77: 181-185, 2020.
5. Yu CY, Huang TW and Tam KW: Management of phyllodes tumor: A systematic review and meta-analysis of real-world evidence. Int J Surg 107: 106969, 2022.
6. Tan PH, Thike AA, Tan WJ, Thu MM, Busmanis I, Li H, Chay WY and Tan MH; Phyllodes Tumour Network Singapore: Predicting clinical behaviour of breast phyllodes tumours: A nomogram based on histological criteria and surgical margins. J Clin Pathol 65: 69-76, 2012.
7. Bogach J, Shakeel S, Wright FC and Hong NJL: Phyllodes Tumors: A scoping review of the literature. Ann Surg Oncol 29: 446-459, 2022.
8. Lim RS, Cordeiro E, Lau J, Lim A, Roberts A and Seely J: Phyllodes tumors-the predictors and detection of recurrence. Can Assoc Radiol J 72: 251-257, 2021.

9. Lashen AG, Toss MS, Ghannam SF, Makhlouf S, Green A, Mongan NP and Rakha E: Expression, assessment and significance of Ki67 expression in breast cancer: An update. J Clin Pathol 76: 357-364, 2023.
10. Finkelman BS, Zhang H, Hicks DG and Turner BM: The Evolution of Ki-67 and Breast Carcinoma: Past observations, present directions, and future considerations. Cancers (Basel) 15: 808, 2023.
11. Boninsegna L, Panzuto F, Partelli S, Capelli P, Delle Fave G, Bettini R, Pederzoli P, Scarpa A and Falconi M: Malignant pancreatic neuroendocrine tumour: Lymph node ratio and Ki67 are predictors of recurrence after curative resections. Eur J Cancer 48: 1608-1615, 2012.
12. La Rosa S: Diagnostic, prognostic, and predictive role of Ki67 proliferative index in neuroendocrine and endocrine neoplasms: Past, present, and future. Endocr Pathol 34: 79-97, 2023.
13. Yamaguchi T, Fujimori T, Tomita S, Ichikawa K, Mitomi H, Ohno K, Shida Y and Kato H: Clinical validation of the gastrointestinal NET grading system: Ki67 index criteria of the WHO 2010 classification is appropriate to predict metastasis or recurrence. Diagn Pathol 8: 65, 2013.
14. Tse GM, Niu Y and Shi HJ: Phyllodes tumor of the breast: An update. Breast Cancer 17: 29-34, 2010.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, *et al*: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 372: n71, 2021.
16. Stang A: Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25: 603-605, 2010.
17. Love J, Selker R, Marsman M, Jamil T, Dropmann D, Verhagen J, Ly A, Gronau QF, Šmíra M, Epskamp S, *et al*: JASP: Graphical statistical software for common statistical designs. Journal of Statistical Software 88: 1-17, 2019.
18. Kuijper A, de Vos RA, Lagendijk JH, van der Wall E and van Diest PJ: Progressive deregulation of the cell cycle with higher tumor grade in the stroma of breast phyllodes tumors. Am J Clin Pathol 123: 690-698, 2005.
19. Kuijper A, van der Groep P, van der Wall E and van Diest PJ: Expression of hypoxia-inducible factor 1 alpha and its downstream targets in fibroepithelial tumors of the breast. Breast Cancer Res 7: R808-R818, 2005.
20. Chan YJ, Chen BF, Chang CL, Yang TL and Fan CC: Expression of p53 protein and Ki-67 antigen in phyllodes tumor of the breast. J Chin Med Assoc 67: 3-8, 2004.
21. Niezabitowski A, Lackowska B, Rys J, Kruczak A, Kowalska T, Mitus J, Reinfuss M and Markiewicz D: Prognostic evaluation of proliferative activity and DNA content in the phyllodes tumor of the breast: Immunohistochemical and flow cytometric study of 118 cases. Breast Cancer Res Treat 65: 77-85, 2001.
22. Shpitz B, Bomstein Y, Sternberg A, Klein E, Tiomkin V, Kaufman A, Groisman G and Bernheim J: Immunoreactivity of p53, Ki-67, and c-erbB-2 in phyllodes tumors of the breast in correlation with clinical and morphologic features. J Surg Oncol 79: 86-92, 2002.
23. Yonemori K, Hasegawa T, Shimizu C, Shibata T, Matsumoto K, Kouno T, Ando M, Katsumata N and Fujiwara Y: Correlation of p53 and MIB-1 expression with both the systemic recurrence and survival in cases of phyllodes tumors of the breast. Pathol Res Pract 202: 705-712, 2006.
24. Sain B, Gupta A, Ghose A, Halder S, Mukherjee V, Bhattacharya S, Mondal RR, Sen AN, Saha B, Roy S and Boussios S: Clinico-Pathological factors determining recurrence of phyllodes tumors of the breast: The 25-year experience at a tertiary cancer centre. J Pers Med 13: 866, 2023.
25. McCarthy E, Kavanagh J, O'Donoghue Y, McCormack E, D'Arcy C and O'Keeffe SA: Phyllodes tumours of the breast: Radiological presentation, management and follow-up. Br J Radiol 87: 20140239, 2014.
26. Chng TW, Lee JY, Lee CS, Li H, Tan MH and Tan PH: Validation of the Singapore nomogram for outcome prediction in breast phyllodes tumours: An Australian cohort. J Clin Pathol 69: 1124-1126, 2016.
27. Choi JE, Kang SH, Tan PH and Bae YK: Recurrence prediction for breast phyllodes tumours: Validation of the Singapore nomogram in Korean women. J Clin Pathol 75: 159-163, 2022.
28. Nishimura R, Tan PH, Thike AA, Tan MH, Taira N, Li HH and Ohsumi S: Utility of the Singapore nomogram for predicting recurrence-free survival in Japanese women with breast phyllodes tumours. J Clin Pathol 67: 748-750, 2014.