REVIEW

Editorial Process: Submission:03/08/2024 Acceptance:09/01/2024

Investigating the Co-Expression Rate of *HER2* and *HER3* Biomarkers in Cancer Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: Many types of cancer express the *HER2/HER3* heterodimer, which is a crucial oncogenic unit. Research has shown that when these two biomarkers are expressed together, it correlates with higher tumor aggressiveness and lower overall survival rate. Therefore, many therapies have been developed to target both biomarkers simultaneously. This study aims to collect data on the co-expression levels of these biomarkers across different types of cancers. **Methods:** A comprehensive search was conducted across PubMed, Scopus, Embase, and Web of Science databases to identify relevant studies. The event rates and their corresponding 95% confidence intervals were calculated. Heterogeneity, subgroup, and meta-regression analyses were conducted based on patients' residency region, age, and gender. The protocol of this study was registered in PROSPERO under ID: CRD42024504256. **Results:** We have detected 60 studies that met all of the inclusion criteria for our research. Out of these, we have focused on a total of 19 studies (with 6,079 participants) related to breast cancer, 9 studies (with 829 participants) related to lung cancer, 6 studies (with 1423 participants) related to gastric cancer, and 4 studies (with 802 participants) related to colorectal cancer for conducting our meta-analysis. According to our results, the co-expression rate of HER2 and *HER3* in breast cancer patients is 18.5% (95%CI 11.7–27.9), in colorectal cancer patients is 17.1% (95%CI 2.4–63.4), in gastric cancer patients is 11.3% (95%CI 4.2–17.2), and in lung cancer patients is 12.7% (95%CI 5.2–22.8). The co-expression of HER2 and *HER3* in lung cancer has a significant association with patients' gender (P=0.038). **Conclusion:** The study found that HER2 and *HER3* biomarkers, which are targets for different therapies, are co-expressed in various types of cancer.

Keywords: Cancer- co-expression- HER2- *HER3*- meta-analysis

Asian Pac J Cancer Prev, **25 (9)**, 2979-2990

Introduction

The human epidermal growth factor receptor (HER) receptor family is widely recognized for its significant impact on various forms of human cancer pathogenesis [1]. The HER family consists of four members, with *HER2* and *HER3* being the two most significant ones [2]. Upon interacting with extracellular ligands, these receptors initiate various downstream pathways that govern a wide range of processes, including differentiation, migration, proliferation, and survival [3].

The *HER2* receptor is found on the cell membrane and can activate tyrosine kinases. The overexpression of the *HER2* receptor plays a crucial role in the process of transformation and tumorigenesis [4]. Different subcategories of human cancers have been observed to exhibit varying levels of *HER2* overexpression, and assessing the *HER2* status is essential in determining the suitability of anti-*HER2* targeted therapies [5]. Nevertheless, *HER3* is unique among the members of the HER family in that it lacks tyrosine kinase activity. Recognizing *HER3*'s role in tumor growth, rapid multiplication, and drug resistance in cancers like breast and non-small cell lung cancer highlights the importance of disabling *HER3* and its signaling pathways to overcome treatment resistance and improve outcomes for cancer patients [6].

As there is no known ligand for *HER2* and *HER3* has a faulty intrinsic tyrosine kinase, *HER2* prefers to combine with *HER3* to form heterodimers [7]. The *HER2*/*HER3* heterodimer is a potent oncogenic unit that is linked to various cancers' progression and poor overall survival [8]. The evasion of apoptosis is significantly influenced by the interaction between *HER2* and *HER3*, which is reliant on

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the presence of the *HER3* ligand (heregulin) [9].

Due to the significance of this co-expression, agents have been designed with the specific purpose of targeting the dimerization of *HER2-HER3*. Pertuzumab serves as an illustration of such an agent. It functions as an antibody that efficiently obstructs the formation of *HER2-HER3* dimers upon ligand binding [10, 11]. Furthermore, certain studies have employed drugs that target *HER2* and *HER3* simultaneously in cancer treatment [12-14].

Despite several studies conducted on the co-expression of *HER2* and *HER3* receptors in different types of cancer, none of these studies have specifically collected data regarding the expression levels of this co-expression across various cancer types. Based on the available data, we hypothesize that many types of cancer express the dimer of *HER2-HER3*. Therefore, the objective of this study was to gather and analyze the results from reliable studies to examine the co-expression level of *HER2* and *HER3* across different types of cancer.

Materials and Methods

Search strategy

This meta-analysis was conducted in compliance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and registered in the PROSPERO registry (CRD42024504256). We searched multiple databases including Scopus, PubMed, Web of Science, and EMBASE to find relevant studies. Additionally, we manually searched the available literature on Google Scholar, covering up to 30 pages, and reviewed the references of the identified studies to locate relevant research. Our search was not limited by language and included studies published until January 2024. To conduct our search, we used the terms "*HER2*," "*HER3*," and "Co-expression," along with their corresponding synonyms. Due to the data type in the present study, we used an epidemiological meta-analysis design.

Study selection and data extraction

In this meta-analysis, we included all case-control studies investigating the *HER2* and *HER3* co-expression levels in cancerous patients. Our main objective is to determine the expression rate of *HER2* and *HER3* co-expression in cancer patients and gather essential data. We have clearly defined exclusion criteria, which include letters, editorials, abstracts, conference abstracts, and publications lacking sufficient information. Furthermore, we have excluded studies that used patients with diseases unrelated to cancer. Two independent investigators (RHM and NA) assessed studies based on predetermined inclusion and exclusion criteria in a blinded manner. Disagreements were resolved through consensus. The data collected was inputted into an Excel spreadsheet that included the primary author's last name, the study's location and date, the total number of cancer patients, the number of patents with *HER2-HER3* dimerization, the mean age of the patients, the ethnicity of patients, and the method applied to evaluate biomarker expression.

Assessing the risk of bias

The quality of the included studies was assessed using the Joanna Briggs Institute Critical Appraisal Instrument (JBI) for systematic reviews of prevalence and incidence [15, 16]. Two authors (RHM and NA) independently conducted the evaluation blindly. In the event of any disagreement, a third person was consulted to resolve the issue. This instrument has been proven to be a reliable and valid tool for evaluating observational studies. The risk of bias was categorized as high if the study scored 49% or below, moderate if the study scored between 50% and 69%, and low if the study scored 70% or above [17].

Statistical analysis

The statistical analysis was performed using the Comprehensive Meta-analysis software version 3, developed in Biostat, USA. The statistical analysis used the total sample size and the number of patients with her2-her3 co-expression to determine the odds ratios and their corresponding 95% confidence intervals. A p-value lower than 0.05 is considered statistical significance. The Cochrane Q and I^2 statistics were used to evaluate the heterogeneity of the studies. If the Cochrane Q P-value was less than 0.1 and the I^2 value exceeded 50%, indicating the presence of statistical heterogeneity, a random-effects model was used to estimate the outcome data. Conversely, a fixed-effects model was employed in other cases. In order to evaluate how confounding variables affected the results of the meta-analysis, subgroup analysis, and meta-regression were performed. Furthermore, a sensitivity analysis was carried out by systematically excluding each study to assess the reliability of the findings.

Results

Study design and description of included studies

The Figure 1 illustrates the process of literature screening and study selection. After conducting an initial online investigation, we obtained a total of 6,624 articles from the EMBASE, PubMed, Scopus, and Web of Science library databases that could be relevant. After carefully examining the titles, abstracts, and keywords, 6524 articles were eliminated from consideration due to duplication or lack of relevance to the present analysis.

Finally, we found 100 studies that report the rates of *HER2-HER3* co-expression in cancer patients. Out of these, 40 studies were excluded due to incomplete information, low quality, and not meeting the exclusion criteria. The remaining 60 studies were selected for the present study, and we have provided their details in Table 1. Out of all the studies conducted, nineteen studies involved 6,079 patients with breast cancer, while nine studies involved 829 patients with lung cancer. Six studies included 1,423 patients with gastric cancer, and four studies included 802 patients with colorectal cancer. The remaining studies focused on other types of cancer.

Risk of bias assessment

The analysis covered various studies and their quality was assessed using the JBI quality assessment checklist

Table 1. Fundamental Features of the Included Studies

Cancer type	First author	Year	Country	Continent	Total number of patients	Number of cases with HER2 and HER3 co-expression	Mean Age or Age Range	Gender	Method of HER2 and HER3 evaluation	JBI Score
Breast cancer	Bobrow [27]	1997	UK	European	53	7	-	F:53 M:0	IHC	77.7
	Suo [28]	2002	Norway	European	97	9	64	F:97 M:0	IHC	100
	Hudelist [29]	2003	Austria	European	74	59	54.2	F:74 M:0	Western blot-analysis	100
	Witton [30]	2003	UK	European	220	26	-	F:220 M:0	IHC	100
	El-Rehim [31]	2004	UK	European	1406	51	53	F:1406 M:0	IHC	100
	Barnes [32]	2005	UK	European	105	8	55	F:105 M:0	IHC	100
	Wiseman [33]	2005	Canada	North American	242	2	-	F:242 M:0	IHC	88.8
	Bianchi [34]	2006	Italy	European	145	40	52.6	F:145 M:40	IHC	88.8
	Yen [35]	2006	USA	North American	35	12	-	F:35 M:0	Western-Blot	88.8
	Kaya [36]	2008	Turkey	European	59	11	59	F:59 M:0	IHC	100
	Haas [37]	2009	Germany	European	171	41	-	F:171 M:0	IHC	100
	Gori [38]	2012	Italy	European	61	31	53	F:61 M:0	IHC	100
	Spears [39]	2012	UK	European	291	124	50.9	F:291 M:0	Proximity ligation assay	100
	Spears [40]	2012	UK	European	692	67	-	F:692 M:0	IHC	100
	Bae [41]	2013	Korea	Asian	235	103	23-77	F:235 M:0	IHC	100
	Czopek [42]	2013	Poland	European	35	16	54.4	F:35 M:0	IHC	88.8
	Jerjees [43]	2014	UK	European	1401	92	54	F:1401 M:0	IHC	100
	Luhtala [44]	2018	Finland	European	308	46	61	F:308 M:0	IHC	100
	Hassanzadeh Makoui [45]	2024	Iran	Asian	444	53	-	F:441 M:3	IHC	100
Biliary tract cancers	Lamarca [46]	2018	UK	European	67	1	65.6	F:35 M:32	IHC	77.7
Bladder cancer	Chow [47]	2001	China	Asian	245	67	63.3	F:80 M:165	IHC	100
	Memon [48]	2006	Denmark	European	88	29	72	F:19 M:69	RT-PCR	88.8

Table 1. Continued

Cancer type	First author	Year	Country	Continent	Total number of patients	Number of cases with HER2 and HER3 co-expression	Mean Age or Age Range	Gender	Method of HER2 and HER3 evaluation	JBI Score
Colorectal cancer	Khelwatty [49]	2014	UK	European	86	20	-	F:37 M:49	IHC	100
	Seo [50]	2015	Korea	Asian	364	21	-	F:59 M:305	IHC	100
	Stahler [51]	2017	Germany	European	208	6	-	-	IHC	77.7
	Khelwatty [52]	2021	UK	European	144	109	-	F:43 M:101	IHC	100
Endometrial cancer	Androutsopoulos [53]	2013	Greece	European	10	9	67.3	-	IHC	77.7
Esophageal adenocarcinoma	Yoon [54]	2014	USA	North American	224	38	-	F: M:	IHC	88.8
Esophagogastric adenocarcinoma	Chan [55]	2016	USA	North American	52	18	66	F:10 M:42	IHC	88.8
Extrahepatic cholangiocarcinoma	Lee [56]	2012	Korea	Asian	224	13	60.9	F:66 M:164	IHC	100
Gastric Cancer	Lee [57]	2013	Korea	Asian	50	13	61	-	Collaborative Enzyme Enhanced Reactive-immunoassay	66.6
	Ja´come [58]	2014	Brazil	South American	200	23	62	F:77 M:124	IHC	100
	He [59]	2015	China	Asian	498	25	59	F:148 M:350	IHC	100
	Tang [60]	2015	China	Asian	121	14	-	F:36 M:85	IHC	100
	Yun [61]	2018	Korea	Asian	502	13	62	F:170 M:332	IHC	100
Glioblastoma	Torp [62]	2007	Norway	European	21	8	30-79	F:9 M:12	IHC	88.8
Head and neck squamous cell carcinoma	Takikita [63]	2011	USA	North American	387	13	61	F:95 M:292	IHC	77.7
Laryngeal squamous cell carcinoma	Almadori [64]	2021	Italy	European	132	14	-	-	IHC	77.7
Lung cancer	Nishio [65]	2006	Japan	Asian	31	13	62	F:11 M:20	IHC	77.7
	Sonnweber [66]	2006	Austria	European	79	21	61	F:18 M:60	IHC	88.8
	Koutsopoulos [67]	2007	Greece	European	209	3	62	F:20 M:189	IHC	88.8
	Fujita [68]	2008	Japan	Asian	52	7	-	-	IHC	77.7
	Xu [60]	2008	China	Asian	90	13	64	F:46 M:44	IHC	100
	Xu [70]	2009	China	Asian	106	12	62	F:51 M:55	IHC	100
	Berghoff [71]	2013	Austria	European	131	7	57	F: M:	IHC	77.7
	Siegfried [72]	2015	USA	North American	86	13	68.2	F:57 M:47	IHC	100
	Manickavasagar [73]	2021	UK	European	45	5	58	F:26 M:19	IHC	88.8

Table 1. Continued

Cancer type	First author	Year	Country	Continent	Total number of patients	Number of cases with HER2 and HER3 co-expression	Mean Age or Age Range	Gender	Method of HER2 and HER3 evaluation	JBI Score
Nasopharyngeal carcinoma	Tulalamba [74]	2014	Thailand	Asian	82	0	48.67	F:25 M:57	IHC	100
Neuroblastic tumors	Izycka-Swieszewska [75]	2011	Poland	European	103	37	-	F:103 M:0	IHC	100
Oral squamous cell carcinoma	Bei [76]	2001	USA	North American	32	10	-	-	IHC	77.7
Osteosarcoma	Wang [77]	2018	China	Asian	60	6	24	F:21 M:39	IHC	100
Ovarian cancer	Simpson [78]	1995	UK	European	46	34	60	F:46 M:0	IHC	88.8
	Puvanenthiran [79]	2018	UK	European	60	37	-	F:60 M:0	IHC	100
Pancreatic cancer	Thomas [80]	2014	France	European	44	5	-	-	IHC	77.7
Papillary thyroid carcinoma	Haugen [81]	1996	Norway	European	56	36	-	-	IHC	66.6
Prostate cancer	Carlsson [82]	2013	China	Asian	12	3	57-74	F:0 M:12	IHC	77.7
Squamous cell carcinomas of head and neck	O-charoenrat [83]	2002	UK	European	54	20	59.7	F:10 M:44	RT-PCR	88.8
Squamous cell carcinomas of oral cavity and base of tongue	Ekberg [84]	2005	Sweden	European	19	3	49-82	F:11 M:8	IHC	77.7
Squamous cell carcinoma of skin	Krahn [85]	2001	Germany	European	5	1	-	-	RT-PCR	66.6
Thymic carcinoma	Weissferdt [86]	2012	USA	North American	24	8	62.3	F:4 M:20	IHC	88.8

for systematic reviews of prevalence and incidence. The studies were rated on a scale of 0 to 100%. Studies with scores below 50% were excluded, and the quality scores of the remaining studies were presented in Table 1.

Meta-analysis results

According to our analysis, the rate of simultaneous expression of *HER2* and *HER3* biomarkers in breast cancer patients is 18.5% (95%CI 11.7–27.9), in colorectal cancer patients is 17.1% (95%CI 2.4–63.4), in gastric cancer patients is 11.3% (95%CI 4.2–17.2), and in lung cancer patients is 12.7% (95%CI 5.2–22.8). Figure 2 shows the corresponding forest plots.

Moreover, we evaluated the concomitant expression rate of *HER2* and *HER3* in various types of cancers. Our analysis of the data gathered from various studies revealed the following co-expression rates: 1.5% in biliary tract carcinoma, 28.9% in bladder cancer, 18.5% in breast cancer, 17.1% in colorectal cancer, 90% in endometrial carcinoma, 17% in esophageal adenocarcinoma, 5.8% in extrahepatic cholangiocarcinoma, 11.3% in gastric cancer, 38.1% in glioblastoma, 12.5% in head and neck squamous cell carcinoma, 10.6% in laryngeal squamous cell carcinoma, 12.7% in lung cancer, 0% in nasopharyngeal carcinoma, 35.9% in neuroblastic tumors, 26.4% in oral squamous cell carcinoma, 10% in osteosarcoma, 67.3% in ovarian cancer, 11.4% in pancreatic cancer, 25% in prostate cancer, 20% in skin squamous cell carcinoma, and 49.8% in thyroid cancer.

Table 2. The Heterogeneity Analysis of the Conducted Studies

Cancer type	Number of included studies	I^2 (%)	Q-test's P value
Breast cancer	19	97.48	P<0001
Colorectal cancer	4	98.64	P<0001
Gastric cancer	6	93.84	P<0001
Lung cancer	9	84.53	P<0001

Heterogeneity, subgroup analysis and meta-regression analysis

After analyzing the data using the I^2 index and Q test, we found that there is a significant heterogeneity among the studies (Table 2). Therefore, we have decided to conduct subgroup analysis and meta-regression tests to determine the potential factors that might be contributing to this heterogeneity using the available data. The results of the subgroup analysis indicate that the difference in the patients' geographical locations does not significantly

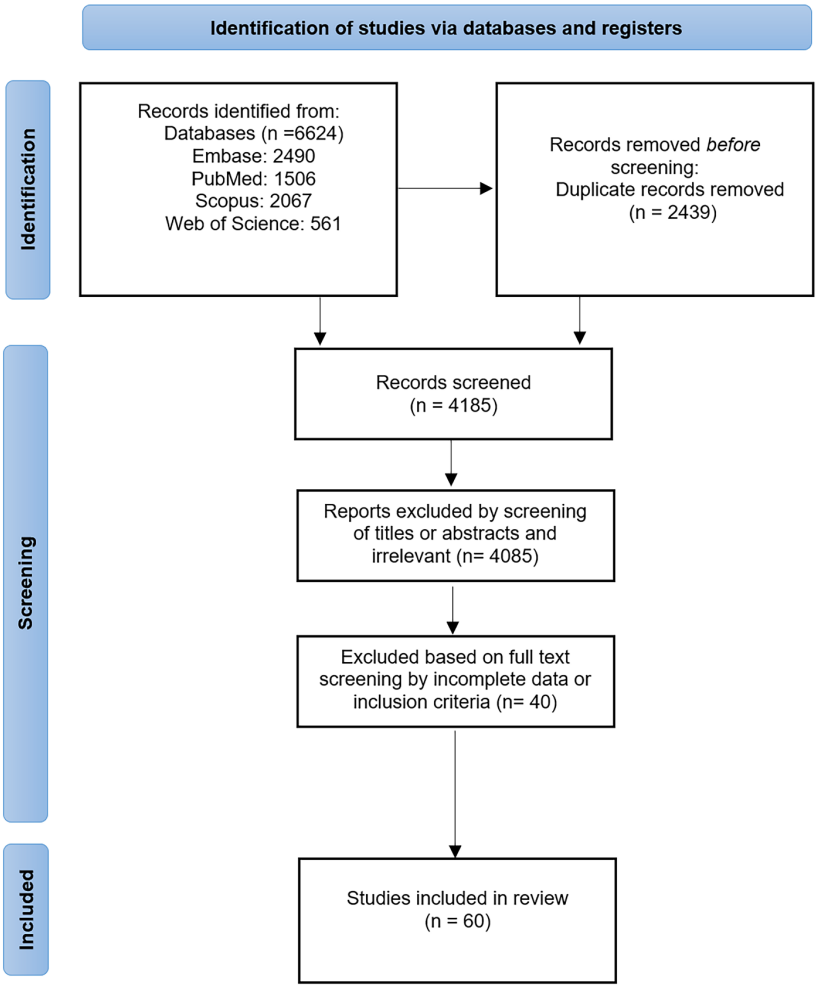

Figure 1. The Flow Diagram of Literature Search and Study Selection

impact the co-expression of *HER2* and *HER3* in breast (P=0.786), gastric (P=0.490) and lung (P=0.456) cancers. Therefore, region of residency cannot be considered as the cause of heterogeneity.

Furthermore, we utilized meta-regression to assess the impact of age on the co-expression of *HER2* and *HER3* in breast and lung cancers, as well as the influence of gender on the co-expression of *HER2* and *HER3* in lung cancer and the cancers prevalent in both males and females. Our findings indicate that age doesn't have a significant impact on the co-expression of *HER2* and *HER3* in breast and lung cancers (P=0.304 and P=0.529 respectively). Although gender had a significant impact on the co-expression of *HER2* and *HER3* in lung cancer (P=0.038), it did not show a significant effect on this co-expression in the combined results of cancers affecting both sexes (P=0.796). As a result, gender may be one of the influential factors in creating heterogeneity in the results of studying the co-expression of *HER2* and *HER3* in lung cancer. Scatter plot diagrams related to our meta-regression analysis are shown in Figure 3.

Sensitivity analysis

We conducted a Sensitivity analysis by excluding one study at a time. The outcomes indicated that the results of our meta-analysis were not significantly changed even when each study was omitted. This further strengthens the credibility and reliability of our research findings.

Discussion

Targeted therapy for tumors expressing the *HER2*/*HER3* heterodimer is crucial due to its significance in tumor development [18]. *HER3* induces resistance to *HER2*-targeted treatment by activating the PI3K/AKT and SRC signaling pathways, which are two crucial molecular mechanisms implicated in the development of resistance to trastuzumab and lapatinib [19]. Due to the issue's importance, the simultaneous expression rate of *HER2* and *HER3* in cancer patients was analyzed.

Our research has found that *HER2* and *HER3* are expressed simultaneously in a wide range of cancer types. The outcomes of our study align with those of Iqbal et al.'s research [1], which demonstrated the presence of *HER2* in different cancer types, and Majumdar et al.'s investigation [6], which showed the existence of *HER3* in various types of cancer. Trastuzumab monotherapy yields response rates ranging from 11% to 26% in metastatic breast cancer [20]. Our study indicates that incorporating concurrent *HER2* and *HER3* therapy in breast cancer and other cancer types could be a beneficial strategy to improve the efficacy of anti-*HER2* treatment.

The data analysis regarding the co-expression of

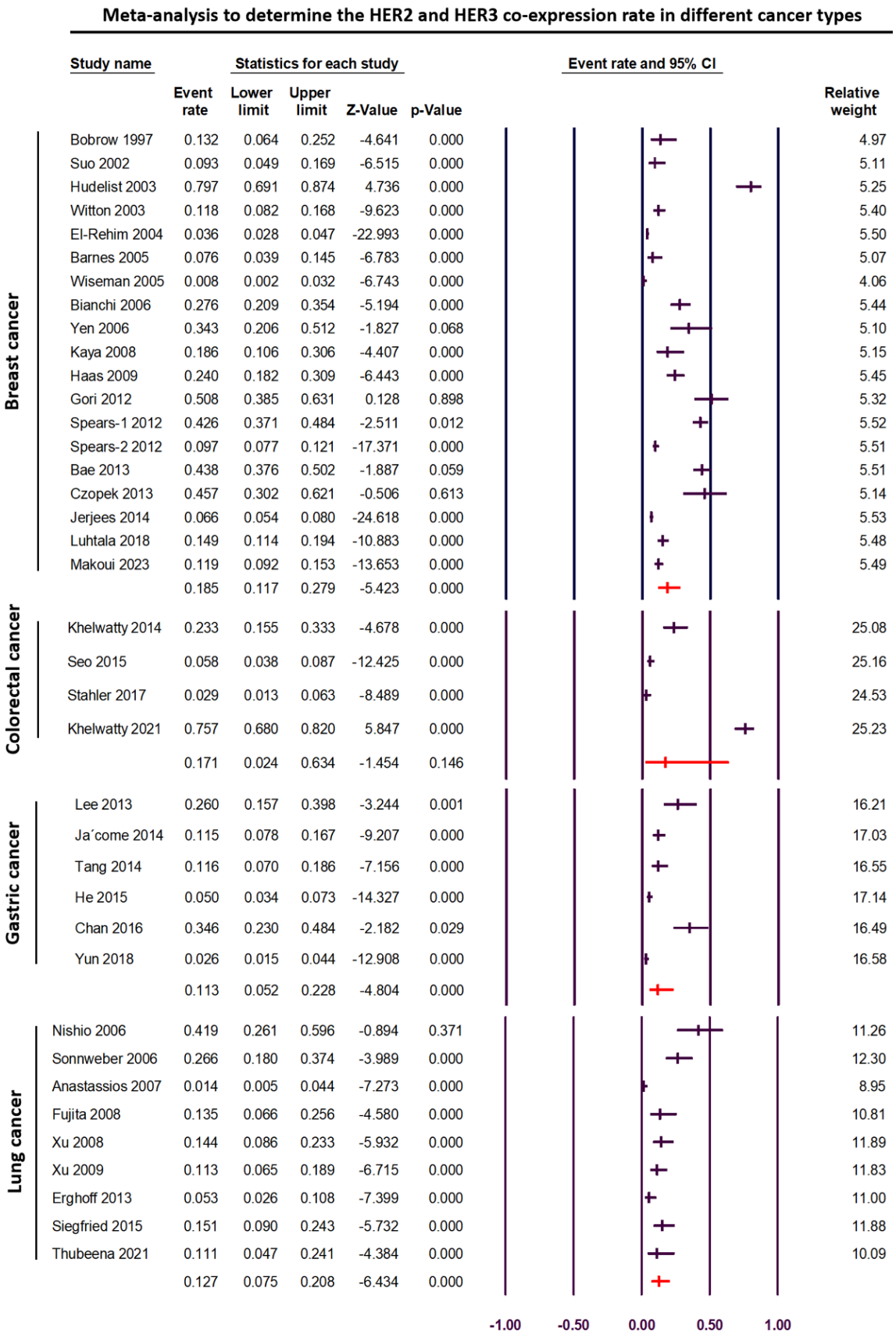

Figure 2. Forest Plots of Studies Examining the Co-Expression Rate of HER2 and HER3 in Breast, Colorectal, Gastric and Lung Cancers.

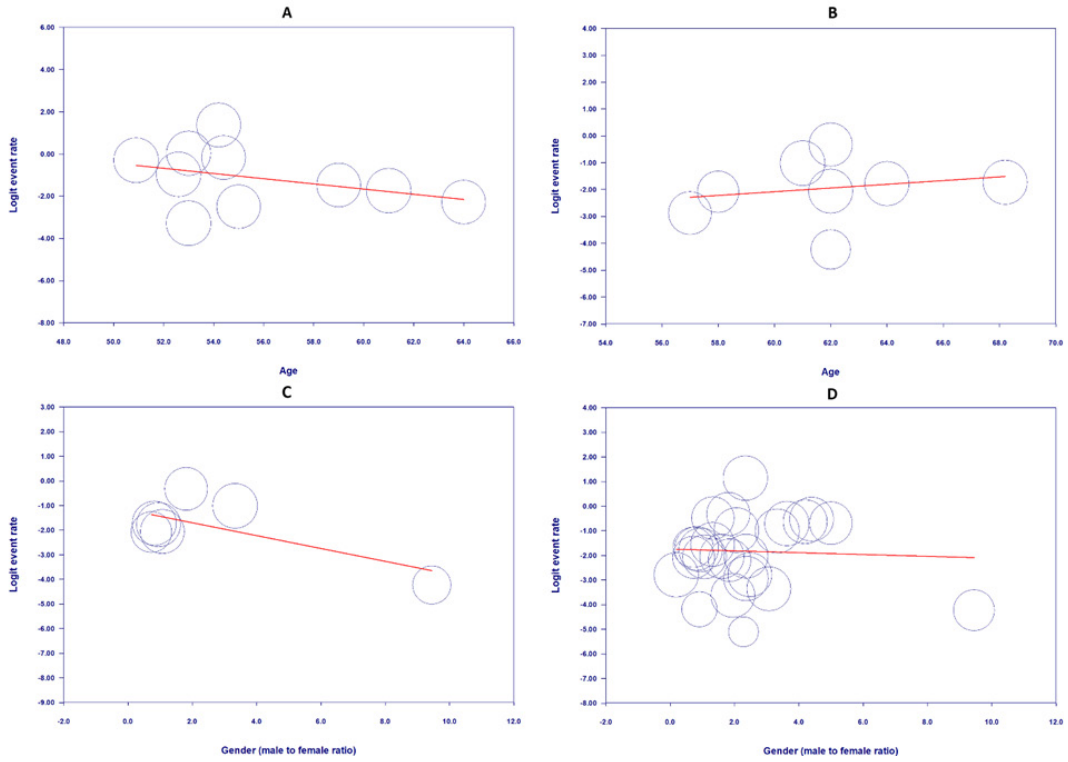

Figure 3. Meta-Regression Linear Prediction Plots that Show the Correlation between Age and the Co-Expression of HER2 and HER3 in Breast and Lung Cancers (A and B, respectively); meta-regression linear prediction plots that show the correlation between gender and the co-expression of HER2 and HER3 in lung cancer and the cancers that affect both males and females (C and D, respectively)

HER2 and *HER3* exhibited significant heterogeneity across studies. Consequently, subgroup analysis and mete-regression were conducted on the number of possible factors, such as median age, gender, and region of residency among the patients included in the study. Out of all the factors analyzed, only gender showed a significant correlation with lung cancer, with the co-expression of *HER2* and *HER3* being significantly higher among women than men. However, to validate this relationship, more studies need to be included in future investigations. There are reports in the literature that have found a correlation between biomarker expression and gender in some types of cancer. One such study by Chen et al. [21] supports our findings and suggests that *HER2* IHC expression levels are associated with gender. The study found that the rate of *HER2* positivity was higher in female patients than in male patients with esophageal squamous cell carcinoma. In a different research study, Fatih et al. [22] found that healthy men have higher levels of *HER2* in their serum than healthy women. This result was contrary to the result of our study. The reason for this discrepancy could be the possibility that this relationship differs in healthy individuals versus those with lung cancer. Additionally, the co-expression with *HER3* may have an impact on the results. According to the studies conducted by Wei et al. [23], Pillai et al. [24], and Ninomiya et al. [25], it has been observed that *HER2* mutations are more prevalent in females than males among patients with lung cancer. These mutations may be linked to increased expression of *HER2*, which could explain our study's findings regarding higher expression of HER-*HER3* in females with lung cancer compared to males. In line with our research, Toschi et al. [26] have found a strong correlation between the female gender and the presence of a positive *HER3* pattern in advanced non-small-cell lung cancer.

Several factors could contribute to the observed heterogeneity that can be investigated in future studies. They include variations in ethnicity, body mass index, differences in the methods used to detect the expression rate of *HER2* and *HER3*, variations in the primary antibodies used for immunohistochemistry staining, differences in the individuals who scored the sample slides, and variances in the temperature of the room where the immunohistochemistry was conducted.

The current research is the first meta-analysis to focus on the co-expression rate of *HER2* and *HER3*. In this investigation, we only included medium and high-quality studies based on the JBI scale. The majority of the studies selected for this analysis used a single technique to measure the expression levels of *HER2* and *HER3*. Additionally, the median age of patients included in the study was nearly uniform. It is important to acknowledge the limitations of our study. Firstly, while efforts were made to standardize the cutoff values for *HER2* and *HER3* in the selected studies, slight variations were observed in certain studies. These variations should be taken into account for future research endeavors. Finally, in this study, meta-analysis was not possible for types of cancer other than breast, colorectal, gastric, and lung due to limited studies available. This highlights the need for

future meta-analyses to be carried out.

In conclusion, the study's findings indicate that several types of cancer, including biliary tract carcinoma, bladder cancer, breast cancer, colorectal cancer, endometrial carcinoma, esophageal adenocarcinoma, in extrahepatic cholangiocarcinoma, in gastric cancer, glioblastoma, head and neck squamous cell carcinoma, laryngeal squamous cell carcinoma, lung cancer, nasopharyngeal carcinoma, in neuroblastic tumors, oral squamous cell carcinoma, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, skin squamous cell carcinoma, and thyroid cancer, exhibit co-expression of *HER2* and *HER3* biomarkers and this heterodimer can be targeted in this cancers.

Author Contribution Statement

MHM and SHF collaborated to develop the idea, design, and plan the study. MHM reviewed the literature, while RHM and NA reviewed the selected studies, checked their quality, and collected the required data. MHM performed statistical analysis of the data and wrote the first draft of the manuscript. All authors contributed to the interpretation of the results and made revisions to the manuscript. All authors have read and approved the final version of the manuscript for publication.

Acknowledgements

We would like to express our appreciation to the authors whose articles were utilized in this research.

Registration and reporting

The protocol of this study was registered in PROSPERO under ID: CRD42024504256.

Ethical approval

Ethical approval is unnecessary for this systematic review and meta-analysis because this is a literature-based study and does not directly involve human or animal subjects.

Conflict of interest

The authors confirm that they have no conflicts of interest.

References

1. Iqbal N, Iqbal N. Human epidermal growth factor receptor 2 (her2) in cancers: Overexpression and therapeutic implications. Mol Biol Int. 2014;2014:852748. https://doi.org/10.1155/2014/852748.
2. Zhang BY, Zhang L, Chen YM, Qiao X, Zhao SL, Li P, et al. Corosolic acid inhibits colorectal cancer cells growth as a novel her2/her3 heterodimerization inhibitor. Br J Pharmacol. 2021;178(6):1475-91. https://doi.org/10.1111/bph.15372.
3. Mishra R, Patel H, Alanazi S, Yuan L, Garrett JT. Her3 signaling and targeted therapy in cancer. Oncol Rev. 2018;12(1):355. https://doi.org/10.4081/oncol.2018.355.
4. Tan ML, Yeap JW, Matawali A. Her receptor, current, and emerging therapeutic targets. In: Rezaei N, editor. Handbook of cancer and immunology. Cham: Springer International Publishing; 2022. p. 1-32.
5. Scholl S, Beuzeboc P, Pouillart P. Targeting her2 in other tumor types. Ann Oncol. 2001;12:S81-S7. https://doi.org/10.1093/annonc/12.suppl_1.S81.
6. Majumder A. Her3:Toward the prognostic significance, therapeutic potential, current challenges, and future therapeutics in different types of cancer. Cells. 2023;12(21):2517. https://doi.org/10.3390/cells12212517
7. Dey N, Williams C, Leyland-Jones B, De P. A critical role for her3 in her2-amplified and non-amplified breast cancers: Function of a kinase-dead rtk. Am J Transl Res. 2015;7(4):733-50.
8. Gandullo-Sánchez L, Ocaña A, Pandiella A. Her3 in cancer: From the bench to the bedside. J Exp Clin Cancer Res. 2022;41(1):310. https://doi.org/10.1186/s13046-022-02515-x.
9. Watanabe S, Yonesaka K, Tanizaki J, Nonagase Y, Takegawa N, Haratani K, et al. Targeting of the her2/her3 signaling axis overcomes ligand-mediated resistance to trastuzumab in her2-positive breast cancer. Cancer Med. 2019;8(3):1258-68. https://doi.org/10.1002/cam4.1995.
10. Liu X, Luan L, Liu X, Jiang D, Deng J, Xu J, et al. A novel nanobody-based her2-targeting antibody exhibits potent synergistic antitumor efficacy in trastuzumab-resistant cancer cells. Front Immunol. 2023;14:1292839. https://doi.org/10.3389/fimmu.2023.1292839.
11. Nami B, Maadi H, Wang Z. Mechanisms underlying the action and synergism of trastuzumab and pertuzumab in targeting her2-positive breast cancer. Cancers (Basel). 2018;10(10). https://doi.org/10.3390/cancers10100342.
12. Rau A, Kocher K, Rommel M, Kühl L, Albrecht M, Gotthard H, et al. A bivalent, bispecific dab-fc antibody molecule for dual targeting of her2 and her3. MAbs. 2021;13(1):1902034. https://doi.org/10.1080/19420862.2021.1902034.
13. Yu X, Ghamande S, Liu H, Xue L, Zhao S, Tan W, et al. Targeting egfr/her2/her3 with a three-in-one aptamer-sirna chimera confers superior activity against her2⁺ breast cancer. Mol Ther Nucleic Acids. 2018;10:317-30. https://doi.org/10.1016/j.omtn.2017.12.015.
14. Robinson MK, Hodge KM, Horak E, Sundberg ÅL, Russeva M, Shaller CC, et al. Targeting erbb2 and erbb3 with a bispecific single-chain fv enhances targeting selectivity and induces a therapeutic effect in vitro. Br J Cancer. 2008;99(9):1415-25. https://doi.org/10.1038/sj.bjc.6604700.
15. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc. 2015;13(3):147-53. https://doi.org/10.1097/xeb.0000000000000054.
16. Munn Z MS, Lisy K, Riitano D, Tufanaru C. Chapter 5: Systematic reviews of prevalence and incidence. In: Aromataris e, munn z (editors). In: JBI Manual for Evidence Synthesis. JBL. 2020. Available from: https://jbi.global/critical-appraisal-tools.
17. Cai Y, Song Y, He M, He W, Zhong X, Wen H, et al. Global prevalence and incidence of hallux valgus: A systematic review and meta-analysis. J Foot Ankle Res. 2023;16(1):63. https://doi.org/10.1186/s13047-023-00661-9.
18. Larsen ME, Lyu H, Liu B. *HER3*-targeted therapeutic antibodies and antibody–drug conjugates in non-small cell lung cancer refractory to EGFR-tyrosine kinase inhibitors. Chinese Medical Journal Pulmonary and Critical Care Medicine. 2023;1(1):11-7. https://doi.org/10.1016/j.pccm.2022.12.001
19. Uliano J, Corvaja C, Curigliano G, Tarantino P. Targeting her3 for cancer treatment: A new horizon for an old target. ESMO Open. 2023;8(1):100790. https://doi.org/10.1016/j.

esmoop.2023.100790.
20. Gajria D, Chandarlapaty S. Her2-amplified breast cancer: Mechanisms of trastuzumab resistance and novel targeted therapies. Expert Rev Anticancer Ther. 2011;11(2):263-75. https://doi.org/10.1586/era.10.226.
21. Chen Y, Zhu SM, Xu XL, Zhao AN, Hu JL. Expression levels of her2 and mrp1 are not prognostic factors of long-term survival in 829 patients with esophageal squamous cell carcinoma. Oncol Lett. 2016;11(1):745-52. https://doi.org/10.3892/ol.2015.3975.
22. Tehrani Fateh S, Behgozin A, Yekani F, Geranpayeh L, Olfatbakhsh A, Moghaddam S, et al. Healthy male individuals possess higher plasma her-2 level than females. Cell J. 2023;25(1):73-5. https://doi.org/10.22074/cellj.2022.562589.1134.
23. Wei XW, Gao X, Zhang XC, Yang JJ, Chen ZH, Wu YL, et al. Mutational landscape and characteristics of erbb2 in non-small cell lung cancer. Thorac Cancer. 2020;11(6):1512-21. https://doi.org/10.1111/1759-7714.13419.
24. Pillai RN, Behera M, Berry LD, Rossi MR, Kris MG, Johnson BE, et al. Her2 mutations in lung adenocarcinomas: A report from the lung cancer mutation consortium. Cancer. 2017;123(21):4099-105. https://doi.org/10.1002/cncr.30869.
25. Ninomiya K, Hata T, Yoshioka H, Ohashi K, Bessho A, Hosokawa S, et al. A prospective cohort study to define the clinical features and outcome of lung cancers harboring her2 aberration in japan (her2-cs study). Chest. 2019;156(2):357-66. https://doi.org/10.1016/j.chest.2019.01.011.
26. Cappuzzo F, Toschi L, Domenichini I, Bartolini S, Ceresoli GL, Rossi E, et al. Her3 genomic gain and sensitivity to gefitinib in advanced non-small-cell lung cancer patients. Br J Cancer. 2005;93(12):1334-40. https://doi.org/10.1038/sj.bjc.6602865.
27. Bobrow LG, Millis RR, Happerfield LC, Gullick WJ. C-erbb-3 protein expression in ductal carcinoma in situ of the breast. Eur J Cancer. 1997;33(11):1846-50. https://doi.org/10.1016/s0959-8049(97)00244-x.
28. Suo Z, Risberg B, Kalsson MG, Willman K, Tierens A, Skovlund E, et al. Egfr family expression in breast carcinomas. C-erbb-2 and c-erbb-4 receptors have different effects on survival. J Pathol. 2002;196(1):17-25. https://doi.org/10.1002/path.1003.
29. Hudelist G, Singer CF, Manavi M, Pischinger K, Kubista E, Czerwenka K. Co-expression of erbb-family members in human breast cancer: Her-2/neu is the preferred dimerization candidate in nodal-positive tumors. Breast Cancer Res Treat. 2003;80(3):353-61. https://doi.org/10.1023/a:1024929522376.
30. Witton CJ, Reeves JR, Going JJ, Cooke TG, Bartlett JM. Expression of the her1-4 family of receptor tyrosine kinases in breast cancer. J Pathol. 2003;200(3):290-7. https://doi.org/10.1002/path.1370.
32. Abd El-Rehim DM, Pinder SE, Paish CE, Bell JA, Rampaul RS, Blamey RW, et al. Expression and co-expression of the members of the epidermal growth factor receptor (egfr) family in invasive breast carcinoma. Br J Cancer. 2004;91(8):1532-42. https://doi.org/10.1038/sj.bjc.6602184.
32. Barnes NL, Khavari S, Boland GP, Cramer A, Knox WF, Bundred NJ. Absence of her4 expression predicts recurrence of ductal carcinoma in situ of the breast. Clin Cancer Res. 2005;11(6):2163-8. https://doi.org/10.1158/1078-0432.Ccr-04-1633.
33. Wiseman SM, Makretsov N, Nielsen TO, Gilks B, Yorida E, Cheang M, et al. Coexpression of the type 1 growth factor receptor family members her-1, her-2, and her-3 has a synergistic negative prognostic effect on breast carcinoma survival. Cancer. 2005;103(9):1770-7. https://doi.org/10.1002/cncr.20970.
34. Bianchi S, Palli D, Falchetti M, Saieva C, Masala G, Mancini B, et al. Erbb-receptors expression and survival in breast carcinoma: A 15-year follow-up study. J Cell Physiol. 2006;206(3):702-8. https://doi.org/10.1002/jcp.20535.
35. Yen L, Cao Z, Wu X, Ingalla ER, Baron C, Young LJ, et al. Loss of nrdp1 enhances erbb2/erbb3-dependent breast tumor cell growth. Cancer Res. 2006;66(23):11279-86. https://doi.org/10.1158/0008-5472.Can-06-2319.
36. Kaya H, Erbarut I, Ozkan N, Bekiroğlu N, Sen S, Abaciğlu U. Immunoexpression of her family, neuregulin, mapk and akt in invasive ductal carcinomas of the breast. Eur J Gynaecol Oncol. 2008;29(4):350-6.
37. Haas S, Gevensleben H, Rabstein S, Harth V, Pesch B, Brüning T, et al. Expression of heregulin, phosphorylated her-2, her-3 and her-4 in her-2 negative breast cancers. Oncol Rep. 2009;21(2):299-304.
38. Gori S, Foglietta J, Mameli MG, Stocchi L, Fenocchio D, Anastasi P, et al. Her-3 status by immunohistochemistry in her-2-positive metastatic breast cancer patients treated with trastuzumab: Correlation with clinical outcome. Tumori. 2012;98(1):39-44. https://doi.org/10.1177/030089161209800105.
39. Spears M, Taylor KJ, Munro AF, Cunningham CA, Mallon EA, Twelves CJ, et al. In situ detection of her2:Her2 and her2:Her3 protein-protein interactions demonstrates prognostic significance in early breast cancer. Breast Cancer Res Treat. 2012;132(2):463-70. https://doi.org/10.1007/s10549-011-1606-z.
40. Spears M, Pederson HC, Lyttle N, Gray C, Quintayo MA, Brogan L, et al. Expression of activated type i receptor tyrosine kinases in early breast cancer. Breast Cancer Res Treat. 2012;134(2):701-8. https://doi.org/10.1007/s10549-012-2076-7.
41. Bae SY, La Choi Y, Kim S, Kim M, Kim J, Jung SP, et al. Her3 status by immunohistochemistry is correlated with poor prognosis in hormone receptor-negative breast cancer patients. Breast Cancer Res Treat. 2013;139(3):741-50. https://doi.org/10.1007/s10549-013-2570-6.
42. Czopek J, Pawlęga J, Fijorek K, Püsküllüoğlu M, Różanowski P, Okoń K. Her-3 expression in her-2-amplified breast carcinoma. Contemp Oncol (Pozn). 2013;17(5):446-9. https://doi.org/10.5114/wo.2013.38564.
43. Jerjees DA, Alabdullah M, Green AR, Alshareeda A, Macmillan RD, Ellis IO, et al. Prognostic and biological significance of proliferation and her2 expression in the luminal class of breast cancer. Breast Cancer Res Treat. 2014;145(2):317-30. https://doi.org/10.1007/s10549-014-2941-7.
44. Luhtala S, Staff S, Kallioniemi A, Tanner M, Isola J. Clinicopathological and prognostic correlations of her3 expression and its degradation regulators, nedd4–1 and nrdp1, in primary breast cancer. BMC Cancer. 2018;18(1):1045. https://doi.org/10.1186/s12885-018-4917-1.
45. Hassanzadeh Makoui M, Mobini M, Fekri S, Geranpayeh L, Moradi Tabriz H, Madjd Z, et al. Clinico-pathological and prognostic significance of a combination of tumor biomarkers in iranian patients with breast cancer. Clin Breast Cancer. 2024;24(1):e9-e19.e9. https://doi.org/10.1016/j.clbc.2023.09.013.
46. Lamarca A, Galdy S, Barriuso J, Moghadam S, Beckett E, Rogan J, et al. The her3 pathway as a potential target for inhibition in patients with biliary tract cancers. PLoS ONE. 2018;13(10):e0206007. https://doi.org/10.1371/journal.pone.0206007.

47. Chow NH, Chan SH, Tzai TS, Ho CL, Liu HS. Expression profiles of erbb family receptors and prognosis in primary transitional cell carcinoma of the urinary bladder. Clin Cancer Res. 2001;7(7):1957-62.
48. Memon AA, Sorensen BS, Meldgaard P, Fokdal L, Thykjaer T, Nexo E. The relation between survival and expression of her1 and her2 depends on the expression of her3 and her4: A study in bladder cancer patients. Br J Cancer. 2006;94(11):1703-9. https://doi.org/10.1038/sj.bjc.6603154.
49. Khelwatty SA, Essapen S, Bagwan I, Green M, Seddon AM, Modjtahedi H. Co-expression of her family members in patients with dukes' c and d colon cancer and their impacts on patient prognosis and survival. PLoS ONE. 2014;9(3):e91139. https://doi.org/10.1371/journal.pone.0091139.
50. Seo AN, Kwak Y, Kim WH, Kim DW, Kang SB, Choe G, et al. Her3 protein expression in relation to her2 positivity in patients with primary colorectal cancer: Clinical relevance and prognostic value. Virchows Arch. 2015;466(6):645-54. https://doi.org/10.1007/s00428-015-1747-2.
51. Stahler A, Heinemann V, Neumann J, Crispin A, Schalhorn A, Stintzing S, et al. Prevalence and influence on outcome of her2/neu, her3 and nrg1 expression in patients with metastatic colorectal cancer. Anticancer Drugs. 2017;28(7):717-22. https://doi.org/10.1097/cad.0000000000000510.
52. Khelwatty SA, Puvanenthiran S, Essapen S, Bagwan I, Seddon AM, Modjtahedi H. Her2 expression is predictive of survival in cetuximab treated patients with ras wild type metastatic colorectal cancer. Cancers (Basel). 2021;13(4). https://doi.org/10.3390/cancers13040638.
53. Androutsopoulos G, Adonakis G, Liava A, Ravazoula P, Decavalas G. Expression and potential role of erbb receptors in type ii endometrial cancer. Eur J Obstet Gynecol Reprod Biol. 2013;168(2):204-8. https://doi.org/10.1016/j.ejogrb.2013.01.007.
54. Yoon HH, Sukov WR, Shi Q, Sattler CA, Wiktor AE, Diasio RB, et al. Her-2/neu gene amplification in relation to expression of her2 and her3 proteins in patients with esophageal adenocarcinoma. Cancer. 2014;120(3):415-24. https://doi.org/10.1002/cncr.28435.
55. Chan E, Alkhasawneh A, Duckworth LV, Aijaz T, Toro TZ, Lu X, et al. Egfr family and cmet expression profiles and prognostic significance in esophagogastric adenocarcinoma. J Gastrointest Oncol. 2016;7(6):838-47. https://doi.org/10.21037/jgo.2016.06.09.
56. Lee HJ, Chung JY, Hewitt SM, Yu E, Hong SM. Her3 overexpression is a prognostic indicator of extrahepatic cholangiocarcinoma. Virchows Arch. 2012;461(5):521-30. https://doi.org/10.1007/s00428-012-1321-0.
57. Lee J, Kim S, Kim P, Liu X, Lee T, Kim KM, et al. A novel proteomics-based clinical diagnostics technology identifies heterogeneity in activated signaling pathways in gastric cancers. PLoS ONE. 2013;8(1):e54644. https://doi.org/10.1371/journal.pone.0054644.
58. Jácome AA, Wohnrath DR, Scapulatempo Neto C, Carneseca EC, Serrano SV, Viana LS, et al. Prognostic value of epidermal growth factor receptors in gastric cancer: A survival analysis by weibull model incorporating long-term survivors. Gastric Cancer. 2014;17(1):76-86. https://doi.org/10.1007/s10120-013-0236-z.
59. He XX, Ding L, Lin Y, Shu M, Wen JM, Xue L. Protein expression of her2, 3, 4 in gastric cancer: Correlation with clinical features and survival. J Clin Pathol. 2015;68(5):374-80. https://doi.org/10.1136/jclinpath-2014-202657.
60. Tang D, Liu CY, Shen D, Fan S, Su X, Ye P, et al. Assessment and prognostic analysis of egfr, her2, and her3 protein expression in surgically resected gastric adenocarcinomas. Onco Targets Ther. 2015;8:7-14. https://doi.org/10.2147/ott.S70922.
62. Yun S, Koh J, Nam SK, Park JO, Lee SM, Lee K, et al. Clinical significance of overexpression of nrg1 and its receptors, her3 and her4, in gastric cancer patients. Gastric Cancer. 2018;21(2):225-36. https://doi.org/10.1007/s10120-017-0732-7.
62. Torp SH, Gulati S, Johannessen E, Dalen A. Coexpression of c-erbb 1-4 receptor proteins in human glioblastomas. An immunohistochemical study. J Exp Clin Cancer Res. 2007;26(3):353-9.
63. Takikita M, Xie R, Chung JY, Cho H, Ylaya K, Hong SM, et al. Membranous expression of her3 is associated with a decreased survival in head and neck squamous cell carcinoma. J Transl Med. 2011;9:126. https://doi.org/10.1186/1479-5876-9-126.
64. Almadori G, Coli A, De Corso E, Mele DA, Settimi S, Di Cintio G, et al. Nuclear her3 expression improves the prognostic stratification of patients with her1 positive advanced laryngeal squamous cell carcinoma. J Transl Med. 2021;19(1):408. https://doi.org/10.1186/s12967-021-03081-0.
65 Nishio M, Taguchi F, Ohyanagi F, Horikike A, Ishikawa Y, Satoh Y, et al. Gefitinib efficacy associated with multiple expression of her family in non-small cell lung cancer. Anticancer Res. 2006;26(5b):3761-5.
66. Sonnweber B, Dlaska M, Skvortsov S, Dirnhofer S, Schmid T, Hilbe W. High predictive value of epidermal growth factor receptor phosphorylation but not of egfrviii mutation in resected stage i non-small cell lung cancer (nsclc). J Clin Pathol. 2006;59(3):255-9. https://doi.org/10.1136/jcp.2005.027615.
67. Koutsopoulos AV, Mavroudis D, Dambaki KI, Souglakos J, Tzortzaki EG, Drositis J, et al. Simultaneous expression of c-erbb-1, c-erbb-2, c-erbb-3 and c-erbb-4 receptors in non-small-cell lung carcinomas: Correlation with clinical outcome. Lung Cancer. 2007;57(2):193-200. https://doi.org/10.1016/j.lungcan.2007.03.009.
68. Fujita M, Ishida M, Tezuka N, Fujino S, Asai T, Okabe H. Her1-4 expression status correlates with the efficacy of gefitinib treatment and tumor cell proliferative activity in non-small cell lung cancer. Mol Med Rep. 2008;1(2):225-30.
69. Xu J, Gao E, Han Y, Zhang Y, Li S, Liu X, et al. Egfr / her2 / her3 expression in tumour and gefitinib treatment in chinese patients with advanced non-small cell lung cancer. Chin J Clin Oncol. 2008;7(8):440-6. https://doi.org/10.1007/s10330-008-0070-7.
70. Xu JM, Han Y, Duan HQ, Gao EM, Zhang Y, Liu XQ, et al. Egfr mutations and her2/3 protein expression and clinical outcome in chinese advanced non-small cell lung cancer patients treated with gefitinib. J Cancer Res Clin Oncol. 2009;135(6):771-82. https://doi.org/10.1007/s00432-008-0512-1.
71. Berghoff AS, Magerle M, Ilhan-Mutlu A, Dinhof C, Widhalm G, Dieckman K, et al. Frequent overexpression of erbb – receptor family members in brain metastases of non-small cell lung cancer patients. APMIS. 2013;121(12):1144-52. https://doi.org/https://doi.org/10.1111/apm.12063.
72. Siegfried JM, Lin Y, Diergaarde B, Lin HM, Dacic S, Pennathur A, et al. Expression of pam50 genes in lung cancer: Evidence that interactions between hormone receptors and her2/her3 contribute to poor outcome. Neoplasia. 2015;17(11):817-25. https://doi.org/10.1016/j.neo.2015.11.002.
73. Manickavasagar T, Yuan W, Carreira S, Gurel B, Miranda S, Ferreira A, et al. Her3 expression and mek activation in non-small-cell lung carcinoma. Lung Cancer Manag.

2021;10(2):Lmt48. https://doi.org/10.2217/lmt-2020-0031.
74. Tulalamba W, Larbcharoensub N, Janvilisri T. Erbb3 as an independent prognostic marker for nasopharyngeal carcinoma. J Clin Pathol. 2014;67(8):667-72. https://doi.org/10.1136/jclinpath-2013-202154.
75. Izycka-Swieszewska E, Wozniak A, Drozynska E, Kot J, Grajkowska W, Klepacka T, et al. Expression and significance of her family receptors in neuroblastic tumors. Clin Exp Metastasis. 2011;28(3):271-82. https://doi.org/10.1007/s10585-010-9369-1.
76. Bei R, Pompa G, Vitolo D, Moriconi E, Ciocci L, Quaranta M, et al. Co-localization of multiple erbb receptors in stratified epithelium of oral squamous cell carcinoma. J Pathol. 2001;195(3):343-8. https://doi.org/10.1002/path.965.
77. Wang SL, Zhong GX, Wang XW, Yu FQ, Weng DF, Wang XX, et al. Prognostic significance of the expression of her family members in primary osteosarcoma. Oncol Lett. 2018;16(2):2185-94. https://doi.org/10.3892/ol.2018.8931.
78. Simpson BJ, Phillips HA, Lessells AM, Langdon SP, Miller WR. C-erbb growth-factor-receptor proteins in ovarian tumours. Int J Cancer. 1995;64(3):202-6. https://doi.org/10.1002/ijc.2910640310.
79. Puvanenthiran S, Essapen S, Haagsma B, Bagwan I, Green M, Khelwatty SA, et al. Co-expression and prognostic significance of the her family members, egfrviii, c-met, cd44 in patients with ovarian cancer. Oncotarget. 2018;9(28):19662-74. https://doi.org/10.18632/oncotarget.24791.
80. Thomas G, Chardès T, Gaborit N, Mollevi C, Leconet W, Robert B, et al. Her3 as biomarker and therapeutic target in pancreatic cancer: New insights in pertuzumab therapy in preclinical models. Oncotarget. 2014;5(16):7138-48. https://doi.org/10.18632/oncotarget.2231.
81. Haugen DR, Akslen LA, Varhaug JE, Lillehaug JR. Expression of c-erbb-3 and c-erbb-4 proteins in papillary thyroid carcinomas. Cancer Res. 1996;56(6):1184-8.
82. Carlsson J, Shen L, Xiang J, Xu J, Wei Q. Tendencies for higher co-expression of egfr and her2 and downregulation of her3 in prostate cancer lymph node metastases compared with corresponding primary tumors. Oncol Lett. 2013;5(1):208-14. https://doi.org/10.3892/ol.2012.996.
83. P Oc, Rhys-Evans PH, Archer DJ, Eccles SA. C-erbb receptors in squamous cell carcinomas of the head and neck: Clinical significance and correlation with matrix metalloproteinases and vascular endothelial growth factors. Oral Oncol. 2002;38(1):73-80. https://doi.org/10.1016/s1368-8375(01)00029-x.
84. Ekberg T, Nestor M, Engström M, Nordgren H, Wester K, Carlsson J, et al. Expression of egfr, her2, her3, and her4 in metastatic squamous cell carcinomas of the oral cavity and base of tongue. Int J Oncol. 2005;26(5):1177-85. https://doi.org/10.3892/ijo.26.5.1177.
85. Krähn G, Leiter U, Kaskel P, Udart M, Utikal J, Bezold G, et al. Coexpression patterns of egfr, her2, her3 and her4 in non-melanoma skin cancer. Eur J Cancer. 2001;37(2):251-9. https://doi.org/10.1016/s0959-8049(00)00364-6.
86. Weissferdt A, Lin H, Woods D, Tang X, Fujimoto J, Wistuba, II, et al. Her family receptor and ligand status in thymic carcinoma. Lung Cancer. 2012;77(3):515-21. https://doi.org/10.1016/j.lungcan.2012.05.108.