# Estrogen receptor-negative/progesterone receptor-positive and her-2 negative breast cancer might no longer be classified as hormone receptor positive breast cancer

Hongjuan Zheng[1], Chenyang Ge[1], Haiping Lin[1], Lunpo Wu[2], Qinghua Wang[1], Shishi Zhou[1], Wanfen Tang[1], Xia Zhang[1], Xiayun Jin[1], Xifeng Xu[1], Zhongwu Hong[1], Jianfei Fu[1], and Jinlin Du[1]

[1]Jinhua Hospital of Zhejiang University
[2]Zhejiang University School of Medicine Second Affiliated Hospital

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**Abstract**

Background: The estrogen receptor (ER)-negative/progesterone receptor (PR)-positive (sPR positive) phenotype is an infrequent and independent biological entity. However, the prognosis of patients with sPR positive and her-2 negative phenotype is still controversial, and it is not always easy to decide treatment strategies for them. Methods: Patients during 2010–2014 were identified from Surveillance, Epidemiology, and End Results (SEER) database. The Kaplan-Meier method was used to evaluate cancer-specific survival (CSS). The propensity score matching (PSM) method was used to balance differences of characteristics in groups. The Life-Table method was used to calculate 5-year CSS rates and the annual hazard rate of death (HRD). Results: A total of 97,527 patients were included, and only 745 (0.76%) patients were sPR positive phenotype. The majority of sPR positive breast cancer were basal-like subtype. Survival analysis showed that the sPR positive breast cancer had similar prognosis comparing to ER-negative/PR-negative (dHR negative) breast cancer, and had the highest HRD during the initial 1-2 years of follow-up, then maintained the HRD of almost zero during the late years of follow-up. Conclusions: The patients with sPR positive and her-2 negative breast cancer, similar to dHR negative breast cancer, had a worse survival, and could benefit from chemotherapy significantly. However, the escalating endocrine therapy was not recommended for sPR positive patients. The patients with sPR positive should be excluded from future clinical trials concerning endocrine therapy.

**Estrogen receptor-negative/progesterone receptor-positive and her-2 negative breast cancer might no longer be classified as hormone receptor positive breast cancer**Hongjuan Zheng[a*], Chenyang Ge[b*], Haiping Lin[c], Lunpo Wu[d, e], Qinghua Wang[a], Shishi Zhou[a], Wanfen Tang[a], Xia Zhang[a], Xiayun Jin[a], Xifeng Xu[a], Zhongwu Hong[f], Jianfei Fu[a#], Jinlin Du[b#a] Department of Medical Oncology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua 321000, Zhejiang Province, China.[b] Department of Colorectal Surgery, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China.[c] Department of Hepatobiliary Surgery, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua, China.[d] Department of Gastroenterology, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China.[e] Institute of Gastroenterology, Zhejiang University, Hangzhou, China.[f] Department of Oncology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua 321000, Zhejiang Province, China. * **Hongjuan Zheng** and **Chenyang Ge** are co-first authors; they contributed equally to the work.# **Jianfei Fu** and **Jinlin Du** are co-corresponding authors. Correspondence to: **Jianfei Fu**, Department of Medical Oncology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, 351 Mingyue Road, Jinhua 321000, Zhejiang Province, China; E-mail:*11218276@zju.edu.cn*; Fax: +86-579-82552856; Correspondence to: **Jinlin Du**, Department of Colorectal Surgery, Affiliated Jinhua

Hospital, Zhejiang University School of Medicine, 351 Mingyue Road, Jinhua 321000, Zhejiang Province, China; E-mail:*djl9090@163.com*;

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**Conflicts of interest**

All authors have declared no conflicting interests.

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**Abstract**

*Background:* The estrogen receptor (ER)-negative/progesterone receptor (PR)-positive (sPR positive) phenotype is an infrequent and independent biological entity. However, the prognosis of patients with sPR positive and her-2 negative phenotype is still controversial, and it is not always easy to decide treatment strategies for them.*Methods:* Patients during 2010–2014 were identified from Surveillance, Epidemiology, and End Results (SEER) database. The Kaplan-Meier method was used to evaluate cancer-specific survival (CSS). The propensity score matching (PSM) method was used to balance differences of characteristics in groups. The Life-Table method was used to calculate 5-year CSS rates and the annual hazard rate of death (HRD). Results: A total of 97,527 patients were included, and only 745 (0.76%) patients were sPR positive phenotype. The majority of sPR positive breast cancer were basal-like subtype. Survival analysis showed that the sPR positive breast cancer had similar prognosis comparing to ER-negative/PR-negative (dHR negative) breast cancer, and had the highest HRD during the initial 1-2 years of follow-up, then maintained the HRD of almost zero during the late years of follow-up. Conclusions: The patients with sPR positive and her-2 negative breast cancer, similar to dHR negative breast cancer, had a worse survival, and could benefit from chemotherapy significantly. However, the escalating endocrine therapy was not recommended for sPR positive patients. The patients with sPR positive should be excluded from future clinical trials concerning endocrine therapy.

**Abbreviations**

ER: Estrogen receptor

PR: Progesterone receptor

sPR positive: ER-negative/PR-positive

SEER: Surveillance, Epidemiology, and End Results

CSS: Cancer-specific survival

PSM: Propensity score matching

HRD: Hazard rate of death

HoR status: hormone-receptor status

IHC: Immunohistochemical staining

dHR negative: ER-negative/PR-negative

dHR positive: ER-positive/PR-positive

IDC: Infiltrative ductal cancer

ILC: Infiltrative lobar cancer

AJCC: American Joint Committee on Cancer

sER positive: ER-positive/PR-negative

HR: Hazard ratio

LOWESS: Locally weighted scatter plot smoothing

**Keywords***:* Breast cancer, sPR positive, the annual hazard rate of death, cancer-specific survival.

## Background

Breast cancer is the greatest threat to women's health and the leading cause of cancer death in young women. In 1973, estrogen receptor (ER) has been recognized as a strong indicator of response to endocrine therapy [1]. Then, ER and progesterone receptor (PR) were gradually established prognostic factors in female breast cancer [2-6]. And steroid hormone receptors were shown to be the strongest predictive markers of response to endocrine therapy in breast cancer [7-10].

There are four hormone-receptor status (HoR status) phenotypes, and the ER-negative/PR-positive (sPR positive) phenotype is infrequent, accounting for 1.0%- 4.10% of all types of malignant breast cancer [11-16]. The existence of the sPR positive breast cancer used to be controversial. Then, the sPR positive phenotype was proved by re-evaluating ER and PR status through immunohistochemical staining (IHC)[13, 17] or analyzing PAM50 expression signature and mRNA level of ESR1 [11, 18]. Besides, Borras and his co-authors established the sPR positive Evsa-T cell line, which also demonstrated the presence of sPR positive breast cancer [19].

Unlike other types of breast cancer, the sPR positive breast cancer had unique clinicopathological characteristics and controversial prognosis[17, 20, 21]. Ke-Da et al. showed that the survival of the sPR positive phenotype was similar to the ER-negative/PR-negative (dHR negative) phenotype [22], while, Ethier et al. indicated that the survival of sPR positive patients was similar to ER-positive/PR-positive (dHR positive) patients [12]. The prognosis of patients with sPR positive and her-2 negative breast cancer is still controversial; therefore, we aim to explore the true prognosis of patients with sPR positive through large-sample clinical data analysis.

In the current study, we systemically studied the clinical features, survival outcomes and the annual hazard rate of death (HRD) of patients with sPR positive and her-2 negative breast cancer.

## Methods

### Study Population

The Surveillance, Epidemiology, and End Results (SEER) database was established by the National Cancer Institute with the aim of collecting information about cancer incidence and survival. This national programme includes18 population-based cancer registries among 14 states across the United States, representing about 30% of the population of the United States. We obtained permission to access the research data (reference number, 12296-Nov2018). The study was approved by the ethics committee of Zhejiang University Jinhua hospital. We used SEER*Stat version 8.3.5(http://seer.cancer.gov/seerstat) to identify patients diagnosed with breast cancer from January 2010 to December 2014. Patients diagnosed after 2014 were excluded to ensure an adequate duration of follow-up. We retrieved records of year and age at diagnosis, gender, race, insurance, marital status, histological type, differentiated grade, location of tumor, T-classification, N-classification, stage TNM, administration of radiotherapy, administration of chemotherapy, ER, PR, her-2, survival months, and cause of death.

The specific inclusion criteria were as follows: (1) site record ICD-O-3 was limited to breast cancer (C500-506; C508-509); (2) gender was limited to female; (3) histological type ICD-O-3 was limited to infiltrative ductal cancer, infiltrative lobar cancer or mixed with both of them (8500/3, 8520/3, 8521/3, 8522/3, 8524/3, 8541/3); (4) the survival time of patients exceeded 1 months, (5) patients were without distant metastasis; (6) the age at diagnosis was limited from 20 to 80; (7) patients were not multiple primary tumors. The exclusion

criteria were as follows: (1) patients were lacking documentation of race, marital status, insurance status, differentiated grade (included grade IV), location of tumor, ER, PR, her-2, T-classification, N-classification; (2) patients were her-2 positive; (3) patients received neoadjuvant therapy; (4) the cause of death was unknown (For the detailed inclusion and exclusion criteria, see the **Supplemental figure 1** ).

### 2.2 *Variable Declaration*

Age was regrouped as 20-40 years old, 41-60 years old, 61-70 years old, 71-80 years old, according our previous study analysis result [23]. Race was divided into white, black and other. Marital status was regrouped as married, single and divorced. Insurance status was divided into insured, medicaid and uninsured. Histological type was grouped as infiltrative ductal cancer (IDC), infiltrative lobar cancer (ILC) and mixture (IDC&ILC). The variable of chemotherapy was only classified as "yes" or "no/unknown", since SEER treatment information cannot accurately distinguish between "no treatment" and "unknown if patients received treatment" [24]. All cases were regrouped according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system. The HoR status of the tumor was stratified to dHR positive, ER-positive/PR-negative (sER positive), sPR positive, and dHR negative.

### 2.3 *Statistical analyses*

The distribution of clinicopathological characteristic in different HoR status groups was analyzed using Chi-Squared tests. Propensity score matching method (PSM) was used to balance differences of characteristics between chemotherapy and non-chemotherapy groups. The propensity score was calculated by logistic regression including covariates of HoR status, T-Classification and N-Classification. The "Matchit" package in R software was used as the nearest method with ratio 1:1 and caliper =0.0001. The cancer-specific survival (CSS), the primary endpoint, was calculated from the date of diagnosis to the date of death of breast cancer. Death attributed to other causes was defined as a censored observation. Survival curves were generated using the Kaplan-Meier method, and the log-rank test was carried out to evaluate the survival differences between groups. The 5-year CSS rates were calculated by Life-Table method. The hazard ratio (HR) of the variables for CSS was estimated using Cox proportional hazard regression model. The Life-Table method was used to calculate HRD. The HRD were plotted at each 6-months interval after diagnosis until month 79, with a total of 13 intervals (intervals 0 to 79). Interpolation was conducted using a locally weighted scatter plot smoothing (LOWESS) function.

R3.5.2 software (http://www.r-project.org/) was used to perform the statistical analyses. When the two-sided P value was less than 0.05, the difference was considered statistically significant.

## 3. Results

### 3.1 Clinicopathological characteristics of patients with her-2 negative breast cancer

We identified 97,527 eligible patients with her-2 negative breast cancer from SEER. The endpoint date of the follow-up was November 2014, with a median follow-up of 48 months (range: 1 to 83 months). There were 0.86% women diagnosed with sPR positive in HoR positive resectable breast cancer, and 0.76% in all resectable breast cancer.

Compared with the sER positive, patients with sPR positive were younger at time of diagnosis (median age 55 versus 62 years,$P$ <0.001), less likely had infiltrative lobar carcinoma (1.61% versus 13.38%, $P$ <0.001), had more poor-differentiated (80.27% versus 36.71%, $P$ <0.001) as well as late-stage breast cancer. More patients with sPR positive received chemotherapy (73.56 vs. 45.27%, $P$ <0.001). However, patients with dHR negative and sPR positive tumors had similar clinicopathological characteristics. The detail information was indicated in **Table 1** .

### 3.2 Univariate and multivariate analysis of CSS

In total, 3,454 (3.07%) patients died of breast cancer. The 5-year CSS rates of patients with sPR positive breast cancer and dHR negative breast cancer were 89.03 % and 87.69%, respectively. The survival of

patients with sER positive and dHR positive were much better, with 5-year CSS rates of 93.57% and 97.81% ($P$ <0.001,**Figure 1** ).

Multivariate analysis revealed that HoR status was an independent prognostic factor. Compared with sPR positive breast cancer, the dHR positive and sER positive breast cancer had favorable survivals (HR=0.29, 95% CI, 0.22-0.36; $P$ <0.001; HR=0.65 ,95% CI, 0.51-0.84; $P$ <0.001, respectively). The detail results were indicated in **Table 2** .

### 3.3 The hazard rate of death (HRD) in different phenotypes of breast cancer

The dHR positive phenotype continued to had a low level of the HRD during the disease progression. The HRD of sPR positive phenotype was higher than the other three phenotypes during the initial 1-2 years of follow-up, and then descended rapidly and successively crossed with the other three phenotypes during the 3-5 years of follow-up. However, the HRD of sPR positive phenotype decreased nearly to zero during the later years of follow-up time (**Figure 2** ).

### 3.4 Analyzing treatment benefits according to HoR status in the PSM cohort

In the initial data, the sample size of patients in the chemotherapy group was fewer than non-chemotherapy group. Also, there were different baseline characteristics between these two groups (**Table 1** ). Therefore, the PSM method was used to balance differences of baseline characteristics. A total of 21,208 patients with chemotherapy were matched with 21,208 patients without chemotherapy (**Supplemental figure 2** ). All covariates included were well balanced between chemotherapy and non-chemotherapy groups in the PSM cohort (**Supplemental table 1** ).

In the PSM cohort, patients with sPR positive and dHR negative phenotypes benefited significantly from chemotherapy both with$P$ <0.001, while patients with sER positive could not benefit from chemotherapy with $P$ =0.052 (**Figure 3** ). Furthermore, we performed an interaction analysis using Cox model between the chemotherapy and HoR status in the PSM cohort (Figure 4). The results showed that the sPR positive phenotype benefited more from chemotherapy than dHR negative phenotype ($P$for interaction = 0.001). Besides, in the non-chemotherapy group, patients with sPR positive phenotype had worse survival than dHR negative phenotype with $P$ =0.034. In the patients with chemotherapy, patients with sPR positive had similar prognosis to dHR negative with $P$ =0.614 (**Supplemental figure 3** ).

### 3.5 Systematic review of the intrinsic subtypes with sPR positive phenotype

Intrinsic molecular subtypes of breast cancer have been thoroughly studied and can indicate the existence of sPR positive phenotype [11, 12, 22]. In total, the sPR positive phenotype had a higher likelihood of being the basal-like subtype (46.15%). Normal-like and her-2 positive subtypes comprised a small proportion, accounting for 4.41%, 9.89%, respectively (**Table 3** ).

## 4. Discussion

Breast cancer with sPR positive is a rare and a biologically distinct subgroup [12, 20, 22]. When considering the causes of sPR positive breast cancer, the mechanisms are quite complicated [19, 25-27]. The secondary loss of ER is one of the hypotheses. Higher estrogen levels in premenopausal females could downregulate the expression of ER protein [26]. Previous studies showed that patients with sPR positive phenotype were more diagnoses in young, who have a relatively higher estrogen level. What's more, patients with sPR positive phenotype were more often with her-2 positive [17, 21] and higher grade [20], which were consistence with our study.

In this study, we identified eligible female patients with her-2 negative breast cancer from SEER to explore the outcomes of patients with sPR positive phenotype. Our results showed that patients with sPR positive phenotype had unfavorable prognosis which was similar with patients dHR negative phenotype, which was consistent with other studies [20, 22, 28]. We have investigated detail clinicopathologic features of sPR positive phenotype and found that the majority of sPR positive breast cancer occurred in younger women with poorly differentiated and late-stage tumors and were rarely of classical lobular type. Besides, the

study of Rakha showed that sPR positive phenotype was more frequently associated with biomarkers of poor prognosis such as positive 53 and basal cytokeratin and reduced E-cadherin expression [20]. All above suggested that sPR positive phenotype is a more aggressive phenotype.

Perou and his co-authors [29] identified four breast cancer subtypes: the basal-like, HER2-enriched, luminal-A, luminal-B and the normal-like breast cancer. Majority of sPR positive tumors tend to be lower mRNA level of ESR1 and basal-like molecular subtype according to Ethier's study (N = 31, 58.49%) [12] and Itoh's study (N = 13, 65%) [18]. Compared with luminal subtypes, patients with basal-like subtype had a poorer survival [30-35] and benefited least from tamoxifen endocrine therapy [36, 37]. Besides, patients with basal-like subtype benefited better from chemotherapy with paclitaxel and anthracycline than luminal subtypes [32, 38-40]. Aleix's study highlighted the higher chemotherapy sensitivity of basal-like subtype [34]. Above all, these results suggest that sPR positive breast cancer might tend to be more sensitive to chemotherapy and less effective in endocrine therapy. Furthermore, these speculations could be confirmed in our study. The Kaplan-Meier and interaction analyses of chemotherapy in different HoR status revealed that patients with sPR positive phenotype could benefit more from chemotherapy when compared with sER positive and dHR negative phenotypes. The particular mechanism of the highly sensitive to chemotherapy of sPR positive phenotype is still unclear. We speculate that it might be related to inadequate chemotherapy to the patients with sPR positive phenotype. What's more, the HRD vividly showed that sPR positive breast cancer suffered a high death risk at the initial 1-2 years. Above all, we proposed that patients with sPR positive should be given more intense chemotherapy just like dHR negative at the beginning.

The study of Bardou and his co-authors showed that patients with sPR positive phenotype, compared with the other three phenotypes, had the worst prognosis when received systemic endocrine therapy in the database of Program Project [41]. Davies's study also revealed that 1236 patients with sPR positive breast cancer did not benefit from 5 years of tamoxifen endocrine therapy with $P$ =0.35 [42]. These results showed that sPR positive breast cancer had less sensitivity of endocrine therapy.

According to the HRD, for sPR positive patients, the risk of tumor death was decreased to nearly zero after 5 years. On the contrary, the HRD of dHR positive and sER positive patients were both continued to stabilized in relatively high levels during the follow-up time. Therefore, for patients with sPR positive, it is advisable to de-escalate rather than highlight the endocrine therapy, and for dHR positive and sER positive patients the escalating endocrine therapy might be more necessary to reduce the risk of recurrence or tumor death in the later time.

In conclusion, patients with sPR positive and her-2 negative phenotype had similar prognosis with triple-negative phenotype. Patients with sPR positive phenotype had higher sensitivity of chemotherapy and lower response to endocrine therapy. In future clinical trials of breast cancer concerning endocrine therapy, patients with sPR positive should be treated with caution or even be excluded. However, further prospective studies referring to response of sPR positive breast cancer to endocrine therapy are recommended.

## Declarations

### Ethics approval and consent to participate

Not applicable. Because this article does not contain any studies with human participants or animals performed by any of the authors.**Consent for publication**Not applicable.**Competing interests**All authors have declared no conflicting interests.**Funding statement**Funding: This study was funded by the major program of the Jinhua Municipal Science & Technology Bureau (grant number 2019-3-004) and the key program of the Jinhua Municipal Science & Technology Bureau (grant number 2014-3-008). The funders had roles in conceptualization, review and editing of the manuscript.

### Authors' contributions

HJ. Z and CY. G: Data curation, Writing- Original draft preparation. HP. L: Methodology. LP. W: Writing - Review & Editing SS. Z: Software. WF. T and QH. W: Validation. X. Z: Formal analysis. XY. J: Project administration. XF. X: Visualization. ZW. H: Funding acquisition JF. F and JL. D:

Conceptualization, Writing - Review & Editing, Supervision. All authors have read and approved the manuscript.**Acknowledgements**We thank professor Barry Nelkin in the Department of Oncology, Johns Hopkins University School of Medicine, for his constructive comments and language editing.**Obtaining Data**All data in this study was identified from the Surveillance, Epidemiology, and End Results (SEER) database (http://seer.cancer.gov/).

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**Legend**

Figure 1: Kaplan-Meier estimate for breast cancer patients with her-2 negative. The patients with sPR positive phenotype had similar prognosis comparing to the dHR negative phenotype with P=0.892. The patients with sER positive or dHR positive had obviously better survival than the sPR positive with P<0.001.

Figure 2: The annual hazard rate of death (HRD) for breast cancer patients with her-2 negative. The HRD of sPR positive phenotype was the highest in all phenotypes during the initial 1-2 years of follow-up, and then descended rapidly and successively crossed with the other three phenotypes during the 3-5 years of follow-up. Finally, the HRD of sPR positive phenotype decreased nearly to zero during the later years of follow-up time.

Figure 3: Chemotherapy benefits in different HR status phenotypes in the PSM cohort with her-2 negative breast cancer. The patients with sER positive phenotype could not benefit from chemotherapy with P=0.052 (B), while patients with sPR positive and dHR negative phenotypes benefited significantly from chemotherapy both with P<0.001 (C and D).

Figure 4: Interaction analysis using Cox model

between the hormone receptor status and chemotherapy in the PSM cohort with her-2 negative breast cancer.

Supplemental Figure 1: The flow chart of inclusion and exclusion criteria.

Supplemental Figure 2: The PSM method was used to balance differences of baseline characteristics including differentiated grade, T-classification, N-classification. A total of 21,208 patients with chemotherapy were matched with 21,208 patients without chemotherapy.

Supplemental Figure 3: Kaplan-Meier estimate for patients with different hormone receptor and chemotherapy status in the PSM cohort. In the patients with non-chemotherapy, patients with sPR positive had worse survival than dHR negative with P=0.034. However, in the patients with chemotherapy, patients with sPR positive had similar prognosis to dHR negative with P=0.614.

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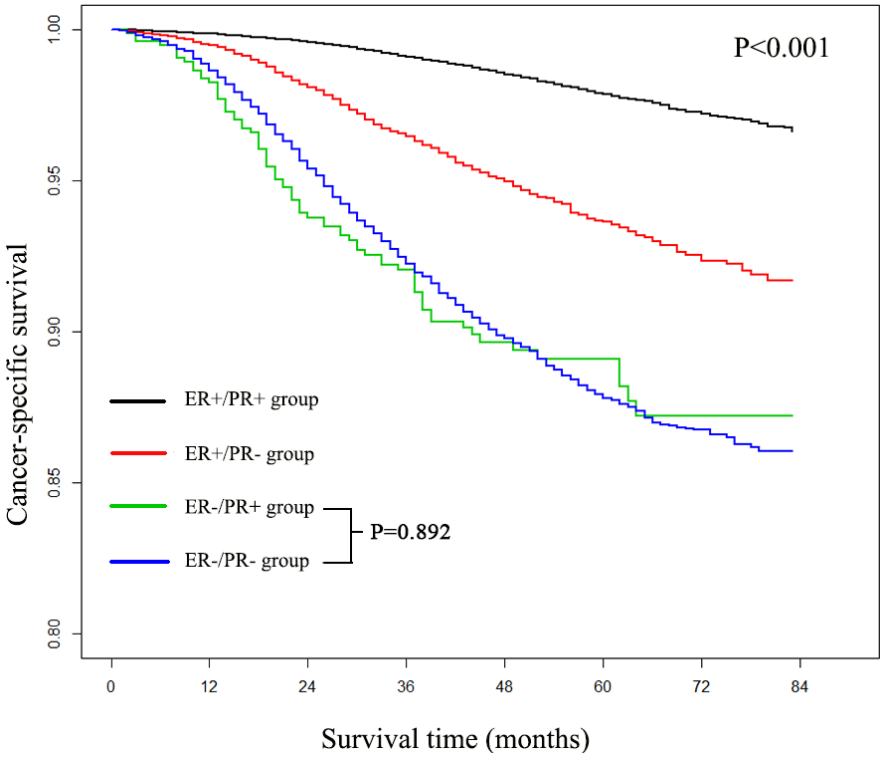
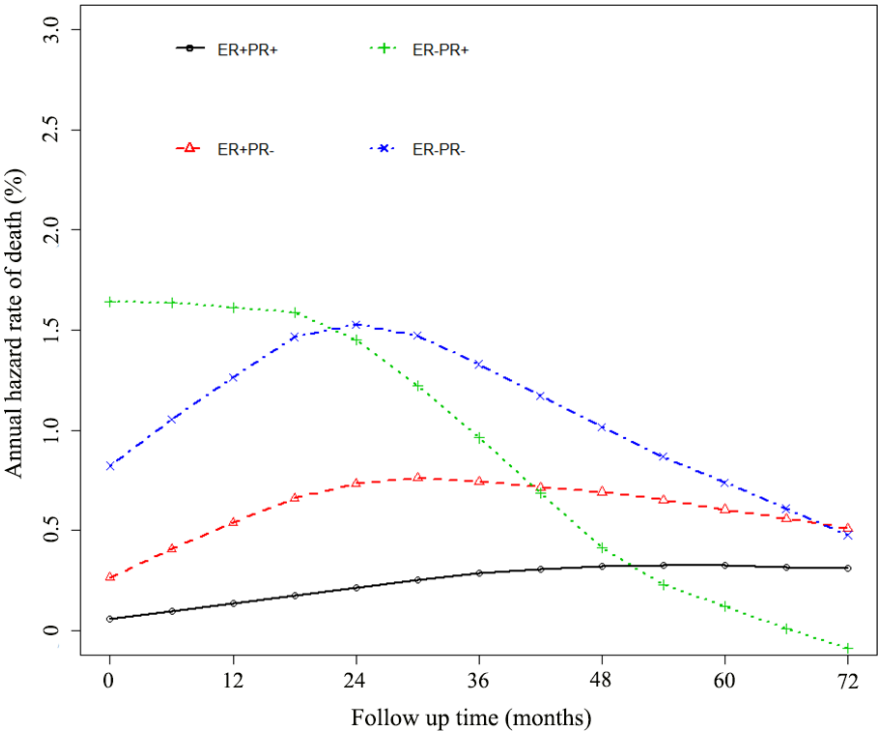
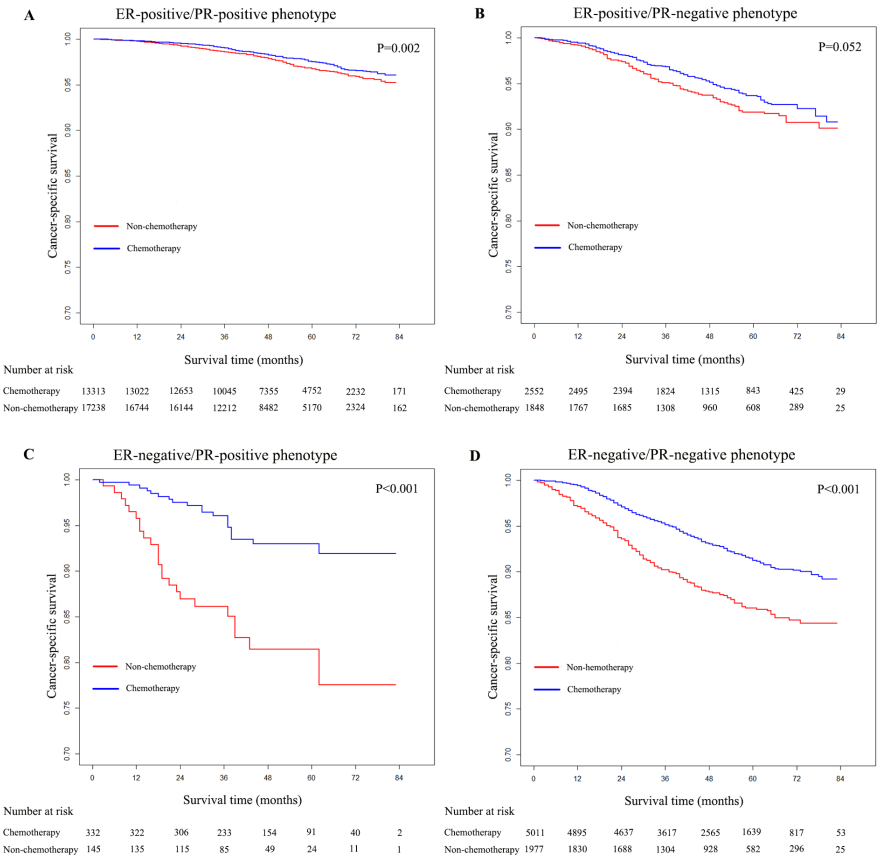
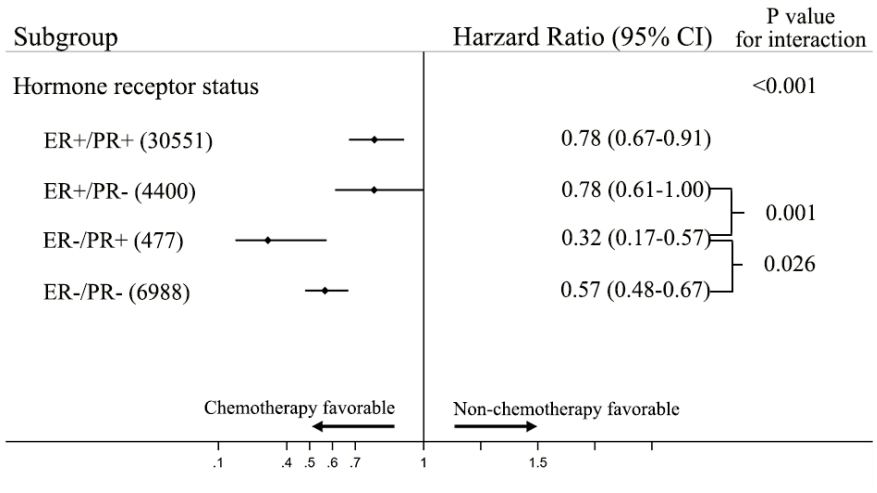
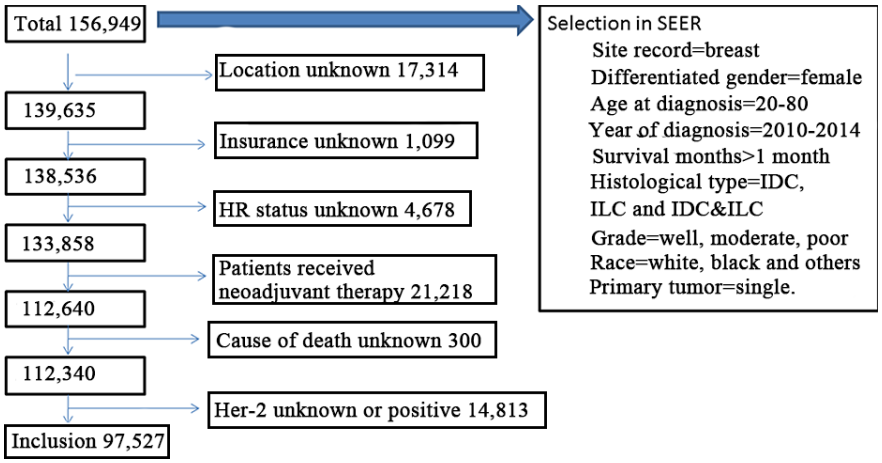
Table 1-3.pdf available at https://authorea.com/users/380689/articles/496576-estrogen-receptor-negative-progesterone-receptor-positive-and-her-2-negative-breast-cancer-might-no-longer-be-classified-as-hormone-receptor-positive-breast-cancer

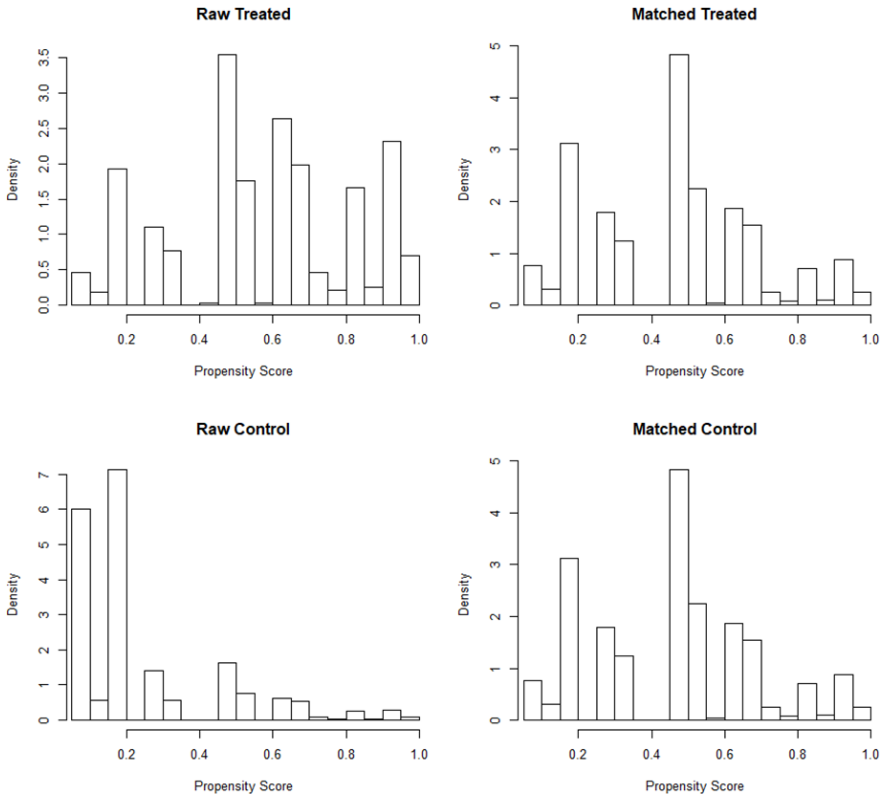


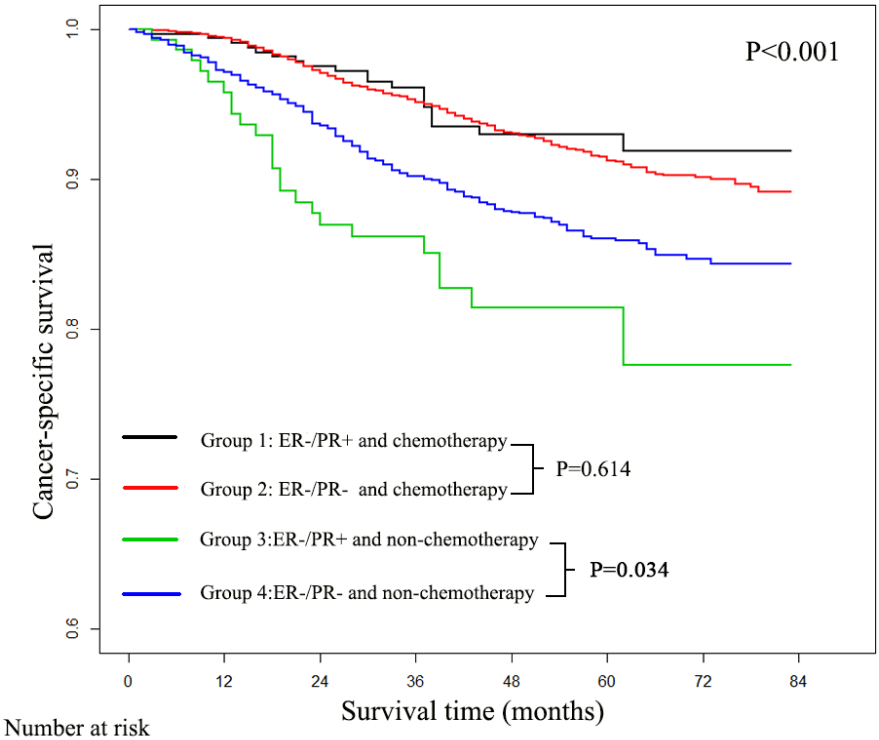









Number at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Group 1 | 332 | 322 | 303 | 226 | 152 | 89 | 37 | 2 |
| Group 2 | 5011 | 4873 | 4561 | 3526 | 2485 | 1563 | 748 | 53 |
| Group 3 | 145 | 134 | 114 | 79 | 49 | 23 | 11 | 1 |
| Group 4 | 1977 | 1830 | 1667 | 1278 | 902 | 559 | 271 | 25 |

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