Research Paper

Association of Neo-Family History Score with pathological complete response, safety, and survival outcomes in patients with breast cancer receiving neoadjuvant platinum-based chemotherapy: An exploratory analysis of two prospective trials

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ABSTRACT

Background: Homologous recombination deficiency is associated with platinum-based chemosensitivity, whereas few studies reported the predictive value of family history of cancer for breast cancer in the neoadjuvant setting. This study aimed to construct a novel family history scoring system and to explore its association with clinical outcomes for patients with breast cancer receiving neoadjuvant platinum-based chemotherapy.

Methods: This study included 262 patients with locally advanced breast cancer enrolled in the SHPD001 and SHPD002 trials from October 2013 to June 2018. The Neo-Family History Score (NeoFHS) was calculated according to cancer type, age at diagnosis, kinship, and number of affected relatives.

Findings: Clinical tumor stage (p=0.048), estrogen receptor status (p=0.001), progesterone receptor status (p=0.036), human epidermal growth factor receptor 2 status (p=0.016), and molecular subtype (p=0.016) were significantly related to NeoFHS. NeoFHS could serve as an independent predictive factor of pathological complete response (pCR) (OR=2.262, 95% CI 1.159-4.414, p=0.017) and an independent prognostic factor of relapse-free survival (adjusted HR=0.305, 95% CI 0.102-0.910, p=0.033). Alopecia (p=0.001), nausea (p=0.001), peripheral neuropathy (p=0.018), diarrhea (p=0.026), constipation (p=0.037) of any grade and leukopenia of grade 3 or greater (p=0.005) were more common in patients with higher NeoFHS.

Interpretation: NeoFHS is a practical and effective biomarker for predicting not only pCR and survival outcomes but also chemotherapy-induced adverse events for neoadjuvant platinum-based chemotherapy in breast cancer. It may help screen candidate responders and guide safety managements.

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1. Introduction

Over the last decades, neoadjuvant chemotherapy (NAC) has become a standard management for patients with locally advanced breast cancer. It has been revealed that patients with pathological complete response (pCR) have improved clinical outcomes including
and subsequently programs cell death under failure to repair or cytotoxic agent that results in DNA double-strand breaks (DSBs) of note, HRD is not capable of explaining all the familial breast cancer. Generally, homologous recombination repair (HRR) gene mutations are identified in only about 20% of breast cancer patients with family history of breast cancer. On the other hand, family history may reflect changes of hereditary substances beyond HRR gene mutations, including variants in other protein-coding genes as well as non-coding RNAs, epigenetic dysregulation, and some unrecognized mechanisms. Previous study suggested that family history of breast, ovarian, or pancreatic cancer might serve as a predictive marker for first-line platinum treatment in metastatic pancreatic adenocarcinoma. However, it remains unclear whether family history could predict chemosensitivity for patients with breast cancer especially those receiving neoadjuvant platinum-based regimen.

Added value of this study

To quantify patients' family history, the Neo-Family History Score system is conducted according to the age-, kinship-, and cancer-specific scores for the affected relatives. This study reveals that Neo-Family History Score is a novel biomarker for predicting not only pathological complete response and survival outcomes but also chemotherapy-induced adverse events for neoadjuvant platinum-based chemotherapy in breast cancer. It may help screen candidate responders and guide safety managements in the future.

Implications of all the available evidence

Family history of cancer may function as a double-edged sword in both protecting cancer cells from chemoresistance and inducing side effects to normal cells. The Neo-Family History Score system could be identified as a practical and effective biomarker for neoadjuvant platinum-based chemosensitivity. Further research is required to provide more insights into the underlying mechanisms.

Research in context

Evidence before this study

The GeparSixto, GeparOcto, TNT, and CBCSG006 trials have revealed that platinum-based chemosensitivity is associated with homologous recombination deficiency (HRD) especially BRCA1/2 mutations. Of note, HRD is not capable of explaining all the familial breast cancer. Generally, homologous recombination repair (HRR) gene mutations are identified in only about 20% of breast cancer patients with family history of breast cancer. On the other hand, family history may reflect changes of hereditary substances beyond HRR gene mutations, including variants in other protein-coding genes as well as non-coding RNAs, epigenetic dysregulation, and some unrecognized mechanisms. Previous study suggested that family history of breast, ovarian, or pancreatic cancer might serve as a predictive marker for first-line platinum treatment in metastatic pancreatic adenocarcinoma. However, it remains unclear whether family history could predict chemosensitivity for patients with breast cancer especially those receiving neoadjuvant platinum-based regimen.

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Implications of all the available evidence

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disease-free survival (DFS) and overall survival (OS) [1], while failure to achieve pCR is the strongest independent risk factor for recurrence especially in human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer (TNBC) [2]. Platinum is a classical cytotoxic agent that results in DNA double-strand breaks (DSBs) and subsequently programs cell death under failure to repair or excessive damage accumulation [3,4]. Cisplatin-based chemotherapy induces superior response in locally advanced breast cancer [5–8]. Our prior research showed that patients with locally advanced breast cancer achieved an encouraging pCR rate (34%-4%) after receiving neoadjuvant cisplatin plus paclitaxel. Much more exciting data was observed in those with HER2-positive breast cancer (52%-4%) and TNBC (64%-7%) [9]. Even so, a considerable number of patients still encounter the failure to achieve pCR. To well distinguish those who respond from those who do not in the neoadjuvant setting, research is warranted to investigate the potential biomarkers for individual chemosensitivity at the initial diagnosis.

Platinum resistance will occur once DSBs trigger excessive DNA damage repair [10], of which homologous recombination repair (HRR) is the major process [11]. Previous evidence has revealed that platinum-based chemosensitivity is associated with mutation of genes involved in HRR, especially BRCA1/2 [12,13]. The GeparSixto trial revealed that homologous recombination deficiency (HRD) independently predicts pCR in TNBC, and improved pCR rate was observed for homologous recombination deficient tumors by adding carboplatin to paclitaxel and nonpegylated liposomal doxorubicin (PMCb) [14]. Of note, HRD is not capable of explaining all the familial breast cancer. Generally, HRR gene mutations are identified in only about 20% of breast cancer patients with family history of breast cancer [15,16]. On the other hand, family history may reflect changes of hereditary substances beyond HRR gene mutations, including variants in other protein-coding genes [15] as well as non-coding RNAs [17], epigenetic dysregulation [18], and some unrecognized mechanisms. The previous study by David et al. suggested that family history of breast, ovarian, or pancreatic cancer might serve as a predictive marker for first-line platinum treatment in metastatic pancreatic adenocarcinoma [19]. Regrettably, it remains unclear whether family history could predict chemosensitivity for breast cancer patients especially those treated with platinum-based regimen.

So far, traditional methods of evaluating family history usually aim to assess incidence [20,21], mortality [22], and BRCA mutation risk [23] instead of chemosensitivity for patients with breast cancer. And those definitions merely include BRCA-related cancer in the kindreds. Notably, at most 55% of breast cancer with family history of both breast cancer and ovarian cancer can be explained by the high-penetrance BRCA1/2 variants [24]. It hints that many other breast cancer susceptibility genes also contribute [15]. Interestingly, patients with family history of cancer other than breast or ovarian cancer generally have HER2-positive disease [25]. Therefore, we hypothesized that family history of BRCA-related cancer and non-BRCA cancer might both influence the biological features of breast cancer. Here we proposed a brief quantitative novel scoring system named Neo-Family History Score (NeoFHS) and postulated that it might serve as a predictive biomarker of platinum-based chemosensitivity for breast cancer in the neoadjuvant setting. In this study, we retrospectively investigated the predictive and prognostic value of NeoFHS in the patients from our platinum-based prospective neoadjuvant trials.

2. Methods

2.1. Patients and study design

We performed a retrospective study on women with T2-4N0-3M0 breast cancer enrolled in two prospective neoadjuvant clinical trials, separately registered as SHPD001 (ClinicalTrials.gov identifier: NCT02199418) and SHPD002 (ClinicalTrials.gov identifier: NCT02221999). Between October 2013 and June 2018, 262 patients enrolled in these two trials at Renji Hospital, School of Medicine, Shanghai Jiao Tong University were available for the analysis. All the patients were from independent families.

Details of the protocols were published previously [9]. In brief, paclitaxel 80 mg/m² was intravenously given on day 1, 8, 15, and 22, combined with cisplatin 25 mg/m² on day 1, 8, and 15 every 28 days for 4 cycles. For HER2-positive patients, trastuzumab was recommended concurrently at a loading dose of 4 mg/kg followed by a maintenance dose of 2 mg/kg, weekly, for 16 weeks. Hormone receptor (HR)-positive patients in SHPD002 were allocated to chemotherapy with or without GnRhA in SHPD002. Surgery was given sequentially after NAC.

This study was presented according to the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guideline [26].
2.2. External validation dataset

An independent cohort that received cisplatin-paclitaxel-based neoadjuvant chemotherapy was included in the analysis as an external validation. Between November 2018 and October 2020, a total of 42 patients were enrolled and their full data were collected.

2.3. Data collection

The baseline data was collected prospectively at enrollment. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, and 25 was used to separate groups. The follow-up information was also prospectively collected.

All the biopsy tissues were diagnosed as invasive breast cancer by Department of Pathology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University. HorR positivity was defined as >1% tumor cell nuclei stained for estrogen receptor (ER) or progesterone receptor (PR) by immunohistochemistry (IHC). HER2 positivity was defined as IHC 3+ or amplification by fluorescence in situ hybridization according to the American Society of Clinical Oncology/College of American Pathologists recommendations 2013 [27]. In terms of Ki67 index, we used 50% to separate groups [28–30]. According to the St Gallen International Expert Consensus [31], the molecular subtype was categorized into luminal A-like (ER or PR positive, HER2 negative, and Ki67 index < 20%), luminal B-like (ER or PR positive; HER2 negative and Ki67 index > 20%, or HER2 positive and any Ki67 index), HER2-enriched (ER negative, PR negative, and HER2 positive), and basal-like (ER, PR, and HER2 negative).

2.4. Calculation of traditional family history scores

Multiple classical tools for identifying BRCA1/2 mutations were recommended by US Preventive Services Task Force (USPSTF) [23]. The Ontario Family History Assessment Tool uses family data on breast, ovarian, prostate, and colon cancer according to onset age for summation, with a score of > 10 implicating doubling of lifetime risk for developing breast cancer (22%). The Manchester Scoring System incorporates family history of female and male breast cancer, ovarian cancer, pancreatic cancer, and prostate cancer according to onset age, with a combined score of 15 corresponding to 10% chance to carry BRCA1/2 mutations. The Pedigree Assessment Tool includes female breast cancer with onset age, male breast cancer, ovarian cancer, pancreatic cancer, and prostate cancer according to onset age, with a value of 1 of 15 corresponding to 10% chance to carry BRCA1/2 mutations. The results were considered significant with p < 0.05.

2.5. Conduction of Neo-Family History Score (NeoFHS)

Considering that cancer type, age at diagnosis, kinship, and affected number may have comprehensive influence on the family background of a patient [23,32,33], we conducted the NeoFHS system to quantify individual family history. It was calculated as the total age-, kinship-, and cancer-specific scores for all the affected relatives (Table 1). The cut-off value of NeoFHS was determined to be 0.5, the higher quartile of all data.

2.6. Outcomes

The outcomes in this study were pCR, relapse-free survival (RFS), distant relapse-free survival (DRFS), visceral metastasis-free survival (VMFS), and safety. The definition of pCR was no residual invasive cancer in the breast and the absence of cancer cells in lymph node samples taken at the time of surgery (ypT0ypN0). RFS was calculated as the time from surgery to first occurrence of locoregional, ipsilateral, contralateral, distant recurrence, and death from any cause.

Table 1

| Factors | Point |
|---------|-------|
| BRCA-related cancer diagnosed under age 50 years | 1 |
| First-degree relative | 1 |
| Second-degree relative | 2 |
| Third-degree relative | 4 |
| BRCA-related cancer diagnosed at or over age 50 years or other cancers diagnosed at any age | 1 |
| First-degree relative | 2 |
| Second-degree relative | 4 |
| Third-degree relative | 8 |

* Point was assigned according to kinship coefficient [57].
* BRCA-related cancer refers to breast, ovarian, prostate, pancreatic, and colon cancer [58].
* Other cancers include lung, esophageal, thyroid, gastric, liver, rectal, nasopharyngeal, bladder, gallbladder, cervical, bone, skin, and tongue cancer, glioma, parotid mixed tumor, lymphoma, and leukemia in this study.

DRFS was defined as the time from surgery to first occurrence of distant recurrence and death from any cause. VMFS referred to the time from surgery until first occurrence of visceral metastasis and death from any cause. Adverse events (AEs) were assessed during study period and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.01.

2.7. Bioinformatics analyses

We derived a gene expression profile GSE75678 from the Gene Expression Omnibus (GEO), and identified the differentially expressed genes (DEGs) between breast cancer patients without family history of cancer and those with family history of any cancer, or BRCA-related cancer, or non-BRCA cancer, respectively. The threshold of DEGs was set as [fold change (FC) ≥ 2.0 and p < 0.05]. Then we performed Gene Ontology (GO) categories and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways by Database for Annotation, Visualization and Integrated Discovery (DAVID) [34,35].

2.8. Statistical analyses

Associations of various family history scores with baseline clinicopathological features and AEs were calculated by chi-squared test or Fisher’s exact test. Logistic regression analyses were used to derive odds ratios (ORs) with 95% confidence intervals (CIs) when we evaluated the correlations of pCR with family history scores and baseline information [age, clinical tumor (T) stage, clinical nodal status, HorR status, HER2 status, Ki67 index, and BMI], and the potential interactions between NeoFHS and clinicopathological features for pCR. To build the multivariate predictive model, the data were randomly split into a training set and a testing set at an 8:2 ratio. The least absolute shrinkage and selection operator (LASSO) algorithm and 10-fold cross validation were used to select optimal predictive parameters. Nomograms were established to display the predicted probabilities of pCR. Calibration curve was examined by Hosmer-Lemeshow test. Receiver operating characteristic (ROC) curves, decision curve analysis (DCA), and clinical impact curves (CICs) were performed to investigate if NeoFHS could promote the ability to predict individual response to NAC. The estimated median follow-up was calculated using the reverse Kaplan-Meier method. Survival rates were compared by Kaplan-Meier curves, examined by log-rank test. Cox proportional hazard regressions were performed to derive hazard ratios (HRs) with 95% CIs. The adjustment factors were baseline clinicopathological variables including menopausal status, clinical T stage, clinical nodal status, HorR status, HER2 status, Ki67 index, and BMI. All analyses were performed by R software version 3.6.3 (http://www.R-project.org). The results were considered significant with p < 0.05.
2.9. Ethics approval and consent to participate

Ethical approvals were granted for the original trials by the Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University (SHPD001, approval ID [2014]14K; SHPD002, approval ID [2017]088). All participants involved in this study signed written informed consents covering the original trials and biomarker research.

2.10. Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and accept responsibility to submit for publication.

3. Results

3.1. Baseline clinicopathological characteristics

Detailed data on family history was available from 262 patients. Among them, 69 (26.3%) patients presented with first-degree family history of any cancer, 37 (14.1%) patients with affected second-degree relatives, and 5 (1.9%) patients with affected third-degree relatives (Fig. 1). In total, 25 patients (9.5%) were at high Ontario risk, 17 patients (6.5%) had high Manchester risk, and 21 patients (8.0%) showed high Pedigree risk. We found an inverse correlation between age and Ontario risk score (p=0.037) as well as Pedigree risk score (p=0.011), and a positive correlation between BMI and Manchester risk score (p=0.009). However, none of these classical family history scores were related to the pathological features of tumors (Supplementary Table 1).

Neither family history of BRCA-related cancer nor family history of non-BRCA cancer was directly related to patients’ clinicopathological characteristics (Table 2). Therefore, we applied the NeoFHS system in all patients to investigate its relationship with tumor features. It suggested that higher T stage (p=0.048), ER negativity (p=0.001), PR negativity (p=0.036), and HER2 positivity (p=0.013) were associated with higher NeoFHS. Besides, patients with HER2-enriched breast cancer were more likely to present with higher NeoFHS, while those with luminal-like tumors tended to have lower NeoFHS (p=0.016). No correlation was detected between NeoFHS and age, menopausal status, nodal stage, Ki67 index, histologic grade, or BMI (Table 2).

3.2. pCR rates

Among 262 patients, 86 (32.8%) achieved pCR while 176 (67.2%) failed to achieve pCR. We detected no differences in pCR rates between the groups separated by Ontario risk score (OR=0.959, 95% CI 0.397–2.319, p=0.926), Manchester risk score (OR=1.125, 95% CI 0.402–3.151, p=0.823), or Pedigree risk score (Fig. 2A; OR=1.025, 95% CI 0.398–2.641, p=0.959; Table 3). However, NeoFHS-high patients achieved a superior pCR rate of 44.9%, whereas the corresponding rate was 27.7% for NeoFHS-low patients (Fig. 2B; OR=2.123, 95% CI 1.224–3.682, p=0.007; Table 3). Multivariate analyses suggested that none of those traditional family history scores were predictive for pCR (Ontario risk score, OR=0.767, 95% CI 0.272–2.161, p=0.616, Supplementary Table 2; Manchester risk score, OR=1.146, 95% CI 0.366–3.589, p=0.815, Supplementary Table 3; Pedigree risk score, OR=0.893, 95% CI 0.301–2.645, p=0.838, Supplementary Table

![Fig. 1. Number of patients with family history of cancer in the first, second, and third-degree relatives.](image-url)
serve as independent predictive factors for pCR (Fig. 2C; Table 4).

The data were randomized into a training set and a testing set at an 8:2 ratio. With LASSO algorithm (Fig. 2D) and cross validation (Fig. 2E), seven predictive features were selected, including NeoFHS, age, T stage, HorR status, HER2 status, Ki67 index, and BMI, based on the training set. A nomogram was created for the predictive model consisting of the extracted variables (Fig. 3A). The corresponding calibration curves showed great agreement between the predicted probabilities and observed pCR outcomes for both the training set ($\chi^2=11.99, p=0.152$; Fig. 3B) and the testing set ($\chi^2=3.47, p=0.902$; Fig. 3C).

The accuracy of different predictive models with or without NeoFHS were compared by ROC curves and decision curves. As a result, the area under curve (AUC) was 0.770 achieved by adding NeoFHS to clinico-pathological variables, which is better than 0.761 for the clinico-pathological characteristics alone for the training set (Fig. 3D). Besides, the DCA consistently depicted more benefits with the model combining NeoFHS with clinico-pathological features (Fig. 3E). For the testing set, the ROC curves (AUC, 0.897 vs 0.847; Fig. 3F) and decision curves (Fig. 3G) both verified the improvement by adding NeoFHS to the clinico-pathological features. The CIC for predicting pCR demonstrated that cost/benefit ratios were lower with the risk threshold less than 0.7 (Fig. 3H).

Furthermore, an independent cohort was included to validate the performance of the predictive model (Fig. 3I). ROC curves supported the benefit by combining NeoFHS with the clinico-pathological features for evaluating response to platinum-based NAC (AUC, 0.897 vs 0.847; Fig. 3J) and decision curves (Fig. 3K) both verified the improvement by adding NeoFHS to the clinico-pathological features. The CIC for predicting pCR demonstrated that cost/benefit ratios were lower with the risk threshold less than 0.7 (Fig. 3L).

### 3.3 Building and assessment of the multivariate predictive model

The data were randomized into a training set and a testing set at an 8:2 ratio. With LASSO algorithm (Fig. 2D) and cross validation (Fig. 2E), seven predictive features were selected, including NeoFHS, age, T stage, HorR status, HER2 status, Ki67 index, and BMI, based on the training set. A nomogram was created for the predictive model consisting of the extracted variables (Fig. 3A). The corresponding calibration curves showed great agreement between the predicted probabilities and observed pCR outcomes for both the training set ($\chi^2=11.99, p=0.152$; Fig. 3B) and the testing set ($\chi^2=3.47, p=0.902$; Fig. 3C).

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HER2, human epidermal growth factor receptor 2; BMI, body mass index.

Fig. 2. Feature extraction for pCR prediction. Notes: (a) The pCR rates by traditional family history scores. (b) Visualization of pCR and Neo-Family History Scores. (c) Heatmap with two-category data (pCR vs no-pCR, NeoFHS high vs low, age ≥35 vs <35 years, T stage T3-4 vs T2, N stage N1-3 vs N0, HorR positive vs negative, HER2 positive vs negative, Ki67 index ≥50% vs <50%, and BMI ≥25 vs <25); (d) LASSO algorithm and 10-fold cross validation for feature selection. Neo-Family History Score, age, clinical T stage, HorR status, HER2 status, Ki67 index, and BMI were extracted with \( \lambda = 0.013 \) [log(\( \lambda \))] = -4.350, while clinical nodal status was excluded. (e) LASSO coefficient profiles of candidate features were successively selected into the predictive model. Abbreviations: pCR, pathological complete response; NeoFHS, Neo-Family History Score; T, tumor; N, nodal; HorR, hormone receptor; HER2, human epidermal growth factor receptor 2; BMI, body mass index.

Table 3
Univariate analysis for predictive factors of pCR in all patients.

| Variables                        | Comparison for OR               | Univariate analysis (n=262) |
|----------------------------------|---------------------------------|-----------------------------|
|                                  | OR 95% CI p value               |                             |
| Ontario risk score               | High vs low                     | 0.959 (0.397, 2.319) 0.926   |
| Manchester risk score            | High vs low                     | 1.125 (0.402, 3.151) 0.823   |
| Pedigree risk score              | High vs low                     | 1.025 (0.398, 2.641) 0.959   |
| Neo-Family History Score         | High vs low                     | 2.123 (1.224, 3.682) **0.007** |
| Age                              | ≥35 vs <35 years                | 0.411 (0.173, 0.974) 0.043    |
| T stage                          | T4 vs T3 vs T2                  | 0.565 (0.391, 0.817) **0.002** |
| Nodal status                     | Positive vs negative            | 1.236 (0.581, 2.626) 0.582    |
| HorR status                      | Positive vs negative            | 0.321 (0.176, 0.587) <0.001   |
| HER2 status                      | Positive vs negative            | 2.707 (1.592, 4.602) <0.001   |
| Ki67 index                       | ≥50% vs <50%                    | 3.292 (1.925, 5.629) <0.001   |
| BMI                              | ≥25 vs <25                      | 0.503 (0.268, 0.944) **0.032** |

Abbreviations: pCR, pathological complete response; OR, odds ratio; CI, confidence interval; T, tumor; HorR, hormone receptor; HER2, human epidermal growth factor receptor 2; BMI, body mass index.

(OR=2.584, 95% CI 1.358–4.919, p=0.004), as well as T2 (OR=6.824, 95% CI 1.296–35.928, p=0.023), T3-4 (OR=2.014, 95% CI 1.082–3.749, p=0.027), node-positive (OR=2.649, 95% CI 1.473–4.761, p=0.001), HorR-positive (OR=2.009, 95% CI 1.026–3.933, p=0.042), HER2-negative (OR=2.333, 95% CI 1.052–5.175, p=0.037), Ki67 ≥50% (OR=2.839, 95% CI 1.169–6.895, p=0.021), and grade 3 tumors (OR=2.175, 95% CI 1.067–4.434, p=0.032; Fig. 4).

In the multivariate analyses, NeoFHS could serve as an independent predictive factor for pCR in T2 (80% vs 37%, OR=7.139, 95% CI 1.083–47.062, p=0.041; Supplementary Table 5), grade 3 (57.4% vs 38.3%, OR=2.332, 95% CI 1.008–5.399, p=0.048; Supplementary Table 6), node-positive (48.6% vs 26.3%, OR=3.088, 95% CI 1.498–6.367, p=0.002; Supplementary Table 7), HorR-positive (37.7% vs 23.2%, OR=2.645, 95% CI 1.164–6.010, p=0.020; Supplementary Table 8), and HER2-negative subgroups (36.8% vs 20.0%, OR=4.786, 95% CI 1.550–14.775, p=0.006; Supplementary Table 9).

There was no interaction detected between clinicopathological variables and NeoFHS for pCR (Fig. 4).

3.5. Relapse-free survival

The median follow-up time was 28.3 months. A total of 30 patients experienced relapse. The Kaplan-Meier estimates
demonstrated that RFS rates did not differ between Ontario high-risk and Ontario low-risk groups (log-rank p=0.0254; adjusted HR=0.341, 95% CI 0.046–2.523, p=0.292; Fig. 5A). No differences were seen for RFS between groups according to Manchester risk score (log-rank p=0.440; adjusted HR=0.447, 95% CI 0.060–3.301, p=0.430; Fig. 5B) or Pedigree risk score (log-rank p=0.328; adjusted HR=0.404, 95% CI 0.054–3.000, p=0.376; Fig. 5C), either. However, NeoFHS was observed to be independently prognostic for RFS (log-rank p=0.066; adjusted HR=0.305, 95% CI 0.102–0.910, p=0.033; Fig. 5D). In node-positive women, patients with higher NeoFHS also achieved longer RFS than those with lower NeoFHS (log-rank p=0.096; adjusted HR=0.317, 95% CI 0.103–0.973, p=0.045; Fig. 5E). The prognostic value of NeoFHS was not significant for RFS in HorR-positive (log-rank p=0.194; adjusted HR=0.444, 95% CI 0.130–1.510, p=0.193) or HER2-negative counterparts (log-rank p=0.133; adjusted HR=0.302, 95% CI 0.069–1.325, p=0.113).

3.6. Distant relapse-free survival

There were totally 26 distant relapse events. For the whole group, neither Ontario risk score (log-rank p=0.321; adjusted HR=0.391, 95% CI 0.052–2.914, p=0.359; Supplementary Fig. 1A),

Table 4

| Variables                      | Comparison for OR | Multivariate analysis (n=262) |
|--------------------------------|-------------------|-----------------------------|
|                                |                  | OR 95% CI p value           |
| Neo-Family History Score       | High vs low      | 2.262 1.159 4.414 0.017     |
| Age                            | ≥35 vs <35 years | 0.367 0.137 0.982 0.046     |
| T stage                        | T4 vs T3 vs T2   | 0.581 0.379 0.892 0.013     |
| Nodal status                   | Positive vs negative | 0.919 0.389 2.170 0.847     |
| HorR status                    | Positive vs negative | 0.398 0.203 0.782 0.008     |
| HER2 status                    | Positive vs negative | 3.294 1.785 6.079 <0.001    |
| Ki67 index                     | ≥50% vs <50%     | 3.190 1.740 5.848 <0.001    |
| BMI                            | ≥25 vs <25       | 0.539 0.266 1.092 0.086     |

Abbreviations: pCR, pathological complete response; OR, odds ratio; CI, confidence interval; T, tumor; HorR, hormone receptor; HER2, human epidermal growth factor receptor 2; BMI, body mass index.
nor Manchester risk score (log-rank p=0.523; adjusted HR=0.469, 95% CI 0.063–3.490, p=0.460; Supplementary Fig. 1B), nor Pedi-gree risk score (log-rank p=0.402; adjusted HR=0.459, 95% CI 0.061–3.424, p=0.447; Supplementary Fig. 1C) was associated with DRFS. Instead, NeoFHS could serve as an independent prognostic factor for DRFS in both total patients (log-rank p=0.053; adjusted HR=0.279, 95% CI 0.080–0.950, p=0.041; Supplementary Fig. 1D) and node-positive subgroup (log-rank p=0.063; adjusted HR=0.274, 95% CI 0.078–0.971, p=0.045; Supplementary Fig. 1E).

### Table 1: Subgroup Analysis for pCR by NeoFHS

| Subgroups          | Events (n)/patients (n) | OR (95% CI) | p value | p value |
|--------------------|-------------------------|-------------|---------|---------|
| Overall            | NeoFHS-low group | NeoFHS-high group | 2.123 (1.224–3.682) | 0.007 |
| Age                | <35 year              | 6/17        | 6/6     | NA     |
|                    | >35 year              | 45/67       | 29/72   | 1.828 (1.022–3.272) | 0.042 |
| Menopausal status  | Premenopausal         | 24/96       | 14/21   | 2.217 (0.999–5.128) | 0.063 |
|                    | Postmenopausal        | 25/88       | 21/47   | 2.035 (0.973–4.259) | 0.059 |
| T stage            | T2                    | 17/44       | 8/10    | 6.824 (1.296–35.928) | 0.023 |
|                    | T3-4                  | 34/138      | 29/48   | 2.014 (1.082–3.749) | 0.027 |
| Nodal status       | Node negative         | 11/32       | 0/6     | NA     |
|                    | Node positive         | 40/152      | 35/72   | 2.649 (1.473–4.761) | 0.001 |
| HorR status        | HorR negative         | 16/33       | 15/25   | 1.94 (0.557–4.563) | 0.385 |
|                    | HorR positive         | 35/151      | 20/53   | 2.009 (1.024–3.933) | 0.042 |
| HER2 status        | HER2 negative         | 24/120      | 14/38   | 2.333 (1.052–5.175) | 0.037 |
|                    | HER2 positive         | 27/64       | 21/40   | 1.515 (0.684–3.352) | 0.306 |
| Ki67 index         | <50%                  | 20/109      | 15/48   | 2.023 (0.928–4.401) | 0.077 |
|                    | >50%                  | 31/75       | 20/30   | 2.839 (1.149–6.895) | 0.021 |
| Histologic grade   | G2                    | 9/68        | 6/24    | 2.185 (0.685–6.971) | 0.187 |
|                    | G3                    | 34/94       | 27/47   | 2.175 (1.047–4.434) | 0.032 |
| Molecular subtype  | Luminal A-like        | 0/17        | 0/4     | NA     |
|                    | Luminal B-like        | 35/334      | 20/49   | 1.951 (0.981–3.881) | 0.057 |
|                    | HER2-enriched         | 5/11        | 10/14   | 3.000 (0.571–15.764) | 0.194 |
|                    | Basal-like            | 11/22       | 5/11    | 0.833 (0.195–3.556) | 0.806 |
| BMI                | <25                   | 41/336      | 29/55   | 2.564 (1.358–4.919) | 0.004 |
|                    | >25                   | 10/48       | 6/23    | 1.341 (0.449–4.289) | 0.621 |

**OR** = odds ratio; **CI** = confidence interval; **NeoFHS** = Neo-Family History Score; **T** = tumor; **HorR** = hormone receptor; **HER2** = human epidermal growth factor receptor 2; **BMI** = body mass index.

**Fig. 4.** Subgroup analysis for pCR by NeoFHS. Notes: ORs and 95% CIs were derived from univariate logistic regression model. Interaction p values were shown between subgroups and NeoFHS. Abbreviations: OR, odds ratio; CI, confidence interval; NeoFHS, Neo-Family History Score; T, tumor; HorR, hormone receptor; HER2, human epidermal growth factor receptor 2; BMI, body mass index.
3.7. Visceral metastasis-free survival

Visceral metastasis events occurred in 18 patients. Similarly, no association of VMFS was detected for total patients with Ontario risk score (log-rank p=0.165; Supplementary Fig. 2A), Manchester risk score (log-rank p=0.263; Supplementary Fig. 2B), or Pedigree risk score (log-rank p=0.197; Supplementary Fig. 2C), while NeoFHS was an independent prognostic factor for improved VMFS in the entire population (log-rank p=0.101; adjusted HR=0.203, 95% CI 0.043–0.952, p=0.043; Supplementary Fig. 2D), and concordantly in patients with node-positive breast cancer (log-rank p=0.115; adjusted HR=0.199, 95% CI 0.041–0.961, p=0.044; Supplementary Fig. 2E).

3.8. Safety

Safety was assessed in all evaluable patients. Overall, common AEs were reported in 242 patients (92.4%). Among the three traditional scoring systems, Ontario risk score was related to more nausea (84.0% vs 57.0%; p=0.009), fatigue (72.0% vs 43.5%; p=0.006), diarrhea (68.0% vs 42.2%; p=0.014), and rash (48.0% vs 27.4%; p=0.032), while Pedigree risk score was correlated to more frequent nausea (80.9% vs 57.7%; p=0.037) and diarrhea (66.7% vs 42.7%; p=0.034) of any grade. In addition, a total of 138 patients (52.7%) experienced grade 3 or greater AEs. Ontario risk score was associated with more anemia events of grade 3 or greater (12.0% vs 3.4%; p=0.041). However, no relationship between AEs and Manchester risk score was found (Supplementary Table 10).

On the other hand, higher NeoFHS was associated with more frequent nausea (75.6% vs 52.7%; p=0.001) and diarrhea (55.1% vs 40.2%; p=0.026) as well. Moreover, alopecia (82.1% vs 60.3%; p=0.001), peripheral neuropathy (70.5% vs 54.9%; p=0.018), and constipation (34.6% vs 22.3%; p=0.037) of any grade were also more common in patients with higher NeoFHS. Additionally, leukopenia of grade 3 or greater was more frequent in the NeoFHS-high group (39.7% vs 22.8%; p=0.005). No difference was detected for other common AEs (Table 5).
Since the predictive ability of pCR was well shown for the NeoFHS system rather than the family history scoring systems assessing BRCA1/2 mutations, we hypothesized that family history of BRCA-related cancer and non-BRCA cancer might both contribute to platinum-based chemosensitivity but through the dysregulation of different genes. To investigate the potential mechanisms of enhanced efficacy and toxicity for patients with higher NeoFHS, we analyzed the gene expression profile GSE75678 to visualize the statistical significance of the DEGs between breast cancer patients without family history of cancer and those with family history of any cancer, or BRCA-related cancer, or non-BRCA cancer, respectively.

As a result, 474 genes were upregulated, and 110 genes were downregulated in patients with family history of any cancer (Supplementary Fig. 3A; Supplementary Table 11–11). The DEGs were utilized to perform pathway analyses. As depicted, the GO terms related to biological process highlighted homophilic cell adhesion, cell death, oxygen transport, leukotriene signaling pathway, heterotypic cell adhesion, cytokine secretion involved in immune response, nervous system development, cell-cell signaling, cell differentiation, cytokine-type endopeptidase activity involved in apoptotic process, glycosphingolipid biosynthetic process, G-protein coupled glutamate receptor signaling pathway, and embryonic heart tube anterior/posterior pattern specification (Supplementary Fig. 3D; Supplementary Table 11–4). The most significant KEGG pathways were hematopoietic cell lineage, calcium signaling pathway, MAPK signaling pathway, proteoglycans in cancer, cytokine-cytokine receptor interaction, and neuroactive ligand-receptor interaction (Supplementary Fig. 3G; Supplementary Table 11–5).

In patients with family history of BRCA-related cancer, there were 959 upregulated genes and 57 downregulated genes (Supplementary Fig. 3B; Supplementary Table 11–2). The GO enrichment suggested that the most critical biological processes were ERK1/2 cascade, platelet activation, platelet degranulation, phosphatidylinositol phosphorylation, protein kinase B signaling, nitric oxide biosynthetic process, long-term synaptic potentiation, protein localization to organelle, ion transmembrane transport, sodium ion transport, central nervous system development, synaptic transmission, insulin-like growth factor receptor signaling pathway, and cellular response to histamine (Supplementary Fig. 3E; Supplementary Table 11–6). While no pathways were enriched by KEGG for the downregulated genes, the key pathways for the upregulated genes were ErbB signaling pathway, HIF-1 signaling pathway, natural killer cell mediated cytotoxicity, proteoglycans in cancer, tuberculosis, MAPK signaling pathway, etc. (Supplementary Fig. 3H; Supplementary Table 11–7).

A total of 579 upregulated genes and 106 downregulated genes were detected in patients with family history of non-BRCA cancer (Supplementary Fig. 3C; Supplementary Table 11–3). The GO enrichment revealed that the most important biological processes included cell adhesion, response to drug, female pregnancy, smoothened signaling pathway, skeletal muscle tissue development, ERK1/2 cascade, B cell activation, protein insertion into mitochondrial membrane involved in apoptotic signaling pathway, leukotriene, inflammatory response, peptidyl-tyrosine phosphorylation, activation of MAPK activity, osteoclast differentiation, release of cytokochrome c from mitochondria, protein phosphorylation, necroptotic process, and p38MAPK cascade (Supplementary Fig. 3F; Supplementary Table 11–8). The KEGG pathway analysis exhibited the top 10 pathways including hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, dilated cardiomyopathy, cholinergic cell lineage, osteoclast differentiation, MAPK signaling pathway, and PI3K-Akt signaling pathway. No KEGG pathways were shown for the downregulated genes as well (Supplementary Fig. 3I; Supplementary Table 11–9).

4. Discussion

As far as we know, our study for the first time succeeded in identifying NeoFHS, a brief novel scoring system we conducted to evaluate the family history of cancer comprehensively, as a predictive biomarker for clinical benefit from platinum-based NAC in patients with breast cancer. It was also the first time to report the relationship between AEs and family history of cancer.

USPSTF has recommended several assessment tools to estimate the likelihood of carrying harmful BRCA1/2 mutations, including Ontario Family History Assessment Tool, Manchester Scoring System, and Pedigree Assessment Tool [23]. We calculated these traditional family history scores and investigated their relationships with tumor features in this study. The findings revealed that none of them were associated with tumor characteristics in our cohorts, although they could accurately identify women with increased possibility of carrying BRCA1/2 mutations [23]. Reportedly, breast cancer with BRCA1 mutation is more often ER-negative and PR-negative, while BRCA2 mutation carriers express similar levels of ER and PR compared with sporadic tumors. Both of the mutation carriers show a lower frequency of HER2-expressing cells [36]. Consistently, Huang et al. reported that family history of breast or ovarian cancer increased the risk of ER-negative and PR-negative, rather than ER-positive or PR-positive breast cancer [37]. However, many other breast cancer susceptibility genes also influence the biological features of breast tumors. For instance, it is more common for breast cancer with reduced ATM expression to be ER-negative and PR-negative [38,39], while low nuclear CHEK2 protein level [39] and germline TP53 mutations [40] are more likely to present with HER2 amplification. Interestingly, Song et al. found that patients with first-degree family history of cancer other than breast or ovarian cancer tended to have HER2-positive disease [25]. Therefore, we postulated that family history of BRCA-related cancer and non-BRCA cancer might contribute to different biological characteristics. In the current study, we
proposed a brief but comprehensive scoring system, NeoFHS, which included both BRCA-related cancer and non-BRCA cancer, as well as age at diagnosis, kinship, and affected number. Partially consistent with previous studies above and fully validating our hypothesis, our data showed that ER negativity, PR negativity, HER2 positivity, higher T stage, and molecular subtype were related to NeoFHS. These findings highlight the necessity and advantage to take various cancer types into comprehensive consideration for the definitions of family history, which we did exactly in the NeoFHS system.

The current study revealed that NeoFHS could serve as an independent predictive factor for pCR in breast cancer receiving platinum-based NAC, especially in node-positive, HorR-positive, and HER2-negative patients. To the best of our knowledge, our study for the first time substantiated that family history of cancer contributed to a better pCR rate, which significantly increased to 44.9% for NeoFHS-high patients from 27.7% for those with lower NeoFHS. Good performance was shown in the predictive model that combined NeoFHS with baseline clinicopathological variables. The external validation dataset further demonstrated this result. So far, emerging evidence indicates that breast cancer arising in BRCA1/2 germline mutation carriers achieves higher response to DNA-damaging agents. Bryski et al. reported that the highest pCR rate for regimens in BRCA1-mutation carriers turned out to be 83% for cisplatin, compared with 22% for AC (doxorubicin and cyclophosphamide) or FAC (fluorouracil, doxorubicin, and cyclophosphamide), 8% for AT (doxorubicin and docetaxel), and 7% for CMF (cyclophosphamide, methotrexate, and fluorouracil) [12]. Concordantly, the GeparOcto trial randomized patients with breast cancer to sequential intense dose-dense epirubicin, paclitaxel, and cyclophosphamide or weekly PM, and its secondary analysis showed a higher pCR rate in patients with germline BRCA1/2 variants than those without [41]. Additionally, the triple-negative trial (TNT), which recruited advanced TNBC, showed a better response to carboplatin plus to docetaxel in germline BRCA1/2 mutation group, with a significant interaction between platinum-based regimen and BRCA1/2 mutation [42]. On these premises, the classical family history scoring systems for assessing BRCA1/2 mutations have potential in pCR prediction. However, we found that Ontario, Manchester, and Pedigree risk score unexpectedly failed to predict pCR in our cohorts. This is consistent with the limited evidence on the association between pCR and family history of BRCA-related cancer. Ding et al. enrolled patients with HER2-positive and node-positive breast cancer to receive neoadjuvant paclitaxel, carboplatin, and trastuzumab, and the pCR rates were 50.0% and 32.9%, respectively, in patients with and without first- or second-degree family history of breast cancer (p=0.086) [43]. The secondary analysis of the GeparSixto trial reported that the pCR rate was 49.1% in the non-carboplatin arm and 61.4% in the carboplatin arm in TNBC with family history of breast or ovarian cancer (p=0.19), whereas the corresponding rate increased from 37% without carboplatin to 53.9% with carboplatin in patients without the same family history (p=0.02) [44]. These facts might be due to their definitions of family history, which did not take into account cancers except breast and ovarian cancer. It prompted us once again to focus on family history of cancer including but not limited to BRCA-related cancer.

In parallel, our data substantiated the prognostic value of NeoFHS in patients treated with neoadjuvant platinum-based chemotherapy, especially in node-positive patients. It indicated that the pCR benefit translated into improved survival outcome in terms of NeoFHS. Our finding is partially supported by the GeparSixto trial, which reported a significant improvement for OS in homologous recombination deficient tumors compared with non-homologous recombination deficient tumors after receiving neoadjuvant PMCb chemotherapy [14]. What makes it different is that NeoFHS would help physicians and patients save both time and expense compared with HRD assay. Till date, previous studies mostly focused on the association of prognosis with family history of BRCA-related cancer. Mohammed et al. reported that patients with family history of breast cancer showed an OS advantage over those without in premenopausal breast cancer [45], Malone et al. revealed that the mortality was significantly lower among young patients with invasive breast cancer and first-degree family history of breast cancer compared with those without [33]. The POSH study suggested that 5-year distant disease-free interval for patients with family history of breast or ovarian cancer in first- or second-degree relatives was better than those without in young patients with ER-negative breast cancer [46]. One noteworthy finding is that Song et al. demonstrated a worse DFS in patients with first-degree family history of cancer other than breast or ovarian cancer [25]. This evidence signifies the importance of non-BRCA cancer to family history when evaluating long-term outcomes. Furthermore, those studies didn’t place restrictions on treatments, and thereby couldn’t ideally reflect the prognostic value of family history for patients receiving neoadjuvant platinum-based regimen. Taken together, it might be reasonable to employ NeoFHS in early assessment of survival outcomes for women with breast cancer administered neoadjuvant platinum-based chemotherapy.

Based on our clinical observations, we speculated that family history of BRCA-cancer and non-BRCA cancer might both contribute to platinum-based chemosensitivity but through different mechanisms. To explore the underlying mechanisms, we performed pathway analyses of the DEGs between breast cancer patients without family history of cancer and those with family history of any cancer, or BRCA-related cancer, or non-BRCA cancer, respectively. As a result, totally different pathways were enriched under the various definitions of family history, suggesting that family history of merely BRCA-related cancer is insufficient to reflect individual genetic background thoroughly. For family history of non-BRCA cancer, the GO analysis showed that a group of the downregulated genes, including FOS, FOSB, and IL-10, were enriched in the response to drug (Supplementary Table S1). Kang et al. discovered that the Fos gene family members, FOS and FOSB, are upregulated in cisplatin-resistant gastric cell lines [47]. Yang et al. found that tumor-associated macrophages could induce paclitaxel resistance via activating IL-10/STAT3/Bcl-2 signaling pathway in breast cancer [48]. Therefore, NeoFHS might well distinguish tumors with hypersensitivity to cytotoxic agents from those without through the function of many other key genes beyond BRCA1/2. Further basic research is required to elucidate the essential difference between family history of BRCA-related cancer and non-BRCA cancer.

In terms of the safety profile, our data suggested that NeoFHS was associated with NAC-induced toxicity, including alopecia, peripheral neuropathy, diarrhea, nausea, constipation, and grade 3-4 leukopenia. This might be partly explained by the fact that not only cancer cells but also normal tissues with HRD would suffer from hypersensitiveness to chemotherapy [49]. Huszno et al. reported that more frequent neutropenia was detected in breast cancer with BRCA1/2 mutation after one cycle of chemotherapy [50]. Furlanetto et al. found that breast cancer with germline BRCA1/2 mutations had higher risk of hematologic toxicities under taxane [51]. Tomao et al. demonstrated that germline BRCA1/2 mutations were associated with higher hematologic toxicity for ovarian cancer undergoing platinum-based chemotherapy [49]. Consistently, our data showed more frequent AEs in patients with high Ontario risk as well as those with high Pedigree risk. It gave us a hint that family history of BRCA-related cancer might be conducive to predicting enhanced toxicity caused by cytotoxic agents. Notably, the results of pathway analyses implicated some other potential mechanisms of AEs, such as dysregulation of calcium signaling pathway and cytokine-cytokine receptor interaction, for those with family history of non-BRCA cancer. Siau and Bennett reported that dysregulation of calcium signaling pathway mediates chemotherapy-evoked neuropathic pain [52]. Zhang et al. revealed that cytokine-mediated signaling pathway is closely related to chemotherapy-induced alopecia [53]. It impelled us to lay
more emphasis on family history of not only BRCA-related cancer but also non-BRCA cancer in chemotherapy-induced AEs. The NeoFHS system may reasonably help us with early prediction and better management for chemotherapy-induced AEs.

Our study has several limitations. First, our data was analyzed retrospectively in a relatively small sample size. There is also a probability of false positive associations among the tests of significance. However, all the data from our clinical trials was collected prospectively, and the results were validated by both internal and external datasets. Therefore, it may indicate potential intrinsic rules to some extent. Further validation is required by enlarged sample size in the prospective cohort. Second, the dataset was heterogenous with respect to different breast cancer subtypes. It’s necessary to prospectively investigate the associations of NeoFHS with pCR in well-defined cohorts before being put to clinical use. In addition, it was not mature to perform analysis for OS. Prolonged follow-up will be warranted.

In summary, family history of cancer may function as a double-edged sword in both protecting cancer cells from chemoresistance and inducing side effects to normal cells. The NeoFHS system could be identified as a practical and effective biomarker for predicting not only chemosensitivity but also chemotherapy-induced AEs. This study may help screen candidate responders and guide safety management in the future. Further researches are required to provide more insights into the underlying mechanisms.

Data sharing statement

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

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Authors Contributions

JS Lu, WJ Yin, and YQ Xu designed and conducted the study. YQ Xu, YP Lin, YH Wang, LH Zhou, SC Xu, YF Wu, J Peng, and J Zhang collected the clinical data. YQ Xu, YP Lin, and YH Wang performed data analysis. YQ Xu drafted the manuscript. WJ Yin and JS Lu revised the manuscript. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101031.

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