Neo-Family History Score Is A Novel Biomarker of Pathological Complete Response, Safety, and Survival Outcomes In Patients With Breast Cancer Receiving Neoadjuvant Platinum-Based Chemotherapy: A Retrospective Analysis of Two Prospective Trials

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Abstract

Background: Homologous recombination repair gene mutations are associated with increased platinum-based chemosensitivity, whereas few studies have reported the predictive value of family history of cancer for breast cancer in the neoadjuvant setting. This study aimed to construct a brief and effective novel family history scoring system and explore its association with pathological complete response (pCR), survival outcomes, and safety for locally advanced breast cancer receiving platinum-based neoadjuvant chemotherapy.

Methods: A total of 262 patients treated with neoadjuvant cisplatin and paclitaxel were included. Neo-Family History Score (NeoFHS) was calculated according to cancer type, age at diagnosis, kinship, and number of affected relatives. Logistic regression was performed to analyze the association between pCR and NeoFHS. Survival rates were compared by Kaplan-Meier curves, examined by log-rank test and Cox proportional hazard regressions.

Results: For all patients enrolled in this study, clinical tumor stage (p=0.048), estrogen receptor status (p=0.001), progesterone receptor status (p=0.036), human epidermal growth factor receptor 2 (HER2) status (p=0.013), and molecular subtype (p=0.016) were significantly related to NeoFHS. The multivariate logistic regression revealed that NeoFHS is an independent predictive factor of pCR (OR=2.262, 95% CI 1.159-4.414, p=0.017), especially in node-positive (OR=3.088, 95% CI 1.498-6.367, p=0.002), hormone receptor-positive (OR=2.645, 95% CI 1.164-6.010, p=0.020), and HER2-negative subgroups (OR=4.786, 95% CI 1.550-14.775, p=0.006). Kaplan-Meier estimates suggested that NeoFHS could serve as an independent prognostic factor for relapse-free survival in the whole group (adjusted HR=0.305, 95% CI 0.102-0.910, p=0.033) and node-positive subgroup (adjusted HR=0.317, 95% CI 0.103-0.973, p=0.045). Furthermore, 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.

Conclusions: Our study revealed that NeoFHS is a practical and effective biomarker for predicting not only pCR and survival outcomes but also chemotherapy-induced AEs for neoadjuvant platinum-based chemotherapy for breast cancer. It may help screen candidate responders and guide safety managements in the future.

Background

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 disease-free survival (DFS) and overall survival (OS),[1] while failure to achieve pCR is the strongest independent risk factor for recurrence.[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 could induce 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 human epidermal growth factor receptor 2 (HER2)-positive breast cancer (52.4%) and triple-negative breast cancer (TNBC; 64.7%). Even so, a considerable number of patients still encounter the failure to achieve pCR.[9] 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 triggers 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 regulation,[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 cancers 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 cancers and non-BRCA cancers 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 patients from our platinum-based prospective neoadjuvant trials.

Methods

Patients and study design

We performed a retrospective study on women with $T_{2-4}N_{0-3}M_0$ breast cancer enrolled in two prospective neoadjuvant clinical trials, separately registered as SHPD001 (ClinicalTrials.gov identifier: NCT02199418) and SHPD002 (ClinicalTrials.gov identifier: NCT02221999). All the patients were from independent families. Ethical approvals were granted for both trials by the Ethics Committee of Renji Hospital, School of Medicine, Shanghai Jiao Tong University. All the enrolled patients signed written informed consents covering translational research.

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 (HorR)-positive patients in SHPD002 were allocated to chemotherapy with or without endocrine therapy [aromatase inhibitor for postmenopausal patients or gonadotropin-releasing hormone agonist (GnRHa) for premenopausal counterparts]. Premenopausal patients with TNBC were randomized to chemotherapy with or without GnRHa in SHPD002. Surgery was given sequentially after NAC.

Between January 2014 and January 2019, 262 patients from these two trials who had undergone breast surgery at Renji Hospital were available for the analysis. This study was presented according to the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines.[26]

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 were 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. According to St Gallen International Expert Consensus,[28] 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).

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, and Ashkenazi Jewish heritage, with a score of ⩾8 as the optimal threshold for referral to genetic counseling. Here, we calculated these traditional family history scores for all the included patients and defined high risk as the score ⩾1 for each tool.

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, 29, 30] we conducted the NeoFHS system to quantify individual family history.

$$\text{NeoFHS} = \sum \text{the age-, kinship-, and cancer-specific score of the affected relative}$$

It was calculated as the total age-, kinship-, and cancer-specific scores for all affected relatives (Table 1). The cut-off value of NeoFHS was determined to be 0.5, the higher quartile of all data.

Table 1 Point assignments for the Neo-Family History Score (NeoFHS) system

Factors	Point [a]
BRCA-related cancer [b] diagnosed <50 years	
First-degree relative	1
Second-degree relative	1/2
Third-degree relative	1/4
BRCA-related cancer diagnosed ⩾50 years or other cancers [C] diagnosed at any age	
First-degree relative	1/2
Second-degree relative	1/4
Third-degree relative	1/8

[a] Point was assigned according to kinship coefficient [31].

[b] BRCA-related cancer refers to breast, ovarian, prostate, pancreatic and colon cancer [23].

[c] Other cancers includes lung, esophageal, gastric, liver, rectal cancer, nasopharyngeal carcinoma, bladder, gallbladder, cervical, bone, skin, and tongue cancer, glioma, parotid mixed tumor, lymphoma, and

leukemia in this cohort.

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 ($ypT_{0/is}$ ypN_0). RFS was calculated as the time from surgery to first occurrence of locoregional, ipsilateral, contralateral, distant recurrence, and death from any cause. 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.

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 any 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 DAVID (https://david.ncifcrf.gov/).

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. The least absolute shrinkage and selection operator (LASSO) algorithm and 10-fold cross validation were used to select optimal predictive parameters. 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. Nomograms were established to display the predicted probabilities of pCR. Calibration curve was examined by Hosmor-Lemeshow test. 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 $p<0.05$.

Results

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).

We applied the NeoFHS system to all patients for investigating 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).

Table 2
Baseline clinicopathological characteristics of all patients

Characteristics	Total	Neo-Family History Score		
		High, N = 78	Low, N = 184	p value
Age				0.686
<35	23 (8.8%)	6 (7.7%)	17 (9.2%)	
⩾35	239 (91.2%)	72 (92.3%)	167 (90.8%)	
Median (range)	52 (23–71)	53 (26–71)	50 (23–70)	
Menopausal status				0.066
Premenopausal	127 (48.5%)	31 (39.7%)	96 (52.2%)	
Postmenopausal	135 (51.5%)	47 (60.3%)	88 (47.8%)	
T stage				**0.048**
T2	56 (21.4%)	10 (12.8%)	46 (25.0%)	
T3	123 (46.9%)	37 (47.4%)	86 (46.7%)	
T4	83 (31.7%)	31 (39.8%)	52 (28.3%)	
N stage				0.164
N0	38 (14.5%)	6 (7.7%)	32 (17.4%)	
N1	189 (74.1%)	61 (78.2%)	128 (69.6%)	
N2	10 (3.8%)	2 (2.6%)	8 (4.3%)	
N3	25 (9.6%)	9 (11.5%)	16 (8.7%)	
ER status				**0.001**
ER negative	89 (34.0%)	38 (48.7%)	51 (27.7%)	
ER positive	173 (66.0%)	40 (51.3%)	133 (72.3%)	
PR status				**0.036**
PR negative	74 (28.2%)	29 (37.1%)	45 (24.5%)	
PR positive	188 (71.8%)	49 (62.8%)	139 (75.5%)	
HER2 status				**0.013**
HER2 negative	158 (60.3%)	38 (48.7%)	120 (65.2%)	

Abbreviations: T, tumor; N, nodal; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BMI, body mass index.

Characteristics	Total	Neo-Family History Score		
HER2 positive	104 (39.7%)	40 (51.3%)	64 (34.8%)	
Ki67 index				0.728
<50%	157 (59.9%)	48 (61.5%)	109 (38.5%)	
⩾50%	105 (40.1%)	30 (59.2%)	75 (40.8%)	
Histologic grade				0.388
G2	92 (35.1%)	24 (30.8%)	68 (37.0%)	
G3	181 (52.8%)	47 (60.2%)	94 (51.1%)	
Unevaluable	29 (11.1%)	7 (9.0%)	22 (11.9%)	
Molecular subtype				**0.016**
Luminal A-like	21 (8.0%)	4 (5.1%)	17 (9.2%)	
Luminal B-like	183 (69.9%)	49 (62.8%)	134 (72.8%)	
HER2-enriched	25 (9.5%)	14 (18.0%)	11 (6.0%)	
Basal-like	33 (12.6%)	11 (14.1%)	22 (12.0%)	
BMI				0.157
<25	191 (71.3%)	55 (65.5%)	136 (73.9%)	
⩾25	71 (28.7%)	29 (34.5%)	48 (26.1%)	

Abbreviations: T, tumor; N, nodal; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BMI, body mass index.

Pcr Rates

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 (OR = 1.025, 95% CI 0.398–2.641, p = 0.959) (Fig. 2A; 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 (OR = 2.123, 95% CI 1.224–3.682, p = 0.007; Fig. 2B; 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 4), whereas NeoFHS was an independent predictive factor for pCR (OR = 2.262, 95% CI 1.159–4.414, p = 0.017). Besides, age (OR = 0.367, 95% CI 0.137–0.982, p = 0.046), T stage (OR = 0.581, 95% CI 0.379–0.892, p = 0.013), HorR status (OR = 0.398, 95% CI 0.203–0.782, p =

0.008), HER2 status (OR = 3.294, 95% CI 1.785–6.079, p < 0.001), and Ki67 index (OR = 3.190, 95% CI 1.740–5.848, p < 0.001) could also serve as independent predictive factors for pCR (Fig. 2C; Table 4). 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.

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.

Table 4
Multivariate analysis for predicting pCR using Neo-Family History Score

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.					

The nomogram was created for the predictive model that combined NeoFHS with the extracted clinicopathological variables (Fig. 3A). The corresponding calibration curve showed great agreement between the predicted probabilities and observed pCR outcomes (χ^2 = 10.39, p = 0.239; Fig. 3B). The accuracy of different predictive models was compared by ROC curves to evaluate the predictive value of NeoFHS. The area under curve (AUC) was 0.795 achieved by adding NeoFHS to clinicopathological variables, better than 0.779 for the clinicopathological characteristics alone, 0.581 for NeoFHS, 0.502 for Ontario model, 0.496 for Manchester model, and 0.499 for Pedigree model (Fig. 3C). The DCA consistently depicted more benefits with the model combining NeoFHS with clinicopathological features (Fig. 3D). The nomogram for predicting pCR demonstrated that cost/benefit ratios were lower with the risk threshold less than 0.7 (Fig. 3E).

Subgroup Analysis Of Pcr Rates

Subgroup analysis suggested that the pCR outcome was positively associated with NeoFHS in patients aged ⩾35 years old (OR = 1.828, 95% CI 1.022–3.272, p = 0.042) and those with BMI less than 25 (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 higher than 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 (80.0% vs 37.0%; 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).

Relapse-free Survival

The median follow-up time was 28.3 months. For all patients, the Kaplan-Meier estimates demonstrated that RFS rates did not differ between Ontario high-risk and Ontario low-risk groups (log-rank p = 0.254; 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).

Distant Relapse-free Survival

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), 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 Pedigree 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 = 0.275, 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).

Visceral Metastasis-free Survival

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).

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). 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).

Table 5
Summary of adverse events according to Neo-Family History Score

Events	Neo-Family History Score		
	High, N = 78	Low, N = 184	p value
Adverse events of any grade			
Leukopenia	67 (85.9%)	161 (87.5%)	0.724
Neutropenia	65 (83.3%)	154 (83.7%)	0.942
Anemia	50 (64.1%)	127 (69.0%)	0.437
Elevated aspartate aminotransferase	15 (19.2%)	31 (16.9%)	0.643
Elevated total bilirubin	45 (57.7%)	82 (44.6%)	0.059
Elevated alanine aminotransferase	35 (44.9%)	77 (41.9%)	0.651
Alopecia	64 (82.1%)	111 (60.3%)	**0.001**
Nausea	59 (75.6%)	97 (52.7%)	**0.001**
Peripheral neuropathy	55 (70.5%)	101 (54.9%)	**0.018**
Diarrhea	43 (55.1%)	74 (40.2%)	**0.026**
Fatigue	43 (55.1%)	78 (42.4%)	0.078
Vomiting	33 (42.3%)	60 (32.6%)	0.134
Hand-foot syndrome	31 (39.7%)	63 (34.2%)	0.396
Epistaxis	31 (39.7%)	65 (35.3%)	0.497
Rash	29 (37.2%)	48 (26.1%)	0.072
Constipation	27 (34.6%)	41 (22.3%)	**0.037**
Adverse events ⩾ Grade 3			
Neutropenia	43 (55.1%)	82 (44.6%)	0.118
Leukopenia	31 (39.7%)	42 (22.8%)	**0.005**
Anemia	3 (3.9%)	8 (4.4%)	0.853
Thrombocytopenia	1 (1.3%)	0	0.298
Vomiting	4 (5.1%)	6 (3.3%)	0.471
Fatigue	3 (3.9%)	5 (2.7%)	0.627
Diarrhea	2 (2.6%)	3 (1.6%)	0.614
Peripheral neuropathy	1 (1.3%)	0	0.298

Events	Neo-Family History Score		
Nausea	1 (1.3%)	1 (0.5%)	0.508
Serious adverse events			
Fever	1 (1.3%)	0	0.298
Diarrhea	0	1 (0.5%)	> 0.99

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 to investigate 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.[32] Consistently, Huang et al. reported that family history of breast or ovarian cancer increased the risk of ER-negative and PR-negative (OR = 1.8, 95% CI 1.2–2.7), rather than ER-positive or PR-positive breast cancer (ER + and PR+, OR = 1.2, 95% CI 0.8–1.7; ER + and PR-, OR = 1.5, 95% CI 0.8-3.0; ER- and PR+, OR = 1.6, 95% CI 0.7–3.2).[33] However, many other breast cancer susceptibility genes also influence the biological features of tumors. For instance, it is more common for breast cancer with reduced ATM expression to be ER-negative and PR-negative,[34, 35] while low nuclear CHEK2 protein level[35] and germline TP53 mutations[36] 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 (p = 0.03).[25] Therefore, we postulated that family history of BRCA-related cancer and non-BRCA cancer might contribute to different biological characteristics. To verify this opinion, we further performed pathway analyses of the DEGs between breast cancer patients without family history of any 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. 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. All 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. So far, emerging evidence has indicated 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 (60.4% vs 46.7%; OR = 1.74, 95% CI 1.13–2.68, p = 0.01).[37] Additionally, the triple-negative trial (TNT), which recruited advanced TNBC, showed a better response to carboplatin than to docetaxel in germline BRCA1/2 mutation group (objective response rate 68.0% vs 33.3%, p = 0.03), with a significant interaction between platinum-based regimen and BRCA1/2 mutation (p = 0.01).[38] 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 unexceptionally 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 (HR = 0.441, 95% CI 0.173–1.123, p = 0.086).[39] 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 (OR 1.65, 95% CI 0.77–3.53, p = 0.19), whereas the corresponding rate increased from 37% without carboplatin to 53.9% with carboplatin in patients without the same family history (OR = 2.0, 95% CI 1.10–3.62, p = 0.02).[40] 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 the pathway analyses of the identified DEGs between patients with family history of non-BRCA cancer and those without family history of any cancer, it highlighted multiple downregulated genes including IL-10 for participating in the response to drug (Supporting information). Yang et al. found that tumor-associated macrophages could induce paclitaxel resistance via activating IL-10/STAT3/Bcl-2 signaling pathway in breast cancer.[41] Therefore, NeoFHS might well distinguish patients 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 parallel, our data substantiated the prognostic value of NeoFHS in patients treated with neoadjuvant platinum, 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 (HR = 0.320, 95% CI 0.158–0.649, p = 0.002).[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 (HR = 6.11, 95% CI 2.81–13.28, p < 0.0001).[42] 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 (RR = 0.5, 95% CI 0.3–0.9).[30] The POSH study suggested that 5-year distant disease-free interval (DDFI) 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 (HR = 0.74, 95% CI 0.57–0.96, p = 0.021).[43] 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 (HR = 2.21, 95% CI 1.28–3.83, p < 0.01).[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 breast cancer receiving neoadjuvant platinum.

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 hypersensitivity to chemotherapy.[44] Huszno et al. reported that more frequent neutropenia was detected in breast cancer with BRCA1/2 mutation after one cycle of chemotherapy (p = 0.0007).[45] Furlanetto et al. found that breast cancer with germline BRCA1/2 mutations had a higher risk of hematologic toxicities under taxane.[46] Tomao et al. demonstrated that germline BRCA1/2 mutations were associated with higher hematologic toxicity in ovarian cancer undergoing platinum-based chemotherapy.[44] 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 by cytotoxic agents. Notably, pathway analyses implicated some other potential mechanisms of AEs, such as dysregulation of calcium signaling pathway and cytokine-cytokine receptor interaction. Siau et al. reported that dysregulation of calcium signaling pathway mediates chemotherapy-evoked neuropathic pain.[47] Zhang et al. revealed that cytokine-mediated signaling pathway is closely related to chemotherapy-induced alopecia.[48] 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. However, all data was collected prospectively in the registered clinical trials. Therefore, it may indicate potential intrinsic rules to some extent. Second, it was not mature to perform analysis for OS. Prolonged follow-up will be warranted. In addition, the sample size was relatively small. However, we did substantiate a profound predictive and prognostic value of NeoFHS for breast cancer treated with NAC. We will expand the sample size for further validation.

Conclusions

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 managements in the future. Further researches are required to provide more insights into the underlying mechanisms.

Abbreviations

BMI: body mass index

CI: confidence interval

DCA: decision curve analysis

DEG: differentially expressed genes

DFS: disease-free survival

DRFS: distant relapse-free survival

ER: estrogen receptor

HER2: human epidermal growth factor receptor 2

HorR: hormone receptor

HR: hazard ratio

HRD: homologous recombination deficiency

HRR: homologous recombination repair

NAC: neoadjuvant chemotherapy

NeoFHS: Neo-Family History Score

OR: odds ratio

OS: overall survival

pCR: pathological complete response

PR: progesterone receptor

RFS: relapse-free survival

ROC: receiver operating characteristics

VMFS: visceral metastasis-free survival

USPSTF: US Preventive Services Task Force

Declarations

Ethics approval and consent to participate

Ethical approvals were granted for both 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 translational research.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

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

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Figures

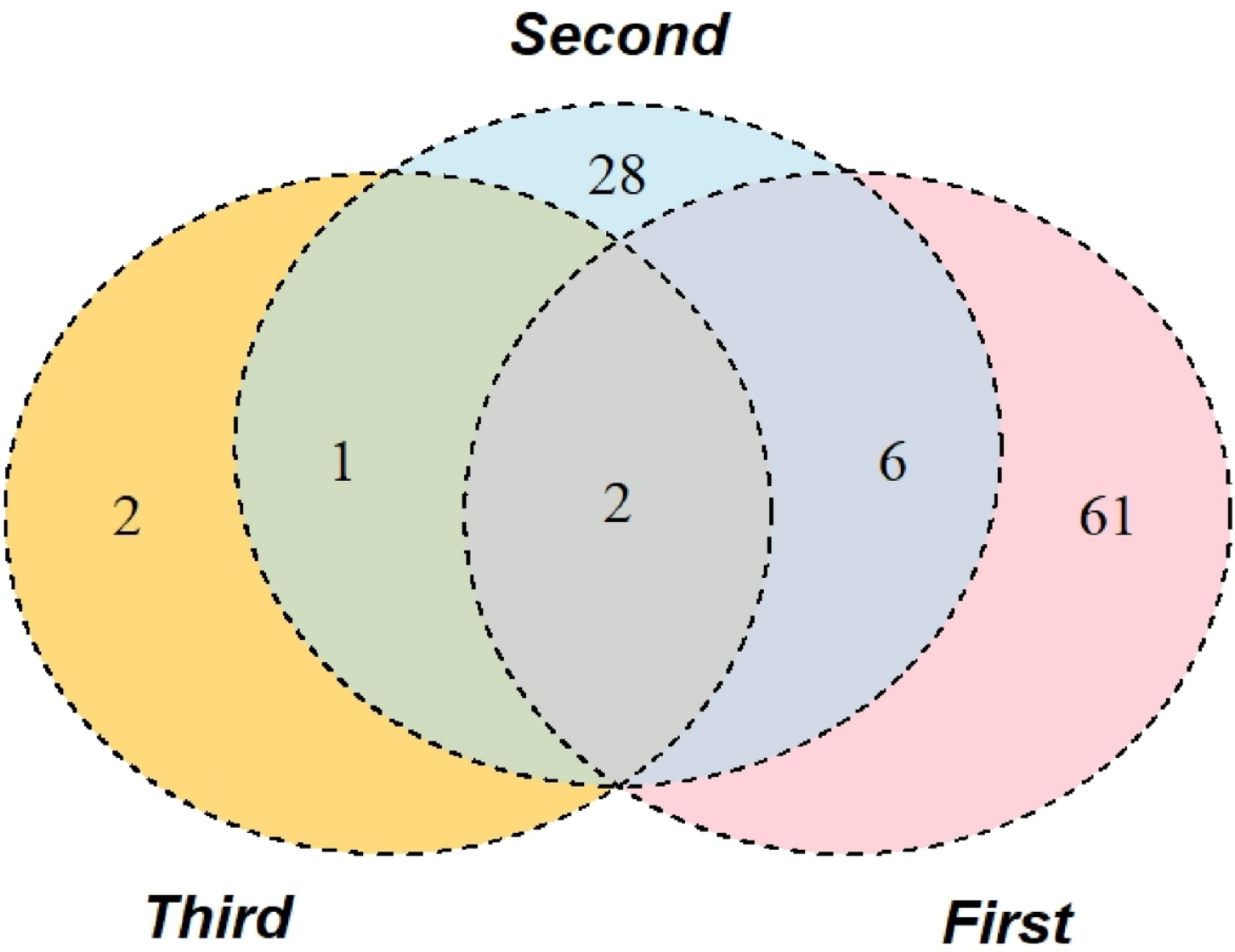

Figure 1

Number of patients with family history of cancer in the first, second, and third-degree relatives

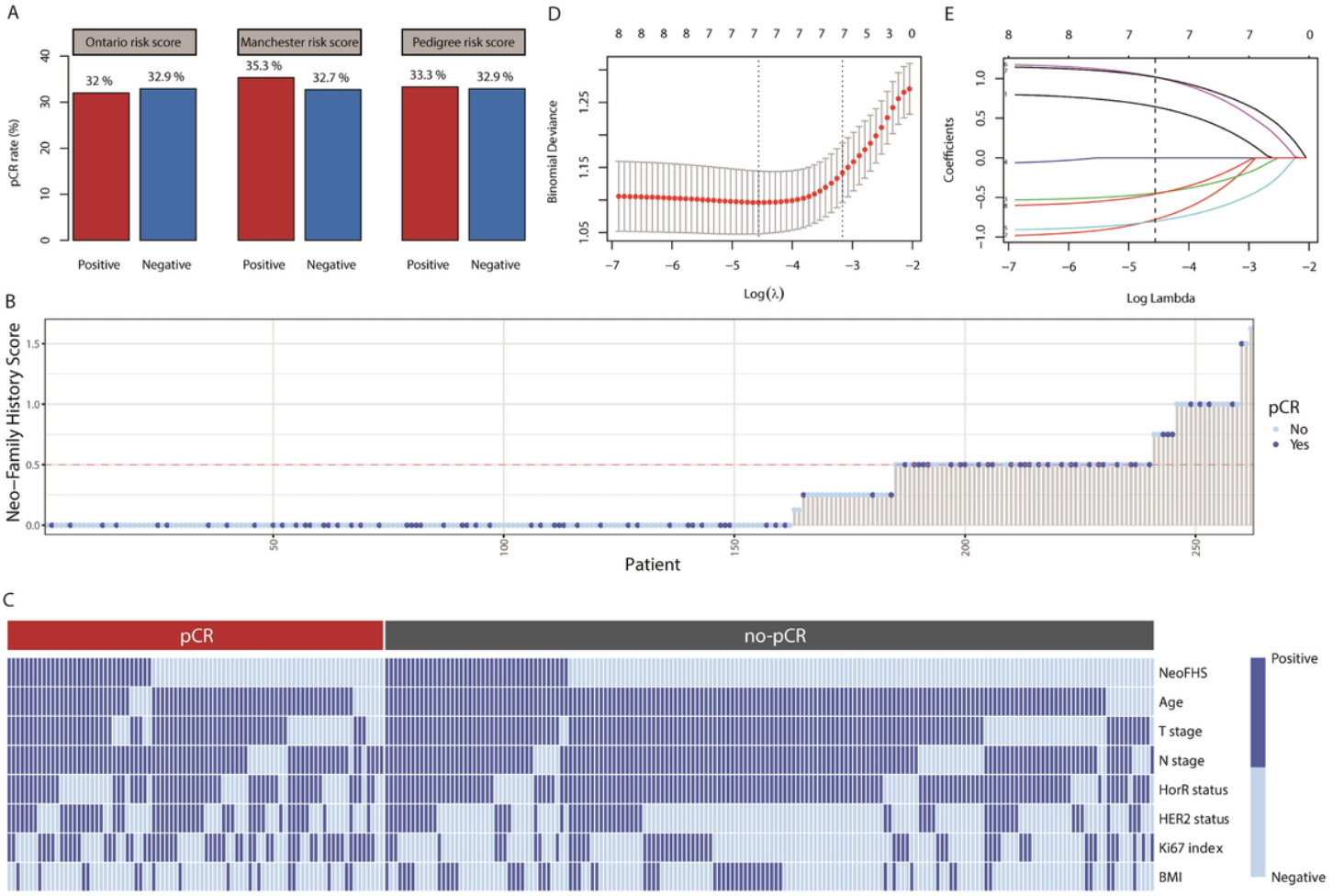

Figure 2

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 positive vs negative, 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 and the clinicopathological variables were all extracted with λ=0.010 [log(λ)=-4.562]. (E) LASSO coefficient profiles of candidate features including Neo-Family History Score and the clinicopathological variables. 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.

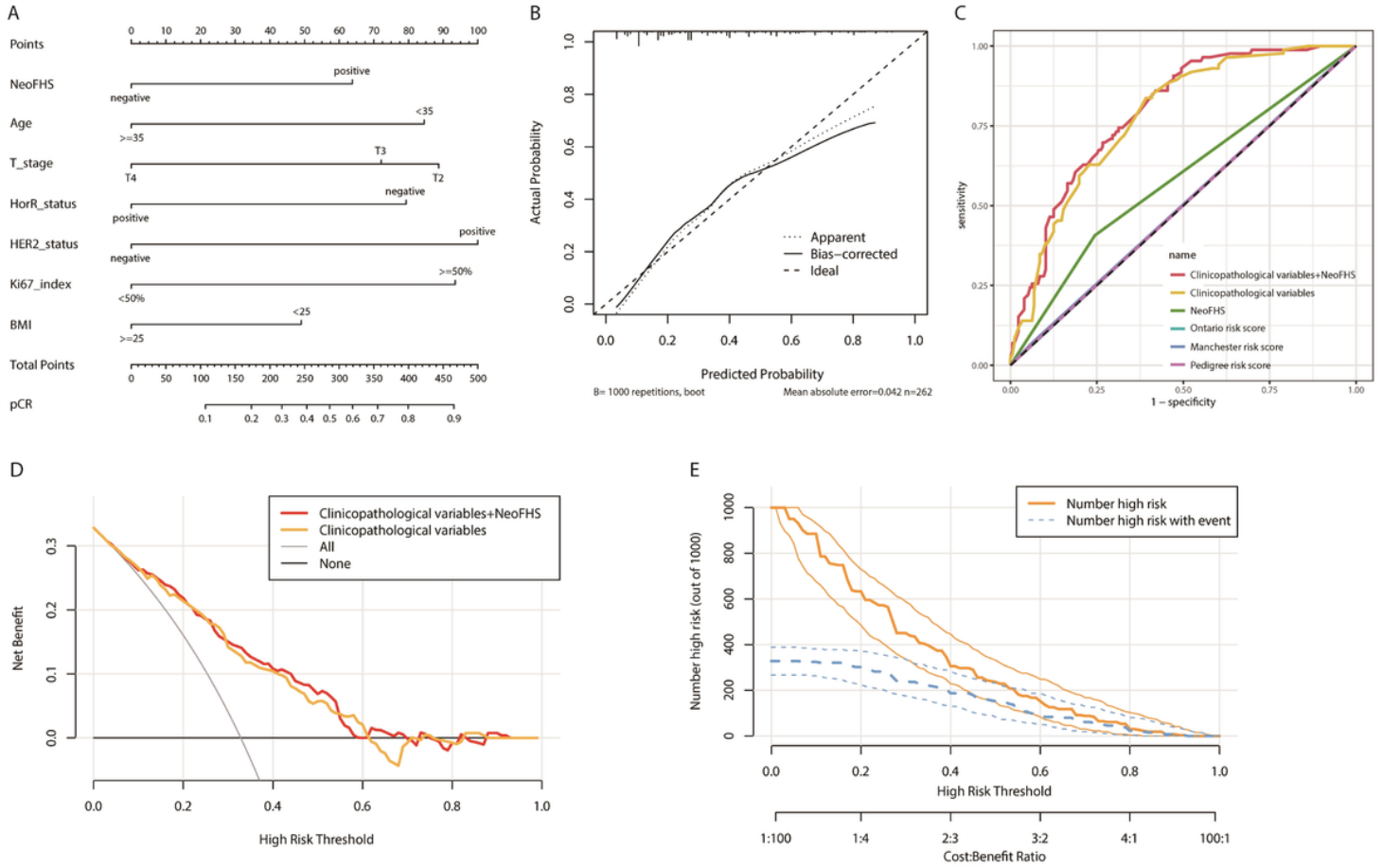

Figure 3

Model building and assessment for pCR prediction Notes: (A) Nomogram based on the predictive model. (B) Calibration curve of the nomogram. (C) Receiver operating characteristic curves of different predictive models (adding NeoFHS to clinicopathological variables, AUC 0.795; clinicopathological variables alone, AUC 0.779; NeoFHS, AUC 0.581; Ontario risk score, AUC 0.502; Manchester risk score, AUC 0.496; Pedigree risk score, AUC 0.499). (D) Decision curve analysis with net benefit versus threshold probabilities. (E) Clinical impact curves of predicting pCR with NeoFHS added to clinicopathological variables. Abbreviations: pCR, pathological complete response; NeoFHS, Neo-Family History Score; T, tumor; HorR, hormone receptor; HER2, human epidermal growth factor receptor 2; BMI, body mass index; AUC, area under curve.

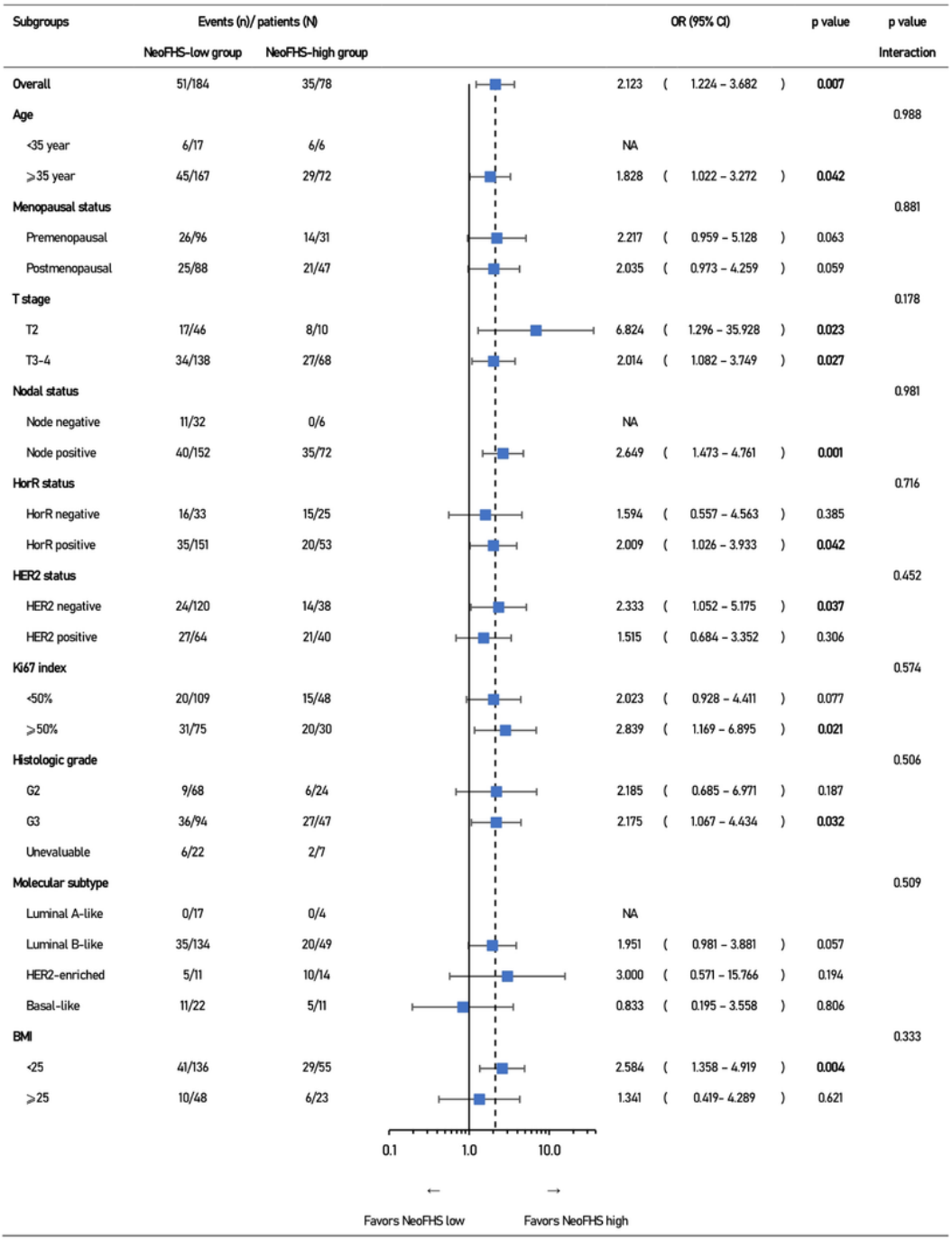

Figure 4

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.

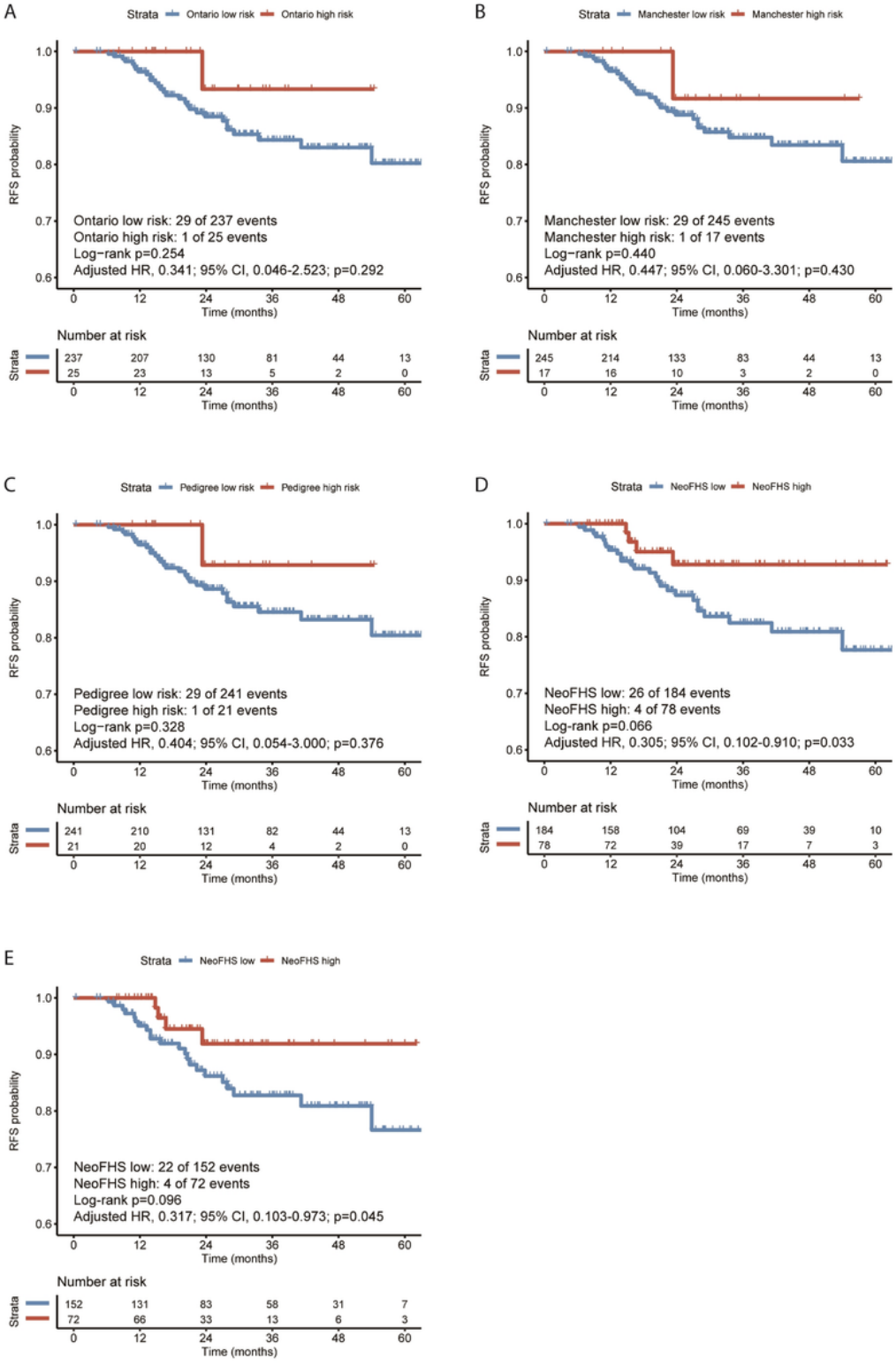

Figure 5

Kaplan-Meier estimates of relapse-free survival according to different family history scoring systems in all patients (A-D) and node-positive patients (E) Abbreviations: RFS, relapse-free survival; HR, hazard ratio; CI, confidence interval; NeoFHS, Neo-Family History Score.

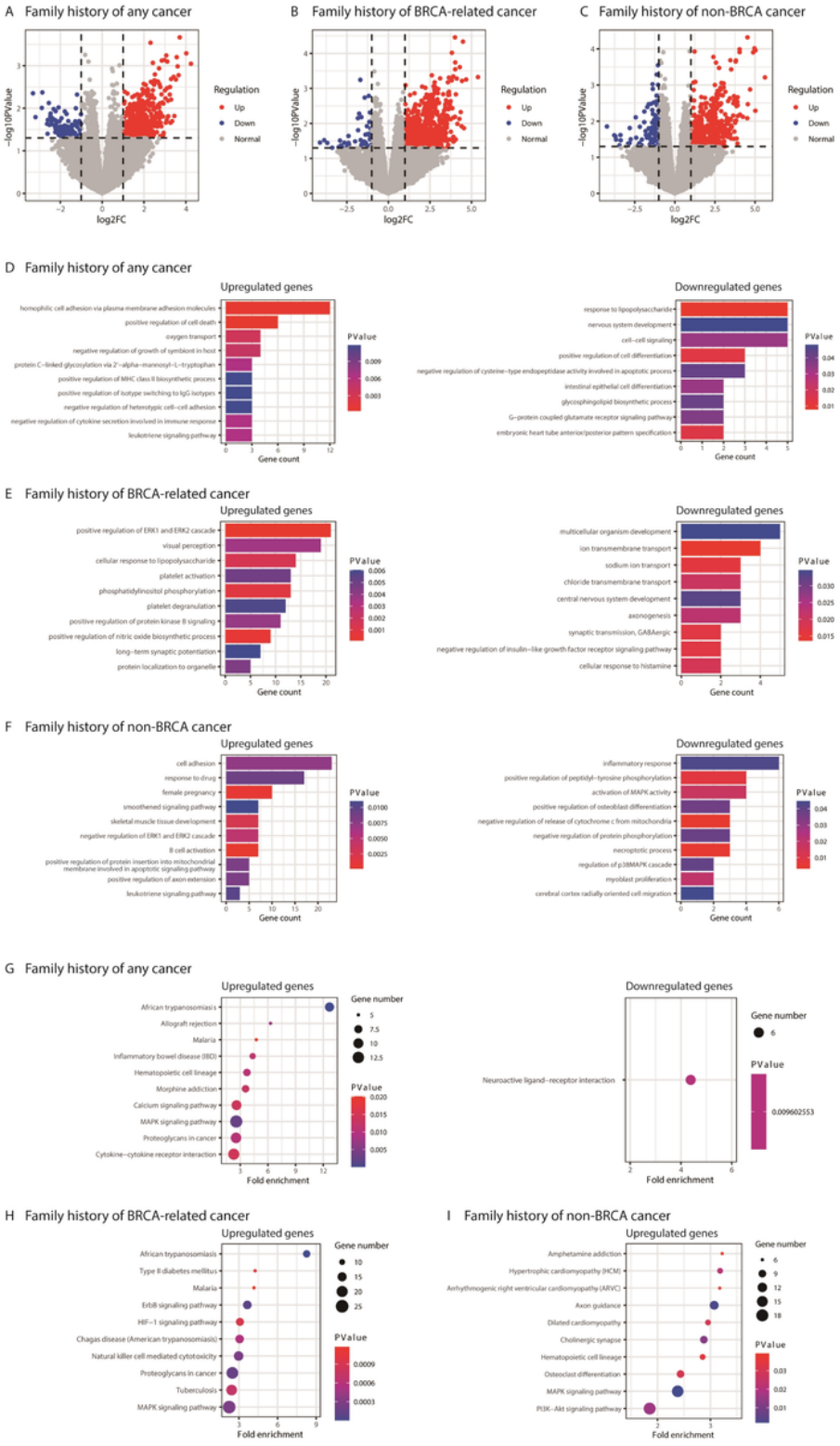

Figure 6

Pathway analyses of differentially expressed genes between patients without family history and those with family history Notes: Volcano plots, GO analysis, and KEGG analysis of differentially expressed genes between patients without family history and those with family history of any cancer (A, D, G), BRCA-related cancer (B, E, H), and non-BRCA cancer (C, F, I). Abbreviations: FC, fold change.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supportinginformation.xlsx
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- supplementtables.docx