

Overexpression of CXXC5 is a strong poor prognostic factor in ER+ breast cancer

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Abstract. CXXC5 is a newly identified CXXC-type zinc finger family protein, which is encoded by the CXXC5 gene localised to the 5q31.3 chromosomal region. Previous studies revealed that CXXC5 is associated with various malignant tumours. The aim of the present study was to investigate the prognosis prediction of CXXC5 in different breast cancer subtypes via the Gene Expression Omnibus database and bc-GenExMiner. CXXC5 overexpression was observed as associated with a poor prognosis for oestrogen receptor positive (ER+) breast cancer. Basal-like breast cancer and triple-negative breast cancer also suggest a poor prognosis, however their CXXC5 expression was low and could not be used as a prognostic factor. The CXXC5 correlated genes and their enriched Gene Ontology (GO) terms were obtained. Among those enriched GO terms, GO:0070062 (extracellular exosome) had the greatest number of associated genes and the associated genes of GO:0000122 (negative regulation of transcription from RNA polymerase II promoter) and GO:0008134 (transcription factor binding) contained CXXC5. These results suggest that overexpression of CXXC5 is a strongly poor prognostic factor in ER+ breast cancer. However, the role of CXXC5 in breast cancer requires further investigation.

Introduction

Breast cancer is one of the most common malignant tumours among women (1). There were precise data from 2012 related to breast cancer incidence and mortality. Across 5 years, from 2008 to 2012, the average incidence rates for white women were the highest, followed by those of black women (2,3). The

current 5-year survival rate of primary breast cancer is relatively high, ranging from 80 to 92% in different populations (4). However, it decreases to <25% when the disease becomes metastatic (4,5). The most important factor to improve the survival rate of patients is to find the most effective treatment, which is guided by tumour cell characteristics (6,7). Once a metastatic lesion is found, accurate characterisation of the tumour cells must be obtained at the start of treatment (8); a possible way to do this is the use of biomarkers (9). Currently, a series of different biomarkers, such as tissue markers, genetic markers, serum markers and non-coding RNA (1,10,11), have been found, but it is much more difficult to assess the effectiveness of the targeted treatment or prognosis of the disease. Therefore, we need to find more biomarkers and determine their clinical utility in future research (9).

CXXC finger protein 5 (CXXC5) is a protein encoded by the CXXC5 gene localised to the 5q31.3 chromosomal region, which is often deleted in myeloid leukaemia (12). Kühnl *et al* (13) reported that CXXC5 could suppress progression of acute myeloid leukaemia (AML) via inhibiting the Wnt pathway and that downregulation of CXXC5 could predict a better prognosis in AML. The study of Bruserud *et al* (14) showed that high CXXC5 expression was related to the stem cell signature of AML that has a bad prognostic impact. We know that 17 β -oestradiol (E2) plays an important role in the homeodynamic regulation of breast tissue functions, and the oestrogen receptor (ER α) is the primary transcript expressed in breast tissue. Yasar *et al* (15) reported that E2-ER α could regulate the expression of CXXC5. Therefore, we knew that there was a certain relationship between CXXC5 and breast cancer. Knappskog *et al* (16) reported that the overexpression of CXXC5 was significantly associated with a bad prognosis in breast cancer. However, the prognostic implications of CXXC5 expression in breast cancers of different molecular types remain unclear. In our study, we used Breast Cancer Gene-Expression Miner v4.0 (bc-GenExMiner v4.0, bcgenex.centregauducheau.fr/BC-GEM/GEM-Accueil.php?js=1) (17), a database that includes a total of 5,861 patients, as the main tool to analyse the role of CXXC5 expression in different breast cancer subtypes. We aimed to show that CXXC5 expression predicts the prognosis of different breast cancer subtypes.

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Materials and methods

GEO data analysis. We obtained the dataset of GDS5666 (18) from Gene Expression Omnibus (GEO; <https://www.ncbi.nlm.nih.gov/geo/>) (19) and analysed it using the Data Analysis Tools of DATASET BROWSER in GEO. Probes of A_51_P234788 (ID_REF) and A_52_P633393 (ID_REF) represented the CXXC5 gene in the platform of GPL7202. We obtained 2 sets of CXXC5 mRNA expression values from these probes. We used the average value of each sample's CXXC5 mRNA expression as the expression value for that sample.

Bioinformatics analysis by bc-GenExMiner v4.0. Using bc-GenExMiner v4.0, we conducted CXXC5 expression analysis, prognostic analysis for CXXC5 through univariate Cox analysis and Kaplan-Meier curve analysis, and gene correlation analysis for CXXC5. Then, we obtained the gene ontology (GO) term results through gene correlation exhaustive analysis. The database of bc-GenExMiner v4.0 had 36 datasets, including a total of 5,861 patients. There were 21 datasets including 3,524 patients for CXXC5 expression analysis and gene correlation analysis among a total of 36 datasets. A total of 3,472 patients from 21 datasets were used for prognostic analysis for CXXC5 with any nodal status, any ER status and any event (AE).

Statistical analysis. In the comparison of CXXC5 expression in primary and metastatic tumours, we used SPSS version 19.0 (IBM SPSS, Armonk, NY, USA) as the software for statistical analysis. Two-tailed unpaired t-tests were used for statistical comparisons. Data are represented as the means \pm standard error of the mean. $P < 0.05$ was considered significant. In other research, the statistical analysis for comparison of CXXC5 expression according to ER and Kaplan-Meier survival curves and univariate Cox analysis was performed by bc-GenExMiner v4.0. Box and whiskers plots are displayed, along with Dunnett-Tukey-Kramer's test and Welch's t-test for every possible clinical criteria for CXXC5 gene.

Results

CXXC5 expression is increased in 4T1-derived metastatic cancer compared to primary cancer. We observed that the expression values of CXXC5 were higher in 4T1-derived metastatic populations than in primary cancers (Fig. 1A). Then, we used bc-GenExMiner v4.0 to determine that CXXC5 upregulation with metastatic relapse (MR) or AE was associated with a poor prognosis of breast cancer (Fig. 1B and C). In the PAM50 breast cancer subtypes, the basal-like subtype had the lowest CXXC5 expression, and CXXC5 expression of luminal tumours was higher than in other types (Fig. 1D).

High level of CXXC5 is a poor prognostic factor in oestrogen receptor positive (ER+) breast cancer. The impact of CXXC5 in breast cancer was considered robust because there were 10 significant results ($P < 0.05$) among the 18 given results (Table I). We determined that the high level of CXXC5 expression is associated with poor prognosis of breast cancer with Nm/ER+/AE, Nm/ER+/MR, N+/ER+/AE, N-/ER+/MR, N+/ER+/MR, Nm/ERm/MR, Nm/ERm/AE, N+/ERm/AE,

N+/ER-/AE and N-/ER+/AE through CXXC5 univariate Cox analysis (Table I). In particular, all breast cancer patients with ER+ status had a poor prognosis. CXXC5 expression was significantly higher in ER+ breast cancer than in ER- breast cancer (Fig. 2A). Using the Kaplan-Meier curve, we ascertained that high CXXC5 expression predicted significantly poor AE-free survival in Nm/ER+ status (HR=1.50; 95% CI, 1.31-1.73; $P < 0.0001$) (Fig. 2B), MR-free survival in Nm/ER+ status (HR=1.70; 95% CI, 1.37-2.10; $P < 0.0001$) (Fig. 2C), AE-free survival in N+/ER+ status (HR=1.51; 95% CI, 1.21-1.87; $P = 0.0002$) (Fig. 2D), MR-free survival in N-/ER+ status (HR=1.56; 95% CI, 1.06-2.27; $P = 0.0228$) (Fig. 2E) and MR-free survival in N+/ER+ status (HR=1.59; 95% CI, 1.16-2.20; $P = 0.0042$) (Fig. 2F). However, CXXC5 expression could not predict AE-free survival in N-/ER+ status ($P = 0.0763$) (Fig. 2G).

Basal-like breast cancer and/or TNBC prognostic analysis for CXXC5. The basal-like breast cancer had lower CXXC5 expression than other subtypes (Fig. 1D). However, basal-like breast cancer could predict bad prognosis, as 75-80% of the triple-negative breast cancers (TNBC) belonged to the group of basal-like breast cancer (20). High levels of CXXC5 expression could predict a bad prognosis in TNBC with MR via CXXC5 univariate Cox analysis (basal-like and/or TNBC) but not in the other group (Tables II and III). However, CXXC5 expression was not associated with prognosis of TNBC with MR through the Kaplan-Meier curve analysis (Fig. 3A). Consistent with the results of CXXC5 univariate Cox analysis (basal-like and/or TNBC), CXXC5 expression was not associated with the prognosis of breast cancer in the other groups (Fig. 3B-F).

Correlated genes with CXXC5. We obtained the correlated genes with CXXC5 in breast cancer through gene correlation exhaustive analysis. Table IV shows the top 10 best positive/negative correlations with CXXC5. Then, we obtained the GO enrichments of the correlated genes with CXXC5 via GO analysis of bc-GenExMiner v4.0 (Table V). Among them, GO:0070062 (extracellular exosome) had the most associated genes, and the associated genes of both GO:0000122 (negative regulation of transcription from RNA polymerase II promoter) and GO:0008134 (transcription factor binding) contained CXXC5.

Discussion

CXXC5 is a newly identified CXXC-type zinc finger family protein (21), which is encoded by the CXXC5 gene localised to the 5q31.3 chromosomal region (12). Previous studies showed that CXXC5 was related to AML, myelodysplastic syndromes, human malignant peripheral nerve sheath tumours, prostate cancer, breast cancer, thyroid cancers and metastatic melanomas (16,22-25). Knappskog *et al* (16) used three independent public microarray datasets, including 599 patients from GEO, to find that CXXC5 was a bad prognostic factor in breast cancer. However, they did not study the effects of CXXC5 on various subtypes in breast cancer.

In our study, using the dataset of GDS5666 from GEO, we found that the expression of CXXC5 was higher in 4T1-derived metastatic populations than in primary breast cancers.

Table I. CXXC5 univariate Cox analysis.

No.	Nodal status	ER status	Event status	P-value	Hazard ratio	95% CI	No. patients	No. events
1	Nm	ER+	AE	<0.0001	1.31	1.22-1.42	2,461	845
2	Nm	ER+	MR	<0.0001	1.53	1.34-1.74	1,450	355
3	N+	ER+	AE	0.0001	1.30	1.14-1.48	846	348
4	N-	ER+	MR	0.0002	1.61	1.25-2.08	542	113
5	N+	ER+	MR	0.0009	1.35	1.13-1.61	475	156
6	Nm	ERm	MR	0.0027	1.15	1.05-1.26	2,017	539
7	Nm	ERm	AE	0.0057	1.09	1.02-1.15	3,472	1,260
8	N+	ERm	AE	0.0162	1.13	1.02-1.25	1,127	503
9	N+	ER-	AE	0.0201	1.26	1.04-1.53	278	155
10	N-	ER+	AE	0.0347	1.15	1.01-1.32	924	277
11	N+	ERm	MR	0.0540	1.15	1.00-1.32	612	224
12	N+	ER-	MR	0.0540	1.32	1.00-1.75	135	68
13	Nm	ER-	AE	0.0784	1.10	0.99-1.22	972	406
14	Nm	ER-	MR	0.1103	1.13	0.97-1.32	547	181
15	N-	ERm	MR	0.1563	1.12	0.96-1.32	762	167
16	N-	ER-	MR	0.5774	1.08	0.82-1.42	205	53
17	N-	ER-	AE	0.7933	0.98	0.81-1.17	361	118
18	N-	ERm	AE	0.8053	0.99	0.89-1.09	1,306	399

CXXC5, CXXC finger protein 5; ER, estrogen receptor; CI, confidence interval; m, mixed; +, positive; -, negative; AE, any event; MR, metastatic relapse. Bold text indicates $P < 0.05$.

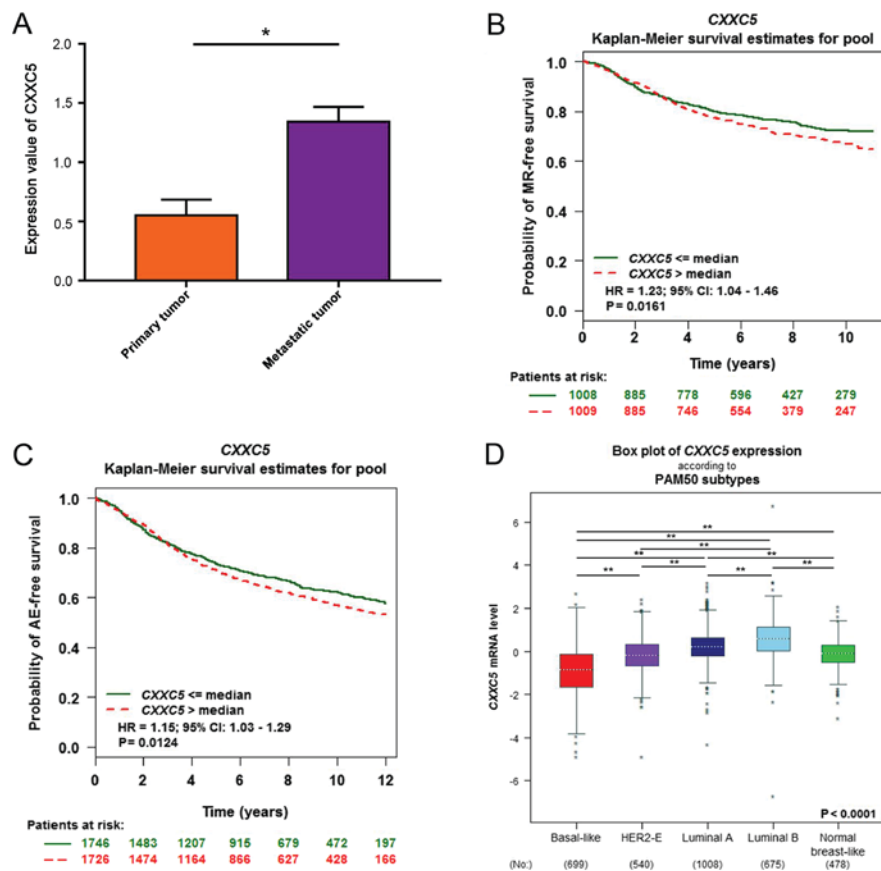


Figure 1. CXXC5 expression is increased in 4T1-derived metastatic cancer compared to primary cancer. (A) Expression value of CXXC5 in 4T1-derived metastatic cancer, compared with primary breast cancer, through data analysis of GDS5666. Student's t-test; * $P < 0.05$. The Kaplan-Meier curve of breast cancer with (B) MR-free (C) and AE-free CXXC5 expression. Data were obtained and analysed by using bc-GenExMiner v4.0. (D) Box plot of CXXC5 mRNA expression according to PAM50 subtype in bc-GenExMiner v4.0. Dunnnett-Tukey-Kramer's test; ** $P < 0.0001$. CXXC5, CXXC finger protein 5; MR, metastatic relapse; AE, any event.

Table II. Univariate Cox analysis (basal-like and/or TNBC) for CXXC5 with MR.

Population	P-value	HR	95% CI	No. patients	No. MR
Basal-like	0.8288	1.02	0.84-1.24	375	109
TNBC	0.0369	1.66	1.03-2.67	80	18
Basal-like + TNBC	0.7465	1.24	0.34-4.54	45	5

CXXC5, CXXC finger protein 5; TNBC, triple-negative breast cancer; CI, confidence interval; MR, metastatic relapse. Bold text indicates $P < 0.05$.

Table III. Univariate Cox analysis (basal-like and/or TNBC) for CXXC5 with AE.

Population	P-value	HR	95% CI	No. patients	No. AE
Basal-like	0.8185	0.99	0.87-1.12	690	251
TNBC	0.4321	1.12	0.84-1.50	194	58
Basal-like + TNBC	0.7343	0.92	0.55-1.52	118	24

CXXC5, CXXC finger protein 5; CI, confidence interval; m, mixed; AE, any event; TNBC, triple-negative breast cancer.

Therefore, CXXC5 might be associated with metastasis. Then, we used expression analysis of bc-GenExMiner v4.0 to find that the expression of CXXC5 was significantly different in PAM subtypes. We established that the high level of CXXC5 expression is associated with poor prognosis of ER+ breast cancer through CXXC5 univariate Cox analysis and Kaplan-Meier curve analysis of bc-GenExMiner v4.0. These results propose CXXC5 as a biomarker and potential therapeutic target in ER+ breast cancer. Although basal-like breast cancer and TNBC could predict bad prognosis, their CXXC5 expression was low. In addition, CXXC5 could not predict their prognosis. Finally, we obtained the CXXC5 correlated genes and enriched GO terms of those genes through gene correlation exhaustive analysis of bc-GenExMiner v4.0. Among those enriched GO terms, GO:0070062 (extracellular exosome) had the most associated genes, and the associated genes of both GO:0000122 (negative regulation of transcription from RNA polymerase II promoter) and GO:0008134 (transcription factor binding) contained CXXC5. These GO terms can guide new investigations into understanding the mechanisms of CXXC5 in breast cancer and propose new treatments for ER+ breast cancer.

There is a limitation to the present study. The mechanism of CXXC5 in breast cancer requires further investigation via *in vitro* and *in vivo* experiments.

In conclusion, we determined that overexpression of CXXC5 was a strongly poor prognostic factor in ER+ breast cancer through the tools of bc-GenExMiner V4.0 based on a database including a total of 5,861 patients. This means that regardless of the clinical stage of breast cancer, high expression of CXXC5 in patients predicts that the disease is more significantly invasive. As is known, gene expression can be measured in many ways. We hope that measuring the expression of CXXC5 may become a routine inspection to assess the prognosis of breast cancer in different patients. In this way, early intervention and treatment could be used, and the survival rate of patients could improve. However, the pathways

Table IV. Top 10 best positive/negative correlated genes with CXXC5.

Gene symbol	Pearson's correlation coefficient	P-value	No. of patients
Positive correlation			
FKBP9P1	0.5858	<0.0001	214
LOC149401	0.5849	<0.0001	155
LOC100288069	0.5806	<0.0001	214
ACTG1P20	0.5784	<0.0001	326
CA12	0.5474	<0.0001	3,524
FOXA1	0.5377	<0.0001	3,524
GATA3	0.5338	<0.0001	3,524
AGR2	0.5287	<0.0001	3,524
PRINS	0.5245	<0.0001	155
AGR3	0.5235	<0.0001	3,023
Negative correlation			
FLJ44715	-0.8160	<0.0001	155
LOC100507412	-0.8069	<0.0001	155
LOC100133683	-0.7873	<0.0001	155
LOC729461	-0.7741	<0.0001	155
LOC728543	-0.7698	<0.0001	155
CEP170P1	-0.6993	<0.0001	155
LOC729324	-0.6529	<0.0001	155
CEP295NL	-0.6524	<0.0001	155
LOC653739	-0.5980	<0.0001	155
LOC100507637	-0.5718	<0.0001	155

CXXC5, CXXC finger protein 5.

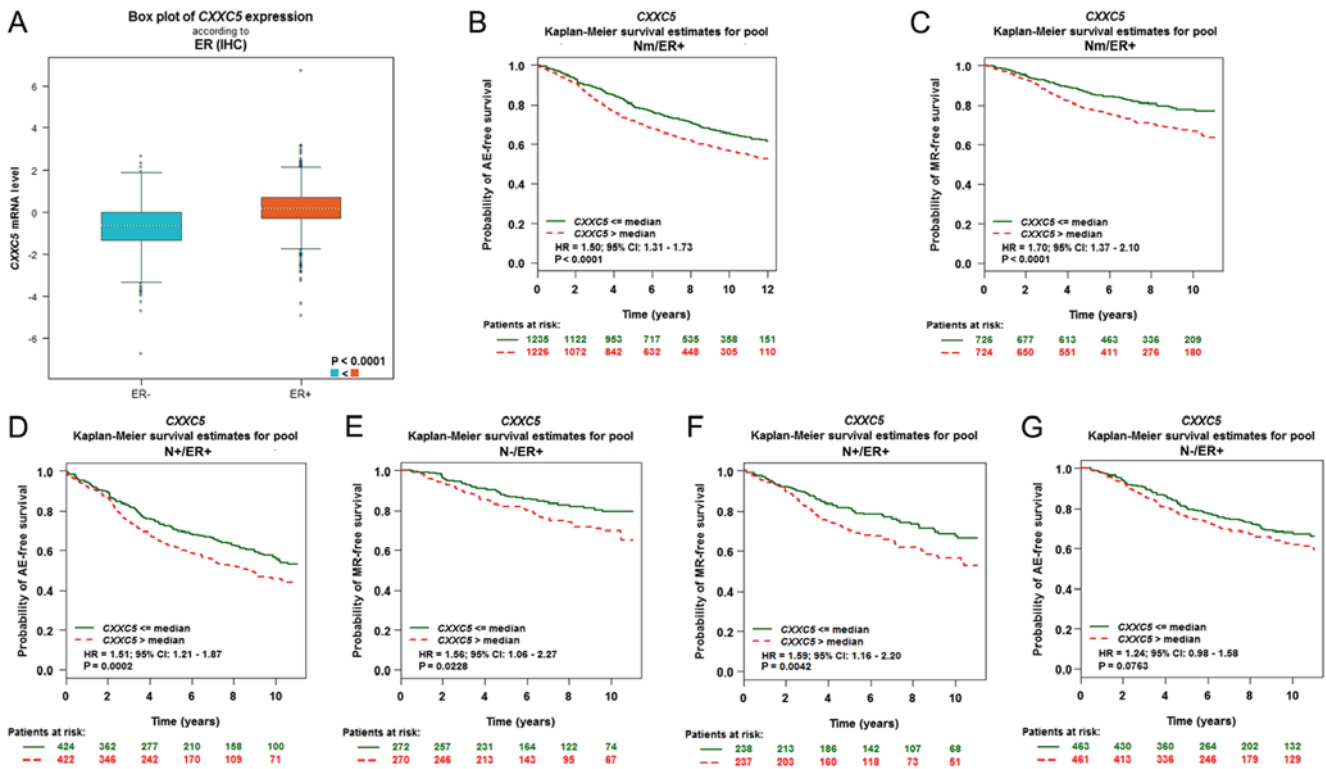


Figure 2. High levels of CXXC5 is a poor prognostic factor in ER+ breast cancer. (A) Box plot of CXXC5 mRNA expression according to ER. The Kaplan-Meier curves of breast cancer with (B) Nm/ER+/AE, (C) Nm/ER+/MR, (D) N+/ER+/AE, (E) N-/ER+/MR, (F) N+/ER+/MR and (G) N-/ER+/AE. All data were obtained and analysed by using bc-GenExMiner v4.0. N, nodal status; ER, oestrogen receptor status; +, positive; -, negative; m, mixed.

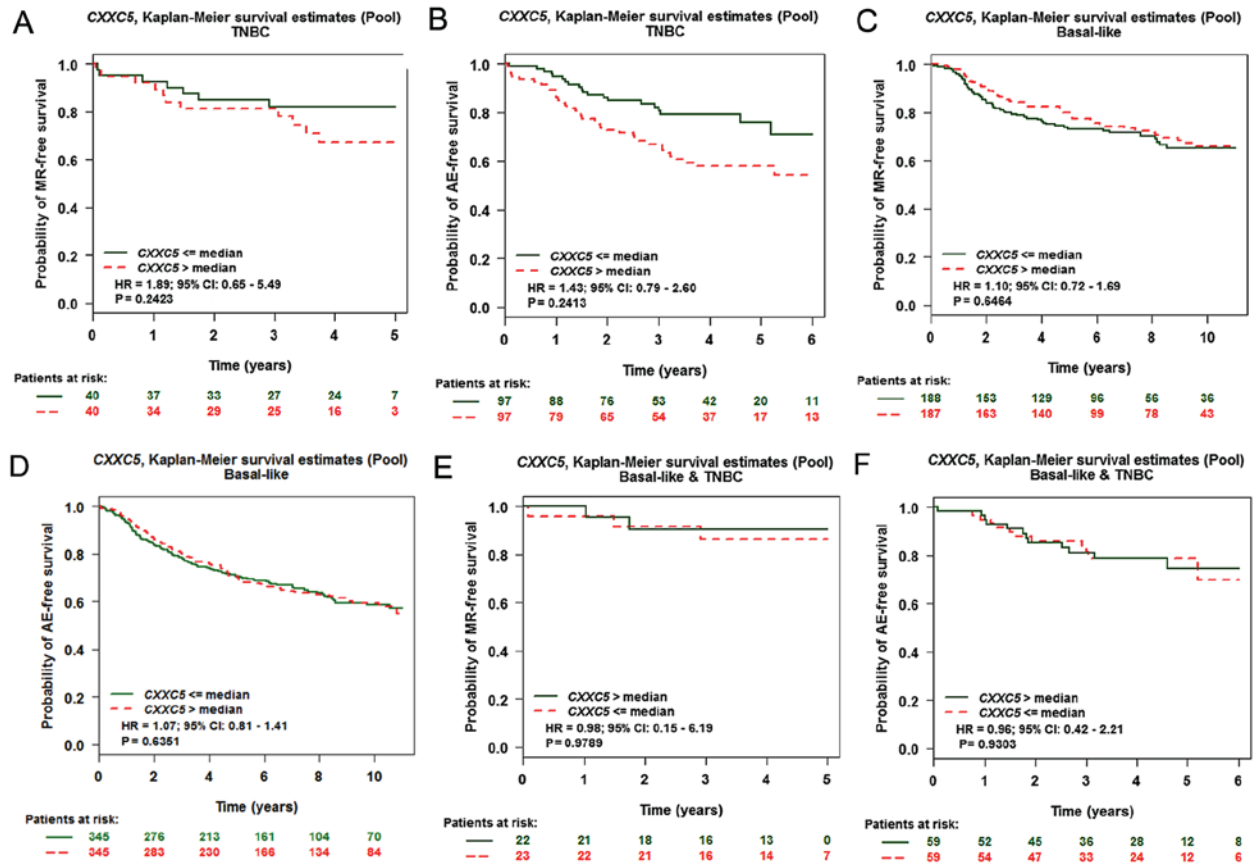


Figure 3. Expression of CXXC5 could not predict the prognosis of basal-like breast cancer and/or TNBC. The Kaplan-Meier curves of TNBC with (A) MR and (B) AE, basal-like breast cancer with (C) MR and (D) AE and basal-like and TNBC with (E) MR and (F) AE. All data were obtained and analysed by using bc-GenExMiner v4.0. TNBC, triple-negative breast cancer; MR, metastatic relapse; AE, any event.

Table V. GO enrichments of correlated genes with CXXC5.

Significant terms	Description	P-value	Associated genes
Biological process			
GO:1902236	Negative regulation of endoplasmic reticulum stress-induced intrinsic apoptotic signaling pathway	4.53x10 ⁻⁵	WFS1, TM6IM6, XBP1
GO:0000122	Negative regulation of transcription from RNA polymerase II promoter	7.14x10 ⁻⁴	CXXC5, FOXA1, GATA3, WFS1, CCND1, SPDEF, DACH1, XBP1, BCL11A, LPIN1
GO:0009653	Anatomical structure morphogenesis	2.25x10 ⁻³	FOXA1, GATA3, KRT18, SOX10
GO:0043627	Response to estrogen	2.40x10 ⁻³	GATA3, ESR1, CCND1
GO:0043433	Negative regulation of sequence-specific DNA binding transcription factor activity	2.64x10 ⁻³	WFS1, ESR1, SIGIRR
Cellular component			
GO:0005902	Microvillus	9.57x10 ⁻⁴	
GO:0030176	Integral component of endoplasmic reticulum membrane	4.59x10 ⁻³	FOXA1, STARD10, SLC9A3R1
GO:0070062	Extracellular exosome	4.53x10 ⁻⁵	WFS1, PIGT, XBP1
		6.21x10 ⁻³	ANXA9, SLC9A3R1, KRT18, TFF3, WWP1, GFRA1, FBP1, MLPH, NME3, CMBL, H2AFJ, HAGH, PVRL2, HSPB1, SERPINA5, TSPAN1, GAMT, PSAT1, PM20D2, FAM171A1, SFT2D2, SLC9A3R1, KRT18
GO:0071944	Cell periphery	7.21x10 ⁻³	
Molecular function			
GO:0008134	Transcription factor binding	1.76x10 ⁻⁴	
		4.10x10 ⁻³	CXXC5, FOXA1, GATA3, ESR1, CCND1, FOXC1, SOX10
GO:0000981	Sequence-specific DNA binding RNA polymerase II transcription factor activity	7.43x10 ⁻³	FOXA1, SPDEF, XBP1, FOXC1
GO:0001078	RNA polymerase II core promoter proximal region sequence-specific DNA binding transcription factor activity involved in negative regulation of transcription	8.49x10 ⁻³	GATA3, DACH1, BCL11A
GO:0044212	Transcription regulatory region DNA binding	8.49E-03	FOXA1, GATA3, XBP1, FOXC1
GO, gene ontology; CXXC5, CXXC finger protein 5; WFS1, wolframin ER transmembrane glycoprotein; TM6IM6, transmembrane BAX inhibitor motif containing 6; XBP1, X-Box binding protein 1; FOXA1, forkhead box A1; GATA3, GATA binding protein 3; CCND1, Cyclin D1; SPDEF, SAM pointed domain containing ETS transcription factor; DACH1, dachshund family transcription factor 1; BCL11A, B-cell CLL/lymphoma 11A; LPIN1, Lipin 1; KRT18, keratin 18; SOX10, SRY-box 10; ESR1, estrogen receptor 1; SIGIRR, single Ig and TIR domain containing; STARD10, StAR related IL-lipid transfer domain containing 10; SLC9A3R1, SLC9A3 regulator 1; PIGT, phosphatidylinositol glycan anchor biosynthesis class T; ANXA9, Annexin A9; TFF3, trefoil factor 3; WWP1, WW domain containing E3 ubiquitin protein ligase 1; GFRA1, GDNF family receptor α 1; FBP1, fructose-bisphosphatase 1; MLPH, melanophilin; NME3, NME/NM23 nucleoside diphosphate kinase 3; CMBL, carboxymethylglutaminase homolog; H2AFJ, H2A histone family member J; HAGH, hydroxyacylglutathione hydrolase; PVRL2, nectin cell adhesion molecule 2; HSPB1, heat shock protein family B (small) member 1; SERPINA5, serpin family A member 5; TSPAN1, tetraspanin 1; GAMT, guanidinoacetate N-methyltransferase; PSAT1, phosphoserine aminotransferase 1; PM20D2, peptidase M20 domain containing 2; FAM171A1, family with sequence similarity 171 member A1; SFT2D2, SFT2 domain containing 2; FOXC1, forkhead box C1.			

of CXXC5 in breast cancer require further investigation. If in-depth research is conducted, we may find the pathways of CXXC5 in breast cancer, and then CXXC5 can be utilized as a potential therapeutic target.

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Availability of data and materials

The data that support the findings of this study are available from GEO database (GDS5666; www.ncbi.nlm.nih.gov/geo/) and Breast Cancer Gene-Expression Miner (bcgenex. centregauducheau.fr/BC-GEM/GEM-Accueil.php?js=1).

Authors' contributions

LF, YW and XC conceived and designed the study. LF and YG analyzed and interpreted the data. LF and YW were the contributors in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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