

# Polymorphisms in *AURKA* and *AURKB* are associated with the survival of triple-negative breast cancer patients treated with taxane-based adjuvant chemotherapy

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**Purpose:** Triple-negative breast cancer (TNBC) is more than a single disease. Identifying biomarkers to further subdivide TNBC patients with distinct outcome is of great importance. It has been reported that single-nucleotide polymorphisms (SNPs) in *Aurora kinase A* (*AURKA*) or *Aurora kinase B* (*AURKB*) are associated with the risk and survival of several cancers. But till now, there is no research about these polymorphisms in TNBC patients.

**Materials and methods:** In this study, we investigated the association between polymorphisms in *AURKA* or *AURKB* gene and prognosis of TNBC patients treated with taxane-based adjuvant chemotherapy. A total of 273 TNBC patients were enrolled. Haploview 4.2 software was used to identify Tag SNPs. Genotyping was conducted using the MassARRAY MALDI-TOF system.

**Results:** We found that *AURKA* rs6099128 GG genotype carriers had significantly worse overall survival (OS) than TT+TG genotype carriers ( $P=0.003$ , HR = 12.499, 95% CI = 2.357–66.298). *AURKB* rs11651993 TT genotype carriers had better disease-free survival (DFS) than TC + CC genotype carriers ( $P=0.018$ , HR = 1.876, 95% CI = 1.116–3.154). *AURKB* rs2289590 CC genotype carriers had worse DFS than CA + AA genotype carriers ( $P=0.021$ , HR = 0.536, 95% CI = 0.315–0.912). After subgroup analysis, rs11651993 TC + CC genotype predicted worse DFS in subgroups of age  $\leq 50$ , post-menopausal, grade unknown (UK), tumor size  $>2$  cm, and lymph node negative. Rs2289590 CA + AA genotype could predict favorable DFS in pre-menopausal, grade 3 and lymph node-positive patients.

**Conclusion:** We first demonstrated that polymorphisms in *AURKA* or *AURKB* gene might predict the OS or DFS of TNBC patients treated with taxane-based adjuvant chemotherapy.

**Keywords:** Aurora kinase, TNBC, polymorphism, prognosis

## Introduction

Breast cancer is the most common cancer and is the leading cause of cancer death in women around the world.<sup>1</sup> It is a very heterogeneous disease and is divided into several subgroups that have different clinicopathological characteristics and prognosis.<sup>2</sup> Triple-negative breast cancer (TNBC) is defined as lacking expression of estrogen receptor (ER), progesterone receptor (PR), and epidermal growth factor receptor 2 (HER2). It is characterized by aggressive behavior, onset at young age, and early relapse.<sup>3,4</sup> TNBC is insensitive to endocrine and HER2-targeted therapy, and therefore, chemotherapy remains the mainstay of treatment. Although some clinical trials found that TNBC is more sensitive to platinum-based chemotherapy,<sup>5,6</sup> taxane/anthracycline-based regimens are still standard and preferred regimens for TNBC patients in the adjuvant setting.<sup>7</sup>

However, not all TNBC patients respond to chemotherapy, which suggests that TNBC is more than a single disease.<sup>8</sup> Identifying biomarkers to further subdivide TNBC patients with distinct outcome is of great importance.

Aurora kinase A (AURKA) and Aurora kinase B (AURKB) are members of the Aurora kinase subfamily of conserved serine/threonine kinases.<sup>9</sup> AURKA localizes to the duplicate centrosomes from the beginning of S phase, shifts to the bipolar spindle microtubules during mitosis, and, finally, moves to perinuclear materials of the daughter cells at the end of mitosis.<sup>10</sup> By contrast, AURKB starts at early G2 and localizes to the chromosomes in prophase, the centromere in prometaphase and metaphase, the central spindle in anaphase, and the mid-body in cytokinesis.<sup>11</sup> AURKA plays a critical role in centrosome duplication and maturation.<sup>12,13</sup> AURKB plays a key role during mitosis by regulating chromosomal alignment, segregation, and cytokinesis, as the catalytic protein of the chromosomal passenger complex (CPC).<sup>11</sup> Deregulation of Aurora kinases leads to impairment of mitotic spindle checkpoints causing abnormal spindle assembly.<sup>9</sup>

It has been reported that single-nucleotide polymorphisms (SNPs) in *AURKA* or *AURKB* are associated with the risk and survival of several cancers including breast cancer,<sup>14</sup> esophageal cancer,<sup>15</sup> and so on. But till now, there is no research about polymorphisms in *AURKA* or *AURKB* and prognosis of TNBC patients. In our study, we first demonstrated that polymorphisms in *AURKA* or *AURKB* gene were associated with the survival of TNBC patients.

## Materials and methods

### Study subjects

Between January 2004 and December 2012, 273 primary TNBC patients treated with taxane-based adjuvant chemotherapy were enrolled in this study. Blood samples were collected from each patient. Patients were followed up until July 30, 2017, to collect data on recurrence and death. The disease-free survival (DFS) time was defined as the time from the date of diagnosis until the date of first locoregional recurrence, first distant metastasis, or death from any cause (whichever came first). Overall survival (OS) was defined as the time from the date of diagnosis to the date of death from any reason or last follow-up.

Formalin-fixed, paraffin-embedded breast cancer tissue samples were obtained from the patients. Immunohistochemistry (IHC) performed with anti-ER and anti-PR antibodies was used to evaluate the ER and PR status. A positive ER and PR status was defined by nuclear staining of more than 1%

according to the guidelines issued by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAPs) in 2010.<sup>16</sup> To determine the HER2 status, IHC or fluorescence in situ hybridization (FISH) was performed.<sup>17</sup> Tumors negative for ER, PR, and HER2 were defined as TNBCs.

### Ethics statement

This investigation was approved by the institutional review board of the Chinese Academy of Medical Sciences Cancer Hospital. It was conducted in accordance with the ethical standards of the Declaration of Helsinki and following the national and international guidelines. Written informed consent was obtained from all patients.

### SNP selection and genotyping

Genotype data from *AURKA* and *AURKB* gene regions encompassing 10 kb of upstream and 3 kb of downstream flanking sequences were extracted from the HapMap Chinese Han population (Hapmap Data Rel 27, Phase II + III, <http://www.HapMap.org>). Haploview 4.2 software (<http://www.broadinstitute.org/mpg/haploview>) was used to identify Tag SNPs. The inclusion criteria were SNPs known in ethnic Han Chinese people and with a minor allele frequency (MAF) of 0.05. Finally, a total of 11 candidate SNPs were selected for genotyping, and information for these SNPs is listed in Table 1. Primers and probes were designed using MassARRAY Typer 4.0 software.

Peripheral blood samples (5 mL) were collected from each subject on recruitment. Genomic DNA was isolated by the routine phenol–chloroform method. Each DNA sample was diluted to a working concentration of 10 ng/mL for genotyping. Genotyping was conducted using the MassARRAY MALDI-TOF System (Sequenom Inc., San Diego, CA, USA)<sup>18,19</sup> at once by the method described in the Sequenom Genotyping Protocol. Twenty percent duplicate samples and negative controls (without DNA) were included for quality assurance of genotyping. Concordance for duplicate samples was 100%. The analysts who carried out the genotyping were blinded to the group information on each sample.

### Statistical analyses

SPSS version 18.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The 5-year DFS rates and 5-year OS rates were estimated by the Kaplan–Meier product limit method for each of the different genotypes and expressed in percentages. Comparisons were made with the log-rank test. HRs of recurrence/metastasis and death with 95% CIs were

**Table 1** Information for the SNPs genotyped in this study

SNPs	Position	Location	Alleles	Gene	MAF in CHB
rs10485805	20:56370727	Intron variant	A/G	<i>AURKA</i>	0.302
rs1468056	20:56390932	Intron variant	C/G	<i>AURKA</i>	0.128
rs2236207	20:56392509	utr variant 5 prime	A/G	<i>AURKA</i>	0.093
rs2298016	20:56384240	Intron variant	C/G	<i>AURKA</i>	0.367
rs6099128	20:56390288	Intron variant	G/T	<i>AURKA</i>	0.167
rs8173	20:56369735	utr variant 3 prime	C/G	<i>AURKA</i>	0.395
rs7503353	17:8204661	Downstream variant 500B	G/T	<i>AURKB</i>	0.163
rs11651993	17:8212456	Upstream variant 2 KB	C/T	<i>AURKB</i>	0.105
rs11869914	17:8211831	Upstream variant 2 KB	G/T	<i>AURKB</i>	0.386
rs2289590	17:8207446	Intron variant	A/C	<i>AURKB</i>	0.267
rs3027257	17:8208935	Intron variant	C/T	<i>AURKB</i>	0.267

**Abbreviations:** CHB, Han Chinese in Beijing; MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

estimated by using the Cox model. The multivariate analysis was adjusted for age ( $\leq 50$  vs  $> 50$ ), histological grade (1–2 vs 3 vs unknown [UK]), tumor size ( $\leq 2$  cm vs  $> 2$  cm), lymph node status (with vs without regional lymph node metastasis), and vascular invasion (with vs without vascular invasion). We performed subgroup analysis for polymorphisms, which were associated with OS or DFS of patients in multivariate analysis. Since there were only 10 patients with rs6099128 GG genotype, we did not perform subgroup analysis for rs6099128. All statistical tests were two sided, and  $P < 0.05$  was considered significant.

## Results

### Clinical characteristics and survival of TNBC patients

A total of 273 patients were enrolled in this study. The median age at diagnosis is 48 years (range, 22–75 years). The 5-year OS rate was 87.1%, and the 5-year DFS rate was 72.8%. Among total patients, 142 (52.0%) and 131 (48.0%) patients were at pre- and post-menopausal stages, respectively. Seventy (25.6%) patients presented with grade 1–2 and 152 (55.7%) with grade 3 tumors. Eighty-four (30.8%), 137 (50.2%), and 52 (19.0%) subjects were diagnosed at stage I, II, and III, respectively. The relationship between clinicopathological characteristics and survival of these patients is summarized in Table 2. Patients with grade 1–2 tumors had a significantly higher 5-year OS rate than those with grade 3 tumors (96.8% vs 79.5%,  $P = 0.039$ , HR = 3.640, 95% CI = 1.071–12.373). Tumor size and lymph node status were significantly related to both DFS and OS. No significant association was observed between age or menopausal status and TNBC survival. After multivariate analysis, tumor size ( $P = 0.024$ , HR = 3.149, 95% CI = 1.166–8.509) and lymph node status ( $P < 0.001$ ,

HR = 11.058, 95% CI = 3.287–37.206) were demonstrated to be independent prognostic factors.

### Polymorphisms in *AURKA* or *AURKB* gene and survival of TNBC patients

The results of relationship between polymorphisms in *AURKA* or *AURKB* and TNBC survival in different genetic models are summarized in Tables 3 and 4. In univariate analysis, *AURKA* rs10485805 GA genotype carriers had worse prognosis than GG genotype carriers ( $P = 0.043$ , HR = 2.177, 95% CI = 1.024–4.628). But after multivariate analysis, there was no association between rs10485805 genotype and OS. In multivariate analysis, *AURKA* rs6099128 GG genotype carriers had significantly worse OS than TT+TG genotype carriers ( $P = 0.003$ , HR = 12.499, 95% CI = 2.357–66.298; Figure 1). Two polymorphisms in *AURKB* were significantly associated with DFS in both univariate and multivariate analyses, including *AURKB* rs11651993 and *AURKB* rs2289590 (Figures 2 and 3). *AURKB* rs11651993 TT genotype carriers had better DFS than TC + CC genotype carriers ( $P = 0.018$ , HR = 1.876, 95% CI = 1.116–3.154). *AURKB* rs2289590 CC genotype carriers had worse DFS than CA + AA genotype carriers ( $P = 0.021$ , HR = 0.536, 95% CI = 0.315–0.912).

### Polymorphisms in *AURKA* or *AURKB* gene and survival of TNBC in different subgroups

In multivariate analysis, *AURKA* rs6099128 was associated with OS, but since there were only 10 patients with GG genotype, we did not explore the relationship in subgroups. As shown in Table 5, we explored the relationship between *AURKB* rs11651993 or rs2289590 and survival of TNBC in

**Table 2** Clinicopathological characteristics and survival of TNBC

Variables	Patients (%)	5-year DFS (%)	HR (95% CI)	P	5-year OS (%)	HR (95% CI)	P
Age (years)							
≤50	166 (60.8)	68.9	1 (Ref)		87.2	1 (Ref)	
>50	107 (39.2)	79.5	0.586 (0.339–1.011)	0.055	86.8	0.876 (0.403–1.901)	0.737
Menopause							
Pre	142 (52.0)	72.1	1 (Ref)		90.1	1 (Ref)	
Post	131 (48.0)	72.9	1.320 (0.806–2.160)	0.270	83.8	1.271 (0.605–2.673)	0.526
Grade							
1–2	70 (25.6)	68.9	1 (Ref)		96.8	1 (Ref)	
3	152 (55.7)	76.9	1.101 (0.609–1.992)	0.750	79.5	3.640 (1.071–12.373)	0.039
UK	51 (18.7)	71.9	0.977 (0.469–2.034)	0.950	91.1	2.219 (0.554–8.891)	0.260
Vascular invasion							
Negative	255 (93.4)	73.5	1 (Ref)		87.1	1 (Ref)	
Positive	18 (6.6)	64.2	1.477 (0.636–3.427)	0.364	82.6	2.108 (0.729–6.097)	0.169
Tumor size							
≤2 cm	127 (46.5)	83.5	1 (Ref)		95.6	1 (Ref)	
>2 cm	146 (53.5)	63.9	2.376 (1.377–4.098)	0.002	80.3	3.983 (1.514–10.478)	0.005
Lymph node							
Negative	162 (59.3)	81.0	1 (Ref)		98.1	1 (Ref)	
Positive	111 (40.7)	61.0	3.039 (1.822–5.068)	<0.001	72.1	13.219 (3.990–43.797)	<0.001
TNM							
I	84 (30.8)	85.4	1 (Ref)		100.0	1 (Ref)	
II	137 (50.2)	75.6	1.814 (0.852–3.860)	0.122	92.9	5.801 (0.742–45.350)	0.094
III	52 (19.0)	45.5	7.272 (3.419–15.468)	<0.001	52.3	36.227 (4.811–272.806)	<0.001

**Abbreviations:** DFS, disease-free survival; OS, overall survival; Ref, reference; TNBC, triple-negative breast cancer; UK, unknown.

**Table 3** *AURKA* or *AURKB* genotypes and DFS

Variables	Patients (%)	5-year DFS (%)	Crude		Adjusted	
			HR (95% CI)	P	HR (95% CI)	P
<i>AURKB</i> rs11651993						
TT	207 (75.8)	76.2	1 (Ref)		1 (Ref)	
TC	58 (21.3)	64.0	1.876 (1.087–3.237)	0.024	1.838 (1.064–3.173)	0.029
CC	8 (2.9)	56.3	2.417 (0.745–7.841)	0.142	2.162 (0.652–7.168)	0.208
TT vs TC + CC			1.934 (1.149–3.254)	0.013	1.876 (1.116–3.154)	0.018
TT + TC vs CC			2.045 (0.639–6.543)	0.228	1.868 (0.570–6.127)	0.302
<i>AURKB</i> rs2289590						
CC	152 (55.7)	68.1	1 (Ref)		1 (Ref)	
CA	105 (38.5)	77.0	0.562 (0.325–0.972)	0.039	0.533 (0.307–0.927)	0.026
AA	16 (5.8)	87.5	0.357 (0.086–1.475)	0.155	0.559 (0.130–2.400)	0.434
CC vs CA + AA			0.531 (0.313–0.902)	0.019	0.536 (0.315–0.912)	0.021
CC + CA vs AA			0.438 (0.107–1.796)	0.252	0.685 (0.161–2.922)	0.609

**Abbreviations:** DFS, disease-free survival; OS, overall survival; Ref, reference.

different subgroups. *AURKB* rs11651993 TC + CC genotype predicted worse DFS in subgroups of age ≤ 50 years, post-menopausal, grade UK, tumor size >2 cm, and lymph node negative. It also predicted shorter OS in subgroups of age > 50 years and grade 3. *AURKB* rs2289590 CA + AA genotype could predict favorable DFS in pre-menopausal, grade 3, and lymph node-positive patients. No significant relationship was observed between rs2289590 and OS in any subgroups.

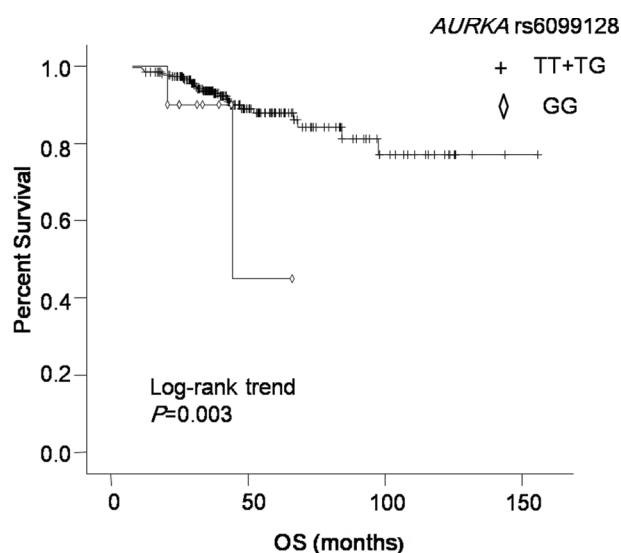
## Discussion

Polymorphisms in *AURKA* or *AURKB* have been reported to be associated with prognosis of some kinds of cancers. Up to now, there is no such comprehensive research that investigated the association between polymorphisms in both *AURKA* and *AURKB* and the outcome of TNBC patients. In our study, we first demonstrated that *AURKA* rs6099128 GG genotype carriers had significantly worse OS than TT + TG genotype carriers, *AURKB* rs11651993 C allele was

**Table 4** *AURKA* or *AURKB* genotypes and overall survival

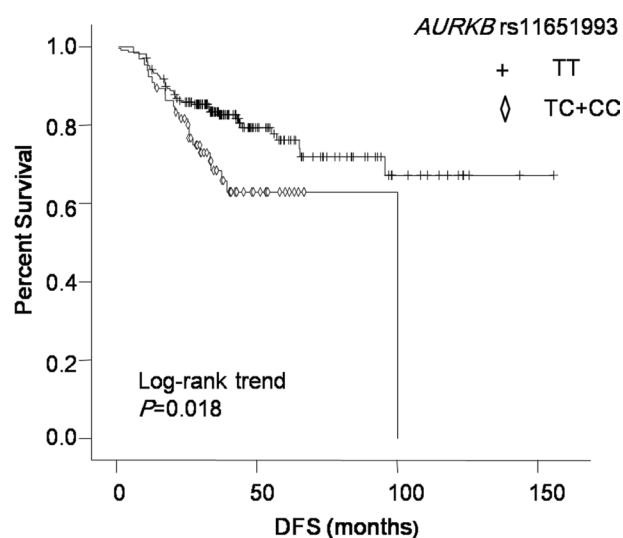
Variables	5-year OS (%)	Crude		Adjusted	
		HR (95% CI)	P	HR (95% CI)	P
<i>AURKA</i> rs10485805					
GG	91.2	1 (Ref)		1 (Ref)	
GA	78.9	2.177 (1.024–4.628)	0.043	1.987 (0.912–4.328)	0.084
AA	100.0	–		–	
GG vs GA + AA		1.757 (0.830–3.719)	0.141	1.605 (0.746–3.451)	0.226
GG + GA vs AA		0.043 (0.000–19.180)	0.312	–	
<i>AURKA</i> rs6099128					
TT	88.4	1 (Ref)		1 (Ref)	
TG	85.5	1.081 (0.434–2.693)	0.868	1.128 (0.448–2.841)	0.799
GG	45.0	3.248 (0.749–14.091)	0.116	12.889 (2.386–69.627)	0.003
TT vs TG + GG		1.296 (0.570–2.945)	0.536	1.440 (0.627–3.308)	0.391
TT + TG vs GG		0.313 (0.073–1.339)	0.117	12.499 (2.357–66.298)	0.003

**Abbreviations:** OS, overall survival; Ref, reference.



**Figure 1** Kaplan–Meier curve of OS for patients with different *AURKA* rs6099128 genotypes.

**Abbreviation:** OS, overall survival.



**Figure 2** Kaplan–Meier curve of DFS for patients with different *AURKB* rs11651993 genotypes.

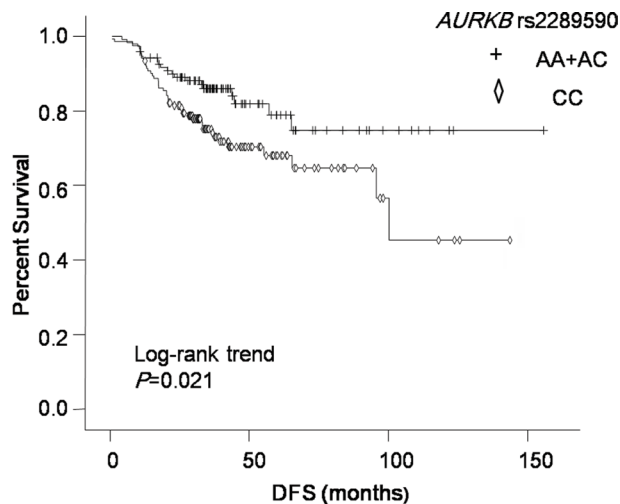
**Abbreviation:** DFS, disease-free survival.

associated with worse DFS, and *AURKB* rs2289590 A allele was significantly associated with better DFS.

*AURKA* gene is an oncogene located on chromosome 20q13. Polymorphisms in *AURKA* gene are associated with risk and intrinsic subtype of breast cancer.<sup>20,21</sup> In the study by Ruan et al,<sup>22</sup> *AURKA* rs10485805 was associated with risk of breast cancer under the recessive genetic model (OR = 0.38, 95% CI = 0.18–0.82,  $P = 0.014$ ); but there is no relationship between rs2298016 and risk in Chinese population. Taylor et al<sup>23</sup> found that rs6099128 had reduced ORs for luminal A (OR = 0.76, 95% CI = 0.60–0.95) and basal-like breast cancer (OR = 0.54, 95% CI = 0.37–0.80). Only a few studies in the literature reported the association between polymorphisms in *AURKA* and OS of breast

cancer. Shi et al<sup>24</sup> found that in the Swedish population, for rs8173, the BC-specific survival was worse in women with at least one G allele, when they had tumors smaller than 2 cm (HR = 2.74, 95% CI = 1.08–6.98) or stage 0–I tumors (HR = 6.94, 95% CI = 1.45–33.22). However, in our research, there is no relationship between genotypes of rs8173 and survival of TNBC. Maybe it is because of the different ethnic groups and different subtypes of BC. Among the six SNPs of *AURKA* investigated in our study, rs1468056 and rs2236207 had never been reported. We found that they were not associated with OS of TNBC. We first demonstrated that *AURKA* rs6099128 GG genotype carriers had significantly worse OS than TT + TG genotype carriers ( $P = 0.003$ , HR = 12.499, 95% CI = 2.357–66.298).

High AURKA expression was strongly associated with decreased survival of breast cancer ( $P = 0.0005$ ), and it was an independent prognostic marker in the study by Nadler et al.<sup>25</sup> In TNBC patients with AURKA high expression, the risk of distant recurrence peaked at the first 3 years and declined rapidly thereafter, whereas patients with AURKA low expression showed a relatively constant risk



**Figure 3** Kaplan-Meier curve of DFS for patients with different *AURKB* rs2289590 genotypes.

**Abbreviation:** DFS, disease-free survival.

of recurrence during the entire follow-up period. Univariate and multivariate analysis showed that overexpression of AURKA predicted poor OS ( $P = 0.002$ ) and progression-free survival ( $P = 0.012$ ) in TNBC.<sup>26</sup> AURKA had been reported to interact and phosphorylate several important proteins involved in stress response and cell cycle checkpoint after DNA damage.<sup>27</sup> Overexpression of AURKA led to diminished transcriptional activity and increased degradation of p53, causing checkpoint defects and genetic instability and ultimately facilitating cancer development and progression.<sup>28</sup>

*AURKB* gene is located on chromosome 17p13. In German population,<sup>29</sup> synonymous *AURKB* rs2241909 (885A>G) polymorphism resulted in an increased familial breast cancer risk for carriers of the homozygous 885G genotype (OR = 1.45, 95% CI = 1.05–2.0,  $P = 0.02$ ). There have been debating data regarding the role of the AURKB expression in cancer prognosis. Zhang et al<sup>30</sup> found that AURKB expression was correlated with the proliferation index ( $P < 0.001$ ) and p53 expression ( $P = 0.014$ ) in breast cancer tissues. Higher expression of AURKB is significantly correlated with the poor survival in these cases ( $P = 0.038$ ). A multivariate Cox regression analysis demonstrated that AURKB expression is an independent prognostic indicator of breast cancer DFS (HR = 1.39, 95% CI = 1.04–1.86). While in the study by Nadler et al,<sup>25</sup> AURKB expression was not

**Table 5** Subgroup analysis of polymorphisms and survival

Variants	Subgroup	DFS		OS	
		HR (95% CI)	P	HR (95% CI)	P
RS11651993 TT vs TC + CC	Age ≤ 50 years	1.942 (1.046–3.606)	0.036	1.093 (0.358–3.333)	0.876
	Age > 50 years	1.913 (0.738–4.956)	0.182	7.309 (1.817–29.402)	0.005
	Pre-menopausal	1.314 (0.581–2.975)	0.512	2.598 (0.842–8.015)	0.097
	Post-menopausal	2.613 (1.309–5.218)	0.006	1.806 (0.612–5.328)	0.284
	Grade 1–2	1.274 (0.442–3.671)	0.654	0.033 (0.000–4.638.821)	0.572
	Grade 3	1.769 (0.864–3.623)	0.119	2.801 (1.086–7.224)	0.033
	Grade UK	3.480 (1.110–10.914)	0.032	4.420 (0.810–24.130)	0.086
	Tumor size ≤ 2 cm	1.844 (0.681–4.991)	0.228	1.149 (0.119–11.093)	0.904
	Tumor size > 2 cm	1.990 (1.080–3.668)	0.027	2.236 (0.966–5.178)	0.060
	LN negative	3.520 (1.526–8.122)	0.003	2.525 (0.210–30.414)	0.466
	LN positive	1.377 (0.689–2.751)	0.365	2.198 (0.965–5.006)	0.061
RS2289590 CC vs CA + AA	Age ≤ 50 years	0.618 (0.337–1.135)	0.121	1.228 (0.487–3.095)	0.663
	Age > 50 years	0.343 (0.113–1.042)	0.059	1.229 (0.354–4.273)	0.745
	Pre-menopausal	0.377 (0.161–0.884)	0.025	0.978 (0.325–2.944)	0.968
	Post-menopausal	0.676 (0.341–1.343)	0.264	1.405 (0.509–3.878)	0.512
	Grade 1–2	0.528 (0.183–1.521)	0.237	1.730 (0.144–20.752)	0.665
	Grade 3	0.358 (0.162–0.789)	0.011	0.780 (0.306–1.989)	0.602
	Grade UK	1.437 (0.481–4.293)	0.516	5.701 (0.661–49.170)	0.113
	Tumor size ≤ 2 cm	0.471 (0.168–1.322)	0.153	2.041 (0.340–12.239)	0.435
	Tumor size > 2 cm	0.543 (0.293–1.006)	0.052	1.084 (0.478–2.461)	0.847
	LN negative	0.549 (0.226–1.334)	0.185	95.034 (0.007–1280606)	0.348
	LN positive	0.507 (0.262–0.983)	0.044	0.858 (0.388–1.896)	0.705

**Abbreviations:** DFS, disease-free survival; OS, overall survival; Ref, reference; UK, unknown.

associated with the survival of breast cancer patients. None of the polymorphisms in *AURKB* of our study has been reported in TNBC. We first found that rs11651993 TC + CC genotype predicted worse DFS in subgroup of age  $\leq 50$  years, post-menopausal, grade UK, tumor size  $>2$  cm, and lymph node negative. It also predicted shorter OS in subgroup of age  $> 50$  years and grade 3. Rs2289590 CA + AA genotype could predict favorable DFS in pre-menopausal, grade 3, and lymph node-positive patients.

All patients in our study received taxane-based adjuvant chemotherapy. Taxanes are microtubule targeting agents (MTAs), which are most widely used drugs in adjuvant setting for TNBC patients. The cytotoxic action of these compounds is mediated primarily through their binding of  $\beta$ -tubulin monomers, leading to microtubule stabilization, thus blocking their depolymerization and subsequently triggering cell cycle arrest at the G2/M phase.<sup>31</sup> Considering the role of Aurora kinases in spindle formation and the reported extent of their deregulation in cancer, we hypothesize that polymorphisms in *AURKA* or *AURKB* might contribute to taxane resistance and then influence the survival of cancer patients. Zhang et al<sup>30</sup> demonstrated that in breast cancer patients who received neoadjuvant chemotherapy (containing sequential taxane and anthracycline-based regimens), elevated expression of *AURKB* contributed to chemoresistance ( $P = 0.011$ ). In taxane-resistance breast cancer cell lines, expression of *AURKA* was significantly higher. Knockdown of *AURKA* not only markedly decreased the expression of P-gp but also downregulated the P-gp function in resistant breast cancer cells. The results indicated that *AURKA* plays a crucial role in paclitaxel-resistant breast cancer.<sup>32</sup>

However, the underlying mechanisms of these SNPs on survival of TNBC are not yet clear and need to be further investigated. By silico analysis of prediction of binding motifs, Mesic et al<sup>33</sup> indicated that polymorphic sites in *AURKA* and *AURKB* could bind different transcription factors. As for *AURKA* rs8173, when the G allele was present, C/EBPalpha, C/EBPbeta, and NF-1 transcription factor binding motifs were recognized, whereas when the same region contained the C allele, additional E2F and RAR- $\beta$  transcription factor motifs were identified. In the case of *AURKB* rs2289590, when the A allele was present, PEA3 and TFII-I binding motifs were recognized. In contrast, when the C allele is present, PEA3, TFII-I, and YY1 binding motifs were identified. Since YY1 expression level and/or activity is associated with unchecked cell proliferation, resistance to apoptosis, metastasis, and tumor cell resistance to chemo-

therapeutics,<sup>34</sup> the binding of an additional YY1 protein in the presence of C allele may alter the level of *AURKB* expression and then influence the survival, which might be a possible explanation for our result that *AURKB* rs2289590 A allele was significantly associated with better DFS.

Previous studies enrolled different subtypes of breast cancer patients, and the regimens are not consistent. In our study, only TNBC patients were enrolled, which can better explain the correlation between polymorphisms in *AURKA* or *AURKB* and survival. There are some limitations of our study. First, this was a retrospective study, so selection bias might exist. Second, the sample size was relatively small, and the prospective large-scale studies are needed to confirm the conclusions. Finally, since we did not explore the mechanisms, further studies on the biological mechanisms are warranted.

## Conclusion

For the first time in TNBC patients receiving taxane-based adjuvant chemotherapy, we demonstrated that *AURKA* rs6099128, *AURKB* rs11651993, and *AURKB* rs2289590 were associated with the survival. Since most polymorphisms have never been reported, more research are needed to verify our results.

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## Disclosure

The authors declare no conflicts of interest in this work.

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