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Prognostic significance of miR-34 rs4938723 T > C polymorphism in triple negative breast cancer patients

Andriani Tsiakou[a,*], Flora Zagouri[b], Eleni Zografos[c], George Samelis[d], Maria Gazouli[c], Despoina Kalapanida[b], Aris Giannos[e], Spyros Marinopoulos[e], Konstantinos Dimitrakakis[e], Andreas Lazaris C.[f], Dimitrios Rigopoulos[a], George Zografos[g]

[a] Department of Dermatology, 'Andreas Syggros' Hospital of Cutaneous & Venereal Diseases, University of Athens, Athens, Greece
[b] Department of Clinical Therapeutics, Alexandra Hospital, University of Athens, Athens, Greece
[c] Department of Biology, University of Athens, Athens, Greece
[d] Department of Oncology, Hippocrateio Hospital, Athens, Greece
[e] Department of Obstetrics and Gymaecology, Alexandra Hospital, University of Athens, Athens, Greece
[f] 1st Department of Pathology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
[g] 1st Propaedeutic Surgical, Department, Hippocrateio Hospital, University of Athens, Greece

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ABSTRACT

Objectives: The aim of this was the assessment of the prognostic role of the rs4938723 C > T polymorphism of the miR-34 in triple negative breast cancer patients.

Methods: Therefore formalin fixed paraffin embedded tissue samples from 114 triple negative breast cancer patients and blood samples from 124 healthy donors were genotyped and subsequently extensive statistical analysis was performed in order to investigate the clinical value of this polymorphism in triple negative breast cancer.

Results: Our statistical analysis disclosed that the majority of patients harboring ductal breast carcinoma (69.4%) have the TC or CC genotypes ($P = .020$). Moreover the survival of the patients was significantly correlated with the occurrence of the TC or CC alleles ($P < .001$). Regarding the correlation of miR-34 polymorphisms with patients' survival we found that women with TC or CC single nucleotide polymorphisms were characterized by shorter disease free survival intervals ($P = .05$). Furthermore triple negative breast cancer patients with TC/CC genotype exhibited shorter overall survival intervals as disclosed by Kaplan Meier analysis ($P < .001$) and Cox regression analysis (HR = 3.2, %95 CI = 2.0–5.5, $P = .008$). Stratified Kaplan-Meier analysis showed that the women harboring the TC or CC genotype along with the ductal histology had significantly shorter survival ($P < .001$). This result was also confirmed by Univariate Cox regression analysis, which showed that women ductal breast cancer and TC or CC genotype are of worse prognosis (HR = 2.35, %95 CI = 2.1–4.65, $P = .003$).

Conclusions: In conclusion, we found that the TC and CC alleles are associated with unfavorable prognosis in triple negative breast cancer patients.

1. Introduction

The pivotal role of miRNAs in carcinogenesis revolutionized our perspectives on cancer patients' management and fueled much interest in recognizing novel cancer markers in this class of small non-coding RNA molecules [1,2]. miRNAs hold promises for their potential use as blood-based and minimally invasive biomarkers since they are surprisingly stable and can be extracted in high quality from easily accessible biological materials e.g. formalin-fixed paraffin-embedded tissues [3,4] and serum [5,6], they are resistant to conditions such as extend storage and repeated freeze/thaw cycles [7] and can be accurately detected and profiled by sensitive and/or high-throughput methods [8,9]. miRNA research has already resulted in fruitful results, making feasible the translation of bench-based observations to clinically applicable tests [10].

Single nucleotide polymorphisms in miRNA genes and target sites represent a recently recognized aspect of the miRNA-related cancer research that is expected to shed light on the mechanistic contribution of miRNAs in carcinogenesis and to provide opportunities for their exploitation in the clinical context [11,12]. single nucleotide

* Corresponding author.
E-mail address: andrianitsiakou@yahoo.gr (A. Tsiakou).

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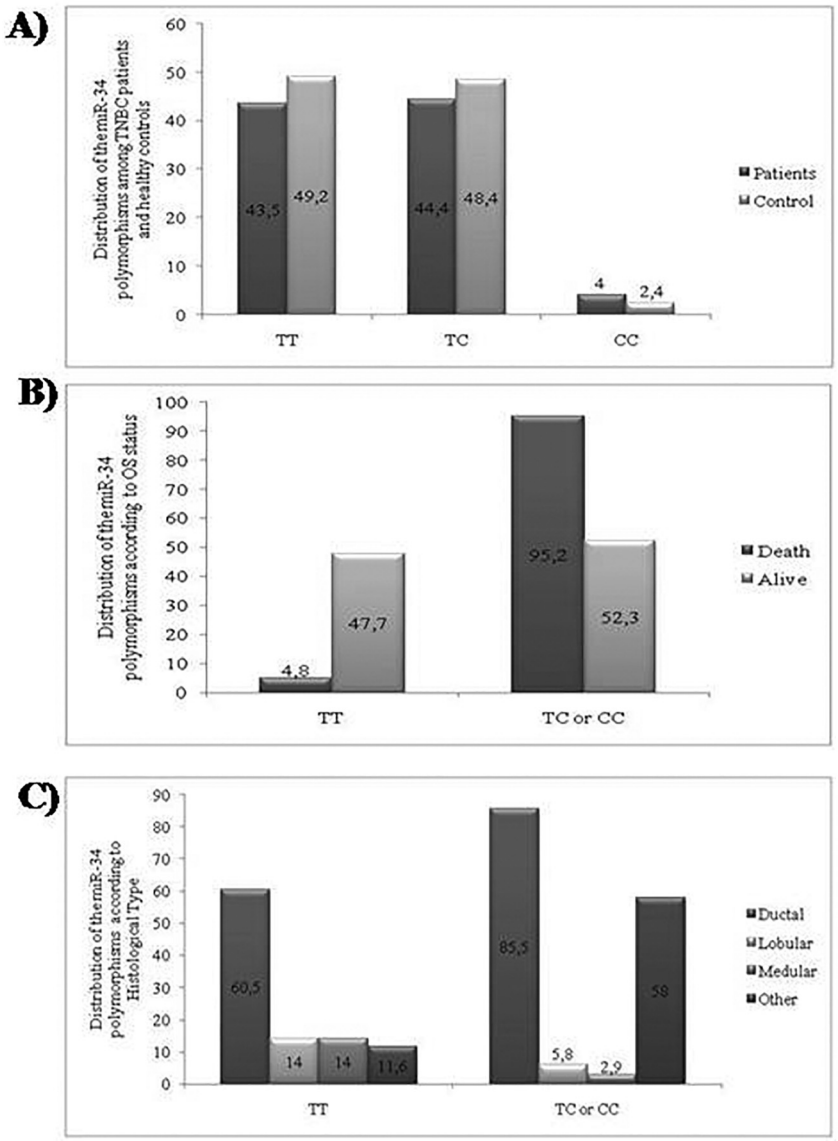

Fig. 1. Distribution of the miR-34 polymorphisms: A) among triple negative breast cancer patients and healthy controls, B) according to overall survival status and C) according to the histological type.

polymorphisms in miRNA genes and/or in miRNA binding sites of protein-coding genes seems to reinforce the already divergent and multifaceted role of miRNAs in gene expression regulation, affecting thereby the cancer susceptibility and development [13,14]. Since the very first study, conducted in 2005, studying the polymorphisms in pre-miRNAs, there is a growing body of literature addressing the contribution of miRNA-related single nucleotide polymorphisms in susceptibility to a wide-range of cancers and their role as novel biomarkers of cancer risk, clinical cancer diagnosis, as well as disease outcome and response to treatment [15,16]. Currently there are several studies regarding the biomarker potential of miRNA-related single nucleotide polymorphisms in breast cancer showing that these single nucleotide polymorphisms can be useful tools in identifying women at high risk for developing this malignancy [17–21].

miR-34 family involves miR-34a, miR- 34b, and miR-34c. The miR-34b, and miR-34c are encoded by a shared primary transcript (pri-miR-34b/c) [22], the promoter of which contains p53-binding sites [23]. Recent studies have shown that the rs4938723 C > T variant in the promoter region of pri-miR-34b/c may affect transcription factor GATA-X binding and consequently pri-miR-34b/c expression [24]. Two recent independent publications have correlated the rs4938723 C > T polymorphism with the risk of hepatocellular [25] and prostate [26] cancer and have shown that it is associated with a higher risk.

The aim of our study was to examine the presence of rs4938723 C > T polymorphism in 114 formalin fixed paraffin embedded tissues isolated by triple negative breast cancer patients and correlated the single nucleotide polymorphism status with the survival of the patients.

2. Materials and methods

2.1. Clinical characteristics of the patients

We analyzed formalin fixed paraffin embedded tissues obtained from 114 triple negative breast cancer patients and 124 blood samples from healthy donors. Detailed medical history, demographic data, clinicopathologic characteristics and follow up survival information were collected for each patient, for statistical analysis (Supl. Table 1).

Research procedures of the study comply with the ethical standards of the World Medical Association Declaration of Helsinki. Approval for the use of the breast tissue samples was acquired by the ethical committee of “Ippokrateio” University Hospital. Informed consent was obtained from all study participants.

2.2. Genotyping

Genotyping of the rs4938723 was analyzed by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The forward and reverse primers were 5'-CTCACCTCCTCTGGGAACCTT-3′ and 5'-AAGGCCATACCATTCAAGACAGTAT-3′, respectively. The *Tas*I restriction enzyme was taken to digest the PCR products as previously described [25].

3. Results

3.1. Differential distribution of miR34 rs4938723 T > C among triple negative breast cancer patients and control cases

The detection of miR34 single nucleotide polymorphism was performed in 114 triple negative breast cancer patients and 124 healthy controls. According to our statistical analysis, the TT and TC allele was found to be equally distributed not only in triple negative breast cancer patients but also in control group. In more details out of the 124 healthy donors, the TT allele was found in 61 (49.2%) women, the TC genotype was detected in 60 (48.4%) healthy donors, while the CC genotype was found in 3 (2.4%) women. In the triple negative breast cancer patients group the corresponding percentages were 43.5% (54 out of the 114 patients), 44.4% (55 out of the 114 patients) and 4% (5 out of the 114) (Fig. 1A, Supl. Table 2). The distribution of miR34 rs4938723 T > C among triple negative breast cancer patients and control cases was not significantly different (chi-square; $P = .445$)

3.2. Correlation of miR34 rs4938723 T > C with patients' clinical variables

By performing chi-square test we demonstrated that, there is no association of miR34 rs4938723 T > C with any of the clinical variables (Supl. Table 3). However, when we stratified the single nucleotide polymorphisms status in the following groups: a) TT, b) TC or CC we found that the survival of the patients is significantly correlated with the occurrence of the TC or CC alleles (chi-quare; $P < .001$, Fig. 1B, Table 1). We also found that 59 out of the 85 patients (69.4%) with ductal breast carcinoma have the TC or CC genotypes (chi-quare; $P = .020$, Fig. 1C, Table 1).

3.3. Survival analysis and prognostic significance of miR34 rs4938723 T > C in triple negative breast cancer patients

Disease-free and Overall survival information were available for 109 triple negative breast cancer patients. Disease free survival was defined as the time interval between the surgical resection of the tumor and the date of the first documented event of either local or regional recurrence, second cancer from breast cancer. Accordingly overall survival was defined as the period between the tumor resection and the disease-related death. In total of 109 triple negative breast cancer patients, 11 patients relapsed (10.1%) and 21 patients died (20.0%). In the group of the patients (11/124) that relapsed 4 (36.4%) carried the TT allele, 7 (63.6%) the TC allele, while none of the patients had the CC allele. Concerning the overall survival status, 13 (61.9%) women were carriers of the TT allele while 7 (33.3%) and 11 (4.76%) had the TC and CC genotypes, respectively (Supl. Table 3).

Survival analysis was performed by Kaplan-Meier and Cox proportional hazards regression models. Kaplan-Meier analysis, performed in the entire study cohort, disclosed that there is no significant association with the disease free survival or overall survival. Next, we performed Kaplan-Meier analysis after dichotomized our study cohort in the following groups: a) TT b) TC or CC. It was found that women with TC or CC single nucleotide polymorphisms were characterized by shorter disease free survival intervals (long rank test; $P = .05$) (Fig. 2A). However Cox univariate regression analysis regarding disease free survival, failed to show any statistical significant result (Table 2). Moreover we also dichotomized our patients in the following groups: a) Ductal histology and CC or TC genotype and b) Lobular or medular histology and TT genotype. However Kaplan- Meier analysis did not reveal any significant correlation between disease free survival and the allele status of the patients.

Concerning overall survival, Kaplan-Meier analysis revealed that there is no significant differentiation of overall survival probability between the three examined genotypes (long rank test; $P > .05$). However, after performing Kaplan-Meier analysis in the above mentioned groups a) TT b) TC or CC, we found that triple negative breast cancer patients with TC/CC genotype exhibited shorter overall survival intervals (long rank test; $P < .001$) (Fig. 2B). Cox regression analysis at the univariate level confirmed that these women were characterized by worse prognosis (HR = 3.2, %95 CI = 2.0–5.5, $P = .008$) (Table 2). Kaplan-Meier analysis between the groups a) Ductal histology and CC or TC genotype and b) Lobular or medular histology and TT genotype showed that the women harboring the TC or CC genotype along with the ductal histology had significantly shorter survival (long rank test; $P < .001$) (Fig. 3). Univariate Cox regression analysis confirmed the above results showing that the women that are characterized by ductal histology and TC or CC genotype are of worse prognosis (HR = 2.35, %95 CI = 2.1–4.65, $P = .003$) (Table 2).

Table 1
Distribution of TT, TC and CC alleles according to classic clinicopathological data.

Variable	Total	miR-34 Polymorphisms		*P* value*
		TT	TC or CC	
DFS status				
Recurrence	11	2 (18.2%)	9 (81.8%)	0.195
No Recurrence	98	41 (41.8%)	57 (58.2%)	
Unknown	15			
OS status				
Death	21	1 (4.8%)	20 (95.2%)	**< 0.001**
Alive	88	42 (47.7%)	46 (52.3%)	
Unknown	15			
Histological type				
Ductal	85	26 (30.6%)	59 (69.4%)	**0.020**
Lobular	10	6 (60.0%)	4 (40.0%)	
Medular	8	6 (75.0%)	2 (25.0%)	
Other	9	5 (55.6%)	4 (44.4%)	
Unknown	12			

4. Discussion

miR-34 plays a central role in the p53 network and it has been found to be down-regulated in multiple types of tumors [27–29]. Concerning breast cancer several data imply the tumor suppressive role of this miRNA [30,31]. The rs4938723 C > T of miR-34 is located within the CpG island of the promoter and is a 423-base pair (bp) upstream from the transcription start site [32]. This single nucleotide polymorphism, which has been annotated in the NCBI SNPs database (rs4938723), may affect a predicted GATA-X transcription factor binding and subsequently affect the expression and carcinogenesis [24,32,33]. The clinical role of miR-34b/c rs4938723 in breast cancer have been addressed by two independent groups, but the results are inconsistent [34,35]. In more details Sanaei et al. referred that the rs4938723 C > T polymorphism is not a risk factor for the occurrence of breast cancer [35], while Bensen et al. found that this single nucleotide polymorphism is associated with breast cancer risk and survival [34].

We analyzed the differential distribution of the rs4938723 T > C polymorphism among triple negative breast cancer patients and healthy controls and we found that there was no statistical significant difference between the two groups ($P = .445$). Our results are in concordance with

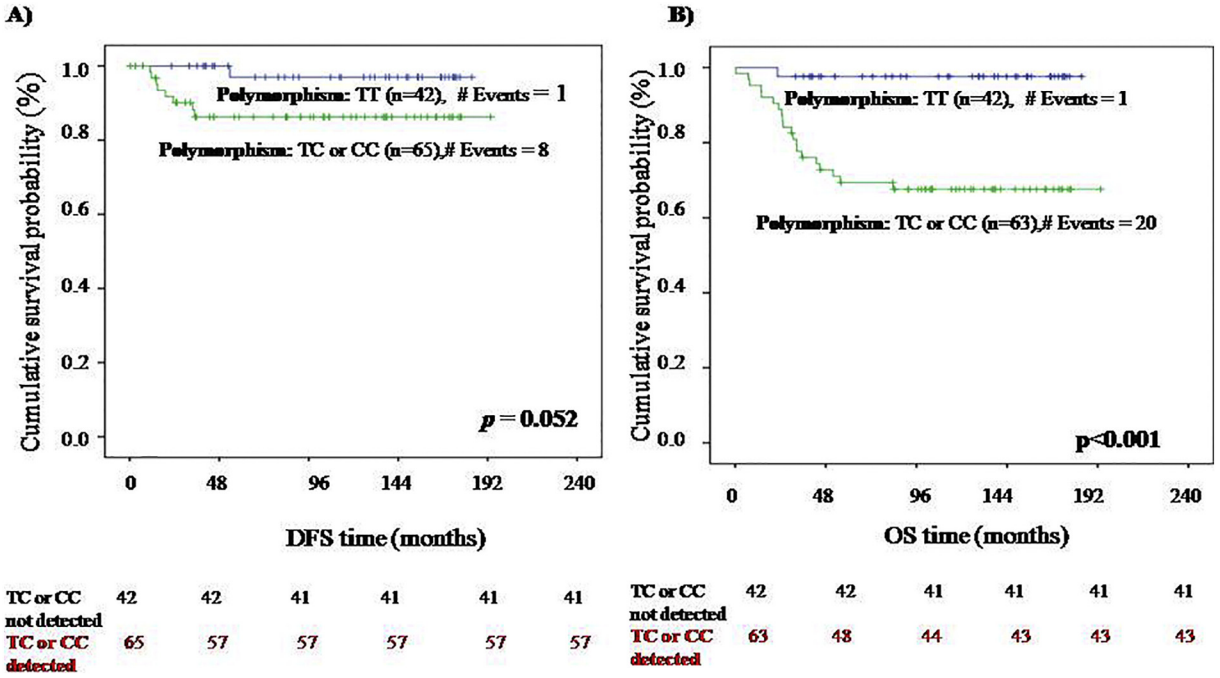

Fig. 2. Kaplan-Meier for the whole cohort of triple negative breast cancer patients of the A) disease free survival curve and B) overall survival curve. *P* values were calculated by log-rank test.

those reported by Bensen *et. al* that showed that the genotype distribution between breast cancer patients and healthy controls is similar [34].

In our study, we also aimed to correlate the genotype status of the rs4938723 C > T of miR-34 with the clinicopathological and survival data of 124 patients with triple negative breast cancer. We found out that the TC or CC genotype is significantly associated with ductal histology (chi-quare; $P = .020$) and breast cancer overall survival (chi-quare; < 0.001). Our survival analysis, which involved Kaplan-Meir and Cox regression analysis, corroborate the above mentioned results regarding overall survival. More specifically Kaplan-Meier analysis showed that triple negative breast cancer patients with TC/CC genotype exhibited shorter overall survival intervals (long rank test; $P < .001$) (Fig. 2B). Cox regression analysis at the univariate level confirmed that these women were characterized by worse prognosis (HR = 15.02, %95 CI = 2.0–112, $P = .008$) (Table 2). Our results are in contrast to those reported by Bensen et al. that showed that CC genotype is associated with enchased overall survival. This discordance could be attributed to the different design of survival analysis, since Bensen et al. studied the TT + TC genotype versus the CC genotype and the study cohort included African American and Caucasian women.

Although the association of TC/CC genotype with unfavorable OS outcome in breast cancer patients seems to be in contradiction with the similar genotype distribution between cancer patients and healthy subjects, similar results have been reported. For example a microarray study by Tripathi et al. exhibited that global gene expression abnormalities occur in normal epithelium of breast cancer patients [36]. Moreover, Schummer et al., showed that many genes, usually associated with cancer pathways, are downregulated in breast cancer compared to normal breast tissue [37].

Taking a step further we performed survival analysis after dichotomized the study cohort in: a) Ductal histology and CC or TC genotype and b) Lobular or medular histology and TT genotype. According to this analysis, women with the TC or CC genotype along with the ductal histology exhibited significantly shorter survival (long rank test; $P < .001$) (Fig. 3). Univariate Cox regression analysis corroborated the above results showing that the women with ductal histology and TC or CC genotype are characterized by worse prognosis (HR = 8.88, %95

Table 2
Univariate analysis of TT, TC and CC alleles regarding DFS and OS.

Variable	Disease free survival (DFS) (n = 103)			Overall survival (OS) (n = 105)		
	HR[a]	95% CI[b]	*P* value	HR[a]	95% CI[b]	*P* value
miR-34 Polymorphisms						
TT	1.00	0.76–2.2	0.088	1.00	2.0–5.5	**0.008**
TC or CC	3.3			3.2		
miR-34/Histology						
TT and Lobular or medular	1.00	0.44–7.13	> 0.05	1.00	2.1–4.65	**0.003**
TC or CC and Ductal	1.78			2.35		
Stage						
I/II	1.00	0.33–5.22	> 0.05	1.00	1.55–8.76	**0.003**
III	1.304			3.69		

Bold value indicates statistical significance.
[a] Hazard ratio, estimated from Cox proportional hazard regression model.
[b] Confidence interval of the estimated HR.

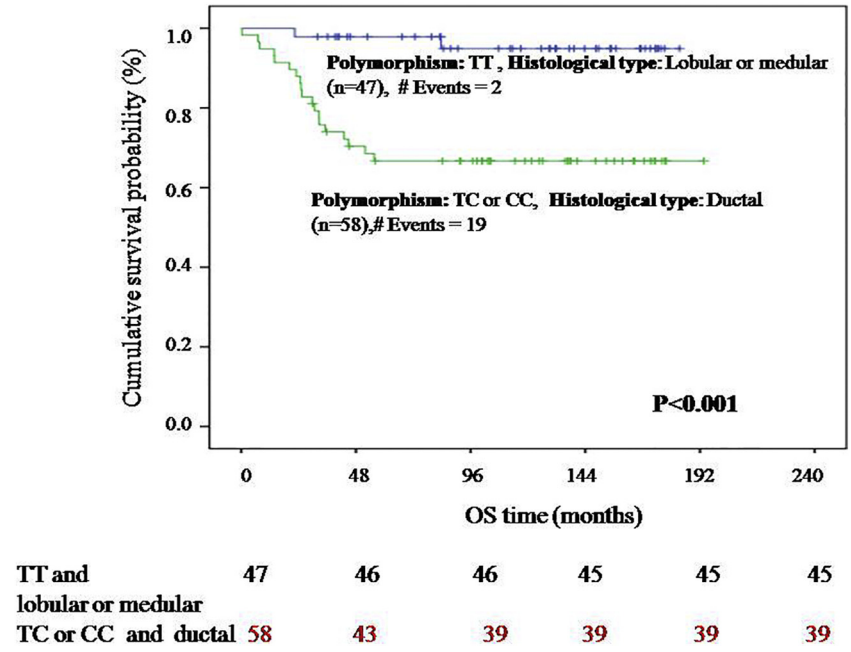

Fig. 3. Kaplan-Meier overall survival curve after stratification of study cohort according to histological type. *P* values were calculated by log-rank test.

CI = 2.1–38.22, *P* = .003) (Table 2).

5. Conclusions

In total our results indicate that the TC and CC alleles are associated with unfavorable prognosis in triple negative breast cancer patients. Taking into consideration that the clinical management of these patients remains a challenging task, the identification of novel markers capable of improving breast cancer patients' prognosis is mandatory. Although our results aided towards this direction, there is still need for their validation on independent multicentric cohorts, since the current study is the first attempt to correlate the rs4938723 C > T of miR-34 in Greek population and is based on a single institution cohort.

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2019.03.009.

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