Low RAB6C expression is a predictor of tamoxifen benefit in estrogen receptor-positive/progesterone receptor-negative breast cancer

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Abstract. Over the last few decades, improved and more individualized treatment has contributed to the increased survival rate of patients with breast cancer. However, certain patients may receive excessive treatment resulting in undesired side effects. In a previous study, it was demonstrated that systemically untreated patients with estrogen receptor (ER)-positive/progesterone receptor (PR)-negative tumors with high Ras-related protein Rab-6C (RAB6C) expression levels (RAB6C$^+$) had prolonged distant recurrence-free survival compared with that of patients exhibiting low RAB6C (RAB6C$^-$)-expressing tumors. The aim of the present study was to investigate whether RAB6C predicts the effectiveness of tamoxifen treatment. The present study used a dataset comprising 486 female patients with ER$^+$ tumors from a randomized study conducted by the Stockholm Breast Cancer Study Group between November 1976 and August 1990. The patients were considered as low-risk if their tumor size was ≤30 mm and their lymph node status was negative. Patients were followed up until distant recurrence, mortality or when 25 years after randomization was achieved, whichever occurred first. For patients with ER$^+$/PR$^-$/RAB6C$^+$ tumors, prolonged distant recurrence-free survival could not be observed if the patients were treated with tamoxifen [hazard ratio (HR), 1.82; 95% confidence interval (CI), 0.69-4.79; P=0.23], whereas patients with ER$^+$/PR$^-$/RAB6C$^-$ tumors had 75% reduced distant recurrence risk (HR, 0.25; 95% CI, 0.09-0.70; P=0.008). In the ER$^+$/PR$^+$ subgroup, patients with RAB6C$^-$ and RAB6C$^+$ tumors benefited from tamoxifen treatment, though it was most evident in the RAB6C$^+$ group (HR, 0.27; 95% CI, 0.13-0.58; P=0.001). The results of the present study indicated that, for patients with ER$^+$/PR$^-$ tumors, those with low RAB6C expression benefited from tamoxifen treatment, whereas no benefit was observed in patients with high RAB6C levels.

Introduction

Breast cancer survival has increased continuously during the last decades, and the 5-year survival rate in Sweden is almost 90% (1,2). Improved and more individualized treatment has contributed to this progress. However, a few patients may be overtreated, possibly with undesired side effects. The majority of patients with estrogen receptor (ER)-positive tumors receive endocrine therapy. In a previous study, our group demonstrated that patients with ER$^+$/progesterone receptor (PR)-positive tumors clearly did benefit from tamoxifen, while the long-term benefit was lower for those with ER$^+$/PR$^-$ tumors (3). Nevertheless, ER$^+$/PR$^-$ tumors are a heterogeneous group, and among them there may be subgroups of patients that do benefit from tamoxifen. Therefore, one subject for further study was the identification of such subgroups.

The ER$^+$/PR$^-$ subgroup is considered to have a more aggressive progression compared with that of the ER$^+$/PR$^+$ subgroup, and according to the St. Gallen criteria, patients with ER$^+$/PR$^-$ tumors are recommended chemotherapy as additional treatment, despite the fact that in this subgroup certain patients may have good prognosis without systemic treatment. Experimental studies have shown that the Ras-related protein RAB6C (RAB6C) inhibits proliferation, invasion and metastasis, suggesting that it acts as a tumor suppressor (4). RAB6C also interacts with p53, which is frequently mutated in breast cancer (5-7). In a concurrent study, it was revealed

that systemically untreated patients with ER⁺/PR⁻ tumors and high RAB6C expression (RAB6C⁺) had prolonged distant recurrence-free survival compared with that of patients with low RAB6C expression (RAB6C⁻) (26). The aim of the present study was to investigate if RAB6C has a treatment predictive value for tamoxifen. For this purpose, data for 486 patients from a randomized clinical trial were used.

Patients and methods

Patients. Patients with operable invasive breast cancer were entered in a previous study of adjuvant tamoxifen therapy conducted by the Stockholm Breast Cancer Study Group (8). Postmenopausal women younger than 70 years of age were randomly administered tamoxifen postoperatively at a dose of 40 mg per day compared with no adjuvant endocrine therapy. Between November 1976 and June 1990, 2,738 patients were recruited into the trial. Among them, 1,780 patients (65%) with no lymph node metastases and a tumor diameter ≤30 mm (established by histological examination) were classified as 'low risk' and did not receive cytotoxic chemotherapy. In this group, 432 patients were treated with breast conserving surgery, including axillary dissection plus radiation to the breast (50 Gy/5 weeks). The remaining 1,348 patients had a modified radical mastectomy and no radiotherapy. Paraffin blocks from 912 low-risk patients were used for the construction of tissue microarrays (TMAs). Of these, 619 tumors were ER⁺, whereof 591 also had data on PR status (3). RAB6C expression could be evaluated for 486 cases among these tumors (Fig. 1).

Hormone receptor status, human epidermal growth factor receptor 2 (HER2) status, grade and RAB6C expression. Data on ER, PR and HER2 was available from previous studies. The status of ER and PR was assessed retrospectively with immunohistochemistry (IHC) using the VENTANA® automated slide stainer (Ventana Medical Systems, Inc.). The primary monoclonal antibodies used were CONFIRM™ mouse anti-ER antibody (clone 6F11) and CONFIRM™ mouse anti-PR antibody (clone 16) (Ventana Medical Systems, Inc.). The cut-off level was set to 10% positively stained tumor cells (9). HER2 was analyzed with IHC as previously described (10). The Nottingham Histological Grade (NHG) was analyzed retrospectively by the same investigator for all tumor samples.

The protein expression of RAB6C was analyzed with IHC, and the staining pattern was evaluated independently by two investigators (JS and TB). The polyclonal rabbit antibody ab200396 (Abcam) was used. The intensity of RAB6C in the nucleus was analyzed and scored as 0, 1, 2 or 3. If the nuclei had an intensity ≥2, the tumor was considered to have high expression of RAB6C (RAB6C⁺). Otherwise, it was considered to have low RAB6C expression (RAB6C⁻).

Ethics approval and patient consent to participate. The present study was performed in accordance with the Declaration of Helsinki. Ethical approval for the use of tumor material was approved by the local Ethical Committee at the Karolinska University Hospital (approval no. KI 97-451 with amendments 030201 and 171027). According to the approval, informed consent from the patients was not required.
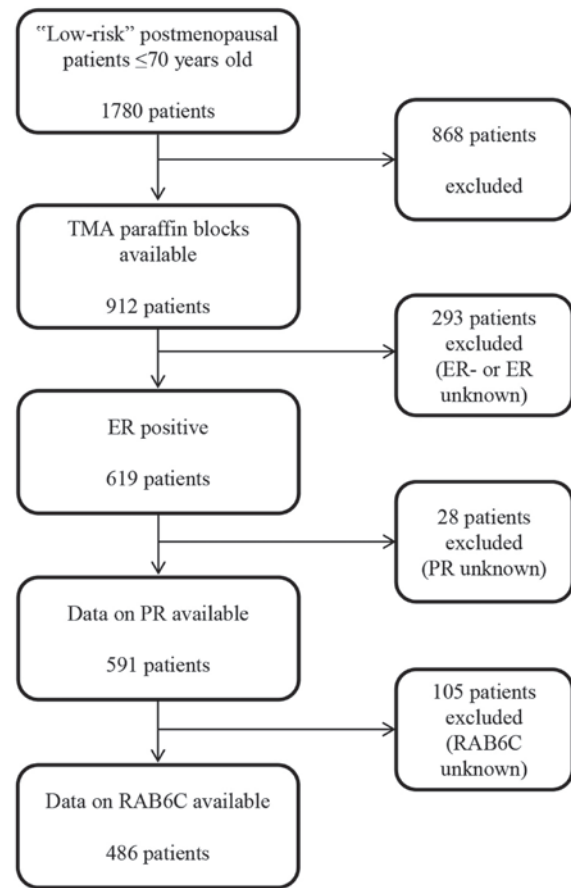

Figure 1. Consort diagram. TMA, tissue microarray; ER, estrogen receptor; PR, progesterone receptor; Ras-related protein Rab-6C.

Statistical analysis. To compare the association between RAB6C and clinical characteristics, the Pearson's χ^2 test was applied. Cumulative distant recurrence-free survival was estimated using the Kaplan-Meier method. The end-point was defined as the first distant recurrence from the patient's primary breast cancer as described by Rutqvist and Johansson (8). Three patients had succumbed to breast cancer but no date of distant recurrence was registered. For these patients, the date of death was used as an event of distant recurrence. The remaining patients were followed up until they had a distant recurrence or succumbed, or for 25 years after randomization, whichever occurred first. Patients were censored at the last follow-up or at mortality due to causes other than breast cancer.

The multivariable analyses with subgroups based on RAB6C status included age, tumor size, HER2, NHG, tamoxifen and the interaction term 'RAB6C x tamoxifen'. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox's proportional hazards model. To test whether there is an interaction between RAB6C and tamoxifen, the Likelihood ratio χ^2 test was applied. The statistical analyses were performed with Stata/SE 13.1 (StataCorp LP).

Results

Patients with ER⁺ tumors did benefit from tamoxifen (HR=0.47, 95% CI=0.31-0.71; P<0.001), which was more evident in patients with ER⁺/PR⁺ tumors (HR=0.39,

Table I. Univariable analysis of distant recurrence rates for tamoxifen-treated patients compared with the control group, stratified by hormonal receptor status.

Subgroup	Number of patients/events		HR (95% CI) TAM+ vs. TAM-	P-value	P for interaction
	TAM+	TAM-			
ER+	259/35	227/61	0.47 (0.3-0.71)	<0.001	
ER+/PR+	177/20	143/39	0.39 (0.23-0.67)	0.001	0.20
ER+/PR-	82/15	84/22	0.65 (0.34-1.25)	0.19	
ER+/PR+/RAB6C+	111/10	75/22	0.27 (0.13-0.58)	0.001	0.14
ER+/PR+/RAB6C-	66/10	68/17	0.63 (0.29-1.37)	0.24	
ER+/PR-/RAB6C+	37/10	41/7	1.82 (0.69-4.79)	0.23	0.004
ER+/PR-/RAB6C-	45/5	43/15	0.25 (0.09-0.70)	0.008	

The control group is the referent (hazard ratio, 1) in each subgroup analysis. ER, estrogen receptor; PR, progesterone receptor; RAB6C, Ras-Related protein Rab-6C.
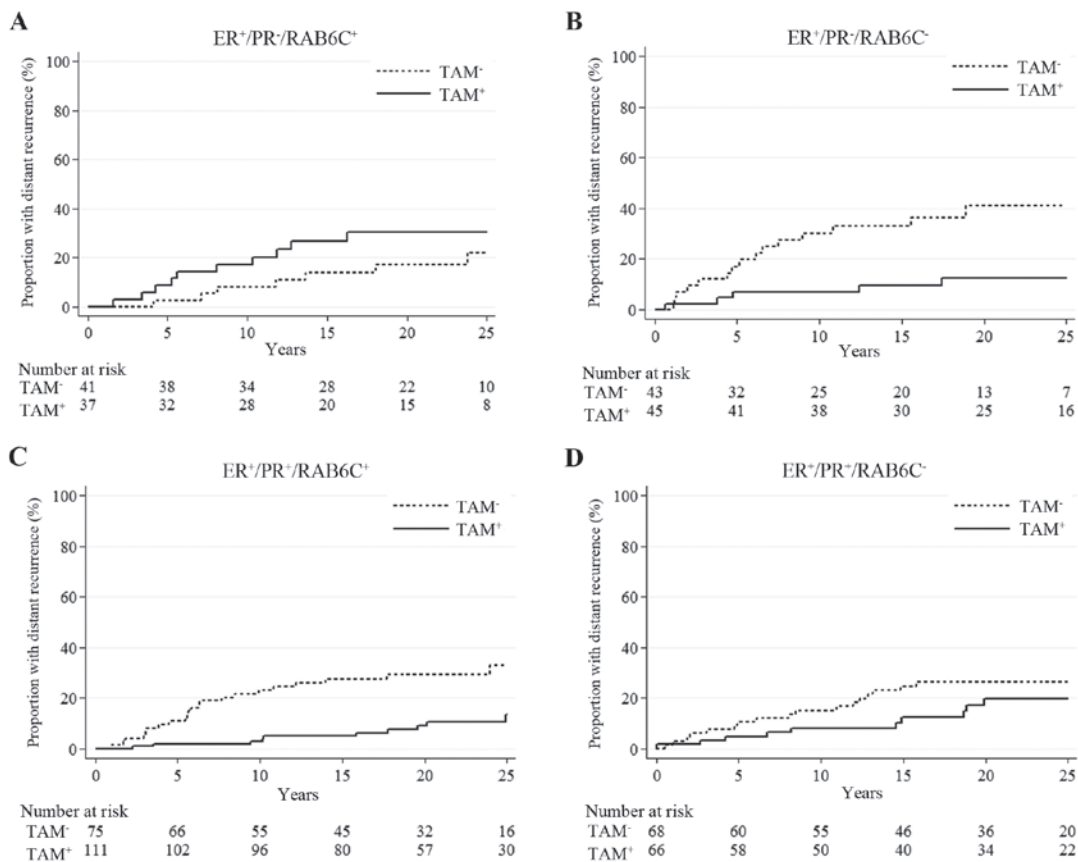

Figure 2. Cumulative distant recurrence risk in relation to tamoxifen treatment in patients with (A) ER+/PR-/RAB6C+ (HR, 1.82; 95% CI, 0.69-4.79; P=0.23), (B) ER+/PR-/RAB6C- (HR, 0.25; 95% CI, 0.09-0.70; P=0.008), (C) ER+/PR+/RAB6C+ (HR, 0.27; 95% CI, 0.13-0.58; P=0.001) and (D) ER+/PR+/RAB6C- (HR, 0.63; 95% CI, 0.29-1.37; P=0.24) tumors. CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor; RAB6C, Ras-related protein Rab-6C; TAM, tamoxifen.

95% CI=0.23-0.67; P=0.001) than in those with ER+/PR- tumors (HR=0.65, 95% CI=0.34-1.25; P=0.19). However, dividing the ER+/PR- tumors by RAB6C status showed that, for those with low RAB6C expression levels, the tamoxifen effect on disease (HR=0.25, 95% CI=0.09-0.70; P=0.008) was comparable to that in patients with ER+/PR+ tumors (Fig. 2).

For patients with ER+/PR-/RAB6C+ tumors, prolonged distant recurrence-free survival was not observed if they were treated with tamoxifen (HR=1.82, 95% CI=0.69-4.79; P=0.23). The different effect of the treatment between the RAB6C+ and RAB6C- groups was indicated by a statistically significant interaction (P=0.004; Table I). In the ER+/PR+ subgroup,

Table II. Multivariable[a] analysis of distant recurrence rates for tamoxifen-treated patients compared with the control group, stratified by hormonal receptor status.

| | Number of patients/events | | HR (95% CI) | | LR interaction term RAB6C x TAM | |
Subgroup	TAM+	TAM-	TAM+ vs. TAM-	P-value	χ^2 value	P-value
ER[+]/PR[+]/RAB6C^{+}	88/7	69/20	0.17 (0.07-0.42)	<0.001	4.63	0.03
ER[+]/PR[+]/RAB6C^{-}	58/10	55/15	0.61 (0.27-1.37)	0.23		
ER[+]/PR[-]/RAB6C^{+}	32/7	32/4	2.18 (0.61-7.78)	0.23	10.17	0.001
ER[+]/PR[-]/RAB6C^{-}	40/4	40/15	0.19 (0.06-0.57)	0.003		

The control group is the referent (hazard ratio, 1) in each subgroup analysis. [a]The analysis includes age, tumor size, human epidermal growth factor receptor 2 status, Nottingham Histologic Grade, RAB6C, TAM and the interaction term 'RAB6C x TAM'. RAB6C, Ras-related protein Rab-6C; TAM, tamoxifen; LR, Likelihood ratio; ER, estrogen receptor; PR, progesterone receptor; HR, hazard ratio; CI, confidence interval.

RAB6C expression did not have a significant influence on benefit from tamoxifen. Both patients with RAB6C^{-} tumors (HR=0.63, 95% CI=0.29-1.37; P=0.24) and RAB6C^{+} tumors (HR=0.27, 95% CI=0.13-0.58; P=0.001) did benefit from tamoxifen, although it was statistically significant only among those with RAB6C^{+} tumors. Of note, the tamoxifen-treated patients with ER[+]/PR[+]/RAB6C^{+} or ER[+]/PR[-]/RAB6C^{-} tumors had excellent distant recurrence-free survival, with a 25-year cumulative proportion of 87% (95% CI=75-93%) and 88% (95% CI=72-95%), respectively. Together, these patients represent 60% of all patients with ER[+] disease treated with tamoxifen.

Established clinical factors were similarly distributed in the tamoxifen-treated and control groups (Table SI). In multivariable analyses divided by PR status and adjusting for age, tumor size, HER2 status and NHG, the results were similar to those obtained in univariable analyses, indicating that the treatment effect of tamoxifen on disease depending on the RAB6C expression was independent of these factors (Tables I and II). In summary, the analyses revealed that it was favorable to treat patients with ER[+]/PR[+] tumors regardless of RAB6C expression status. In contrast to high RAB6C expression, low RAB6C expression predicted benefit from tamoxifen for patients with ER[+]/PR[-] tumors.

Discussion

The hormone receptors ER and PR are important markers for breast cancer treatment. While tumors that are positive for both receptors are associated with prolonged survival when patients are treated with endocrine therapy, ER[+]/PR[-] tumors are considered to have a more aggressive phenotype (11). Patients with this tumor subtype are mostly treated with both endocrine therapy and chemotherapy, but there are probably subgroups of patients with these tumors who have high survival rates with more limited treatment. In a concurrent study, the results indicated that RAB6C may identify such patients (26). The present study further investigated the role of RAB6C in a retrospective study based on clinical data with patients randomized to be treated with endocrine therapy (tamoxifen) or included in the control group. Among patients

with ER[+]/PR[-] tumors, tamoxifen treatment showed different effects depending on RAB6C expression, and patients with low RAB6C expression did benefit from tamoxifen. For patients with ER[+]/PR[+] tumors, there was no statistically significant difference in treatment effect on RAB6C^{+} or RAB6C^{-} disease.

The relevance of PR for tamoxifen benefit has been discussed in various studies (3,12-16). Several of them concluded that patients with ER[+]/PR[+] tumors did benefit from tamoxifen treatment, whilst patients with ER[+]/PR[-] tumors benefit less. There is a need to identify patients with ER[+]/PR[-] tumors that do benefit from tamoxifen. The results of the present study confirmed that patients with ER[+]/PR[+] tumors benefit from tamoxifen, whereas for those with ER[+]/PR[-] tumors, the effect depends on RAB6C status. Potential physical interactions between RAB6C and the hormone receptors need to be evaluated in further studies. A number of samples from the original cohort was missing on the TMAs. However, in a previous study, the results showed no bias in the missing cases with respect to tumor size, ER status or tamoxifen treatment (17).

The knowledge of RAB6C is limited, although it is known to be a member of the RAB6 family and consists of a single exon. RAB6C shares 97% identity with the *RAB6A'* transcript, leading to the hypothesis that *RAB6C* was generated by retrotransposition of a fully processed *RAB6A'* mRNA, and encodes a functional protein different from that coded by RAB6A' (18). *RAB6C* is most highly expressed in brain, prostate, testis, breast and cervical tissues, and appears to participate not only in breast cancer (18,19). In cervical cancer, *RAB6C* promoter methylation analysis has been shown to have high sensitivity and specificity in distinguishing between malignant, premalignant and normal tissue, while in squamous cell carcinoma of the tongue, patients with low *RAB6C* expression levels had poorer survival times than those with high *RAB6C* expression (20,21). This is also in line with our study on the prognostic value of RAB6C in breast cancer (26). Furthermore, the long non-protein coding RAB6C antisense RNA 1 (RAB6C-AS1) is frequently overexpressed in gastric and breast cancer, and often deleted in prostate and pancreatic cancer and in brain tumors. Its gene is located in the same chromosomal region as RAB6C and both genes are often co-expressed (22). Results from previous experimental

studies on breast cancer cell lines indicated that RAB6C has properties as a tumor suppressor with the capability to inhibit proliferation, invasion and metastasis, and promote apoptosis (4,18). It has also been suggested that *RAB6C* may increase sensitivity to various drugs (23-25). The present study investigated the predictive value of RAB6C in relation to tamoxifen therapy with data from a randomized clinical study. For untreated control patients with ER$^+$/PR$^-$ tumors, those with tumors expressing low RAB6C levels had a higher recurrence rate than untreated patients with tumors expressing high RAB6C levels. A higher number of events in the control group with low RAB6C expression increased the probability of observing differences between treated and untreated patients. Therefore, the data showing a difference in benefit from tamoxifen therapy in patients with ER$^+$/PR$^-$ tumors depending on the RAB6C expression, should be interpreted with care. Additional data are needed before clinical practice may be influenced. For patients with ER$^+$/PR$^-$ tumors, more tailored therapy is required, and the results of the present study may contribute to the identification of clinically relevant subgroups.

Acknowledgements

Funding

Availability of data and materials

The datasets used and/or analyzed during the present study is available from the corresponding author on reasonable request.

Authors' contributions

HF, JC and OS conceived the study and participated in the study design and coordination. TF and BN provided the study materials, collected clinical follow-up data and hormone receptor data from patients and performed clinical interpretations. TB and JS performed the laboratory experiments and scored RAB6C. HF performed the statistical analysis and drafted the manuscript. HF, JC, OS, TB, JS, BN and TF

interpreted the results, provided critical revision. All authors read and approved the final manuscript.

Ethics approval and patient consent to participate

The present study was performed in accordance with the Declaration of Helsinki. Ethical approval for the use of tumor material was approved by the local Ethical Committee at the Karolinska University Hospital (Stockholm, Sweden) (approval no. KI 97-451 with amendments 030201 and 171027). According to the approval, informed consent from the patients was not required.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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