Androgen receptor and FOXA1 in breast cancer: Prognostic insights from a treatment-naïve historical cohort

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Abstract

Background: We re-evaluated archival breast cancers treated with surgery alone to determine the intrinsic prognostic value of androgen receptor (AR) and FOXA1 expression, using contemporary immunohistochemistry applied to tissue microarrays. **Methods**: Primary breast cancers surgically treated at our institution between 1979 and 1982 were reviewed. TMAs were created from three invasive areas, and all pathological features were reassessed using current protocols. **Results**: Of 935 cases, 758 were evaluable. Subtypes were ER+/HER2− (71%), ER+/HER2+ (6%), ER−/HER2+ (10%), and ER−/HER2− (13%). AR positivity (≥10%) occurred in 69%, 57%, 45%, and 17% of these groups, respectively, and strong AR expression was associated with improved distant recurrence–free survival (p = 0.0239). FOXA1 was highly expressed except in ER−/HER2− tumors but showed no prognostic value overall or within ER-positive disease. **Conclusion**: In this treatment-naïve cohort, strong AR expression predicted improved prognosis, while FOXA1 did not show independent prognostic value.

Introduction

- We are conducting an ongoing project using archival tissue samples from primary breast cancer cases treated with surgery alone at our institution, without any adjuvant systemic therapy. This treatment-naïve cohort provides a unique opportunity to assess the intrinsic prognostic significance of biomarker expression, free from the confounding effects of systemic therapy.
- AR is a steroid hormone receptor expressed in a subset of breast cancers and has attracted growing interest as a potential prognostic and therapeutic marker. [1]
- Forkhead-box protein A1 (FOXA1) is a pioneer transcription factor that enhances ER activity and plays a key role in mammary gland biology. It is a well-established favorable prognostic marker in ER-positive, HER2-negative breast cancer. Although FOXA1 expression is also observed in other subtypes, including ER-negative tumors, its clinical significance outside ER-positive disease is unclear. Whether FOXA1 reflects intrinsic tumor biology or simply serves as a surrogate for endocrine responsiveness remains unresolved.[2-4]
- In this study, we report the results of immunohistochemical analyses for AR and FOXA1 in a treatment-naïve historical cohort, aiming to clarify their intrinsic prognostic relevance across breast cancer subtypes.

Materials and Methods

- We retrospectively analyzed primary breast cancer cases operated on at our institution between 1979 and 1982, from which Tissue microarrays (TMAs) were constructed by sampling three representative areas of the invasive tumor component.
- All pathological features, including immunohistochemical markers, were re-evaluated using current standardized protocols.
- Cut off value FOXA1 positive: 10%[5], FOXA1-high: ≥75% (ROC curve)
  AR positive: 10%[6], AR-high: Allred score 7-8[7]

Results

- Among 935 eligible cases, **758** were available for FOXA1 immunohistochemical evaluation in the invasive component.
- The median follow-up period was **16.1** years.

Table 1 Clinicopathological characteristics according to FOXA1 and AR expression status

		FOXA1-positive n=636	FOXA1-negative n=97	P-value	AR-positive n=450	AR-negative n=308	P-value
Age (median, range)		50 (24-88)	49 (25-88)	0.17	48 (27-88)	50 (24-88)	0.10
Stage	I	359 (56)	52 (54)	0.08	266 (59)	157 (51)	0.08
	II	222 (35)	42 (43)		150 (34)	124 (40)	
	III	55 (9)	3 (3)		33 (7)	27 (9)	
HG	I	144 (23)	3 (3)	**<0.001**	112 (25)	40 (13)	**<0.001**
	II	331 (52)	16 (17)		240 (53)	121 (39)	
	III	161 (25)	78 (80)		98 (22)	147 (48)	
ER	(-)	88 (14)	78 (80)	**<0.001**	50 (11)	121 (39)	**<0.001**
	(+)	548 (86)	19 (20)		400 (89)	187 (61)	
PR	(-)	170 (27)	87 (90)	**<0.001**	99 (22)	168 (56)	**<0.001**
	(+)	466 (73)	10 (10)		351 (78)	140 (46)	
HER2	(-)	524 (83)	92 (95)	**0.0014**	388 (87)	246 (80)	**0.02**
	(+)	109 (17)	5 (5)		60 (13)	61 (20)	
Subtype	ER+HER2-	502 (79)	19 (20)	**<0.001**	372 (83)	166 (54)	**<0.001**
	ER+HER2+	44 (7)	0 (0)		27 (6)	20 (7)	
	ER-HER2+	65 (10)	5 (5)		33 (7)	41 (13)	
	ER-HER2-	22 (4)	73 (75)		16 (4)	80 (26)	

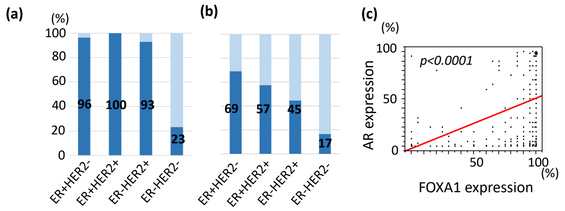


Figure 1. Expression patterns of FOXA1 and AR according to intrinsic subtype and their correlation. (a) FOXA1 expression, (b) AR expression, and (c) their positive correlation (*p < 0.0001*).

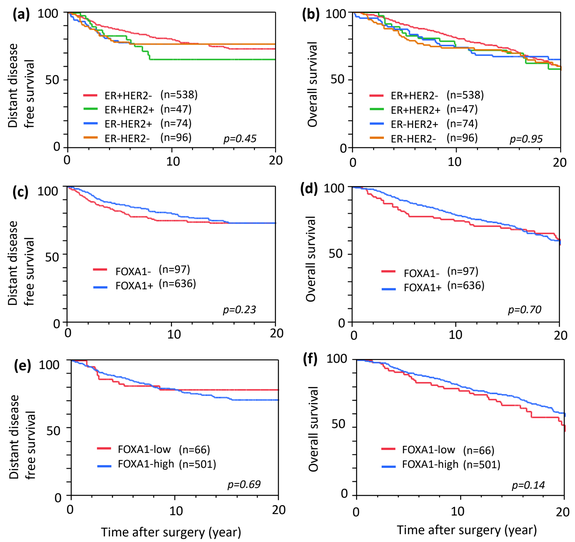


Figure 2. Kaplan-Meier survival curves of DDFS and OS. (a, b) Prognosis according to breast cancer subtypes in the entire cohort of 756 patients. (c, d) Prognosis according to FOXA1 positivity and negativity (cutoff 10%). (e, f) Prognosis according to high and low FOXA1 expression (cutoff 70%) in ER+HER2– breast cancer.

Summary of Results

- HER2 expression was significantly higher in FOXA1-positive tumors, whereas it was lower in AR-positive tumors.
- FOXA1 expression was observed not only in ER-positive tumors but also in a subset of ER-negative cases.
- AR and FOXA1 expression showed a positive correlation.
- In prognostic analyses, FOXA1 did not show a significant difference in DDFS or OS even when restricted to the ER+HER2– subgroup, whereas analyses based on AR expression demonstrated that AR-high patients had significantly better outcomes.

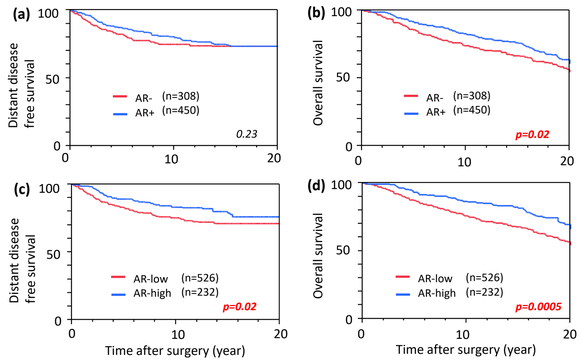


Figure 3. Kaplan-Meier survival curves of DDFS and OS. (a, b) Prognosis according to AR positivity and negativity (cutoff 10%). (c, d) Prognosis according to high and low AR expression (cutoff Allred score 7-8)

Discussion

FOXA1 and HER2 association

- Present study: potential link between FOXA1 and HER2 expression
- Reports in clinical breast cancer specimens remain limited
- In vitro studies have shown the FOXA1–HER2 interaction in previous reports[8,9]
  - ✓ FOXA1 = critical factor for maintaining HER2 expression
  - ✓ Co-expression of FOXA1 and HER2 observed in same cells
  - ✓ Loss of FOXA1 → reduced cell viability
  - ✓ FOXA1-driven transcriptional programs influence response and resistance to HER2-targeted therapy

Prognostic impact of FOXA1

- Previous studies: FOXA1 = strong prognostic factor in ER+HER2– breast cancer[2]
- Present study (treatment-naïve cohort): no significant prognostic effect
- In prior cohorts with adjuvant endocrine therapy, favorable outcomes in FOXA1-high cases may reflect treatment effect, suggesting FOXA1 itself is not an independent prognostic factor. These findings indicate FOXA1 may reflect endocrine responsiveness rather than intrinsic tumor behavior, and its role in late recurrence—especially in ER-negative disease—deserves further study.

Conclusions

In this treatment-naïve cohort, strong AR expression predicted improved prognosis, while FOXA1 did not show independent prognostic value.

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References

1. *Transl Breast Cancer Res.* 2023 PMID 37946721
2. *Dev Biol.* 2022 PMID 12297093
3. *Cancers(Basel)* 2021 PMID 34680352
4. *J Clin Invest.* 2021 PMID 34101624
5. *Hum Pathol.* 2016 PMID 26527523
6. *Mod Pathol.* 2011 PMID 21552212
7. BMC Cancer. 2019 PMID 31888566
8. *NPJ Breast Cancer.* 2021 PMID 33980863
9. *Cells.* 2022 PMID 35203384

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