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Influence of Patient Age on the Biological Profile and Prognosis of Operable Early-Stage Breast Cancer

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ABSTRACT

Breast cancer (BC) exhibits age-related alterations in its biological characteristics. This study aimed to investigate the natural progression of these changes. A total of 2,383 women with clinically T0-2N0-1M0 BC, treated with primary surgery and appropriate adjuvant therapy at a specialized BC center, were included. Tissue microarrays were prepared from surgical specimens, and indirect immunohistochemistry was performed to assess a comprehensive panel of 16 relevant biomarkers. Significant decade-wise changes were observed in the expression patterns of biomarkers associated with luminal phenotypes (estrogen receptor [ER], progesterone receptor [PgR], human epidermal growth factor receptor 2 [HER2], E-cadherin, MUC1, Bcl2, CK7/8, CK18) and basal phenotypes (CK5/6, CK14, p53, Ki67), as well as in lymph node involvement, histological grade, and tumor size ($p < 0.05$). Ages 40 and 70 years emerged as key milestones marking shifts in these biological patterns. Older women with ER-positive tumors demonstrated significantly higher metastasis-free and breast cancer-specific survival rates, whereas no age-related differences were observed in ER-negative tumors. Overall, BC biology evolves with advancing age, with <40 years representing a phase of aggressive phenotypes, >70 years corresponding to less aggressive characteristics, and the 40–70-year range constituting a transitional phase.

Keywords: Biology, Breast cancer, Aging, Clinical outcome

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Introduction

Breast cancer (BC) remains the most frequent malignancy among women and a leading cause of cancer-related deaths globally [1]. Its incidence increases with age, and accumulating evidence suggests that the biological profile of tumors also shifts over time. Older patients are more likely to develop lobular carcinoma, whereas younger women tend to present with aggressive histological subtypes, such as medullary carcinoma [2–4]. Similarly, tumor grade exhibits age-related variation: higher-grade tumors (grade III) are more common in younger women, while lower-grade tumors (grades I–II) predominate in older patients [3, 5, 6]. At the molecular level, ER expression generally rises with age, whereas HER2 and Ki67 levels tend to decrease, consistent with a trend toward less aggressive tumor phenotypes in the elderly [2, 7].

Although it remains uncertain whether aging itself directly drives these differences, a cascade of biological alterations is likely to occur over time, influencing tumor behavior and clinical outcomes [8]. Nevertheless, there is limited longitudinal or systematic data characterizing how BC biology evolves across age groups. One potential approach is to examine patterns of biomarker expression across a wide age spectrum. To date, few studies have undertaken this, often with small panels of conventional markers (ER, PgR, HER2, Ki67, Bcl2) and heterogeneous, multicenter retrospective data, limiting their interpretability [9, 10].

In response to these limitations, this study adopted a structured approach with three aims:

1. To investigate age-related trends in BC biological features, including a comparison of ER-positive and ER-negative tumors given their distinct clinical behaviors.

2. To evaluate whether shifts in biological characteristics correlate with differences in clinical outcomes among age groups.
3. To examine whether treatment approaches vary in relation to observed outcome differences.

Results and Discussion

The cohort consisted of 2,383 women, including 1,808 patients from the Nottingham Tenovus series (age 18–70 years) and 575 patients from the Elderly Primary Breast Cancer series (age 70–91 years). Patients were stratified by decade: ≤30 years (n = 19), 31–40 (n = 144), 41–50 (n = 496), 51–60 (n = 599), 61–70 (n = 551), 71–80 (n = 484), and ≥81 (n = 90).

Biological features

Age-dependent patterns of biomarkers

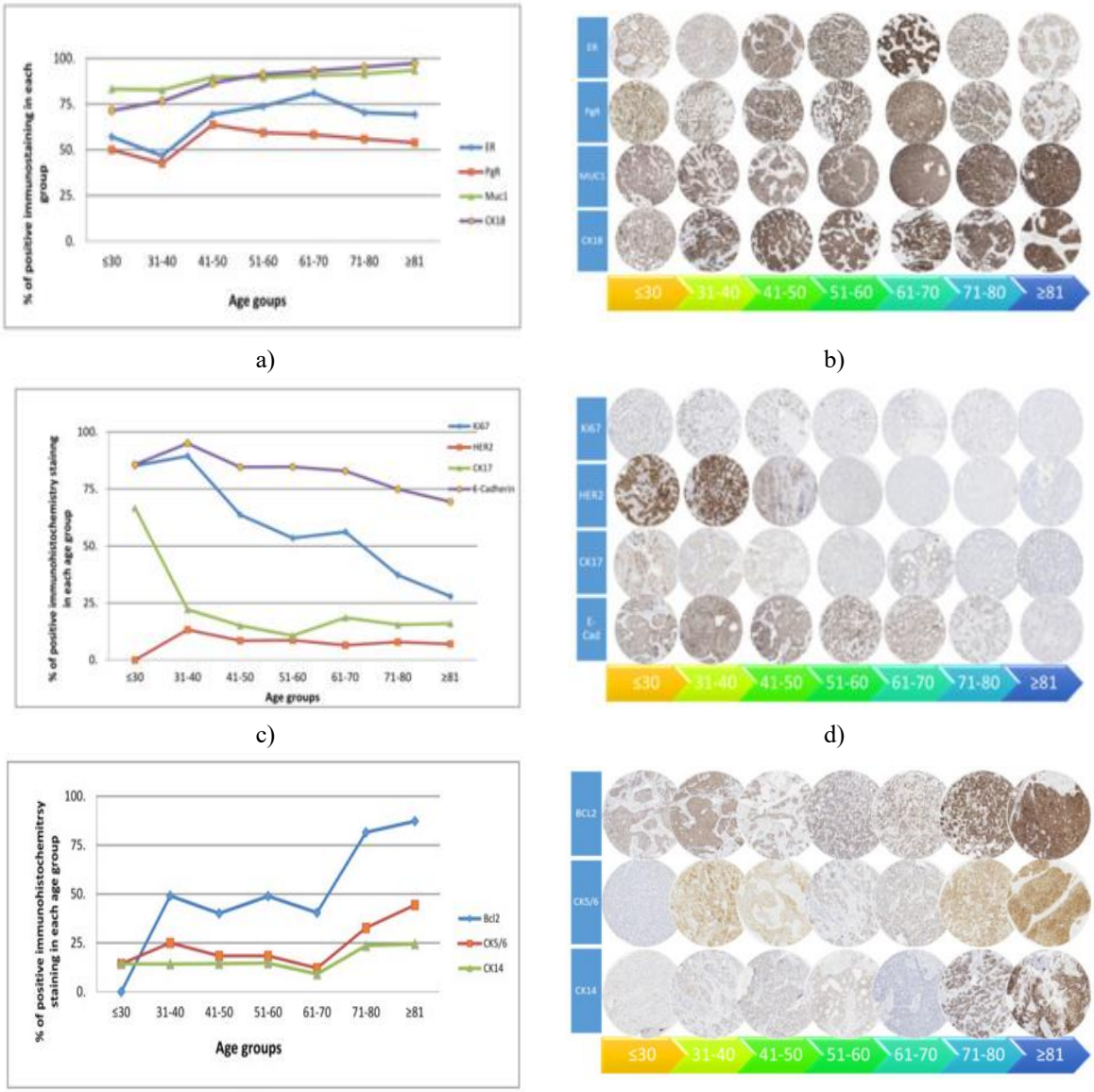
Analysis revealed distinct age-related shifts in biomarker expression, with significant changes observed in ER ($p < 0.001$), PgR ($p = 0.003$), HER4 ($p < 0.001$), E-cadherin ($p < 0.001$), Ki67 ($p < 0.001$), p53 ($p = 0.003$), CK5/6 ($p < 0.001$), CK7/8 ($p = 0.006$), CK14 ($p < 0.001$), CK17 ($p < 0.03$), CK18 ($p < 0.001$), and Bcl2 ($p < 0.001$). These transitions were particularly marked at ages 40 and 70, identifying them as key biological milestones **(Table 1)**. Additional tumor characteristics, including lymph node involvement ($p = 0.01$), tumor size ($p < 0.001$), and histological grade ($p < 0.001$), also displayed clear age-related patterns **(Table 1)**.

Table 1. Age standardised pattern of biological markers in early operable primary breast cancer.

Biomarker (n)	**≤30 n (%)**	**31–40 n (%)**	**41–50 n (%)**	**51–60 n (%)**	**61–70 n (%)**	**71–80 n (%)**	**≥81 n (%)**	p-Value
Lymph node stage								
1	7(50)	62 (50.8)	281 (62.0)	378 (64.1)	395 (68.6)	192 (57.1)	38 (57.6)	0.01
2	4 (28.6)	44 (36.1)	133 (29.4)	168 (28.5)	133 (23.1)	106 (31.5)	21 (31.8)	
3	3 (21.4)	16 (13.1)	39 (8.6)	44 (7.5)	48 (8.3)	38 (11.3)	7 (10.6)	
Histological Grade								
1	0	5 (4.1)	83 (18.3)	131 (22.2)	110 (19.0)	51 (12.1)	13 (12.9)	<0.001
2	2 (14.3)	25 (20.5)	140 (30.9)	200 (34.0)	209 (36.1)	166 (39.2)	46 (45.5)	
3	12 (85.7)	92 (75.4)	230 (50.8)	258 (43.8)	260 (44.9)	206 (48.7)	42 (41.6)	
Pathological size								
0.1–3.0 cm	9 (64.3)	100 (82.0)	402 (88.9)	533 (90.5)	537 (92.7)	377 (80.2)	87 (77.0)	<0.001
3.1–5.0 cm	3 (21.4)	16 (13.1)	41 (9.1)	45 (7.6)	40 (6.9)	84 (17.9)	19 (16.8)	
>5.0 cm	2 (14.3)	6 (4.9)	9 (2.0)	11 (1.9)	2 (0.3)	9 (1.9)	7 (6.2)	
ER positive (n = 2333)	8 (57.1)	57 (46.7)	314 (69.3)	436 (73.8)	470 (81.0)	322 (70.3)	79 (69.3)	<0.001
PgR (n = 2278)	7 (50.0)	51 (42.5)	281 (63.7)	339 (59.4)	327 (58.3)	255 (55.9)	62 (53.9)	0.003
HER2 (n = 2297)	0	16 (13.3)	37 (8.5)	50 (8.7)	37 (6.5)	37 (7.9)	8 (7.0)	0.232
Ki67 (n = 2020)	12 (85.7)	84 (89.4)	239 (63.7)	255 (53.5)	251 (56.2)	183 (37.3)	34 (27.9)	<0.001
P53 (n = 2267)	3 (21.4)	53 (44.2)	133 (30.2)	152 (26.6)	127 (22.6)	156 (34.8)	43 (39.1)	<0.001
Bcl2 (n = 1221)	0	28 (49.1)	73 (40.1)	110 (48.9)	90 (40.5)	345 (81.6)	96 (87.3)	<0.001
Muc1 (n = 1962)	10 (83.3)	86 (82.7)	330 (89.7)	413 (89.6)	419 (90.7)	409 (91.5)	101 (93.5)	0.133
BRCA1 (n = 1979)	11 (84.6)	83 (80.6)	313 (82.8)	393 (83.4)	403 (86.1)	152 (34.5)	36 (34.3)	<0.001

CK5/6 (n = 2274)	2 (14.3)	30 (25.0)	82 (18.4)	105 (18.4)	69 (12.1)	146 (32.7)	48 (44.4)	<0.001
CK7/8 (n = 2296)	13 (92.6)	119 (99.2)	441 (98.9)	573 (99.0)	571 (99.7)	440 (97.1)	108 (97.3)	0.006
CK14 (n = 2193)	2 (14.3)	17 (14.2)	64 (14.4)	84 (14.7)	51 (9.1)	91 (23.6)	25 (24.5)	<0.001
CK17 (n = 1160)	2 (66.7)	8 (22.2)	24 (15.1)	32 (10.7)	80 (18.6)	17 (15.5)	186 (16.0)	0.035
CK18 (n = 2176)	10 (71.4)	91 (76.5)	361 (86.4)	490 (91.4)	501 (93.1)	417 (95.2)	110 (97.3)	<0.001
CK19 (n = 2292)	12 (85.7)	111 (92.5)	425 (95.3)	547 (94.3)	538 (94.6)	424 (94.0)	109 (97.3)	0.481
E-Cadherin (n = 2289)	12 (85.7)	115 (95.0)	374 (84.6)	488 (84.7)	469 (82.9)	344 (74.9)	77 (69.4)	<0.001

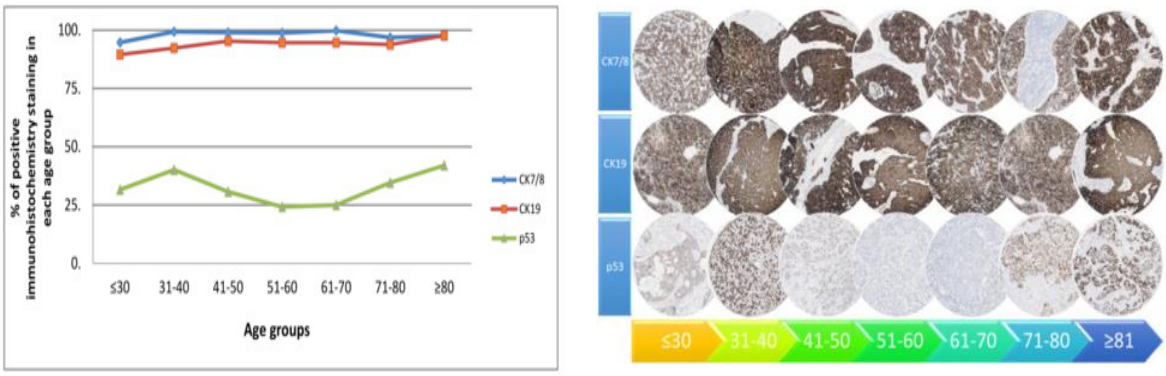
The overall age stratified expression of biomarkers showed four patterns **(Figure 1)**:



a) b)

c) d)

e) f)



g) h)

Figure 1. Age-Related Patterns of Biomarker Expression in Early Operable Primary Breast Cancer Treated by Surgery

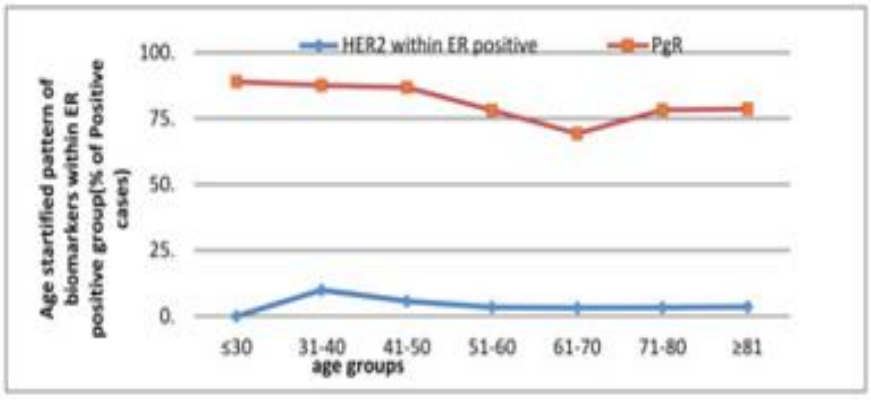
(a, b) Biomarkers showing a gradual increase starting at 40 years (magnification ×20 in B).
(c, d) Biomarkers exhibiting a gradual decrease from 40 years (magnification ×20 in D).
(e, f) Biomarkers demonstrating a rise at 70 years (magnification ×20 in F).
(g, h) Biomarkers with two peaks, rising at 40 years, declining, and increasing again at 70 years (magnification ×20 in H).

Key patterns observed:

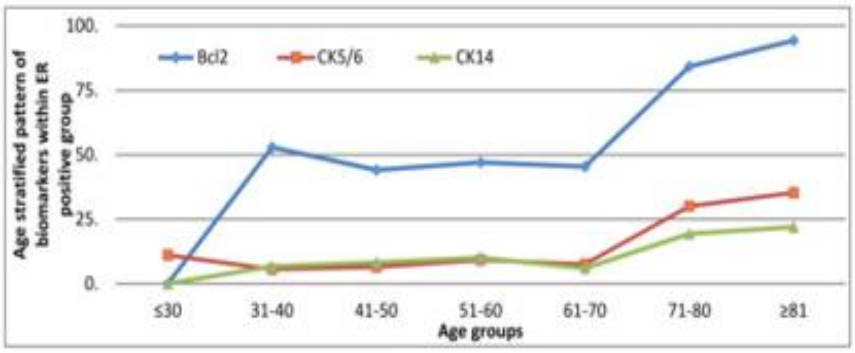
1. **Gradual rise from 40 years:** ER, PgR, MUC1, CK18
2. **Gradual decline from 40 years:** Ki67, HER2, CK17, E-cadherin
3. **Increase at 70 years:** Bcl2, CK5/6, CK14
4. **Two-peak pattern:** CK7/8, CK19, p53 (first peak at 40 years, second at 70 years)

Based on these biomarker trajectories, patients were categorized into three age groups for further analysis: <40 years, 41–69 years, and ≥70 years. Representative immunohistochemical staining patterns are illustrated in **Figure 1**.

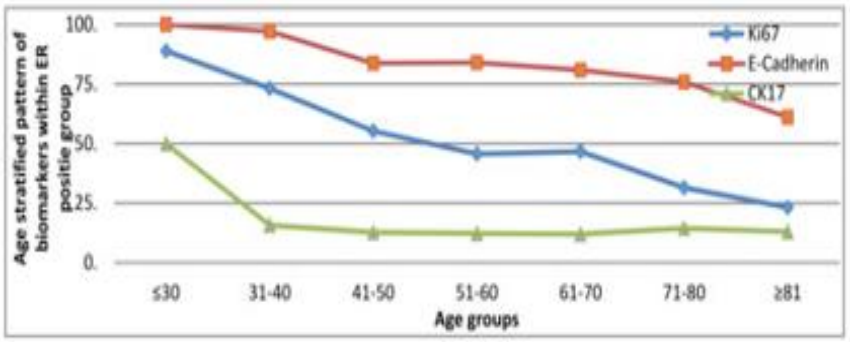
Biomarker patterns by ER status
ER-positive tumors
Within the ER-positive subgroup, distinct age-related trends in biomarker expression were observed **(Figure 2)**:



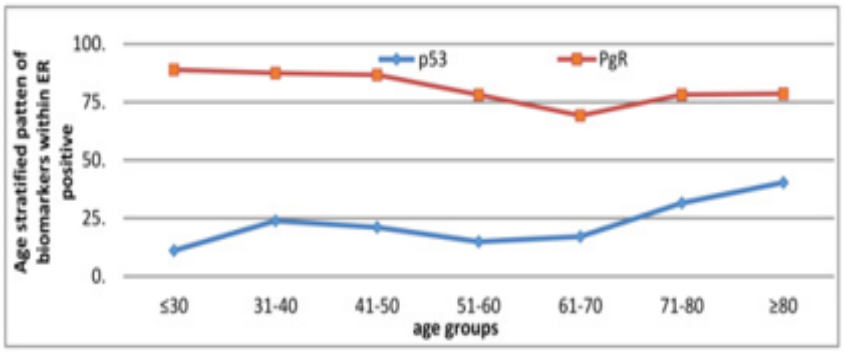
a)



b)



c)



d)

Figure 2. Age-Related Patterns of Biomarker Expression in ER-Positive Early Operable Breast Cancer Treated by Surgery

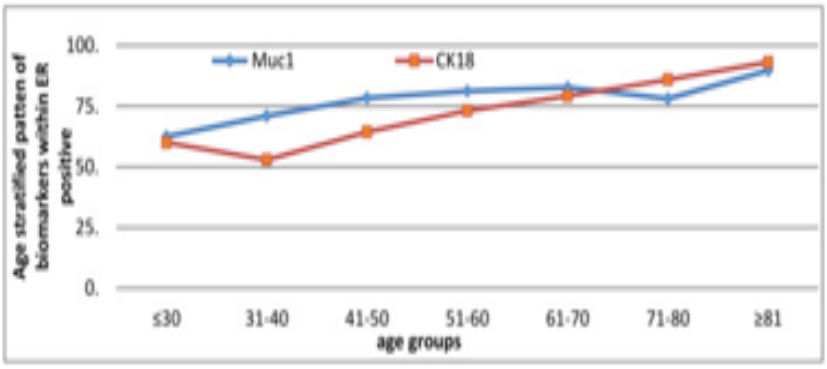
(a) Biomarkers showing a decline around 40 years.
(b) Biomarkers exhibiting a rise at 70 years.
(c) Biomarkers with a consistent decline across ages.
(d) Biomarkers displaying two peaks at 40 and 70 years.

Observed patterns:

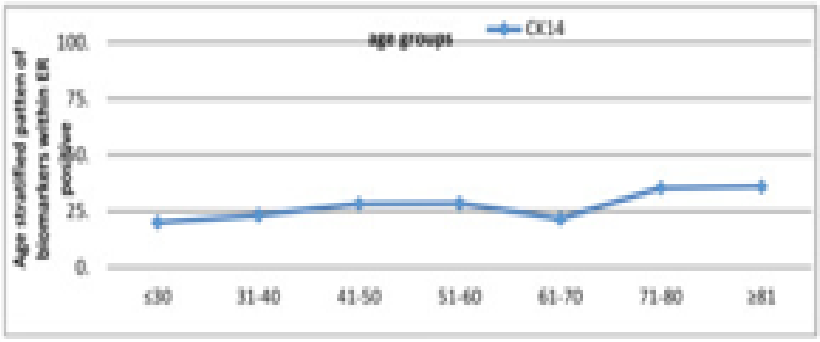
1. **Rise at 40 years:** HER2
2. **Rise at 70 years:** Bcl2, CK5/6, CK14
3. **Decline with advancing age:** Ki67, E-cadherin
4. **Two peaks (40 and 70 years):** p53, PgR
5. **Stable expression across ages:** MUC1, CK18, CK7/8, CK19 (>80% positivity)

ER-negative tumors

In the ER-negative subgroup, distinct age-related biomarker patterns were observed **(Figure 3)**:



a)



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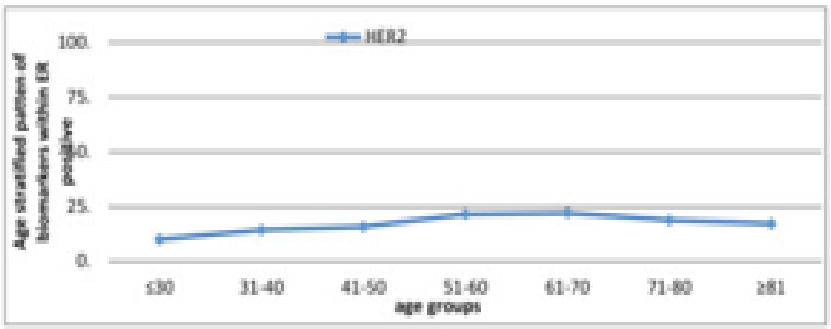
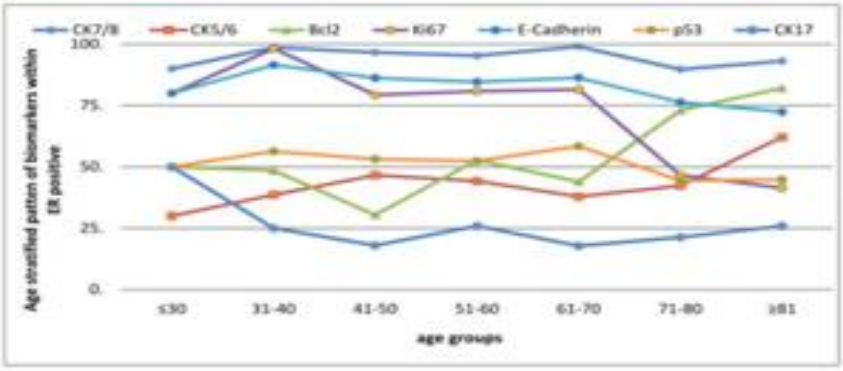


c)



d)

Figure 3. Age-Related Patterns of Biomarker Expression in ER-Negative Early Operable Breast Cancer Treated by Surgery

(a) Biomarkers showing a gradual rise with age

(b) Biomarkers with a rise at 70 years.

(c) Biomarkers exhibiting a decline at 70 years.

(d) Biomarkers with two peaks at 40 and 70 years.

Observed patterns

1. **Rise at 40 years:** MUC1, CK18
2. **Rise at 70 years:** CK14
3. **Rise at 30 years followed by decline at 70 years:** HER2
4. **Two peaks (40 and 70 years):** Bcl2, CK5/6, Ki67, CK7/8, E-cadherin, p53, CK17
5. **Stable expression:** PgR remained largely negative (93.9%)

Clinical outcomes

Breast cancer–specific and metastasis-free survival

Older patients demonstrated significantly higher 5-year breast cancer–specific survival (BCSS): ≤40 years = 75%, 41–69 years = 86%, ≥70 years = 90% (p = 0.04). Within the same age groups, patients with ER-positive tumors had higher BCSS than those with ER-negative tumors in the 41–70 and ≥70-year groups. When analyzing only ER-positive tumors, BCSS increased with age, with older women showing superior survival compared to younger patients.

Metastasis-free survival (MFS) was also significantly higher in older women with ER-positive tumors (p = 0.03). In contrast, for ER-negative tumors, both BCSS and MFS did not vary significantly across age groups **(Table 2)**.

Table 2. Clinical outcome of early operable primary breast cancer—comparison among age groups based on oestrogen receptor status.

Outcome Measure	≤40 Years	41–70 Years	≥70 years	p-Value
5-year Metastases free survival (%)				
ER positive	68	85	87	0.003
ER negative	68	70	71	0.81
5-year Breast cancer specific survival (%)				
ER positive	85	89	94	0.03
ER negative	70	73	75	0.88

Treatment patterns

Younger patients were more frequently treated with intensive regimens, including adjuvant chemotherapy and radiotherapy, whereas a substantial proportion of older women underwent surgery without adjuvant chemotherapy. In contrast, adjuvant endocrine therapy was prescribed more often in older women with ER-positive tumors compared to younger patients (<40 years = 32%, 41–70 years = 41%, ≥70 years = 64%). A detailed summary of treatment patterns is presented in **Table 3**.

Table 3. Pattern of treatment of early operable primary breast cancer—comparison among age groups based on oestrogen receptor status.

	Surgery Only	Surgery Followed by Chemotherapy + /− Radiotherapy	Surgery Followed by Endocrine Therapy + /− Radiotherapy	Surgery Followed by Radiotherapy
ER negative age groups n (%)				
≤40	5 (6.7)	61 (81.3)	0	9 (12.0)
41–70	59 (16.3)	124 (34.3)	108 (29.8)	71 (19.6)
>70	122 (72.2)	0	18 (10.7)	29 (17.2)
ER positive age groups n (%)				
≤40	14 (1)	29 (36.7)	17 (21.5)	19 (24.1)
41–70	326 (28.5)	94 (8.2)	463 (40.5)	260 (22.7)
>70	116 (29.1)	2 (0.5)	257 (64.4)	24 (6.0)

Our findings indicate that the biological characteristics of breast cancer evolve gradually with age. Based on age-stratified patterns, three distinct biological groups were identified: ≤40 years, 41–70 years, and >70 years, a pattern that persisted in both ER-positive and ER-negative subgroups.

Tissue aging is associated with increased cancer risk due to factors such as cumulative estrogen exposure, reduced DNA repair capacity (including p53 mutations), and age-related immune decline [10–13]. However, the mechanisms by which aging drives changes in tumor biology remain incompletely understood.

In this study, ER expression generally increased with age, consistent with previous reports [2, 9, 10, 14]. The slight decline observed at age 70 may reflect selection bias, as the cohort included only surgically treated patients, excluding many older women managed with primary endocrine therapy, who are likely ER-positive.

Other biomarkers showed distinct trajectories—consistent rises, falls, or biphasic patterns—with age. These findings align with prior literature on ER, PgR, HER2, luminal and basal cytokeratins, Ki67, and EGFR [2, 9, 10, 15]. Notably, this is the first study to describe age-stratified biomarker patterns by ER status, using a large panel of markers with long-term clinical outcomes.

The observed p53 patterns differed from previous reports [2, 9, 10, 15], which generally noted decreasing positivity with age. In our cohort, p53 expression decreased in ER-negative tumors but increased in ER-positive tumors, suggesting a possible link between long-term estrogen exposure and accumulation of somatic p53 mutations in older women. Further in vitro studies are warranted to clarify the role of p53 in age-related breast carcinogenesis.

Overall, the biomarker profiles delineate three age-related groups:

1. **≤40 years:** low ER, PgR, luminal cytokeratins, and Bcl2; high Ki67, HER2, and p53—reflecting aggressive tumor biology.
2. **41–70 years:** transitional phase with intermediate biomarker expression.
3. **>70 years:** opposite profile to the youngest group, consistent with less aggressive biology.

These patterns also correlate with menopausal status: <40 years generally premenopausal, >70 years postmenopausal, and 41–70 years including pre-, peri-, and early post-menopausal women. This supports the hypothesis that circulating estrogen levels influence tumor biology. Mechanistically, younger women may exhibit proto-oncogene-driven carcinogenesis, whereas older women may be more affected by dysfunction in tumor suppressor pathways, though these relationships remain incompletely understood.

Clinical outcomes reflected these biological differences. Older women demonstrated superior breast cancer–specific survival (BCSS) and metastasis-free survival (MFS), particularly in ER-positive tumors. Among ER-negative tumors, survival did not differ significantly by age, despite younger patients receiving more aggressive therapies. Adjuvant chemotherapy usage declined with age in ER-positive tumors, while endocrine therapy was increasingly employed in older women (>70 years, 64%). These findings are consistent with existing literature, suggesting that age-related differences in tumor biology, rather than treatment intensity, largely drive survival outcomes.

The strengths of this study include a large, single-center cohort encompassing all age groups, prospectively collected tumor samples, standardized tissue microarray construction, and centralized biomarker assessment. Limitations include the exclusion of older women managed non-surgically, potentially overrepresenting ER-negative tumors in the oldest group.

Materials and Methods

Patients

This study included women with early-stage operable breast cancer (clinically T0–2N0–1M0) who underwent primary surgery without prior therapy. Two well-characterized patient cohorts treated at a single center using standardized protocols were included: women ≤70 years from the Nottingham Primary Breast Cancer series (n = 1,808) [16] and women ≥70 years from the Nottingham Elderly Primary Breast Cancer series (n = 575) [17]. Patients were stratified by decade at diagnosis: ≤30, 31–40, 41–50, 51–60, 61–70, 71–80, and ≥80 years.

Ethical approval was granted by the Nottingham City Hospital Research Ethics Committee (C2020313). Tumor samples were collected prior to the Human Tissue Act; patient consent was deemed not necessary by the Ethics Committee. Tissue microarrays were constructed from high-quality surgical specimens for centralized biomarker analysis.

Tumor analysis

Tissue microarrays (TMAs) were constructed from formalin-fixed paraffin-embedded surgical specimens [18]. Hematoxylin and eosin staining was used to identify the most representative tumor areas. Single 0.6 mm cores from each representative region were transferred into TMA blocks using a manual Beecher tissue microarrayer (MP06, Beecher Instruments Inc., Sun Prairie, WI, USA). One core per tumor was included.

Indirect immunohistochemistry (IHC) was performed using the StreptAvidin Biotin Complex and EnVision methods [19]. Immunostaining was scored using McCarty's H-score (range 0–300), which incorporates both staining intensity and the percentage of positive cells [20]. Cut-offs for biomarker positivity were determined using X-tile bioinformatics software [21], with previously defined thresholds provided in [7].

A panel of 16 biomarkers was analyzed, including hormone receptors (ER, PgR), HER2, Ki67, luminal markers (CK7/8, CK18, CK19, MUC1, E-cadherin, Bcl2, HER4), and basal markers (BRCA1, CK5/6, CK14, CK17, p53). Given the distinct clinical behavior of ER-positive and ER-negative tumors, analyses were performed separately for these subgroups to compare biological patterns and clinical outcomes.

Clinical outcome

Clinical outcomes were assessed as breast cancer–specific survival (BCSS) and metastasis-free survival (MFS), defined from the date of diagnosis to death from breast cancer or to the detection of distant metastases, respectively.

Statistical analysis

Data were analyzed using SPSS version 18.0 (Chicago, IL, USA). The Kruskal–Wallis test was initially applied to detect overall group differences, followed by Mann–Whitney U tests to identify pairwise differences, with results confirmed by Chi-square tests. Survival analyses were conducted using Kaplan–Meier methods, with significance assessed by Log-rank and generalized Wilcoxon tests. A p-value <0.05 was considered statistically significant.

Conclusion

This study demonstrates that breast cancer biology changes progressively with age, with favorable prognostic markers increasing over time. Three biologically distinct age groups were identified, with key cut-off points at 40 and 70 years. Older patients, particularly those with ER-positive tumors, exhibited superior clinical outcomes, whereas no age-related survival differences were observed in ER-negative tumors. Treatment patterns reflected this biology, with younger patients receiving more aggressive adjuvant therapies compared to older women.

These findings suggest that advancing age is associated with less aggressive tumor biology and improved survival. Further studies are needed to elucidate the cellular mechanisms and age-related alterations in the tumor microenvironment that drive these changes, to optimize the management of women with different breast cancer phenotypes.

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Conflict of Interest: None

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Ethics Statement: None

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