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Distinct Biology and Inferior Outcomes of Breast Cancer in Young Adults and Adolescents

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Abstract

This study sought to characterize the distinctive features of breast cancer in young adults and adolescents (AYA; <40 years) relative to other age groups within estrogen receptor–positive/human epidermal growth factor receptor 2–negative disease, taking into account the influence of age-related hormonal status. Patients were stratified into four age-defined groups: adolescents and young adults (AYA; 15–39 years), perimenopausal (40–54 years), menopausal (55–64 years), and older adults (≥65 years). Clinicopathological characteristics and tumor biology were interrogated through gene set variation analysis and the xCell algorithm, leveraging transcriptomic data from large publicly available cohorts of estrogen receptor–positive/HER2-negative breast cancer, including SCAN-B (n = 2,381) and METABRIC (n = 1,353). Analysis restricted to estrogen receptor–positive/HER2-negative disease demonstrated that tumors arising in adolescents and young adults were characterized by more aggressive pathological features, including increased lymph node involvement and a higher prevalence of high-grade histology (Nottingham grade 3; $P < 0.001$). Outcome analyses suggested poorer prognosis in this age group, with disease-specific and overall survival appearing less favorable, particularly when contrasted with patients in the perimenopausal age range. Across both METABRIC and SCAN-B cohorts, transcriptional activity related to late estrogen responsiveness showed a consistent inverse relationship with age ($P \leq 0.001$). At the molecular level, tumors from younger patients displayed elevated signatures of homologous recombination deficiency, reflected by increased BRCAness and DNA repair activity relative to older counterparts ($P < 0.05$). Pathway-level interrogation further revealed that AYA tumors preferentially activated gene programs associated with cell cycle progression and oncogenic signaling, including mTORC1, unfolded protein response, and PI3K–AKT–mTOR cascades ($P < 0.03$). Interestingly, these biological patterns were also evident in small tumors (<2 cm), suggesting that tumor size alone does not account for the observed molecular aggressiveness. Immune microenvironment profiling indicated that breast cancers in adolescents and young adults harbored a distinct immune landscape, with increased infiltration of cytotoxic T lymphocytes, regulatory T cells, Th2 cells, and classically activated (M1) macrophages, alongside a relative depletion of alternatively activated (M2) macrophages ($P < 0.03$). In addition, somatic mutation analysis revealed age-associated differences in genomic alterations, with higher mutation frequencies in AHNAK2, GATA3, HERC2, and TG, and reduced prevalence of KMT2C mutations in AYA tumors compared with those from older patients. Among estrogen receptor–positive/HER2-negative tumors, those occurring in adolescents and young adults displayed heightened proliferative activity and a more immune-enriched microenvironment than tumors from older patients.

Keywords: Adolescent and young adult generation, AYA, Breast cancer, BRCAness, Gene expression, Generation gap

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Introduction

The term adolescents and young adults (AYA) refers to individuals typically defined as being younger than 40 years of age. Each year in the United States, approximately 89,000 cancer diagnoses occur within this population, most commonly involving the thyroid, skin,

colorectal tissue, and breast, collectively representing about 5% of all newly diagnosed cancers nationwide. Although the incidence of breast cancer (BC) rises progressively with advancing age, AYA patients still account for roughly 5% of all BC cases, corresponding to nearly 12,000 new diagnoses annually in the United States [1, 2]. Notably, among cancers affecting the AYA population, BC exhibits both the highest incidence and the greatest mortality burden [3].

Breast cancers diagnosed in AYA patients are widely recognized as clinically aggressive. Compared with tumors arising in older individuals, AYA-associated BC more frequently presents with unfavorable characteristics, including a higher prevalence of aggressive molecular subtypes—such as triple-negative disease and human epidermal growth factor receptor 2 (HER2) overexpression—larger primary tumor size, and increased rates of lymph node involvement and distant metastasis [4–6]. These cancers are also more strongly linked to familial predisposition and inherited genetic alterations, and affected patients often experience poorer survival outcomes relative to older age groups [1, 7]. However, much of the existing literature evaluates outcomes across broad age categories [8], limiting the ability to discern biologically and clinically meaningful differences among specific age-defined subgroups and potentially introducing confounding effects. A deeper understanding of breast cancer biology in the AYA population is therefore critically important, particularly given the substantial societal roles younger individuals often hold, including employment responsibilities, childrearing, and caregiving for elderly family members. Over the past decade, significant advances have been made in the development and approval of novel therapeutic agents for breast cancer. A detailed understanding of tumor biology is fundamental both for identifying new therapeutic targets and for refining treatment indications. Despite evidence that AYA patients frequently experience worse prognoses than their older counterparts, the biological underpinnings of breast cancer in this population remain insufficiently characterized, in part due to the relative rarity of these cases. Consequently, treatment decisions for AYA patients generally adhere to guidelines established for older populations. Improving outcomes for AYA patients therefore requires a more precise understanding of the biological features that distinguish their disease.

The present study was designed to define the biological characteristics of breast cancer in AYA patients, with particular emphasis on the estrogen receptor (ER)-positive/HER2-negative subtype, where tumor behavior is strongly influenced by age-related hormonal factors and prior data are limited. By leveraging transcriptomic analyses to compare tumors across distinct age groups, this work seeks to clarify age-dependent biological differences. Elucidating the unique molecular features of breast cancer in adolescents and young adults may ultimately inform the development of targeted therapeutic strategies tailored specifically to this underserved population.

Materials and Methods

Study cohorts

This research aims to delineate the unique aspects of breast cancer (BC) in adolescents and young adults (AYA), focusing primarily on the ER-positive/HER2-negative subtype, by contrasting it with cases in older age categories. For this purpose, two extensive, independent datasets were employed, offering detailed clinicopathological and gene expression profiles from BC patients. The analysis incorporated publicly available information on ER-positive/HER2-negative BC from the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) [9] (n = 1353 of 1903 total BC cases), gathered from tumor repositories in the UK and Canada, as well as the Swedish Breast Cancer Analysis Network (SCAN-B: GSE96058) [10, 11] (n = 2381 of 3273 total BC cases), assembled in Sweden. Relevant clinicopathological and transcriptomic details were retrieved through cBioportal [12] and the Gene Expression Omnibus (RRID:SCR_005012). Recognizing the influence of menopausal status linked to age as a critical patient-related factor in BC, the cohorts were categorized into four age brackets: AYA (15–39 years), perimenopausal (40–54 years), postmenopausal (55–64 years), and older adults (65+ years). Overall survival (OS) was calculated as the duration from diagnosis or the beginning of therapy until death due to any reason, whereas disease-specific survival (DSS) was calculated as the duration from diagnosis or therapy start until death caused by BC.

Biological analysis

To evaluate the activity of individual hallmark cancer signaling pathways, gene set variation analysis (GSVA) was performed utilizing gene sets from the Molecular Signatures Database (MSigDB) [13]. For each breast

cancer case, a GSVA score was computed based on transcriptomic profiles [14], following previously described methodologies [15, 16]. The **BRCAness score**, developed by our group [17], was used to estimate the predictive status of homologous recombination deficiency. Additionally, the relative infiltration of various immune cell types within the tumor microenvironment was determined using the xCell algorithm [18]. All these biological analyses were conducted using transcriptomic data from ER-positive/HER2-negative tumors in both cohorts.

Statistical methods

For all analyses, group differences were assessed using Fisher's exact test**,** the Mann–Whitney U test**,** or the Kruskal–Wallis test**,** depending on the data type. Survival outcomes were estimated using the Kaplan–Meier approach, with statistical comparisons performed via the log-rank test. Data organization and preliminary calculations were conducted in Microsoft Excel (version 16; Microsoft Corp, Redmond, WA; RRID:SCR_016137)**,** whereas all statistical analyses and graphical outputs were produced in **R** (version 4.1.0; R Foundation, Vienna, Austria)**.** Statistical significance was set at a threshold of $P < 0.05$.

Consent to participate and ethics approval

This study analyzed de-identified human data previously collected in other investigations; therefore, informed consent was waived.

Results and Discussion

Clinicopathological features by age in the METABRIC cohort

Using the full METABRIC dataset, we compared clinicopathological characteristics of breast cancer across age groups, with a focus on adolescents and young adults (AYA). Tumors in the AYA population were generally larger and exhibited more advanced disease than those in older patients. The AYA group also tended to show higher rates of lymph node involvement and a greater frequency of high-grade (Nottingham grade 3) tumors. Additionally, triple-negative breast cancer and HER2-positive subtypes were more prevalent among AYA patients.

When analyses were restricted to ER-positive/HER2-negative tumors, both tumor size and pathological T stage appeared elevated in the AYA and older adult groups. Lymph node metastases, including the number of affected nodes, were more common in AYA patients, resulting in overall more advanced pathological stages. High-grade tumors (Nottingham grade 3) were particularly enriched in the AYA group but not in the older cohort. Progesterone receptor positivity was observed more frequently in AYA and perimenopausal patients. Although there was a trend toward higher BRCA mutation prevalence in AYA tumors, the differences did not reach statistical significance.

Survival trends in ER-Positive/HER2-negative breast cancer

Next, we evaluated survival outcomes across age groups within the METABRIC cohort. AYA patients exhibited a tendency toward poorer disease-specific survival (DSS) and overall survival (OS) compared with perimenopausal and menopausal individuals, both in the full cohort and in the ER-positive/HER2-negative subgroup **(Figure 1)**. Cox proportional hazards models were used to estimate hazard ratios for OS and DSS for each age group relative to AYA patients.

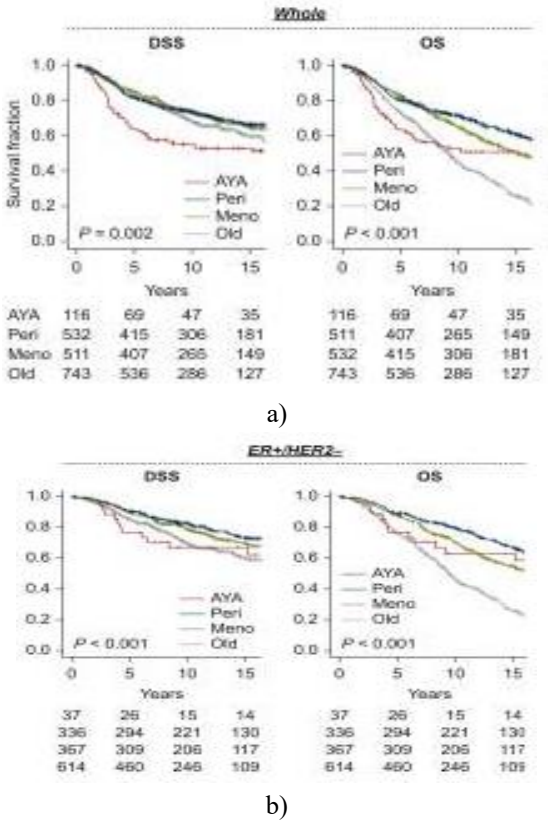


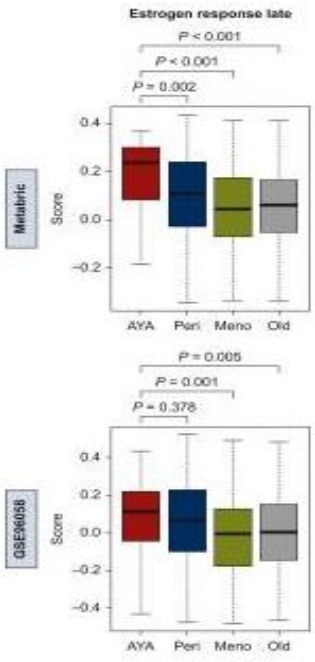
Figure 1. Survival outcomes across age groups in overall and ER-positive/HER2-negative breast cancer. Kaplan–Meier curves show disease-specific

survival (DSS) and overall survival (OS) stratified by age: adolescents and young adults (AYA; 15–39 years, red), perimenopausal (40–54 years, blue), menopausal (55–64 years, olive), and older adults (≥65 years, gray). Case numbers in the METABRIC cohort were as follows: whole cohort, AYA/peri/meno/old = 116/532/512/743; ER-positive/HER2-negative subgroup, AYA/peri/meno/old = 37/336/367/613.

In the ER-positive/HER2-negative subgroup, tumors from AYA patients exhibited significantly elevated DNA repair signaling and BRCAness, alongside increased activity of pathways associated with cell proliferation and oncogenic signaling. Notably, these included mTORC1, unfolded protein response, and PI3K/AKT/mTOR pathways, compared with older age groups.

We further examined estrogen response signaling across age groups within ER-positive/HER2-negative tumors **(Figure 2a)**. As anticipated, late estrogen response activity, quantified using the MSigDB 'Hallmark estrogen response late' gene set, was highest in younger patients, consistent with greater ovarian estrogen production.

ER+/HER2



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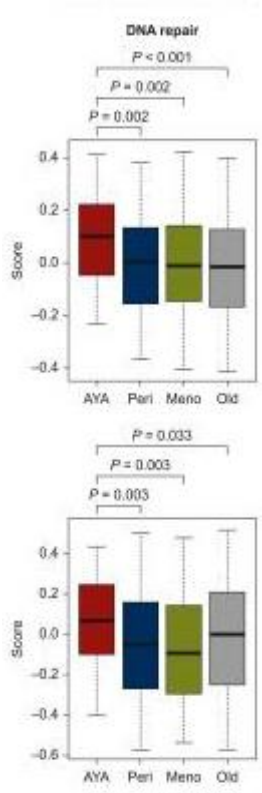

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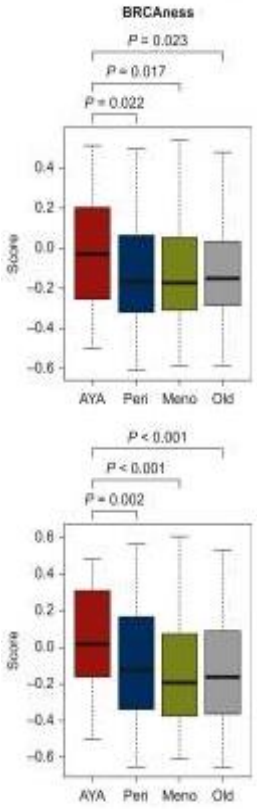

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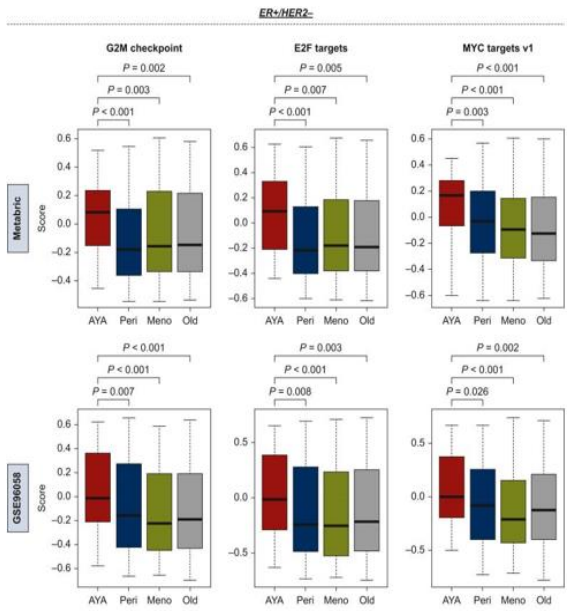

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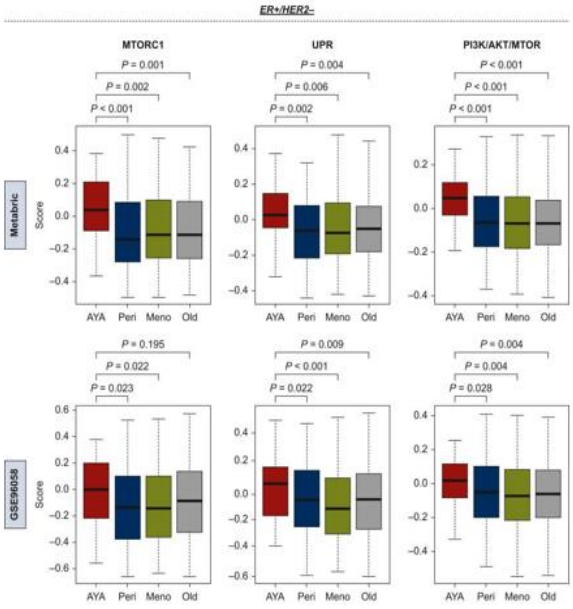


e)

Figure 2. Comparison of molecular signaling across age groups in ER-positive/HER2-negative breast cancer. The activity of late estrogen response (a), DNA repair pathways (b), BRCAness (c), cell proliferation–related gene sets (G2M checkpoint, E2F targets, MYC targets v1; d), and additional oncogenic pathways, including mTORC1, unfolded protein response (UPR), and PI3K/AKT/mTOR signaling (e), was evaluated across four age categories: adolescents and young adults (AYA, red), perimenopausal (peri, blue), menopausal (meno, olive), and older adults (gray) in both METABRIC (AYA/peri/meno/old = 37/336/367/613) and SCAN-B (GSE96058, AYA/peri/meno/old = 52/604/585/1140) cohorts. Statistical comparisons between AYA and other age groups were performed using the Mann–Whitney U test.

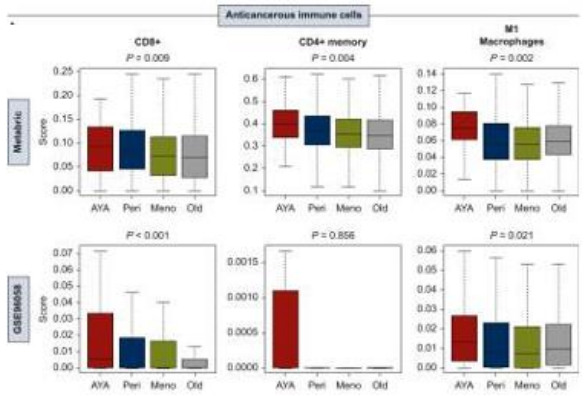
Considering the well-documented link between early-onset breast cancer and BRCA mutations, we quantified DNA repair and BRCAness across age groups using scoring systems established in prior studies [17–22]. In both METABRIC and SCAN-B datasets, tumors from AYA patients displayed significantly elevated DNA repair activity and higher BRCAness scores compared with older groups **(Figures 2b and 2c)**, highlighting the enhanced homologous recombination deficiency in ER-positive/HER2-negative tumors in this younger population.

We then assessed the activation of key cancer-related pathways using gene set variation analysis to explore age-specific tumor biology. The AYA group showed pronounced enrichment of cell proliferation–associated gene sets, including G2M checkpoint, E2F targets, and MYC targets v1 **(Figure 2d)**. Additionally, multiple pro-tumorigenic signaling pathways, such as mTORC1, unfolded protein response, and PI3K/AKT/mTOR, were markedly upregulated in AYA tumors compared with older patients. These patterns were consistently observed in both cohorts **(Figure 2e)**, indicating that ER-positive/HER2-negative breast cancers in adolescents and young adults are distinguished by heightened cell cycle activity and activation of multiple oncogenic signaling networks.

Age-dependent differences in immune infiltration in ER-positive/HER2-negative breast cancer

To assess age-related variation in the tumor immune microenvironment, we examined immune cell composition in ER-positive/HER2-negative breast cancers. In the METABRIC cohort, tumors from adolescents and young adults (AYA) showed higher levels of antitumor immune cells, including $CD8^+$ cytotoxic T cells, M1 macrophages, Th2 cells, and $CD4^+$ memory T cells**,** while immunosuppressive populations, such as regulatory T cells and M2 macrophages**,** were comparatively reduced **(Figures 3a and 3b)**. Analyses in the SCAN-B (GSE96058) cohort largely confirmed these findings, although $CD4^+$ memory T cell enrichment was not consistently observed. These results indicate that the

composition and intensity of immune infiltration in ER-positive/HER2-negative breast cancer are influenced by patient age, with younger patients exhibiting a more immunologically active tumor microenvironment.



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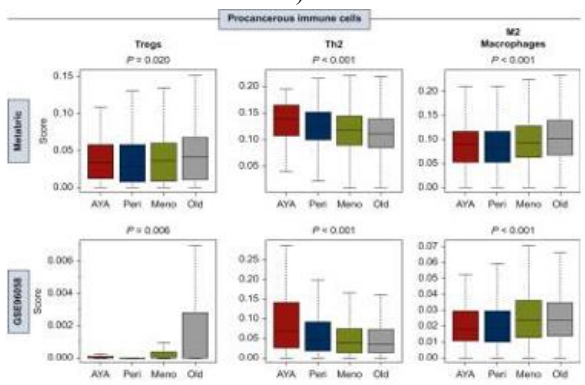
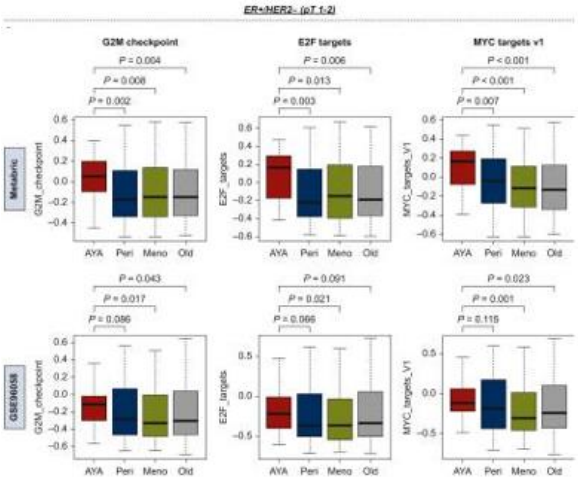


b)

Figure 3. Immune cell composition in ER-positive/HER2-negative breast cancer across age groups. Boxplots display the fraction of infiltrating immune cells for (a) antitumor populations, including $CD8^+$ T cells, $CD4^+$ memory T cells, and M1 macrophages**,** and (b) protumor populations, such as regulatory T cells, Th2 cells, and M2 macrophages**,** stratified by age: adolescents and young adults (AYA, red), perimenopausal (peri, blue), menopausal (meno, olive), and older adults (gray). Data are shown for both METABRIC (AYA/peri/meno/old = 37/336/367/613) and SCAN-B (GSE96058, AYA/peri/meno/old = 52/604/585/1140) cohorts. Group differences were assessed using the Kruskal–Wallis test**.**

Enhanced proliferation and oncogenic signaling in small tumors of AYA patients

indicated that tumor size was generally larger in AYA and older patients. This observation raised the question of whether increased tumor size in AYA reflects intrinsically high proliferative activity or whether larger tumors in older patients are attributable to delayed detection, possibly due to socioeconomic factors. To address this, we examined the enrichment of cell proliferation–related gene sets in ER-positive/HER2-negative tumors smaller than 5 cm. Even among these smaller tumors, AYA patients exhibited significantly higher proliferation signaling compared with other age groups, including older adults **(Figures 4a and 4b)**. These findings suggest that ER-positive/HER2-negative breast cancers in AYA patients are inherently more proliferative, whereas tumors in older patients may grow more slowly, with larger size at diagnosis likely reflecting delayed presentation rather than aggressive biology.



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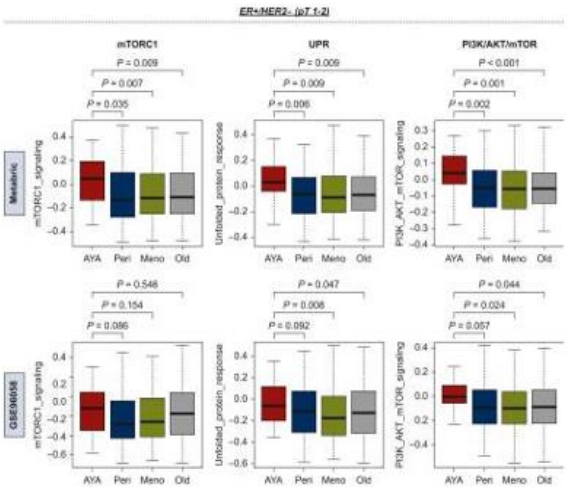

b)

Figure 4. Age-related differences in proliferation and oncogenic signaling in small ER-positive/HER2-

negative tumors. Boxplots show the activity of (a) cell proliferation–associated gene sets (G2M checkpoint, E2F targets, MYC targets v1) and (b) additional pro-tumorigenic pathways (mTORC1, unfolded protein response [UPR], PI3K/AKT/mTOR) in T1 and T2 tumors across age groups: adolescents and young adults (AYA, red), perimenopausal (peri, blue), menopausal (meno, olive), and older adults (gray). Data are presented for both METABRIC (AYA/peri/meno/old = 37/336/367/613) and SCAN-B (GSE96058, AYA/peri/meno/old = 52/604/585/1140) cohorts. Comparisons between AYA and each older group were performed using the Mann–Whitney U test.

Distinct mutation patterns in AYA ER-Positive/HER2-negative breast cancer

We next examined the prevalence of somatic mutations among 20 genes frequently altered in breast cancer. Tumors from AYA patients exhibited higher mutation rates in several genes, including AHNAK2, GATA3, HERC2, and TG, whereas mutations in KMT2C were less frequent compared with other age groups **(Figure 5)**. No significant differences were observed in mutation frequencies among the perimenopausal, menopausal, and older adult groups. These findings indicate that ER-positive/HER2-negative breast cancers in AYA patients are characterized by distinct mutational profiles relative to older age groups.

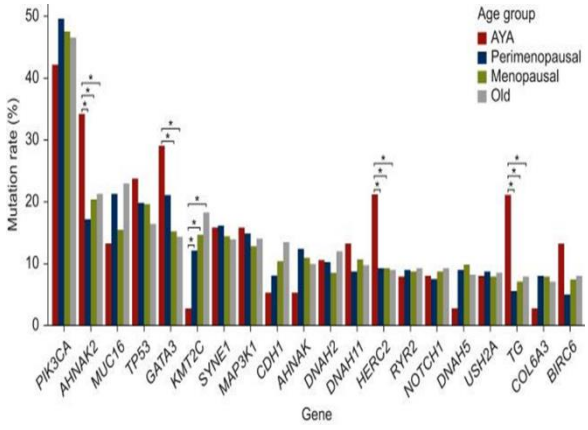

Figure 5. Age-specific differences in mutation frequency in ER-positive/HER2-negative breast cancer. Barplots depict the mutation rates of 20 genes commonly altered in breast cancer across age groups: adolescents and young adults (AYA, red), perimenopausal (peri, blue), menopausal (meno, olive), and older adults (gray) in the METABRIC cohort (AYA/peri/meno/old = 37/336/367/613). Statistical comparisons between AYA and each older age group were performed using Fisher's exact test**,** with asterisks (*) indicating P-values < 0.05.

In this study, breast cancer (BC) patients were categorized into four age groups: adolescents and young adults (AYA, 15–39 years), perimenopausal (40–54 years), menopausal (55–64 years), and older adults (≥65 years). Tumors in AYA and older patients were generally larger than those in intermediate age groups. AYA tumors were also more likely to present with lymph node involvement and advanced disease stage, and Nottingham grade 3 histology was more frequently observed. Progesterone receptor positivity was enriched in AYA and perimenopausal patients. Survival analyses revealed that AYA patients tended to experience poorer disease-specific survival (DSS) and overall survival (OS), especially relative to perimenopausal patients, with the trend being most pronounced in ER-positive/HER2-negative BC.

Analysis of ER-positive/HER2-negative tumors showed that late estrogen response signaling decreased progressively with age. Regarding the tumor immune microenvironment, AYA tumors exhibited higher infiltration of $CD8^+$ T cells, M1 macrophages, regulatory T cells, and Th2 cells, whereas M2 macrophages were consistently less abundant across both METABRIC and SCAN-B cohorts. AYA tumors also demonstrated elevated BRCAness and DNA repair activity, alongside upregulation of cell proliferation pathways (G2M checkpoint, E2F targets, MYC targets v1) and oncogenic signaling (mTORC1, unfolded protein response, PI3K/AKT/mTOR). Notably, these patterns persisted even in small tumors, suggesting that enhanced proliferative capacity is an intrinsic feature of AYA BC rather than a consequence of delayed detection.

Genetic predisposition is believed to play a larger role in BC among younger patients due to limited exposure to environmental risk factors. Indeed, AYA BC is frequently linked to family history and germline mutations, particularly in the context of hereditary breast and ovarian cancer syndrome [23]. In our cohort, the AYA group showed a trend toward higher BRCA mutation frequency, although differences were not statistically significant. BRCAness, a marker of homologous recombination deficiency resembling BRCA mutation effects, has emerged as a clinically relevant biomarker. Tools such as the 'myChoice' assay

are used in ovarian cancer to guide PARP inhibitor therapy, and our previously developed BRCAness score allows similar assessment in BC [17]. In this study, both DNA repair signaling and BRCAness scores were higher in AYA ER-positive/HER2-negative tumors, indicating potential sensitivity to PARP inhibitors.

Beyond DNA repair, proliferation-related genes such as MYCN, KPT5, and BUB1 have been reported to be elevated in AYA BC, and higher expression of VEGFA, MIBL2, and ANGPTL4 is associated with poorer disease-free survival across subtypes [24]. Our findings align with these reports and may explain the aggressive growth and poorer prognosis observed in AYA BC. Additionally, signaling pathways including mTORC1, unfolded protein response, and PI3K/AKT/mTOR were significantly upregulated in AYA tumors in both METABRIC and SCAN-B cohorts, whereas no substantial differences were observed among older age groups [25–27]. These results underscore the distinct molecular biology of AYA BC and suggest potential targets for therapy, consistent with recommendations for targeting tyrosine kinases, DNA repair, and PI3K/mTOR/AKT pathways in AYA sarcomas [28].

The classification into four age groups also accounts for dramatic shifts in estrogen levels during young, perimenopausal, and postmenopausal stages [29]. Differences in estrogen signaling may influence tumor biology, particularly in hormone receptor–positive BC. Our data showed that estrogen response activity in tumor tissue varied by age group **(Figure 2)**, and elevated estrogen signaling in AYA may contribute to increased cell proliferation, potentially explaining their poorer outcomes. Ovarian suppression in premenopausal patients may improve prognosis, consistent with findings from the SOFT study [30], and may also help explain differences in chemotherapy efficacy noted in TAILORx [31] and RxPONDER [32] trials due to chemotherapy-induced menopause.

Estrogen also modulates immune function. Estradiol (E2) influences $CD4^+$ and $CD8^+$ T cells, macrophages, Th cells, and regulatory T cells, and promotes secretion of proinflammatory cytokines such as TNF-α, IL-6, IL-8, and MCP-1 [33]. Menopause-associated estrogen decline is linked to increased inflammatory cytokine production [34]. Estrogen also affects dendritic cell differentiation, survival, and costimulatory molecule expression [35, 36] and can enhance T-cell proliferation in vitro [33]. Furthermore, estrogen signaling through ERα regulates thymic development and T-cell maturation [37], and ERRα supports T-cell metabolism and proliferation [38]. In vivo, E2 treatment reduces $CD4^+$ and $CD8^+$ T-cell presence in mammary tissue [39]. Consistent with these observations, our data showed slight age-related decreases in $CD4^+$ and $CD8^+$ T-cell infiltration, emphasizing the importance of considering both immune status and age-specific estrogen levels when designing treatment strategies.

Recent advances in hormone receptor–positive BC therapy, including CDK4/6 inhibitors [40, 41]**,** PIK3CA inhibitors [42]**,** ESR1 inhibitors [43]**,** and PIK3CA/AKT/PTEN inhibitors [44]**,** often rely on tumor genomic profiling. Our study indicates that AYA BC harbors unique genetic alterations, suggesting opportunities for developing age-specific targeted therapies.

A major strength of this analysis is the validation of findings across two large, independent cohorts with diverse backgrounds, minimizing sampling bias. METABRIC used microarray-based transcriptomics, whereas SCAN-B used RNA sequencing, yet consistent patterns were observed. Limitations include the predominance of White patients, lack of detailed treatment data, and small proportion of AYA patients (3% in METABRIC, 2% in SCAN-B), which may limit generalizability. Additionally, the retrospective nature of the study underscores the need for large prospective investigations to better understand the clinical and molecular characteristics of AYA BC.

Conclusion

ER-positive/HER2-negative breast cancer in adolescents and young adults (AYA) is characterized by elevated proliferative activity and increased immune cell infiltration relative to older age groups. Gaining a detailed understanding of these unique biological features could facilitate the development of novel therapies and tailored treatment strategies specifically for the AYA population.

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Conflict of Interest: None

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Ethics Statement: None

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