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ORIGINAL RESEARCH

Breast cancer in adolescents and young adults has a specific biology and poor patient outcome compared with older patients

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Background: We aimed to clarify the features of adolescents and young adults (AYA: younger than 40 years old) breast cancer (BC) compared with other age groups in estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative BC, given the effects of age-related hormonal status.

Methods: The cohorts analyzed were divided into AYA (15-39 years old), perimenopausal (40-54 years old), menopausal (55-64 years old), and old (65+ years old). Clinicopathological and biological features were analyzed using gene set variation analysis and xCell algorithm using transcriptome profiles from large public databases of ER-positive/HER2-negative BC (METABRIC; $n = 1353$, SCAN-B; $n = 2381$).

Results: In the ER-positive/HER2-negative subtype, pathological lymph node positivity, and Nottingham grade 3 were higher among AYA (all $P < 0.001$). AYA patients had a trend toward worse disease-specific and overall survival, particularly compared with the perimenopausal group. Estrogen response late signaling decreased with age (all $P \leq 0.001$ in both METABRIC and SCAN-B cohorts). AYA was associated with significantly higher BRCAness and DNA repair than the other groups (all $P < 0.05$ in both cohorts). AYA significantly enriched cell proliferation-related and procancerous gene sets [mTORC1, unfolded protein response, and phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling] when compared with the others (all $P < 0.03$ in both cohorts). Interestingly, these features have also been observed in tumors <2 cm. Infiltration of $CD8^+$, regulatory, T helper type 2 cells, and M1 macrophages was higher, while M2 macrophages were lower in AYA (all $P < 0.03$ in both cohorts). Finally, ER-positive/HER2-negative BC in AYA patients has different features of gene mutations, including *AHNAK2*, *GATA3*, *HERC2*, and *TG*, which were observed at a higher rate in AYA, and *KMT2C*, which was observed at a lower rate in AYA, compared with other age groups.

Conclusions: ER-positive/HER2-negative BC in AYA was highly proliferative with high immune cell infiltration compared with the other age groups.

Key words: adolescent and young adult generation, AYA, breast cancer, BRCAness, gene expression, generation gap, hallmark signaling

BACKGROUND

'AYA' is an acronym that stands for adolescents and young adults, which is commonly defined as patients younger than 40 years old. Approximately 89 000 AYA cases are diagnosed with cancer in the thyroid, skin, colorectal, and breast in the United States each year, accounting for ∼5% of all cancers diagnosed in the country. As the incidence of breast cancer (BC) increases with age, patients in AYA account for 5% of all BC cases, which are ∼12 000 every year in the United States.[1,2] By contrast, BC has the highest incidence and causes of death among cancers in the AYA.[3] BCs diagnosed among AYA are known to be clinically aggressive, with a higher likelihood of aggressive subtypes [triple-negative BC or human epidermal growth factor receptor 2 (HER2)-overexpressing], larger tumor size, and a higher likelihood of lymph node and distant metastases, compared with older patients.[4-6] They are strongly associated with family history and genetic germline alterations, and survival outcomes are often worse in AYA patients than in older patients.[1,7] However, previous studies have reported clinical outcomes over broad age ranges,[8] precluding comparisons by clinically important age ranges that could introduce confounding

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factors. It is vital to understand the disease biology of the AYA population and how it differs from the other age groups, especially because younger AYA populations are key players in society, with jobs, small children, and aged parents with caregiving responsibilities.

In recent years, several drugs have been developed and approved for the treatment of BC. Understanding the biology of BC is necessary for the development of novel drugs and for determining appropriate indications. Despite the fact that the prognosis of AYA patients is worse than that of older patients, owing to their rarity, their biology has not been well studied, and their treatment follows the same guidelines as other age groups. In other words, understanding the biology of AYA patients with BC is essential for improving the prognosis of BC in AYA. The aim of this study was to elucidate the biology of BC in AYA patients, particularly in the estrogen receptor (ER)-positive/HER2-negative subtype, where disease biology is affected by age-related hormonal status and an area with a paucity of prior data. We compared the biological characteristics of BC among age groups using transcriptome data. Understanding the unique biology of AYA patients with BC is expected to provide clues for developing new drugs and treatment strategies specifically for these patients.

MATERIALS AND METHODS

Study cohorts

This study aims to clarify the specific features of AYA BC, especially the ER-positive/HER2-negative subtype by comparing it with the other age groups. To carry out this study, we used two large independent cohorts where clinicopathological and transcriptomic data of patients with BC were available. Our study utilized data from public databases on ER-positive/HER2-negative BC, including the Molecular Taxonomy of Breast Cancer International Consortium[9] [METABRIC ($n = 1353$ among 1903 BC cases)], which was collected from tumor banks in the UK and Canada, and the Swedish Breast Cancer Analysis Network[10,11] [SCAN-B: GSE96058 ($n = 2381$ among 3273 BC cases)], which was collected in Sweden. Clinicopathological and transcriptomic data were obtained using cBioportal[12] and Gene Expression Omnibus (RRID:SCR_005012). Furthermore, to consider age-related menopausal status, which is an important host factor for BC, in this study, each analyzed BC cohort was divided into four groups by age: AYA (15-39 years old), perimenopausal (40-54 years old), menopausal (55-64 years old), and old (65+ years old). Consolidated Standards of Reporting Trials (CONSORT) diagram of the study in the both METABRIC and SCAN-B cohorts are presented in Supplementary Figures S1 and S2, available at https://doi.org/10.1016/j.esmoop.2024.103737.

Overall survival (OS) was defined as the time from the date of diagnosis or the start of treatment to death from any cause, and disease-specific survival (DSS) was defined as the time from the date of diagnosis or the start of treatment to death from BC.

Biological analysis

To assess the enhancement level of each hallmark cancer signaling pathway, gene set variant analysis was carried out using the Molecular Signatures Database (MSigDB) gene set collection.[13] The gene set variation score was calculated with transcriptomic data for each BC case,[14] as previously reported.[15,16] The BRCAness score was established by our group[17] as a predictive BRCAness status. The infiltrating fraction rate of several immune cells in the tumor microenvironment was calculated using the xCell algorithm.[18] These biological analyses were carried out using the transcriptome of all samples from patients with ER-positive/HER2-negative BC in each cohort.

Statistical methods

As mentioned in each figure legend, group comparisons were analyzed using Fisher's, Mann—Whitney *U*, and Kruskal—Wallis tests. The Kaplan—Meier method was used for survival analysis using the log-rank test. Data were generated using Microsoft Excel (version 16; Microsoft Corp, Redmond, WA; RRID:SCR_016137), and data plots and analyses were generated using R software (version 4.1.0; R Foundation, Vienna, Austria). Statistical significance was defined as $P < 0.05$.

Ethics approval and consent to participate

As this study examined human data that had been generated in the past by other studies, informed consent was not obtained.

RESULTS

Clinical feature of each generation in the METABRIC cohort

We first investigated the differences in the clinicopathological features of AYA with other age groups in whole BC dataset using the METABRIC cohort. We found that tumors were larger and more advanced in the AYA group than among the other groups. There was a trend toward higher pathological lymph node positivity and Nottingham grade 3 among AYA. AYA was significantly associated with triple-negative BC and higher HER2 positivity (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103737). We next focused on ER-positive/HER2-negative BC. There was a trend for tumor size at diagnosis and pathological T-category to be larger in the AYA and old groups (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103737). The lymph node metastasis-positive rate and the number of lymph node metastases were higher in the AYA group compared with the other groups. The pathological stage was also more advanced in the AYA group. Nottingham histological grade 3 tumors were higher in the AYA group, but not in the old group. Progesterone receptor positivity was higher in the AYA and perimenopausal groups compared with the other groups. The AYA group tended to have higher BRCA mutation rates than other groups, but did not show significant differences.

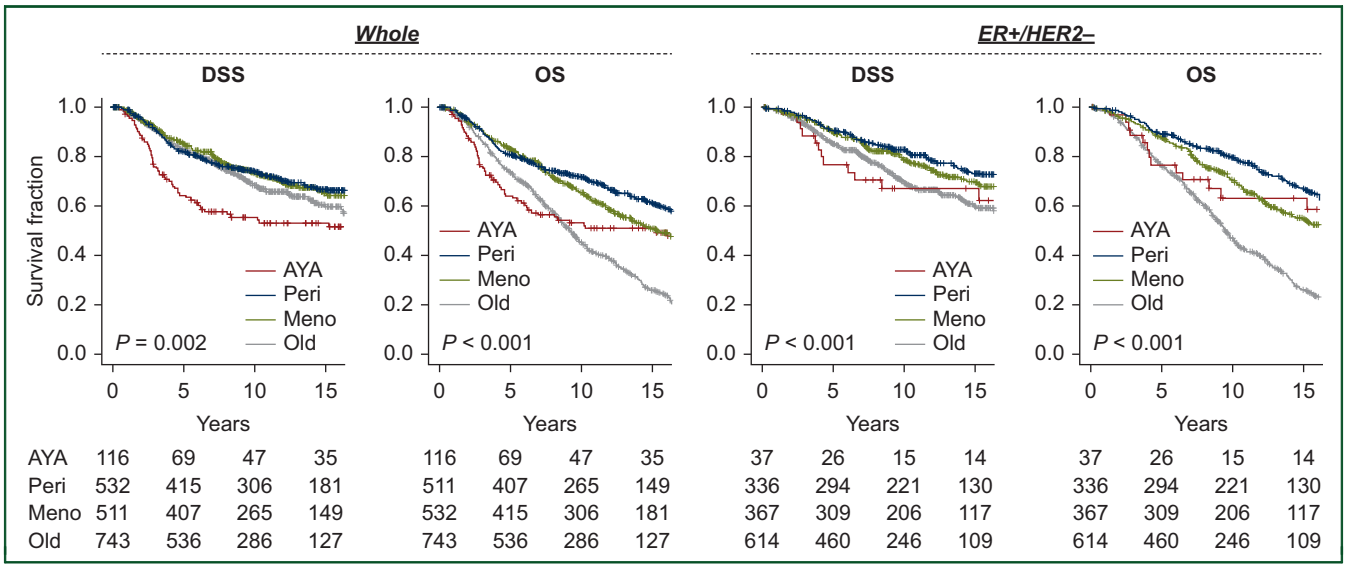


Figure 1. Patient survival outcomes by the age groups of whole and estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC). Kaplan–Meier curves with log-rank disease-specific survival (DSS) and overall survival (OS) among each age group [red, adolescents and young adults (AYA; 15-39 years old); blue, perimenopausal (peri; 40-54 years old); olive, menopausal (meno; 55-64 years old); and gray, old (65+ years old)] in the whole (number of cases: AYA/peri/meno/old = 116/532/512/743) and ER-positive/HER2-negative BC of the METABRIC (number of cases: AYA/peri/meno/old = 37/336/367/613) cohort.

ER-positive/HER2-negative BC in the AYA group shows a trend toward worse survival compared with other age groups

We next investigated the differences in patient survival among age groups in the METABRIC cohort. We found that AYA has a trend toward worse DSS and OS compared with perimenopausal and menopausal groups in the whole BC dataset, as well as ER-positive/HER2-negative BC (Figure 1). A hazard ratio of DSS and OS for each age group compared with the AYA group was calculated in the whole cohort and ER-positive/HER2-negative BC using a Cox proportional hazards analysis (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103737).

ER-positive/HER2-negative BC in the AYA group was significantly associated with high levels of DNA repair signaling and BRCAness, as well as enhanced cell proliferation-related and other procancerous signaling, including mTORC1, unfolded protein response, and PI3K/AKT/mTOR signaling, compared with the other age groups

First, we investigated the levels of estrogen response signaling by age group in ER-positive/HER2-negative BCs (Figure 2A). As expected, late responses to estrogen, estimated using the 'Hallmark estrogen response late' gene set in MSigDB, were significantly higher in younger generations, given estrogen production from ovaries.

As it is known that juvenile BC is likely to be associated with BRCA mutation, we investigated the levels of DNA repair and BRCAness among each age group in the ER-positive/HER2-negative subtype in the METABRIC and SCAN-B (GSE96058) cohorts using the scores we previously reported.[17-22] We found that AYA was significantly associated with high levels of DNA repair and BRCAness compared with other age groups in ER-positive/HER2-negative BC (Figure 2B and C). These results were consistent in both cohorts, suggesting that ER-positive/HER2-negative BC in AYA patients has enhanced DNA repair and BRCAness compared with other age groups.

To investigate the biology of AYA in the ER-positive/HER2-negative subtype, we next compared the activation of hallmarks of cancer pathways using gene set variant analysis scoring between AYA and other age groups in ER-positive/HER2-negative BC. We found that the AYA ER-positive/HER2-negative BC group had significantly higher levels of cell proliferation-related gene sets, including the G2M checkpoint, E2F targets, and MYC targets v1 (Figure 2D). Furthermore, they had significantly higher levels of other procancerous signaling, including mTORC1, unfolded protein response, and phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling, which was consistent in both METABRIC and SCAN-B (GSE96058) cohorts (Figure 2E). These results suggest that AYA has specific biological functions, such as enhanced cell proliferation-related gene signaling as well as several other procancerous pathways in ER-positive/HER2-negative BC.

ER-positive/HER2-negative BC in AYA was significantly infiltrated with high levels of anticancerous immune cells compared with the other age groups

We next investigated the differences in immune cell infiltration in ER-positive/HER2-negative BC according to age group. We found that the younger age groups tended to have higher infiltration of several immune cells, including $CD8^+$ T cells, $CD4^+$ memory T cells, M1 macrophages, and T helper type 2 cells, and lower infiltration of regulatory T cells and M2 macrophages in the METABRIC cohort

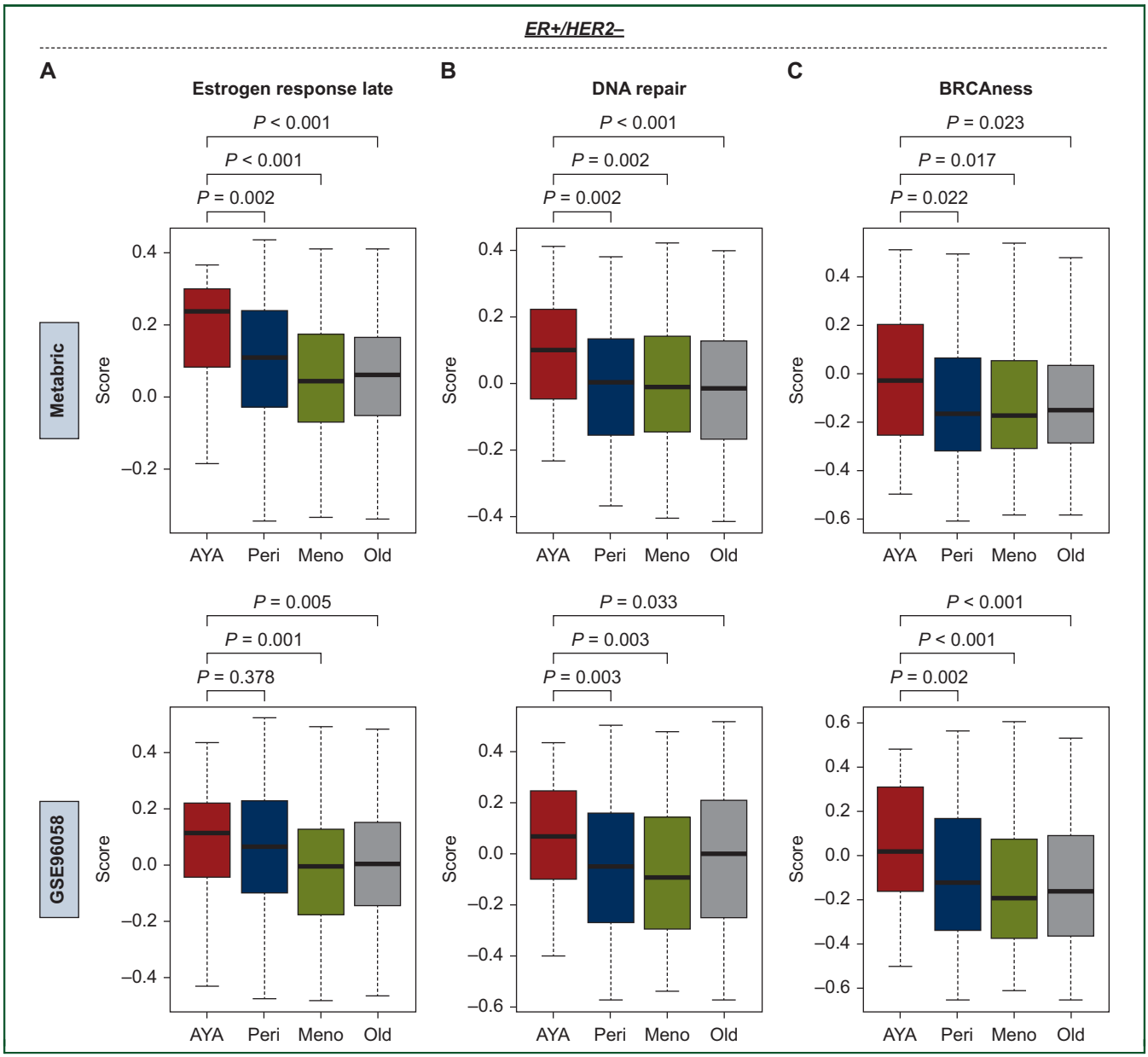


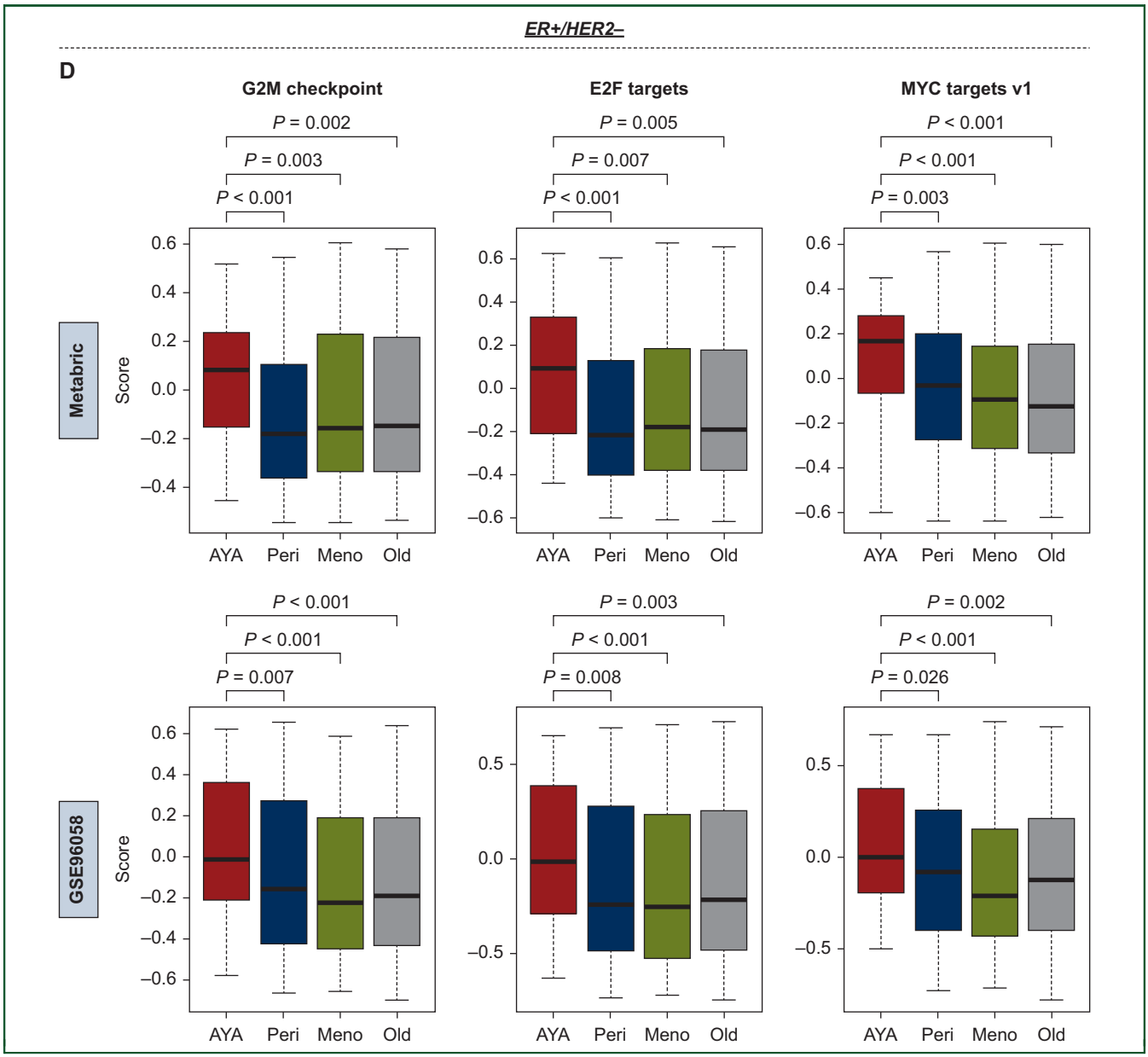
Figure 2. Comparison of the level of estrogen response, DNA repair, BRCAness, and other procancerous gene signaling among adolescents and young adults (AYA) and the other age groups in the estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative subtype. Boxplots of the score level of (A) gene set defining late response to estrogen; (B) DNA repair signaling; (C) BRCAness score; (D) cell proliferation-related gene sets, including G2M checkpoint, E2F targets, and MYC targets v1; and (E) other procancerous gene sets, including mTORC1, unfolded protein response (UPR), and PI3K/AKT/mTOR, by each age group [red, AYA; blue, perimenopausal (peri); olive, menopausal (meno); and gray, old] in both METABRIC (number of cases: AYA/peri/meno/old = 37/336/367/613) and SCAN-B (GSE96058, number of cases: AYA/peri/meno/old = 52/604/585/1140) cohorts. The *P*-value was calculated to compare AYA with other age groups with ER-positive/HER2-negative BC using the Mann−Whitney *U* test.

AKT, protein kinase B; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase.

(Figure 3A and B). These results were validated by the SCAN-B (GSE96058) cohort, except for CD4+ memory T cells, suggesting that the fraction of immune infiltration into BC may differ by age.

AYA was significantly and consistently associated with enhanced cell proliferation-related and procancerous signaling compared with the other generations in small ER-positive/HER2-negative BC

In Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103737, we found that the tumor size was significantly larger in AYA and old patients, which led us to wonder whether this is because the cancer cells are aggressively proliferating or due to late presentation given socioeconomic reasons, such as poor access. To this end, enrichment of cell proliferation-related gene sets was compared between AYA and other age groups in ER-positive/HER2-negative tumors <5 cm. We found that even among small tumors, AYA showed higher cell proliferation signaling levels than other groups, including old patients (Figure 4A and B). These results show that AYA BC exhibits enhanced cell proliferation, whereas older tumors do not, suggesting that the latter are more likely to be slow-growing, with delayed diagnoses possibly due to late presentation.



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ER-positive/HER2-negative BC in AYA has different features of gene mutation compared with other age groups

Finally, we compared the mutation rates among each group of 20 genes with high mutation rates in BC. We found that BC in the AYA group had higher rates of several gene mutations, including AHNAK2, GATA3, HERC2, and TG, compared with other groups, and a lower rate of mutations in the KMT2C gene compared with other groups (Figure 5). Furthermore, there was no significant difference in the mutation rates for any of the genes among the other three groups. These results suggest that AYA patients with BC may have different gene mutation characteristics compared with other age groups.

DISCUSSION

In this study, we divided the BC patients into four age groups: AYA (15-39 years old), perimenopausal (40-54 years old), menopausal (55-64 years old), and old (older than 65 years old) in each cohort. We found that the tumor size was larger in the AYA and old groups compared with the other groups. AYA-BC was associated with lymph node positivity and a higher disease stage. Nottingham histological grade 3 was significantly higher in the AYA group than in the other groups. Progesterone receptor positivity was higher in the AYA and perimenopausal groups than in other groups. AYA BC has a trend toward worse disease-specific and OS than other groups, particularly compared with the perimenopausal group. The difference in survival was more pronounced in patients with ER-positive/HER2-negative BC. In biological analyses of the ER-positive/HER2-negative subtype, we found that estrogen response late signaling showed a decreasing trend with increasing age. The infiltration fraction of several immune cells, including $CD8^+$ T cells, M1 macrophages, regulatory T cells,

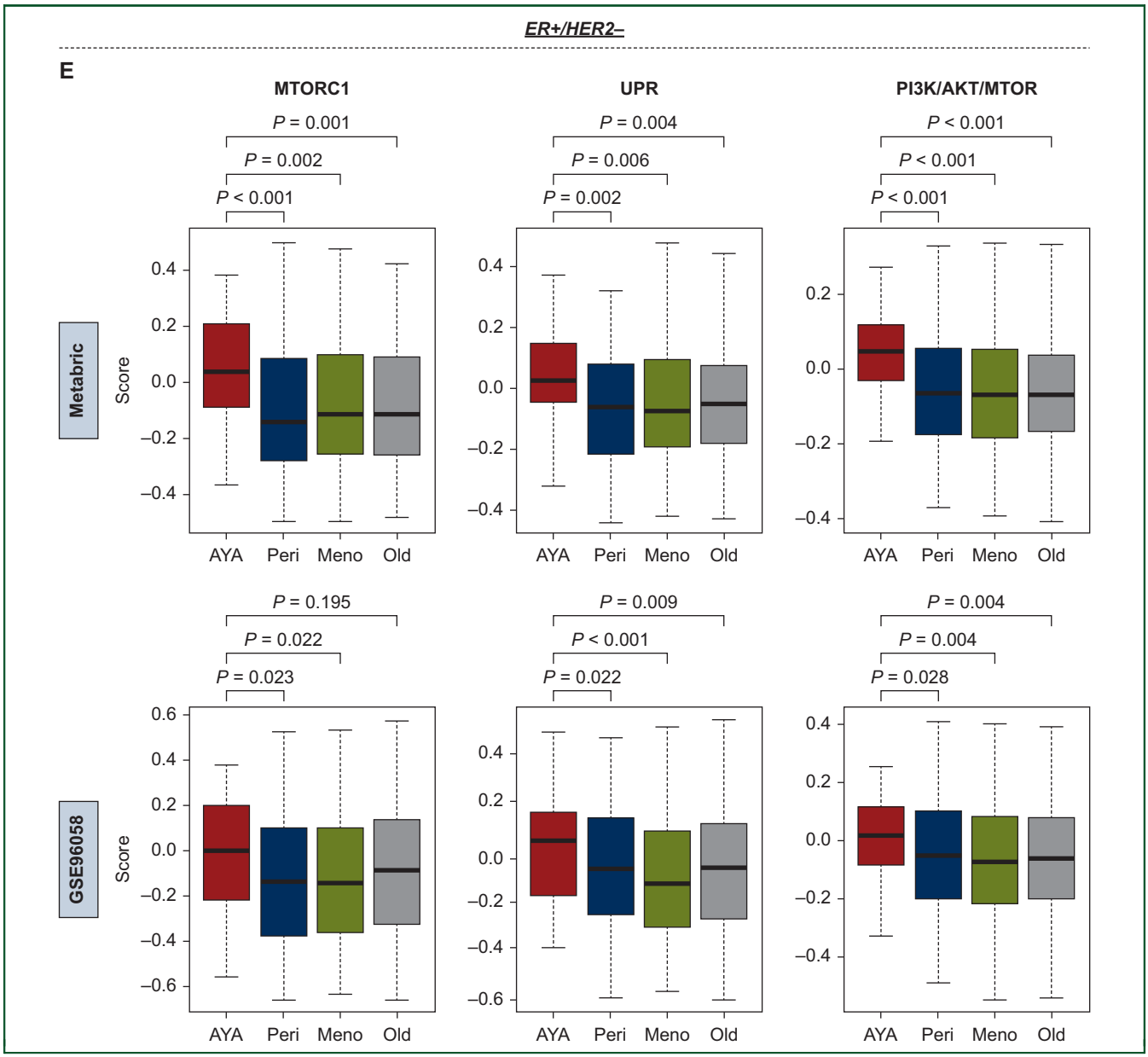

Figure 2. **Continued.**

and T helper type 2 cells, was significantly higher, while M2 macrophages were consistently significantly lower in AYA in the two cohorts. AYA BC showed significantly higher BRCAness and DNA repair compared with other age groups and had significant enrichment in cell proliferation-related (G2M checkpoint, E2F targets, and MYC target v1) and procancerous gene sets (mTORC1, unfolded protein response, and PI3K/ACT/mTOR signaling), when compared with other age groups consistently in the two cohorts. Interestingly, similar features have been observed in small tumors.

Both genetic and environmental factors are involved in cancer development. As younger people have fewer years of accumulated environmental factors, the genetic component is presumed to be higher. In fact, BC in AYA is often associated with a family history of cancer and germline mutations, with hereditary breast and ovarian cancer syndrome being the most common.[23] In our study, the AYA group had a trend toward having a higher rate of BRCA mutations than other groups, but did not show significant differences. Recently, BRCAness, which estimates the degree of homologous recombination deficiency mimicking BRCA gene mutations, has emerged as a biomarker in the field. In ovarian cancer, a tool called 'myChoice' that measures BRCAness is already in clinical use to determine patient selection for poly(ADP-ribose) polymerase (PARP) inhibitors. We have previously reported a novel BRCAness score to quantify the BRCAness status of BC.[17] In this study, not only the BRCAness scores but also the DNA repair signaling was higher in AYA compared with the other groups, particularly in ER-positive/HER2-negative BC. This indicates a high rate of detection of homologous recombination deficiency in AYA and a high likelihood of sensitivity to PARP inhibitors.

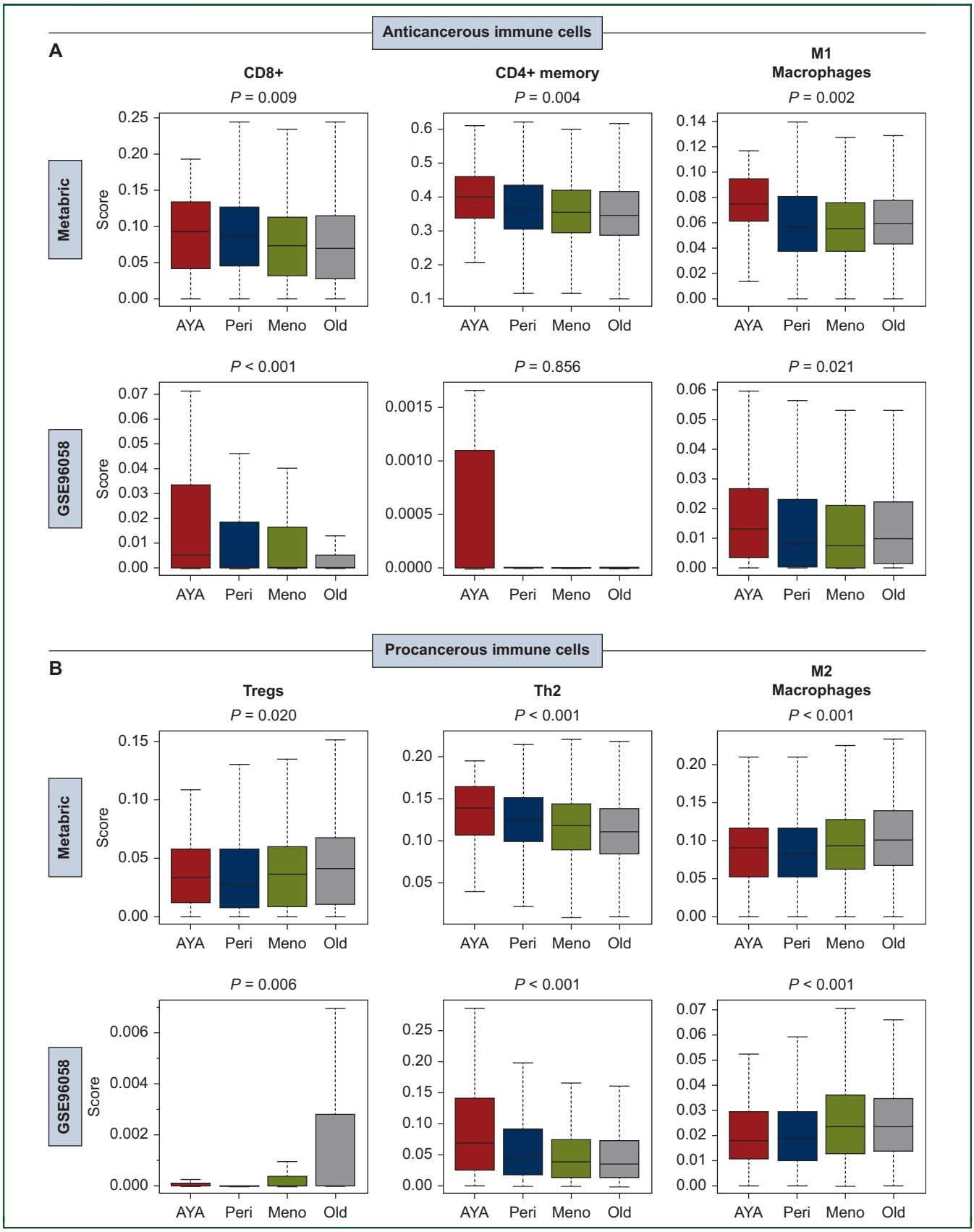

Figure 3. Immune cell infiltrations in estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC) by the age groups. Boxplots of infiltration fraction of (A) anticancerous immune cells; $CD8^+$ T cells, $CD4^+$ memory T cells, and M1 macrophages, and (B) procancerous immune cells; regulatory T cells, T helper type 2 (Th2) cells, and M2 macrophages by each age group [red, adolescents and young adults (AYA); blue, perimenopausal (peri); olive, menopausal (meno); and gray, old] in both METABRIC (number of cases: AYA/peri/meno/old = 37/336/367/613) and SCAN-B (GSE96058, number of cases: AYA/peri/meno/old = 52/604/585/1140) cohorts. The Kruskal–Wallis test was used for the analysis.

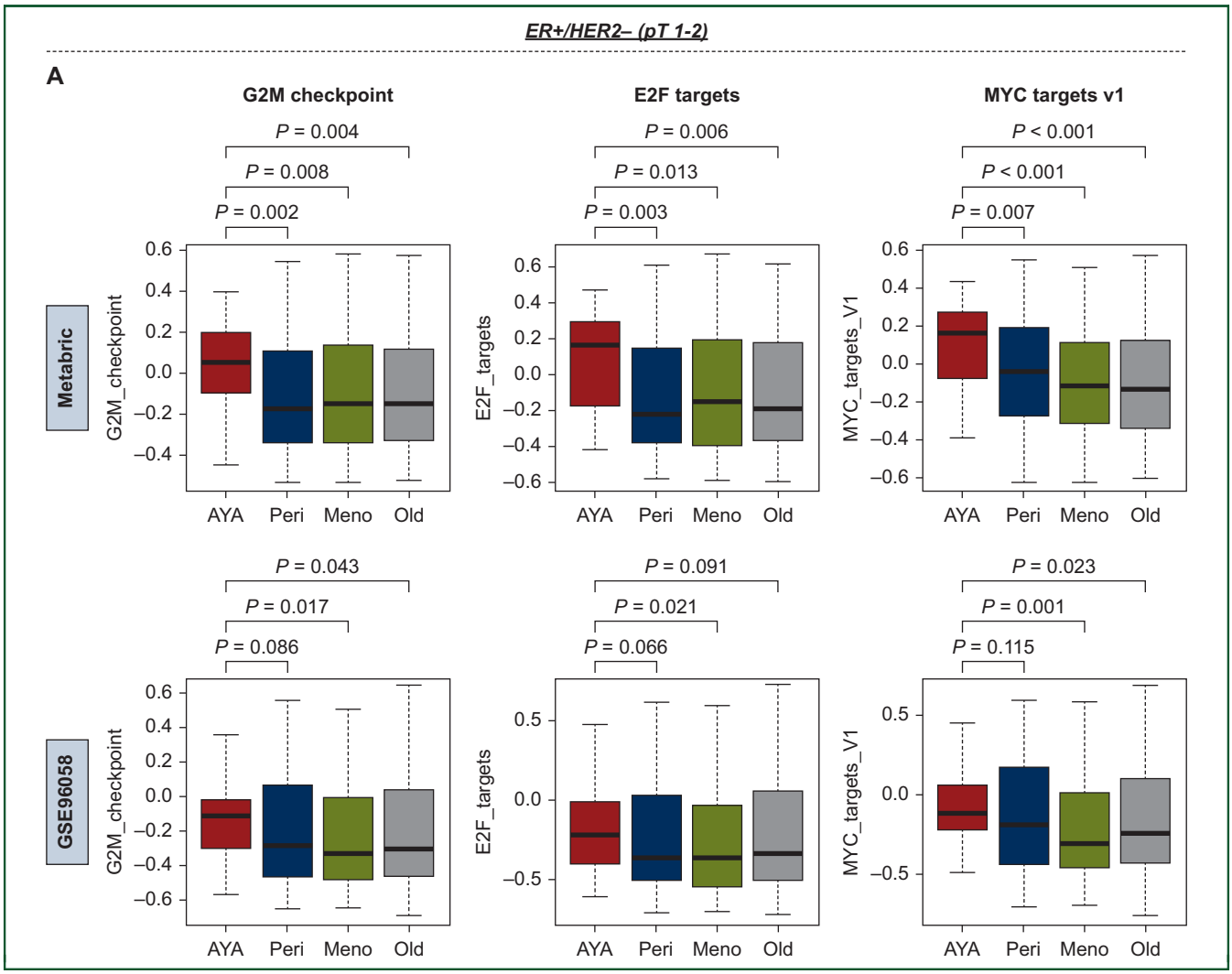

Figure 4. Comparison of the level of cell proliferation-related and procancerous signaling among adolescents and young adults (AYA) and the other age groups in T-categories 1 and 2 of estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC). Boxplots of the score level of (A) cell proliferation-related gene sets, including G2M checkpoint, E2F targets, and MYC targets v1, and (B) other procancerous gene sets, including mTORC1, unfolded protein response (UPR), and PI3K/AKT/mTOR, by each age group [red, AYA; blue, perimenopausal (peri); olive, menopausal (meno); and gray, old] in both METABRIC (number of cases: AYA/peri/meno/old = 37/336/367/613) and SCAN-B (GSE96058, number of cases: AYA/peri/meno/old = 52/604/585/1140) cohorts. The *P*-value was calculated to compare AYA with each of the other groups in T-categories 1 and 2 of ER-positive/HER2-negative BC using the Mann–Whitney *U* test.
AKT, protein kinase B; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase.

From a biological perspective, it has been reported that cell proliferation-related genes, including *MYCN*, *KPT5*, and *BUB1*, are significantly higher in AYA. In addition, high expression of *VEGFA*, *MIBL2*, and *ANGPTL4* was significantly associated with worse disease-free survival for all subtypes.[24] Our results are consistent with this previous report, which may explain the rapid growth and poor prognosis of AYA BC. Furthermore, we have previously reported that several signaling pathways other than cell proliferation-related signaling were predominantly enhanced in AYA, including mTORC1, unfolded protein response, and PI3K/AKT/mTOR signaling using the pathway scoring method.[25-27] These findings were consistently observed in the two independent large cohorts. Interestingly, no significant differences in these signaling levels were observed among the other three age groups. This supports the notion that AYA BC has distinct biology. The association between AYAs and these three hallmarks of cancer signaling in BC was understudied. Reports examining treatment recommendations for AYAs with bone and soft tissue sarcoma based on genetic analysis recommended that most patients receive agents targeting tyrosine kinases, DNA repair, and the PI3K/mTOR/AKT pathway.[28]

In this study, we divided patients into four age groups because estrogen levels dramatically vary during the young, perimenopausal, and postmenopausal periods.[29] Differences in estrogen levels with age should be fully considered when investigating the biology of BC, particularly hormone receptor-positive BC. Estrogen levels are difficult to ascertain because of diurnal variation; however, our study showed that estrogen response signaling levels in BC tissues differed among the four age groups, as shown in Figure 2. Furthermore, estrogen response levels may play a role in the cell proliferation of ER-positive BC among AYA, potentially contributing to a poor prognosis. Ovarian function

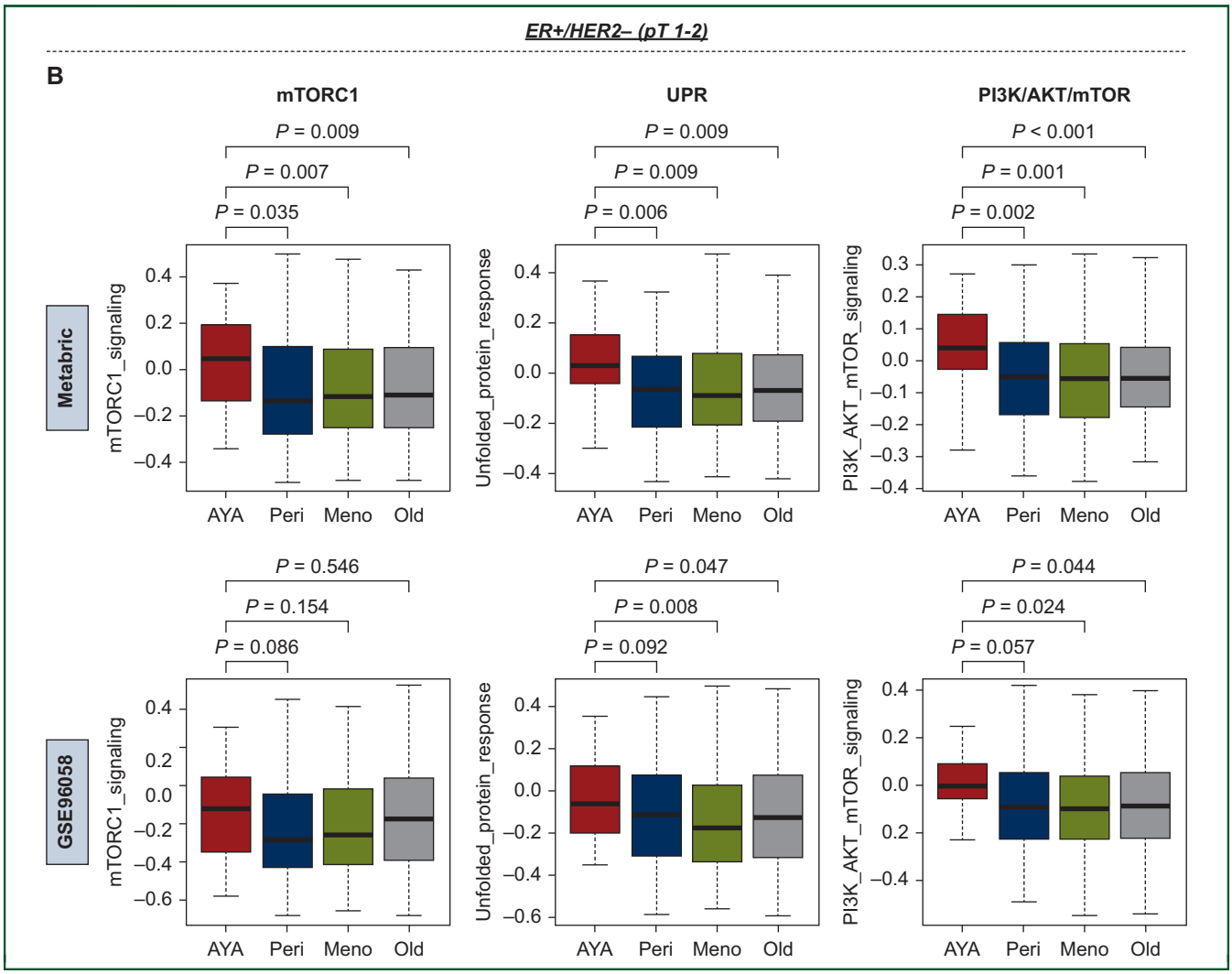

Figure 4. **Continued.**

suppression in AYA patients could, therefore, improve prognosis. This may partly explain the findings observed in the SOFT study,[30] which demonstrated that the addition of ovarian function suppression significantly improved disease-free survival and OS in premenopausal women with BC, particularly those younger than 35 years. This also partly explains the observed difference in the activity of chemotherapy between pre- and postmenopausal patients with ER-positive BC in the TAILORx[31] and RxPONDER[32] trials, due to chemotherapy-induced menopause, which may lower estrogen levels in premenopausal patients.

Estrogen itself has been reported to affect not only the immune response but also several immune cells such as CD4+ T cells, CD8+ T cells, macrophages, Th cells, and regulatory T cells. Estradiol (E2) upregulates the expression and secretion of various proinflammatory cytokines and chemokines such as tumor necrosis factor-alpha, interleukin-6 and interleukin-8, and monocyte chemoattractant protein 1.[33] A reduction in hormone levels has been associated with an increase in proinflammatory cytokine production, especially with a decline in ovarian function related to menopausal status.[34] Dendritic cells (DCs) induce differentiation and survival and increase the expression of costimulatory molecules by estrogen *in vitro* models.[35] It was also reported that T-cell proliferation was stimulated by E2 pretreatment in cocultures of mature DCs with T cells.[33] Furthermore, E2 modulates functional DCs from the bone marrow.[36] These reports suggest the need to monitor the effects of ER inhibitors on different immune cell functions, not only the inhibition of cancer cells, but also the migration of immune cells to lymphoid organs or avoiding their anergic phenotype. Furthermore, E2 has been reported to affect the maturation, development, and size of T cells mainly by ERα signaling, a process known as thymic atrophy.[37] Estrogen-related receptor-α (ERRα) is a key regulator that supports T-cell functions because the inhibition of ERRα decreases several glycolytic genes implicated in inflammatory cytokine production and T-cell proliferation *in vitro*.[38] E2 administration in a mammary involution mouse model diminished CD4+ and CD8+ T cells in the mammary tissue, highlighting the effects of this hormone on the function of these immune cell types.[39] In our study, the infiltrating fractions of CD4+ and CD8+ T cells also decreased with increasing age, although the difference was

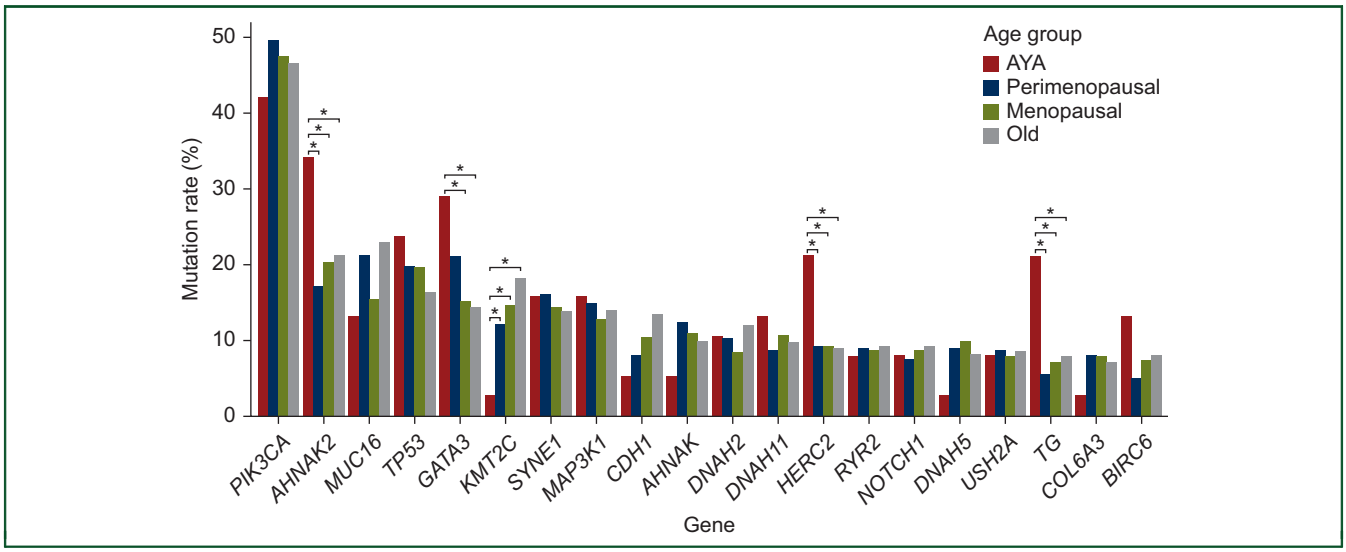

Figure 5. Comparison of the mutation rate among adolescents and young adults (AYA) and the other age groups in estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC). Barplots of the mutation rate among each group of 20 genes with high mutation rates in breast cancer [red, AYA; blue, perimenopausal (peri); olive, menopausal (meno); and gray, old] in the METABRIC (number of cases: AYA/peri/meno/old = 37/336/367/613) cohort. The *P*-value was calculated to compare AYA with each of the other groups of ER-positive/HER2-negative BC using Fisher's test. * indicate *P* value smaller than 0.05.

minimal. Future treatment strategies need to be carefully considered and planned, considering the immune status of the tumor and age-specific estrogen levels.

In recent years, several agents have been developed for the treatment of hormone receptor-positive BC, especially targeted agents, such as CDK4/6 inhibitors,[40,41] PIK3CA inhibitors,[42] ESR1 inhibitors,[43] and PIK3CA/AKT/PTEN inhibitors.[44] These drugs were selected for treatment by examining DNA mutations. Our study showed that BC in AYA is associated with genetic mutations, which are distinct from other age groups. These findings may lead to the development of molecularly targeted drugs specific to the AYA BC population.

The strength of this study is that the results were validated using multiple large independent cohorts from completely different backgrounds, regardless of epidemiological, national, regional, racial, ethical, and clinical differences, which minimized sampling biases. We evaluated METABRIC and SCAN-B cohorts separately because the transcriptome was measured by gene expression microarray in METABRIC, whereas RNA-sequencing was used in SCAN-B. Even with the different technology used, we observed consistent findings among the two cohorts. At the same time, our study has several limitations. Racial differences in genetic and environmental factors are particularly large[4,45]; therefore biological studies are required for each race. The transcriptomic data used for analysis in this study consisted mostly of White patients with BC, and it may be necessary to create cohorts of other races, such as Asians, that include transcriptomic data with AYA and to investigate their features. Analyzed cohorts lack details on the treatment regimens that the patients received, and it is assumed that all the patients received the 'standard-of-care' treatment. Whether or not the patient underwent systemic therapy, and which drugs were used can be significant confounders of the survival analysis and this is a limitation of this study. One of the biggest limitations is the very small sample size of the AYA group compared with other age groups (3% in the METABRIC cohort and 2% in the SCAN-B cohort). Future cohorts focusing on AYA are needed. Furthermore, although this study used ∼10 000 patient sample data, the research was limited to a retrospective study, and large prospective studies are needed to clarify the features of AYA-BC, especially patient outcomes.

Conclusions

ER-positive/HER2-negative BC in AYA is highly proliferative, with high immune cell infiltration compared with other age groups. A clear understanding of disease biology may lead to the development and discovery of new drugs and treatment strategies specific to AYA patients.

FUNDING

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DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

Molecular Taxonomy of BC International Consortium (METABRIC) and SCAN-B (GSE96058) data are publicly available without any restrictions via cBioportal or Gene Expression Omnibus (GEO).

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