Breast cancer treatments activate genes associated with biological ageing. The study, published in the *Journal of the National Cancer Institute*, 8 October, suggests that chemotherapy, radiation, and surgery all lead to statistically significant increases in cellular senescence and DNA damage response genes.

“While we expected to see increased gene expression linked to biological aging in women who received chemotherapy, we were surprised to find similar changes in those who only underwent radiation or surgery,” says study lead author Judith Carroll, from UCLA Health Jonsson Comprehensive Cancer Center, in Los Angeles.

“The results suggest women who receive treatment for breast cancer have a pattern of gene expression that indicates increased DNA damage and inflammation, which could be important targets for recovering from cancer and having a better quality of life in survivorship,” adds senior author of the study Julienne Bower, also from the UCLA Health Jonsson Comprehensive Cancer Center.

Treatment advances have improved breast cancer survival, with data from Cancer Research UK showing that over three-quarters of breast cancer patients now survive for 10 years or more. However, breast cancer is linked to accelerated aging, impacting physical abilities, independence, and lifespan. “Survivors can experience increased fatigue, cognitive complaints, insomnia, peripheral neuropathy, and physical functional declines, among other symptoms. There’s also some evidence that there’s increased risk for earlier onset of age-related comorbidities and frailty,” Carroll tells *Cancerworld*.

The current study focused on 184 patients with stage 0–III breast cancer who had taken part in the RISE study, a longitudinal analysis of cancer-related fatigue, and who had gene expression data available. Carroll and colleagues assessed peripheral blood mononuclear cell gene expression using RNA sequencing on quality-verified RNA at baseline (prior to chemotherapy, radiotherapy, or surgery), and then at six, 12 and 18 months post-treatment. The investigators measured p16INK4a, a protein that inhibits cells from replicating, which has been proposed as a marker of biological ageing. They also looked at DNA damage response (a damage response index determined from 30 genes known to be altered when cells undergo DNA damage); SenMayo (a measure reflecting intracellular changes known to be specific to senescent cells); and the senescence-associated secretory phenotype (focused on inflammatory signals).

Results showed that women receiving chemotherapy with or without radiotherapy (n=73) had higher odds (odds ratio=2.97, 95%CI 1.52–5.8) of having detectable p16INK4a immediately following treatment compared with women undergoing radiotherapy (n=76) or surgery alone (n=37).

In all treatment groups, the proportion of women expressing 16INK4a over the follow-up period increased (P<0.001), with no correlation by treatment.

For all treatment groups, increases were found for DNA damage response (P<0.001); SenMayo (P<0.001); and the senescence-associated secretory phenotype (P<0.001).

“Although chemotherapy did have a slightly different pattern, similar to what others have shown, we also noted changes in women who did not receive chemotherapy,” says Carroll. “We anticipated that, among women who received chemotherapy, we’d see the largest increases in these different genes, since prior work has shown increased gene expression specifically in this group. But little research has disentangled whether this pattern is unique in these women compared to others undergoing treatment for breast cancer who receive surgery alone or radiation.”

The results, say the authors, shed light on some of the pathways that drive the later symptoms breast cancer patients all too often report. “These biological pathways could be important targets for intervention to alleviate the lasting impact of cancer treatment and improve quality of life for survivors,” says Carroll.

The team now hope to undertake more research with larger sample sizes for women receiving surgery alone or with radiation, but not chemotherapy, to better identify other possible factors. Ultimately, new treatments could be developed to be delivered after the initial cancer is gone to help alleviate symptoms and improve quality of life. But first, the investigators plan to explore factors that could be implemented right away, such as exercise, good sleep and stress management.

Similar processes, the authors suggest, are likely to occur following treatment with other cancers. “The evidence is particularly strong when the participants are followed for a long time, like in childhood cancer survivors,” says Carroll.