Men with prostate cancer living in disadvantaged neighbourhoods show significantly higher activity of stress-related genes than those living in other neighbourhoods. The observational study, published in *JAMA Network Open*, 12 July, found that neighbourhood disadvantage was positively associated with the expression of a number of stress-related genes, some of which are proinflammatory and could contribute to making tumours more aggressive.

"Our study findings suggest that neighborhood disadvantage adversely impacts stress-related genetic pathways in the body. We believe that this may in turn increase an individual's risk of aggressive prostate cancer," study senior author Kathryn Hughes Barry, tells *Cancerworld*. "Since African American individuals are more likely to reside in disadvantaged areas than White individuals," she adds, "this may contribute in part to the higher risk of aggressive prostate cancer among African American men." Barry, who is Assistant Professor at the University of Maryland School of Medicine and a cancer epidemiologist at the Greenebaum Comprehensive Cancer Center, believes that understanding the mechanisms that contribute to an individual's risk of aggressive prostate cancer could ultimately lead to interventions that lower the burden of aggressive disease and related racial disparities.

In African American men the incidence of prostate cancer is more than 1.5 times higher than for White men in the United States, and mortality twice as high. As well as being more likely to be diagnosed with advanced prostate cancer (due to reduced access to health care and screening), African American men are more prone to aggressive forms of the disease, which are more likely to be fatal. Increasing literature supports the concept of neighbourhood socioeconomic deprivation, which disproportionately affects African American individuals, being associated with a higher likelihood of being diagnosed with an advanced or aggressive prostate cancer. Evidence for the link between living in stressful neighbourhoods and cancer was reviewed in a 2022 *Cancerworld* feature.

For the current study, Barry and colleagues hypothesised that neighbourhood disadvantage would affect the expression of stress-related genes, which in turn would contribute to an increased risk of aggressive prostate cancer.

The cross-sectional study included 218 men with prostate cancer, of whom 168 (77%) were African American and 50 (23%) White, who had undergone radical prostatectomy at the University of Maryland Medical Center between August 1992 and January 2021. To be eligible, subjects needed to have RNA expression data from prostate tumour tissue and a valid residential address at time of diagnosis.

RNA expression data was obtained using an assay called the Human Clariom D array, which measures the activity level of genes and transcripts throughout the genome (138,745 transcripts). For the current study, the team focused on two different sets of genes, for a total of 105 stress-related genes. The first set encompassed genes in the Conserved Transcriptional Response to Adversity (CTRA), while the second set included stress-related signalling genes (genes in the serotoninergic, adrenergic, glucocorticoid, dopaminergic, and muscarinic systems). "Many of the genes that we studied have been previously linked with prostate cancer risk, progression, or death," explains Joseph Boyle, the first author of the study, from the Massey Comprehensive Cancer Center at Virginia Commonwealth University.

Neighbourhoods where patients lived at time of diagnosis were evaluated using two indexes of neighbourhood deprivation (Area Deprivation Index and Neighbourhood Deprivation Index), taking into account neighborhood-level income, education, employment and housing quality. The team also looked at racial segregation (using the Racial Isolation Index) and historical 'redlining', where certain neighbourhoods in the past were systematically denied mortgage applications or refinancing. "While the redlining occurred many years ago, this led to long-term disinvestment and disadvantage

that has been linked with worse health outcomes in the present day, including cancer outcomes," explains Barry.

Results showed that African American participants experienced greater neighbourhood disadvantage than White participants. The median Area Deprivation Index score was 115 for African American men vs 92 for White men, while the median Racial Isolation Index was 0.68 for African American men vs 0.11 for White men.

The Area Deprivation Index was found to be associated with higher RNA expression for 11 stress-related genes – *HTR6* ($P<0.001$, serotonin pathway), *HTR4* ($P=0.003$, serotonin pathway), *HTR3D* ($P=0.006$, serotonin pathway), *IFIT5* ($P=0.009$, type I interferon responses), *IFIT2* ($P=0.009$, type I interferon responses), *CXCL8* ($P=0.01$, proinflammatory), *FOSL2* ($P=0.02$, proinflammatory), *IL1β* ($P=0.02$, proinflammatory), *MX2* ($P=0.03$, type I interferon responses), *IFI44L* ($P=0.04$, type I interferon responses), and *FOS* ($P=0.05$, proinflammatory).

Several of the genes (*HTR6, IFIT2, MX2*, and *FOS*) were associated with more than one measure of neighbourhood disadvantage. After multiple-comparison adjustments, the association between the Area Deprivation Index and *HTR6*, a gene in the serotonin pathway, remained statistically significant ($\beta=0.003$, $SE=0.001$; $P<0.001$; Benjamini-Hochberg q-value=0.01).

HTR6 encodes a receptor that is part of the 7-transmembrane G protein-coupled receptor family, and plays a role in activating the cyclic AMP-dependent signalling pathway. "This receptor is hypothesized to be involved in regulating cholinergic neuronal transmission. Among other roles, the cholinergic system is important in regulating immune response, and its dysregulation is thought to contribute to some inflammatory and autoimmune conditions. There is also evidence that expression of *HTR* genes may be associated with lethal prostate cancer," write the authors.

It was also noteworthy that the investigators observed positive associations between neighbourhood disadvantage and several proinflammatory genes (*CXCL8, FOSL2, IL1B, FOS*, and *PTGS1*). "An individual's RNA levels can change in response to stress, and we and others hypothesise that resulting biologic effects, such as increased inflammation, may contribute to an increased risk of aggressive prostate cancer," says Barry.

Next, the team plans to conduct a larger follow-up study including men from other regions across the US, to assess whether findings will be replicated and to increase their generalisability. "One of the limitations of our current study is that we only had address information at diagnosis for the study participants. In our future work, we aim to gather additional residential information, so we can investigate the role of neighbourhood disadvantage over an individual's lifetime," says Barry.

In the long term, one potential clinical application of this field of research could be that information on an individual's RNA expression profile could be harnessed for precision medicine. For example, says Barry, RNA expression profiles could be used to identify healthy men at higher risk of developing aggressive disease who would benefit from more frequent prostate screening, or to identify patients diagnosed with prostate cancer who are more likely to progress and who might benefit from different clinical management. "It's an interesting idea that, in the future, therapeutic interventions could be developed to reduce elevated expression of these genes, but much more work would need to be done – including experimental studies and clinical trials – before considering this possibility," says Barry.