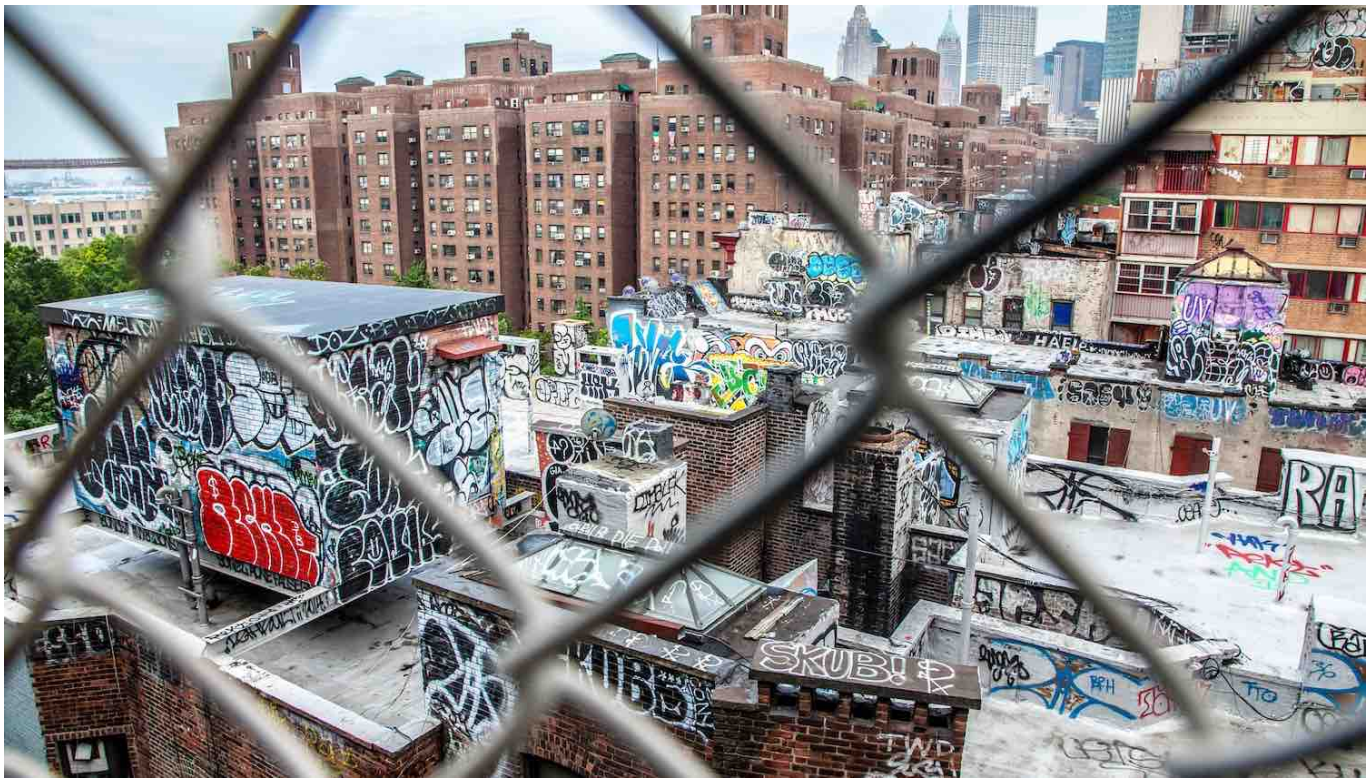
Cancerworld

From social determinants to cancer outcomes: the cell biology behind the disparities

Janet Fricker / 29 April 2022



Raised levels of stress are a normal response to being diagnosed with cancer, and asking patients about their psychological and emotional wellbeing is, or should be, a normal part of attending to their quality of life. But can stress directly affect the course of the cancer and ultimately impact on survival?

A growing body of evidence suggests it can, and specifically that responses to living in stressful neighbourhoods, and feelings of social isolation, can trigger physiological responses that promote tumour growth and migration.

At the annual conference of the American Association of Cancer Researchers, April 8–13 2022, this link between stress responses and promoters of tumour growth took centre stage at the Presidential Symposium, on 'Aging, Stress and Cancer'.
Electra Paskett, who holds the Chair of Cancer Research at Ohio State University, set the scene, as the opening speaker. Paskett has a special interest in cancer disparities and says she uses a 'team

science' approach to understanding what lies behind the disparities and how to intervene to counter them.

Her message relating to clinical practice was clear. Bad health outcomes are the result of social and environmental determinants, where stress is an important factor at play. Patients living in 'unfavourable' neighbourhoods are likely to have worse cancer outcomes. It should therefore be routine practice to increase the level of care and support provided for these patients to try to mitigate some of the increased risk.

> "Where patients live should be considered the new 'vital sign'"

"For a long time we have been blaming bad health outcomes on individuals. But that's wrong, there are upstream factors such as where you live causing stress," she said. "Stress has an effect not only on development of cancer but across the cancer control continuum influencing everything from detection and survivorship to supportive care." Healthcare providers can and should help, she stressed. "If we find patients live in 'hot' areas we should intervene to provide them with better care."

Pressing the point home, Paskett suggested that "where patients live" should be considered the new 'vital sign', because it is such a reliable health-related indicator and signals need for support.

Epidemiology of neighbourhood risk

The association between cancer outcomes and adverse socio-economic factors and environment has been shown in many studies.

In 2021 a retrospective study by Kirsten Beyer, published in *Journal of Clinical Oncology*, found a strong association between breast cancer survival and neighbourhoods classified by mortgage companies as 'hazardous to investment' using the controversial 'redlining index'.

The study used data from the SEER-Medicare cancer registry on more than 27,000 women with an initial diagnosis of stage I-IV breast cancer, made between 2007 and 2009, and followed up until 2015. Figures for all-cause mortality among women with no comorbidities (more than half the sample) showed survival among women living in neighbourhoods classified as least hazardous to investment was almost 40% higher than among those classified most hazardous. Among those living in areas classified 'moderate' or 'low' hazard, the survival advantage was 27% and 10% respectively. A similar pattern was found for breast cancer-specific mortality, and the disparities remained after controlling for health insurance.

> Women living in the most deprived neighbourhoods had significantly shorter
> overall survival compared to those living in the least

A study by Gerlareh Sadigh, published in February 2022, in *JAMA Oncology*, strengthened the evidence linking neighbourhood to cancer outcomes. The study aimed to investigate racial

disparities in survival outcomes for early hormone receptor-positive breast cancer after adjusting for insurance status and neighbourhood deprivation. It used a post hoc analysis of data on more than 9,700 women recruited to the TAILORx trial – a prospective randomised clinical trial looking at the use of genomic signatures to select treatment for women with early-stage breast cancer.

The Sadigh study found that black race compared with white race was associated with a statistically significantly shorter relapse-free interval (HR 1.39, $P = 0.02$) and overall survival (HR 1.49, $P = 0.009$), after adjusting for insurance and neighbourhood deprivation level. But it also found that women living in neighbourhoods in the highest deprivation quartile had shorter overall survival compared to those living in the lowest quartile regardless of self-identified race (HR 1.34, $P=0.04$) – an effect size similar to that reported in the Beyer study the previous year.

Epidemiology of stress risk

Other studies have looked at cancer incidence and outcomes related to specific stressful experiences. Paskett mentioned a 2017 study by Siegal Sadetzki, published in *Cancer*, which showed that holocaust survivors had an increased risk for cancer at all sites (HR 1.06, $P<0.001$), with the differences found to be most striking for colorectal cancers (HR 1.12, $P=0.07$) and lung cancers (HR 1.37, $P=0.008$). Psychological responses to a myriad of acute stressors leading to prolonged heightened anxiety was one of the major factors explored in that study that could explain the raised cancer risk.

The role of stress in explaining worse cancer outcomes emerged as an unexpected finding from a 2009 epidemiological study, published in *Cancer*, of 3.7 million cancer cases documented in the US SEER registry, which aimed to explore why being married versus single at diagnosis seemed to lead to better cancer outcomes. The dominant assumption at the time was that the survival impact was mediated by increased support, potentially leading to better compliance with therapy. But the study found important differences between the relative outcomes for single people, depending on whether they had never been married, or were separated, or widowed or divorced, indicating that single status in itself may not be the main driver.

While survival for all single patients was worse on average than for married patients, the difference was markedly greater for patients who were separated at the time of diagnosis, followed by widowed, divorced, and never married patients. The survival rates for patients who were separated were 72% those of married patients at five years (lower by almost one-quarter), and 64% at 10 years (lower by almost one-third).

The findings led the authors to point to the need to investigate possible direct physiological relationships between stress levels and cancer outcomes: “While other socioeconomic variables could contribute to this phenomenon, further research into the immunologic correlates of the acutely stressful condition of marital separation should be conducted,” they concluded.

> “Factors influencing the course of cancer at a molecular level are intimately tied to ‘upstream’ social and environmental determinants”

Here was the second key message that Paskett wanted to get across to the cancer researchers attending the AACR 2022 Presidential Symposium: The factors influencing the course and outcomes

of cancer at a molecular level are intimately tied to 'upstream' social and environmental determinants, and efforts to improve cancer outcomes need to understand the links and look for ways to intervene.

From social determinants to molecular drivers: Joining the dots

Paskett highlighted in particular research done at the University of Chicago to explain data showing black women in Chicago were much more likely to die of breast cancer than white women (38.3 vs 23.6 per 100,000), and that the disparity had been rapidly growing.

In a study published in 2008, Sarah Gehlert and Funmi Olopade found that black women living in predominantly black Chicago neighbourhoods were isolated due to poverty, crime, and fractured communities. They experienced stress as a result of being afraid to go out and not being able to form casual relationships with neighbours.

To understand causal links between isolation and cancer, a team of investigators from across many departments at the University of Chicago – including the University's Institute for Mind and Biology and Departments of Comparative Human Development, Psychology, Pathology, and Medicine – used an animal model. Their study, published in *PNAS* in 2009, showed that, at 15 months, Sprague-Dawley rats genetically prone to developing breast cancer had very significantly higher tumour burdens if they had been kept on their own in isolated conditions compared to their litter mates who had been kept in groups.

Furthermore, when exposed to stress, cortisone levels of isolated rats took much longer to return to normal levels (if ever) than rats kept in groups. The team concluded that higher reactivity to stress led to tumours developing through heightened secretion of glucocorticoids.

> "The model offers a framework to identify mechanisms whereby psychosocial stressors increase growth and malignancy of breast cancer"

They also noted that "an array of behavioural measures demonstrated that socially isolated females possessed an anxious, fearful, and vigilant phenotype," and proposed that their model could be used as a framework for studying the interaction of social neglect with genetic risk, "to identify mechanisms whereby psychosocial stressors increase growth and malignancy of breast cancer".

The findings stimulated further studies into the connection between stress and the course of a cancer in both animals and humans, said Paskett, which have confirmed that CNS perceptions of stress lead to activation of the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis. "The stress hormones that are released modulate the activity of multiple components of the tumour microenvironment, affecting tumour cell growth, migration, invasive capacity, angiogenesis, and activate oncogenic viruses and alter immune function," she said. "The way I explain it is that if the immune system is always revved and there's an abnormal virus or cancer cell it won't have enough bandwidth to go and attack it."

A multi-level, multimodal approach

For Gehlert, who was director of the University of Chicago's Center for Interdisciplinary Health

Disparities Research (CIHDR) at the time of the 2008 and 2009 studies, the relevance of the findings stretched well beyond the specific disparities in breast cancer outcomes between black women and white women in Chicago that they were investigating.

What was important was the value of the approach they used – the "CIHDR approach" – of following the links in the chain from the social determinants to the impact at cellular level, starting "at the top, with race, poverty, disruption, and neighborhood crime," moving onto "isolation, acquired vigilance, and depression; then to stress-hormone dynamics; and finally to cell survival and tumor development."

That same approach could equally be used to investigate different disparities and different cancers/diseases.

It was a point that Paskett too took pains to emphasise. Into this model can be fed overarching contextual factors, she said, including society, discrimination, work environments, family demands (marital status and care giving roles) and individual factors (such as body mass index and genetics).

The purpose of such work, of course, would be not just to understand disparities, but develop strategies to address them. At a clinical level, recognising the higher risk for a poor cancer outcome associated with living in a deprived and stressful neighbourhood as 'a vital sign' could be one way to do this. Possible interventions suggested by Paskett included "providing health navigators to help patients complete what doctors recommend by assessing barriers to care and then addressing those individual barriers."

More effective, of course, would be action at a public health level to address the disparities in the array of overlapping and interacting social determinants that can be linked – using the CIHDR model – to the changes in cell behaviour that promote cancer growth and jeopardise outcomes.