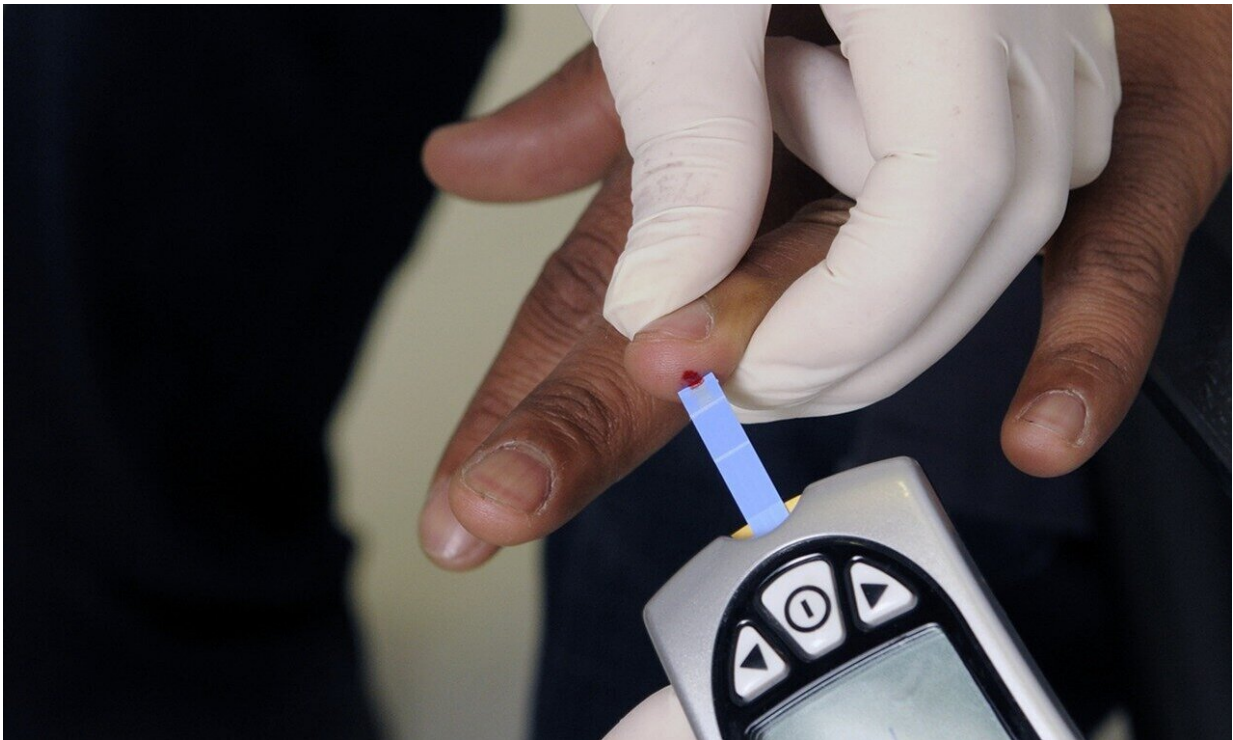


High cholesterol fuels cancer by fostering resistance to a form of cell death

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Chronically high cholesterol levels are known to be associated with increased risks of breast cancer and worse outcomes in most cancers, but the link has not been fully understood.

In a study appearing online Aug. 24 in the journal *Nature*

Communications, a research team led by the Duke Cancer Institute has identified the mechanisms at work, describing how [breast cancer cells](#) use cholesterol to develop tolerance to stress, making them impervious to death as they migrate from the original tumor site.

"Most [cancer cells](#) die as they try to metastasize—it's a very stressful process," said senior author Donald P. McDonnell, Ph.D., professor in the departments of Pharmacology and Cancer Biology and Medicine at Duke University School of Medicine. "The few that don't die have this ability to overcome the cell's stress-induced death mechanism. We found that cholesterol was integral in fueling this ability."

McDonnell and colleagues built on earlier research in their lab focusing on the link between high cholesterol and estrogen-positive breast and gynecological cancers. Those studies found that cancers fueled by the estrogen hormone benefitted from derivatives of cholesterol that act like estrogen, stoking cancer growth.

But a paradox emerged for estrogen-negative breast cancers. These cancers are not dependent on estrogens, but high cholesterol is still associated with worse disease, suggesting a different mechanism might be at work.

In the current study using [cancer cell lines](#) and mouse models, the Duke researchers found that migrating cancer cells gobble cholesterol in response to stress. Most die.

But in the what-doesn't-kill-you-makes-you-stronger motif, those that live emerge with a super-power that makes them able to withstand ferroptosis, a [natural process](#) in which cells succumb to stress. These stress-impervious cancer cells then proliferate and readily metastasize.

The process appears to be used not only by ER-negative breast cancer

cells, but other types of tumors, including melanoma. And the mechanisms identified could be targeted by therapies.

"Unraveling this pathway has highlighted new approaches that may be useful for the treatment of advanced disease," McDonnell said. "There are contemporary therapies under development that inhibit the pathway we've described. Importantly, these findings yet again highlight why lowering cholesterol—either using drugs or by dietary modification—is a good idea for better health."

More information: Dysregulated cholesterol homeostasis results in resistance to 2 ferroptosis and increased cancer cell metastasis, *Nature Communications* (2021).

Provided by Duke University Medical Center

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