

Nobel-winner Watson: Do antioxidants promote cancer?

- 19 March 2013 by [James Watson](#)
- Magazine issue [2908](#). [Subscribe and save](#)
- For similar stories, visit the [The Big Idea](#) and [Cancer](#) Topic Guides

Antioxidant foods and pills could heighten the risk of cancer and diabetes, argues the co-discoverer of the structure of DNA

ANTIOXIDANTS have long been touted as powerful disease-preventing agents. Billions of dollars are spent annually on antioxidant supplement pills. Untold additional sums are spent by health-conscious consumers loading up on antioxidant-rich foods like blueberries and blackberries. However, claims that these products let human beings live healthier and longer lives do not stand up to [serious scrutiny](#).

Many, many clinical trials reveal that they lead to virtually [no improvement in the functioning of our cardiovascular systems](#). There is less data about antioxidants and cancer but the most recent large-scale trial to see whether the antioxidant vitamin E prevents cancer was halted when not only was no benefit shown, but slightly [more prostate cancer was observed in vitamin E takers](#).

It is easy to see how antioxidants came to be regarded as an aid to health. The oxidising molecules, or oxidants, that they neutralise in our bodies, though essential to normal biological function, are toxic in excess. They damage DNA and proteins, and so can cause cancer. But this simplistic view overlooks [evidence that a more complex system is at play](#) (*Open Biology*, [doi.org/kpp](https://doi.org/10.1098/rsob.140100)). For example, vegetables such as Brussels sprouts and broccoli that have been linked with anti-cancer benefits may actually generate these benefits through [their ability to promote pro-oxidative cellular processes](#) rather than antioxidative ones.

The fact that antioxidant dietary supplementation might lead to more not less cancer should come as no surprise to the world's better-informed cancer therapists, who know that ionising radiation treatment kills cancer cells largely through creation of oxidants called reactive oxygen species (ROS). And though it was generally believed that major chemotherapy drugs like paclitaxel kill each cancer through different means, there now is a [growing consensus that they too are highly effective generators of the powerful oxidant](#) superoxide, the hydrogen radical and hydrogen peroxide, the three major components of ROS.

This at last explains the long-disturbing findings that when a cancer becomes resistant to one form of chemotherapy, it simultaneously becomes resistant to all the other, better chemotherapy agents, as well as to further radiation therapies.

Recent research on pancreatic cancer has demonstrated that in cells of aggressive, resource-hungry tumours, antioxidant levels are greatly elevated. These endogenous antioxidants – synthesised by the body – arise to keep ROS from triggering sensors that initiate a process called apoptosis, or programmed cell death. This raises an important possibility: if we can learn how to reduce antioxidant levels specifically in cancer cells, we may be able to successfully treat many types of late-stage cancers that are now incurable.

Cell killer

To understand how we might achieve this goal, we first need to understand better how the body controls antioxidant levels. In the absence of ROS, levels of cellular antioxidants are normally kept to very low levels by an enzyme called Keap 1 ubiquitin ligase. This destroys a transcription factor – a molecule that controls gene expression – called Nrf2 that is used to [turn on synthesis of the major antioxidants](#). When, however, ROS levels rise to therapeutically effective levels, [Nrf2 transcription factors somehow become liberated](#) and direct the synthesis of some 10 different antioxidants that destroy ROS.

I suspect that once a cell is committed to moving through the cell cycle to replicate, it turns up antioxidant synthesis to protect the vulnerable single-stranded chains of replicating DNA. Though most cancer therapists have long suspected that cells undergoing division are most vulnerable to cell-killing agents, the truth may be just the opposite. The recent important observation that populations of [stem cells have relatively high antioxidant levels](#) may be due in part to their higher content of cells undergoing cell division.

The realisation that high antioxidant levels can explain why ROS-driven therapy stops working represents a big conceptual step forward. But what prospect do we have of developing drugs that preferentially kill cancer stem cells without exhibiting significant toxicity to non-cancerous cells? Fortunately there exists one such drug, Metformin, already in wide use for stopping the progression of type 2 diabetes.

Relatively safe to use and the most prescribed drug in the world, Metformin has long been the world's most effective anti-type 2 diabetic weapon. In the past five years, [evidence has steadily accumulated](#) that its use results in 20 to 40 per cent lower incidence of many major cancers, such as those of the lung, [pancreas](#) and colon.

Other evidence also points to Metformin's cancer preventative properties. Kevin Struhl's laboratory at Harvard Medical School in Boston screened more than 1000 drugs already approved for medical use against non-cancerous disorders to see if any of them also had anti-cancer potential. Their most effective candidate was Metformin. They also discovered that [Metformin preferentially kills cancerous mesenchymal stem cells](#), the most untreatable of all cancer cells. It does this by unleashing the ROS-driven apoptotic death pathway in cells that possess antioxidants in sufficient amounts to nullify even traces of ROS-driven apoptosis. As soon as possible, work should commence to measure the antioxidant levels in cancer stem cells exposed to Metformin.

Cancer is not the only disease in which antioxidants may play a role. Type 2 diabetes may arise when antioxidants block essential ROS signalling to the liver, which normally heightens insulin sensitivity and lowers the rate of glucose synthesis.

The essential role of ROS in maintaining healthy liver function emerged in 2009 from [seminal experiments](#) carried out by Michael Ristow's laboratory at the University of Jena, Germany. These showed that physical exercise prevents type 2 diabetes via increased ROS production traceable to stressed electron transport systems in mitochondria (the tiny organs in cells that produce energy, partly via chains of reduction and oxidation reactions). Yet exercise had no such positive effect in those who simultaneously consumed daily doses of antioxidant vitamin C and E supplements.

The same mechanism – stressed mitochondrial-generated ROS – is also likely to be at the heart

of why [men who frequently exercise have some 20 per cent lower incidence of colon cancer](#).

This evidence leads me to suspect that many nascent cancers are nipped in the bud through normal fluctuations in ROS levels. We return, thus, to our initial question: are supplemental, external sources of antioxidants helping anyone?

I believe the question must be asked as to whether daily consumption of antioxidant foods and pills significantly heightens the risk not only of cancer but also type 2 diabetes. However, finding out if regular consumers of antioxidants have an elevated risk of disease will not be easy due to inherently incomplete data about the actual frequency and doses consumed. Testing in animal models is unlikely to provide results of sufficient power or persuasiveness to settle the question.

Perhaps we should only test antioxidants on individuals at risk of neurodegenerative disease. A rationale for this is provided by a number of studies which show evidence that Parkinson's disease can arise from unintended exposure to strong oxidants. We still do not know why people with Parkinson's disease come down with 30 per cent fewer solid cancers of all forms, but it could be due to (genetically caused) lower levels of antioxidants.

At present we clearly possess insufficient facts to let the world uncontroversially move toward a truly healthy use of either oxidants or antioxidants. In trying to learn more, we must never forget that preventing a disease almost inevitably costs less than its cure.

This article appeared in print under the headline "Antioxidant antidote"

Profile

James Watson won a Nobel prize in 1962 for co-discovering the structure of DNA. He later helped establish the Human Genome Project and became director of the Cold Spring Harbor Laboratory, New York, focusing on the study of cancer