Will an Aspirin a Day Keep Cancer Away?

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The first hint of protective factor of aspirin

- In the late 1970s by a surgeon in Melbourne
- He wanted to figure out why his country had a relatively high rate of colorectal cancer.
- He and colleagues interviewed more than 700 cancer patients and comparable number of healthy people
- Conclusion => Australians‘ penchant for beer, fatty foods and red meet all seemed to predispose them to disease
- But they also found a surprising protective factor => people who regularly used aspirin were 40% less likely to develop colorectal cancer than those didn‘t take the drug
Studies from UK

- Offered the first evidence from placebo-controlled clinical trials that regularly taking low doses of aspirin wards off other types of cancer as well.
- The studies found that death rates from several tumor types were as much as 37% lower.
- People who developed a cancer => taking aspirin seemed to slow the spread of tumors to other parts of the body.
- „It’s just about the first proof of principle that a simple compound of any kind can reduce the risk of several cancers“
These reports have raised attractive possibility that aspirin could serve as the first anticancer drug for general population.

Debate about the risks and benefits.

Other suggestion => medical societies and policymakers should also consider aspirin‘s general cancer-fighting effects.

The research lost momentum in the past decade when one NSAID drug, Vioxx, was pulled off the market because of safety concerns.

What is the mechanism by which aspirin and other NSAIDs protect against cancer???
How does taking aspirin ward off cancer?

- Researchers still don’t understand the mechanism

- Aspirin (acetylsalicylic acid) inhibits two forms of enzymes known as cyclooxygenases (COX) that convert arachidonic acid into lipids called prostaglandins
  - COX-1 protect the stomach lining
  - COX-2 involved in inflammation

- Researchers have concluded that aspirin prevents cancer mainly by blocking the activity of COX-2 (the same inflammation-driven responses that help tissue recovery from wound injury may also help tumors grow)

- Some new clinical studies of low-dose aspirin suggest that COX-2 isn’t directly involved at all => low doses this drug doesn’t block COX-2 but still impairs platelets via the COX-1 pathway
How does taking aspirin ward off cancer?

- Studies suggest that platelets blunt immune attack on cancer cells and help them take root in a new place.
- Other experiments suggest that activated platelets can also stimulate the COX-2 pathway in adjacent cells => this would explain how aspirin could block early stages of colorectal cancer.
- Drugs that target only COX-2 (Vioxx, Celebrex) unacceptably raised heart attack risk => efforts to make an alternative to standard aspirin haven’t yet panned out.
Comeback

- Aspirin and some other NSAIDs first bore out their promise in trials published starting in 2000 => people who had precancerous colon polyps removed and others genetically prone to colorectal cancer
- Epidemiological evidence has suggested that aspirin could have broader anticancer effects => it’s not conclusive
- This evidence come from studies in which people answered questions about their past use of medications
- Hopes for aspirin fell in 2005
- Vioxx, Celebrex
Results

- First result => aspirin was taken daily => 37% fewer deaths from cancers after 5 years
  - Found that people who taken regularly aspirin had more stomach bleeds => these incidents were not fatal => people recovered and the bleeding risk went down after several years on aspirin

- Second result => people on aspirin who developed cancer were 36% less likely to have tumors that had spread

- Third result => remarkable consistency in the drop on cancers among aspirin users in epidemiologic studies and clinical trials
Chan and his suggest

- Chan is part of an international panel on cancer prevention that, in response to the Rothwell studies, plans to update its stance on aspirin published 3 years ago.
- The panel suggest that people take low doses of aspirin daily starting around age 50 and stopping by age 70.
- Also is important when doctors should screen patients for the ulcer-causing *Helicobacter pylori* bacterium => positive test => treating this people by antibiotics before putting them on aspirin (reduce the risk of bleeds).
U.S. researchers suggest

- It’s time to update guidelines on the risks and benefits of daily aspirin use
- The group had endorsed its preventive prowess for heart attack and stroke => discounted its anticancer effects
- The potential to protect against both cancer and heart disease could tip the balance toward recommending aspirin for many more healthy adults
- Others are more cautious about recommending aspirin => only people with a particular genetic profile will see their cancer risk go down if they take aspirin
Researchers from Houston in Texas are also wary => they thought they could put aspirin in the drinking water => but they admitted that everybody needed a more personalized approach

All may become clearer soon after reports on longer-term effects of aspirin on cancer risk => this will be crucial

Thun says: „We don‘t want to mess this up“. 
THANK YOU FOR YOUR ATTENTION 😊
When lymphocytes run out of steam

Emanuuel Martin et al.
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immune cells

crucial part in protection against micro-organisms - viruses and bacteria

T cells and B cells

response is driven by antigen receptors on the cells’ surface

leads to rapid cell proliferation and immune protection

Proliferation depends on metabolic adaptation
children from several unrelated families developed a severe immunodeficiency at birth or at a very young age.

persistent infections with viruses such as Epstein-Barr and varicella zoster

infections from bacteria such as pneumococcus

patients might be suffering from an inherited immunodeficiency that compromises lymphocyte function.
Sequencing of DNA from the affected children all carried a mutation in CTPS1 -> absence of this enzyme in the patients’ lymphocytes

CTPS1 is one of two forms of CTP synthase enzymes

production of cytidine nucleotide triphosphate (CTP)

required for cellular DNA and RNA synthesis
normal lymphocytes express both CTPS1 and CTPS2
CTPS1 is present at low levels - markedly expressed in activated lymphocytes
CTPS2 is already expressed at high levels in non-activated lymphocytes
Analyses of T and B cells from the CTPS1-deficient patients
cells’ capacity to synthesize DNA and proliferate following stimulation of the antigen receptor was severely compromised
Intracellular levels of CTP were also very low
- Defects were reproduced when CTPS1 expression was artificially reduced in normal lymphocytes.
- When 3-deazauridine, a pharmacological inhibitor of CTPS enzymes, was used to suppress their activity, defects were corrected when CTPS1 was introduced into cells of CTPS1-deficient patients by retrovirus-mediated gene transfer.
- When CTP was added to the cells’ culture medium.
findings show that CTPS1 and its product, CTP, are required for lymphocytes to proliferate intensely during antigen-induced activation.

In the absence of CTPS1, antigen-stimulated lymphocytes do not produce sufficient quantities of CTP, causing defects in DNA synthesis and cell proliferation.

These effects explain in large part why CTPS1-deficient children develop life-threatening viral and bacterial infections.
even though CTPS2 is expressed in lymphocytes, it cannot replace CTPS1

possible explanation for this is that CTPS1 is much more active than CTPS2

possibly to modifications such as phosphorylation or co-factor binding that could influence the enzymes’ aktivity

differences between CTPS1 and CTPS2 remains to be clarified
The data also raise the provocative possibility that pharmacological inhibitors of CTPS1 could be useful tools for treating human diseases associated with excessive or uncontrolled lymphocyte proliferation:

- transplant rejection
- graft-versus-host disease
- some forms of cancers such as leukaemia and lymphoma
CTPS inhibitor 3-deazauridine has already been shown to display some therapeutic efficiency against leukaemic cells *in vitro*

Although it probably also inhibited targets other than CTPS in these cells

development of more-specific inhibitors of CTPS1 will help the further investigation of this possible therapeutic methods
Thank you for your attention.