Spotlight

Should we stop investing in chemoprevention trials in oncology?

Opening opinion: Yes

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As a family doctor in an inner-city, fairly deprived practice, I want to reduce the above-average risk of cancer in my patients. I routinely advise them to engage in physical activity, lose weight, stop smoking, and reduce alcohol consumption—because these factors are known to be associated with cancer. But it is a lot of effort for little gain; implementing prevention lacks a strong research base, and many questions about reducing risk factors remain unanswered.

Chemoprevention sits awkwardly in the cancer prevention world. When researchers and activists call for more prevention research they are not generally talking about pills—rather, four in ten cancers are linked to lifestyle. As indicated at the Union for International Cancer Control World Cancer Leaders Summit in 2014, more than 10% of the world's adult population is obese, and 25% of cancer cases in high-income countries are related to diet and physical activity. At least 1 billion people still use tobacco worldwide, which is responsible for 20% of all cancer deaths. An analysis from the Organisation for Economic Co-operation and Development (OECD) suggests that implementing a package to improve diet, increase physical activity, and reduce obesity in Europe would, after 10 years, lead to gains of more than 3 million years of life free of cancer.

Therefore, although we know that some interventions work in promoting healthy lifestyles, we still do not know how to implement prevention systems, in which all relevant agencies work together to prevent or reduce the impact of public health problems; indeed, this was the conclusion of the UK's National Prevention Research Initiative after four rounds of funding. Prevention needs research on synthesis and translation, communication, and implementation. Furthermore, research on the cost-effectiveness of public health interventions and modelling of long-term impact on disease outcomes is vital, but under-resourced.

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But isn't research on chemoprevention a legitimate expenditure? Well, suggesting disinvestment in any area of cancer research is unpopular, but decades of chemoprevention research have so far not delivered—we are no closer to finding a successful chemopreventive intervention that has significant benefits. Even aspirin, which has been shown to reduce colorectal cancer incidence hasn't so far had an effect on cancer-specific mortality, and note that in the USA there are 100 000 hospital admissions related to non-steroidal anti-inflammatory drugs and 16 500 deaths annually. Hormonal agents, such as tamoxifen, raloxifene, and the aromatase inhibitors, have been shown to reduce breast cancer incidence, but we still lack evidence for mortality reductions. Trials with nutrients have, at best, produced mixed results; the carotenoids failed to reduce lung cancer mortality, and selenium is only selectively protective for prostate cancer (as are 5α-reductase inhibitors). These have all been huge, expensive trials, and even when there is evidence of health benefits, people seem unwilling to take a tablet that might mitigate against some future risk of cancer—note the poor uptake of tamoxifen in high-risk women with breast cancer.

Of course, none of these failures means we should abandon chemoprevention research; as we enter an era of personalised medicine, we need to increase our armamentarium of interventions that might reduce risk in targeted groups. However, this debate is about investment in large-scale, population-based, chemoprevention trials, and we should only contemplate such trials if we are convinced that the candidate drug has potential to reduce mortality, with acceptable levels of adverse effects. We should also determine whether people would be prepared to take the medication, as current evidence suggests that the population is, at best, ambivalent about treating theoretical future risk of cancer. Furthermore, the harmful effects associated with candidate drugs will be experienced by large numbers of people who do not stand to benefit.

Preventive research is a finite resource—every penny that we spend on expensive chemoprevention trials means less research on lifestyle and public health strategies to reduce the burden of preventable cancers across the world. Let's remember that 80% of the world's burden of cancer is in

low-income and middle-income countries; on a global scale, if we could fund research on ways to reduce vaccine-preventable cancers, tackle tobacco and alcohol use, and implement low-cost screening we could bring about cancer mortality reduction on a scale that no chemopreventive approach could currently deliver. Seen through the lens of global equity, it is difficult to justify huge investment in chemoprevention; an affordable, effective agent that could be used across the world seems a distant prospect.

In summary, chemoprevention research should continue, but it needs to change and we should be cautious about repeating the mistakes of the past. There is a huge research agenda in cancer prevention research, and limited research funding; we are obliged to choose areas with the potential to bring the most benefit to the most people.

Counter opinion: No

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Prevention of cancer has been the leading contributing factor to a 27% reduction in cancer mortality observed between 1991 and 2016 in the USA. Seven approaches to prevention are proven to work: the avoidance of exposure to cancer risk factors such as tobacco and sun; the adoption of healthy lifestyles, including food choices and exercise; screening for and treating cancer precursors, such as removal of colorectal adenomas; vaccination against hepatitis B and HPV; treatment of viral infections, such as HIV and hepatitis C; organ removal in individuals at very high risk for certain cancers; and chemoprevention, actively consuming or applying a natural or synthetic substance that reduces the risk of cancer. Although chemoprevention has not been widely adopted, this approach offers some unique advantages. It does not require major changes in behaviour, can be relatively inexpensive, can be made widely available around the world, and can target cancers for which other approaches to prevention and treatment are ineffective. To date, these theoretical advantages have not been realised, and confidence in chemoprevention as a strategy warranting continuing research investment has waned; some argue for curtailing investment in chemoprevention research and particularly ending investment in large chemoprevention clinical trials. Although continued modification of our approach to chemoprevention research is needed, curtailing our investment in chemoprevention research would be a mistake.

There are four chief arguments for abandoning further chemoprevention research. First, many chemoprevention trials, particularly for vitamins and various natural substances, have failed to consistently find a cancer prevention benefit and some have found harms. Second, these trials are expensive and demanding to perform. Third, chemoprevention has not been widely adopted into clinical care. Finally, other approaches to prevention, such as healthier lifestyles and screening, are not being implemented equitably or completely. None of these arguments individually or in combination justifies the serious step of ending investment in chemoprevention research, including clinical trials.

Thoughtful investment in chemoprevention research should continue, and this research must be expanded to address the appropriate uptake of cancer preventive therapy into clinical practice. Chemoprevention has been shown to work in some settings. The selective oestrogen receptor antagonists, raloxifene and tamoxifen, reduce the risk of breast cancer by as much as 40% in populations of women at increased risk for breast cancer and aromatase inhibitors prevent oestrogen-positive breast cancers. 5-α reductase inhibitors reduce the risk of developing prostate cancer. Oral contraceptives reduce the risk of ovarian cancer. COX-2 inhibitors reduce colorectal cancer risk and aspirin prevents some colorectal cancers and might reduce the risk for gastric, oesophageal, and other cancers. Second, the era of precision medicine now allows clinicians to tailor therapies to the characteristics of individual patients. Studies to tailor cancer screening to individual risk are being conducted. Future research to find potential agents to prevent cancer should be based on identification of specific molecular targets in populations with identifiable genetic, epigenetic, or environmental exposures that define populations at higher than average risk. Identification of relevant biomarkers can facilitate a stepwise approach to evaluating potential agents. Third, the fact that clinical uptake has been surprisingly low should not be interpreted as meaning that chemoprevention will not or should not be more widely implemented.

The reverse is true. Preventive therapy with prescription medications that are associated with costs and side-effects is a linchpin of our approach to reducing cardiovascular disease in individuals with specific risks for disease. Cancer preventive therapy, a far more accurate and appealing description than chemoprevention, can and should become more acceptable to clinicians and the public. Although efforts to promote adoption of a healthy lifestyle are crucial and necessary, just as they are in the prevention of cardiovascular disease, for many patients, taking a pill is far easier and more practical. Increasing cancer screening is a high public health priority but is not available in many low-income and middle-income countries. Again, promoting an affordable proven cancer preventive therapy might be more feasible and widely available. Finally, finding a medication that can prevent a cancer that is not otherwise known to be amenable to prevention or screening has the potential to substantially reduce the burden of cancer. But there is no hope of discovering such a therapy if we stop conducting the research and the clinical trials to find it.