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EDITORIAL

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Time to abandon early detection cancer screening

1 | INTRODUCTION

Ever since 1971, when the US President signed the "War on Cancer"[1] National Cancer Act, screening has been a hallmark in cancer control. The fundamental idea was that more cancers would be cured if they were detected and treated before symptoms arise. During the following decades, astronomic amounts of money and great hopes were invested to implement population-based screening programs.

Over time, prioritization of cancer screening has hardly declined. The expectation of success has rather increased and, for example, the attendance to mammography screening for early detection of breast cancer has indeed been used as a quality indicator of the health care system.[2] Aggressive efforts to diagnose pre-symptomatic cancer becomes an attractive resort to accelerate the reduction in cancer mortality. Until relatively recently, this remained an elusive goal.[3] Currently, declines in cancer mortality have been documented for several cancers. However, the lion's share for this improvement seems to have been due to therapeutic advances rather than screening.

Nevertheless, several investigators continue to argue that screening has made a substantial contribution to this improvement for breast cancer[4] and others claim that reducing screening intensity for prostate cancer can be detrimental.[5] Clearly, such screening efforts continue to have strong supporters. Moreover, the advent of new biomarkers, for example genetic or epigenetic test panels[6] rekindle wider interest in screening for cancer control. Many biotech companies and start-ups are fiercely building a case for the adoption of new methods of massive testing for screening purposes.

Screening has remained enthusiastically recommended by health care providers as an indicator of commitment, progress and success. The value of early detection of cancer by screening has an intuitive appeal both to medical practitioners and the general population. Promotion of population-based cancer screening remains a key activity for many cancer societies and charities. Many patient organizations—dominated by cancer survivors many of whom are convinced that screening saved their lives—have become powerful advocates. A cadre of scholars have based their scientific careers on theoretical and empirical studies of cancer screening. And an even larger community of health care providers make their living on screening, diagnostic workup, treatment and surveillance of cancer patients.

Screening is big business: more screening means more patients, more clinical revenue to diagnostic and clinical departments, and more survivors in need of care and follow-up.[7] Critics are met with fierce opposition[8] and not much changes. We believe, however, that a major, radical change is urgently needed after more than four decades of enormous investments and failing expectations.

2 | EARLY DETECTION VERSUS PREVENTIVE SCREENING

Cancer screening is based on two fundamentally different principles: early detection and prevention.[9] The classical screening approach and the focus of our essay is early detection of already invasive cancer in the entire population. Examples are mammography screening for breast cancer and prostate-specific antigen (PSA) screening for prostate cancer. The assumption is that a meaningful proportion of cancers are initially curable with screening, but progress to a metastatic and incurable stage without screening. The primary aim of early detection screening is to reduce cancer mortality because it cannot reduce cancer incidence (in fact, it *increases* cancer incidence through overdiagnosis, see below). However, as treatments for symptomatic cancers are getting more effective and many more cancers that at the advent of cancer screening could only be cured through early detection are now well manageable when patients have become symptomatic.

Conversely, preventive screening tests are designed to detect and remove precursors of cancer rather than established malignant lesions. Examples are Pap-smear screening for cervical cancer and colonoscopy screening for colorectal cancer. Their main effect is to reduce the risk of cancer through a reduction of cancer incidence, following removal of precancerous lesions.[9] The reduction in cancer mortality is achieved through the reduction of the incidence. Of course, prevention screening tests may concurrently also achieve early detection of asymptomatic malignancies. Unfortunately, however, most cancer types have no

established readily detectable precursor lesion. Early detection therefore remains the only available goal of screening for most human malignancies.

3 | SCREENING EFFECTIVENESS

3.1 | Early detection screening

Early detection screening aims at reducing cancer mortality, but such benefit is disappointingly small or not existing. For several malignancies—including neuroblastoma,[10] lung cancer with chest radiographs[11] and ovarian cancer with the tumour marker CA 125[12]—population-based screening efforts were abandoned due to lack of effectiveness, poor performance of the screening test, unacceptable overdiagnosis or a combination of these concerns. For some malignancies, early detection screening strategies are still occasionally proposed for specific high-risk patients (eg, low-dose helical computer tomography imaging for smokers[13] or for BRCA carriers). Nevertheless, when it comes to screening the entire population at a given age, today, the centre of the stage in early detection cancer screening is dominated by mammography for breast cancer and PSA-testing for prostate cancer.

It is beyond the scope of this essay to review the overwhelming literature on mammography[14] and PSA screening.[15] An updated meta-analysis of available trials[16] shows no or very limited evidence for improvement in prostate cancer mortality with PSA screening. Only trials with obvious quality deficits have suggested a benefit for breast cancer-specific mortality with mammography.[7] We acknowledge that a reduction in all-cause mortality may be hard to demonstrate following screening for only one specific cancer. All-cause mortality is, however, the only outcome that cannot be misclassified and takes into account iatrogenic causes of death attributable to screening. Summary relative risk estimates for all-cause mortality are 0.99-1.00 for both PSA screening and mammography with extremely tight confidence intervals.[7,16] Recent observational data from population-based screening programs in Norway,[17] the Netherlands[18] and Denmark[19] also do not support any clinically meaningful breast cancer mortality benefit with mammography screening.[14]

Lead time bias, the amount of time between the detection of a cancer through screening and its expected detection if no screening had been done, is the key artefact in the screening process. We acknowledge that from the standpoint of the patient, treating an advanced or metastatic tumour is not equivalent to treating a small, localized one. However, if there is no mortality benefit with early detection screening, this is equivalent to self-deceit.According to a recent meta-analysis, PSA screening leads to seven more diagnoses of prostate cancer per 1000 men screened due to overdiagnosis, while at the same time, the effect on prostate cancer mortality is either zero or at best 1 less death per 1000 patients screened for 10 years.[16] When one balances the societal burden of having seven more patients going through surgery and adjuvant therapy for an early cancer detected by screening, versus at best one fewer with more advanced stages requiring more aggressive treatment, it is doubtful that the latter scenario is preferable.

3.2 | Preventive screening

Preventive screening has been adopted widely for cervix and colorectal cancer. The benefits seem stronger and more uncontroversial than for early detection screening. Data from randomized trials for cervical preventive screening tests are scarcely available, but observational data suggest large benefits.[20,21] For colorectal cancer, randomized trials with flexible sigmoidoscopy show that cause-specific incidence and mortality is reduced[22]; randomized trials on colonoscopy screening are currently underway.[23]

4 | OVERDIAGNOSIS

The concept of overdiagnosis of cancer was largely unknown until the1990 s, and it was fiercely disputed as a real clinical problem introduced by cancer screening until a few years ago. It is now clear that overdiagnosis is one of the overarching problems with cancer screening.[15,24–27] Paradoxically, the higher the harm of overdiagnosis through screening, the more people survive with a label of cancer (because it is overdiagnosed, it would never have harmed or killed them if undetected), and the more popular screening gets. Patient advocate groups grow bigger with people who believe screening saved their life, and more people are convinced to get screened.

Overdiagnosis is defined as the detection of a disease or condition that would not cause symptoms or death during an individuals' lifetime. Overdiagnosis is not a significant challenge in the management and treatment of symptomatic patients. In population-based cancer screening, however, where entire populations of asymptomatic and presumptively healthy individuals are subjected to testing for potential disease, overdiagnosis is a major harm. The more repetitive the screening and the more frequent the presence of asymptomatic malignant lesions, the greater the risk of overdiagnosis. Hence, for every cancer death averted, numerous individuals receive a cancer diagnosis they would not have experienced if they had not been screened.[26]

With more screening tests pushed to the market and advertised in the current era of personalized diagnostics, people who have more access to these (often expensive)

tests may actually be at higher risk of overdiagnosis and mismanagement. Paradoxically, the wealthy may experience worsening health due to excessive screening and iatrogenic disease as they consume more misleading, wasteful information than less wealthy citizens and more disadvantaged populations.[28]

Overdiagnosis is a potential problem for both early detection and preventive screening. More than 20% of breast cancers and more than half of all prostate cancers are most likely overdiagnosed. For preventive screening, overdiagnosis of precancerous lesions (such as colorectal polyps or premalignant cervical neoplasia) is also a challenge. The number of patients affected is larger than for cancer, but the treatment is often less invasive and harmful.

5 | HARM

As recent investigations show that most population screening programs have not been successful in reducing cancer mortality, the question arises whether they have caused any harm —beyond just wasted resources and side-effects of treatment that can be frequent and severe. The short answer is, inevitably, yes. To intervene in healthy populations and convey to a proportion of individuals that they might have cancer but need further diagnostic workup to confirm or exclude the diagnosis may have profound implications. That the message causes worry and existential concerns goes without saying, that a confirmed cancer diagnosis causes severe, stress-induced psychiatric and somatic outcomes for patients is now also firmly established[29,30] regardless of whether the cancer is overdiagnosed, curable or already metastatic and lethal. Existential fear, tough treatment choices, invasive treatments with short- and long-term quality of life impairments, fear of recurrence, stigma, social isolation and other strains associated with the reality of having cancer probably all contribute to that, on average, almost one in every three cancer patients meet criteria for a psychiatric disorder.[31]

The rise in the incidence of psychiatric disorders in this population starts before a cancer diagnosis is confirmed, or during the diagnostic process, with a peak in incidence just after cancer diagnosis.[30] This steep rise in psychiatric disorders coincides with a similar rise in suicide,[29,32] iatrogenic and noniatrogenic injuries[33] and severe cardiovascular events.[29,32] Population-based screening programs ensure that an unnecessarily large proportion of the population are thrown into this cascade of hazards encountered through the diagnostic process and after receiving a diagnosis of cancer.

6 | DISCUSSION

After almost half a century, the war on cancer has not been decisively won. Key advances have occurred mostly for treatment rather than for prevention. Therefore, we propose to radically reconsider strategies and priorities within the realm of cancer control.[34] Cancer screening remains promoted as a fundamental component of current and future cancer control despite constantly growing evidence that more harm than benefit is created for most commonly used tests. The currently prevailing nudging of the population towards cancer screening tests with little effect and a doubtful benefit-harm balance should be stopped. People should be informed unpassionately and objectively, and informed nonparticipation should be an accepted choice. Consequently, high attendance for such screening needs to be abandoned as a quality indicator for healthcare.

Following widespread use, the evidence that early detection screening tests such as mammography and PSA screening convey a positive benefit-harm ratio have decreased, not increased. The substantial overdiagnosis of cancer is no longer disputed. This has led for example the Swiss Medical Board to propose abolishing mammography screening programs.[35] After almost three decades of opportunistic PSA-testing on an industrial scale, and extensive assessment of mortality trends, the evidence of benefit is still so unconvincing that the US Preventive Services Task Force is now leaving it entirely to patients and doctors to decide what to do.[15] The harms, on the other hand, are of such a magnitude that even the developer of the PSA-test —in a unique op-ed in New York Times—regretted his discovery because it has created so much suffering.[36]

The lack of success with early detection cancer screening is not entirely surprising. The cell that first undergoes malignant transformation must multiply many times before a cancer becomes detectable when the number of cells is in the order of 10^9. With enormous variability in growth rate, this process usually takes many years or decades; for breast cancer, it may start already in-utero.[37] The advancement of diagnosis through screening with one or a few years (the lead time) therefore represents only a small fraction of the time-period during which tumour growth and progression takes place. The assumption that many cancers progress from a curable to an incurable stage during this short period may thus be too optimistic.

Predictions that future screening tools might perform better than existing ones are abundant. For example, novel, highly sensitive imaging techniques, detection of circulating tumour-DNA and proteomic biomarkers are in the pipeline.[6] Needless to say, we share the hope that screening tests with better performance than those available today will see the light of day. However, we are also concerned that these tests, as they are added to the armamentarium of screening, may also lead to further overdiagnosis, overtreatment (with harms unrelated to any possible benefit) and stigma along with escalating costs for screening programs, diagnostic workup, treatment and surveillance. And there is no guarantee that overdiagnosis following increased diagnostic intensity is

confined to the cancers for which documentation is already overwhelming: neuroblastoma, malignant melanoma and cancers of the thyroid, breast and prostate. Overdiagnosis of most cancer sites and types might indeed be an unavoidable consequence of increased diagnostic intensity.[24]

7 | CONCLUSION AND NEXT STEPS FOR DE-IMPLEMENTATION

During half a century, early detection screening imposed indiscriminately on the entire population to detect asymptomatic cancer has been highly promoted, almost glorified, as a strategy to improve cancer control. Long-established prerequisites for implementation of screening programs have been ignored.[38] And there has been little publicly heard discourse about the profound ethical dilemmas—applicable also to randomized trials[39]—when the general population is approached for a large-scale medical experiment. Over time, both the scientific and the health care community have been surprisingly unwilling to embrace accumulating evidence that wide population-based early detection screening for cancer has not fulfilled our expectations, and indeed induced considerable harm to a large population of healthy individuals.

Based on the past track record, the future of population-based cancer screening may lie more in preventive screening rather than early detection of already invasive cancer. Therefore, population-based early detection approaches should be abandoned. This will liberate enormous resources that may be devoted to effective cancer prevention programs and other interventions that have strong evidence for improving public health. It may also liberate resources for discovering whether early detection can be successfully applied in selected high-risk individuals instead of population-wide. Such examples of high-risk population screening include, but are not limited to, helical CT scans for lung cancer in heavy smokers; surveillance for hepatocellular carcinoma in cirrhosis; or intensive mammography screening in BRCA carriers. It may also affect preventive screening strategies, for example intensive colorectal cancer screening in people with hereditary polyposis. The rapid accumulation of evidence on new biomarkers and candidate precision tools offers also new opportunities for more circumscribed, precision screening in relatively small groups of high-risk people. Nevertheless, whether such precision screening can maximize benefits and reduce the burden of overdiagnosis and harms remains an open question.

The cancer prevention and control community should face a difficult public and provider education challenge. If early detection screening is indeed less useful and more harmful than we thought, a major question is how to disentangle from its widespread population-level endorsement. One option is to aim for de-implementing its use at a population level. This should preferably be done in an organized fashion using research methodology to be able to measure its effects. A second option would be to shift and narrow recommended age ranges and decrease the frequency of screening intervals, thus reducing the total uptake of these screening tests. A third option would be to focus more on the shared decision-making aspects of screening. For example, one could present screening recommendations as a choice of what illness one would prefer not to experience, rather than a demonstrated strategy to prolong one's life.[40] This may be more realistic and respectful of people's wishes rather than making screening completely unavailable. Nevertheless, we still need to be honest to ourselves and to our patients about what screening can achieve and what (mostly) it cannot achieve.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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