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A risk-based framework to decide who benefits from screening

Philip E. Castle and

Department of Epidemiology and Population Health, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461, USA; and the Global Coalition Against Cervical Cancer, 3800 Fairfax Drive, Arlington, Virginia 22203, USA

Hormuzd A. Katki

Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Rockville, Maryland 20850, USA

Abstract

We believe that current controversies surrounding screening might be better approached by shifting the question from ‘does screening work?’ to ‘for whom does screening work?’ We propose a ‘rule-out/rule-in’ principle as an intellectual basis and starting point for screening. Finally, we advocate the ‘equal management of equal risks’ principle as an unifying framework for developing simplified and consistent screening guidelines and practice.

We read with great interest the article on population-based cancer screening by Shieh *et al.*[1] that was recently published in *Nature Reviews Clinical Oncology*. Shieh *et al.*[1] highlight the various challenges for population-base cancer screening, including heterogeneity of the tumours and overdiagnosis/overtreatment that contributes to harms of screening. We would like to offer a different, but complementary, perspective on cancer screening, informed by our experience from serving on guidelines committees for cervical-cancer screening[2], and from proposing risk-based approaches to lung-cancer screening.

While Shieh *et al.*[1] focused on disease detection, we propose that the primary goal of screening is twofold: first, ruling out disease, for individuals with a negative test result, thereby providing reassurance of freedom from cancer; second, detection of treatable disease among those with a positive test result. Indeed, the former is the main benefit derived from screening because most people will not ultimately develop the cancer in question; therefore, biomarkers that can effectively rule out cancer should be the primary focus for screening programmes. For example, negative Papanicolaou (Pap)-test smears provide much less reassurance against cervical cancer than negative human papillomavirus (HPV) tests[3]. Thus, cervical screening programmes are increasingly incorporating HPV testing to rule out disease in ~80–95% of women, who are at sufficiently low cancer risk to be screened at an extended interval, thereby reducing the potential harms of screening.

Correspondence to P.E.C., castle.philip@gmail.com.

Competing interests statement

The authors declare no competing interests.

Biomarkers used in screening for the early detection of other cancers, however, might not be as powerful as HPV for ruling- out individuals at low risk. Consequently, many individuals at low risk of cancer must endure frequent screening and an increased chance of false-positive findings with invasive sequelae. A better approach might be to *a priori* rule out individuals at low risk of the disease from screening altogether. For example, the US National Lung Screening Trial (NLST) involved a high-risk subgroup of smokers, and showed that performing three annual CT screens, compared with annual chest radiography, reduced lung-cancer mortality by 20%; however, only 1% of the CT-prevented lung-cancer deaths occurred in the 20% of patients with the lowest 5-year risk of lung cancer[4]. Indeed, risk modelling indicates that 90% of CT-preventable lung-cancer deaths in the USA might occur in the 50% of ever-smokers at the highest disease risk[5]. Hence, half of ever-smokers could potentially be immediately ruled-out of CT lung screening programmes.

Thus, the decades-long acrimonious debate about ‘does lung screening work?’ can be resolved by answering instead ‘for whom does lung screening work?’: namely, those at sufficiently high-risk of cancer. A benefit for CT lung screening would probably not have been revealed if the NLST had included many low-risk smokers or, even worse, non-smokers. Historically, however, screening has been focused on the general population — not selected based on risk, except that associated with age — in which the target disease is uncommon. Decreasing disease prevalence increasingly degrades test performance, notably the positive predictive value (PPV), except when the test is exceptionally accurate[6]. Furthermore, a low disease prevalence can make it hard to judge whether small gains in the negative predictive value (NPV) of screening provide substantial reassurance against an already rare disease. Typically, tests or diagnostics are used among subgroups of individuals whose *a priori* risks are higher, such as those with symptoms, in whom the disease is more common and the PPV of the test is thus greatly improved. Even HPV testing is not recommended for all women, owing to both poor specificity and PPV in women aged <25 years, who have a high prevalence of benign HPV infections and early or equivocal precancerous lesions that have only limited invasive potential and commonly regress spontaneously[7]. Given that excisional treatment of precancerous lesions might cause preterm obstetrical delivery[8], treatment of low-risk, potentially regressive lesions in women of reproductive age should be avoided.

Once disease is ruled-out in individuals at low risk, further investigation for disease is warranted in the high-risk subgroup. A second, more-specific test or procedure can be applied to this smaller subgroup to ‘rule in’ and/or diagnose the disease, and can be more invasive and more expensive because it will be used in a subgroup whose potential benefit is greater than that of the general population. Except for the most-common diseases diagnosed with very accurate tests (for example, at a disease prevalence of 0.1%, a test must be at least 99% specific in order to have a positive predictive value ≥10%), no single test can effectively rule out and rule in disease; for example, Pap triage testing or other more-specific tests are required to rule in which women with a positive result of HPV testing should be sent for colposcopy and biopsy[9]. Thus, cancer screening must be envisioned as a two-step process: screening to rule out disease, followed by tests to rule in, diagnose, and treat the disease, as needed, in the remaining population.

The rule-out and rule-in steps are inseparable; however, one must recognize that the 'rule-out' step is a public health activity that involves metrics including effectiveness and cost-effectiveness, whereas the 'rule-in' step is typically a medical intervention that uses metrics of diagnostic yield. Specifically, a good screening programme should rule out individuals at low risk of developing untreatable or fatal cancer, and among those ruled in, the chance of finding treatable disease (either precancer or early stage cancer, treatment of which prevents cancer or cancer death) should be high.

'Rule-out/rule-in' screening guidelines would ideally account for not only the full history of screening and diagnostic tests, but also prescreening epidemiological risk factors, to achieve the principles of 'precision prevention'; however, precision prevention is also 'complex prevention' because simple blanket interventions for all are substituted with interventions that are precisely tailored to a person's risk factors and test results. This paradigm is daunting, but has been approached in cervical-cancer screening through the development of a risk-based framework[10]. The core principle of this approach is 'equal management of equal risks', whereby women at the same risk are managed similarly, regardless of the different combinations of risk factors and test results that can underlie the risk. Such a strategy, based on risk thresholds or bands, provides uniform standards for how frequently women should be screened (who should be ruled out), who should undergo colposcopy (who should be ruled in), and when treatment in warranted. Risk factors or biomarkers that do not meaningfully change the screening or management of large numbers of individuals, by shifting them into different risk bands, probably should not be introduced into risk models.

The equal management of equal risks principle can be assessed by checking whether subgroups of people with higher risk truly have greater benefit (risk reduction) from undergoing screening than lower-risk individuals. For example, lung-cancer risk increases with the diagnosis of additional pulmonary conditions, such as emphysema, bronchitis, or chronic obstructive pulmonary disease. In the NLST, smokers with 0–1 pulmonary conditions benefited from CT lung screening, whereas those with multiple pulmonary conditions (that is, those at highest risk) did not[4]. Perhaps those with multiple pulmonary conditions are already too sick to handle the rigours of lung-cancer therapy or are more likely to succumb to their pre-existing conditions or future co-morbidities, and thus do not benefit from earlier detection. These findings were statistically insignificant[4], but demonstrate that the equal management of equal risks principle needs to be checked because, according to this concept, those with multiple lung diseases should have had not only a benefit, but also the highest benefit.

Speculatively, these principles might be applied to screening for cancers in other organs, such as prostate-specific antigen (PSA) testing for prostate cancer, to provide a roadmap to improve the benefit-to-harm ratio[11]. For example, rather than basing guidelines on PSA levels, this biomarker can be combined with other risk factors in a risk calculation, on which clinical management could be based[11]. Repeatedly low PSA values might enable patients at very low risk of prostate cancer to be ruled-out of further screening entirely, whereas those deemed at merely low risk might be ruled out for many years[11]. Importantly, only patients at high risk of prostate cancer should be ruled in, with higher risk thresholds used to determine who needs immediate biopsies, reducing both the population harms and the detection of

potentially indolent disease[11]. If the *post-hoc* results from the PIVOT trial[12] are borne out in the clinic, those at intermediate risk or with low-grade prostate cancer might return fairly safely for further tests at short intervals, until increased risk sufficient for them to be ruled in for clinical action is predicted. Moreover, research should be focused on developing a triage biomarker to identify which individuals with a 'positive' test based on PSA risk, or which patients with low-grade prostate cancer should be ruled-in for further intervention, similar to the approach used in cervical screening for women with a positive HPV result.

Great hopes for cancer screening can still be realized, but will require a nuanced approach that starts with the question 'for whom does screening work?' We propose that new screening strategies start by screening only the highest-risk populations, who will gain the greatest benefit, to garner public acceptability. For screening programmes to have meaningful public health benefits, however, they must eventually include people at intermediate risk, who typically contribute the bulk of the cancers, which will require triage tests or algorithms to rule in only those at sufficiently high risk to warrant the next level of intervention. We propose basing 'rule-out/rule-in' screening guidelines entirely on risk, on the basis of the equal management of equal risks principle for simplified and consistent management.

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