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A framework provided an outline toward the proper evaluation of potential screening strategies

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Abstract

Objectives: Screening tests are often introduced into clinical practice without proper evaluation, despite the increasing awareness that screening is a double-edged sword that can lead to either net benefits or harms. Our objective was to develop a comprehensive framework for the evaluation of new screening strategies.

Study Design and Setting: Elaborating on the existing concepts proposed by experts, a stepwise framework is proposed to evaluate whether a potential screening test can be introduced as a screening strategy into clinical practice. The principle of screening strategy evaluation is illustrated for cervical cancer, which is a template for screening because of the existence of an easily detectable and treatable precursor lesion.

Results: The evaluation procedure consists of six consecutive steps. In steps 1–4, the technical accuracy, place of the test in the screening pathway, diagnostic accuracy, and longitudinal sensitivity and specificity of the screening test are assessed. In steps 5 and 6, the impact of the screening strategy on the patient and population levels, respectively, is evaluated. The framework incorporates a harm and benefit trade-off and cost-effectiveness analysis.

Conclusion: Our framework provides an outline toward the proper evaluation of potential screening strategies before considering implementation.

Keywords: Cancer screening; Screening evaluation; Cervical cancer; Screening strategy; Harm benefit; Framework

1. Introduction

Almost 40 years ago, Wilson and Jungner [1], for the World Health Organization, formulated a number of criteria (called ‘‘principles’’), which a screening strategy should meet. One of the criteria was that there should be a suitable screening test or examination detecting latent or early phases of the target disease. Unfortunately, still no comprehensive guideline exists concerning the assessment of screening strategies. Moreover, the specific context of screening applied to large groups of apparently healthy persons among whom the disease usually is rare, makes the evaluation of screening strategies a difficult, delicate, and costly exercise.

In this article, we propose a comprehensive framework for the evaluation of new screening strategies, using cervical cancer screening as a case example. When dealing with terms such as screening tests, strategies, or programs, clear definitions should be made. Evaluation of a potential screening strategy, involving a new screening test, comprises the test, patient, and population level. Generally, it includes the determination of age ranges and screening intervals and assessment of its cost-effectiveness. Although the effectiveness of a screening program depends on the properties of the screening test itself, other factors including natural history of the disease, screening organization, level of participation of the target population, compliance with follow-up and efficacy of workup, and treatment of the screen-detected lesion also determine the success [2–5]. The evaluation of screening programs in all their aspects, however, lies beyond the scope of this article, which focuses on the evaluation of new screening strategies.

Our reasoning starts from the assumption that before a possible screening strategy is considered, a clear decision has been made on the exact aim and the general target of the intervention. The aim should be formulated as the net benefit for the screenees and in terms of avoiding

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What is new?

Key findings

- The development of a comprehensive framework building further on the existing concepts, based on a stepwise evaluation process including a harm and benefit trade-off and cost-effectiveness analysis of the screening tests before introduction into clinical practice as a screening strategy.

What is the implication and what should change now?

- New screening tests should go through a proper evaluation process before considering implementation as a screening strategy, to avoid doing more harm than benefit.

worsening public health. The broad target population can be, depending on the target condition, either an age and sex subgroup of the general population or a high-risk subgroup, for example, people working or living in specific conditions or exposed to risk factors [6]. These general ideas will guide the researcher to precise screening intervals and target populations chosen for the individual observational studies and trials.

1.1. Methodological considerations that are specific for the evaluation of a screening strategy

When people actively present with a health problem that requires treatment, they accept that the diagnostic process or treatment carries some risk of inflicting harm. When the same processes are applied to healthy people, the acceptable level of risk is much lower. Additionally, motivation for screening often is encouraged by invitations and often includes some degree of social pressure.

1.1.1. Cervical cancer screening

Screening can effectively prevent cervical cancer. The International Agency for Research on Cancer estimated that well-organized cytologic screening for cervical cancer precursors every 3−5 years between ages of 35 and 64 years can reduce the incidence of cervical cancer by 80% or more among the women screened [7]. Nevertheless, cervical cancer was worldwide the third most common cancer in women and the fourth most common cause of cancer death and even the most common cause in many developing countries in 2008 [8]. It occurs at a relatively young age when women are actively involved in their careers or caring for their families, resulting in proportionally more life-years lost compared with most cancers [8]. The rationale of cervical cancer cytologic screening is to identify and treat high-grade cervical intraepithelial neoplasia (CIN) or precancerous lesion and prevent its progression to invasive cancer. The mean time of initial dysplasia to invasion is at least 10 years, and the probability of detection increases as the preclinical phase progresses [9,10]. Removing these precursor lesions is effective in avoiding progression to invasive malignancy. Although screening for cervical cancer is well established, there were until recently no randomized clinical trials to demonstrate its effectiveness. The observational evidence, however, showing a reduced incidence of and mortality from cervical cancer is widely accepted [11,12]. The recognition of a strong causal relationship between the persistent high-risk human papillomavirus (HPV) infection of the genital tract and occurrence of cervical cancer has resulted in the development of several HPV detection systems providing new preventive strategies that could potentially result in an even greater reduction in incidence and mortality than cytology.

1.1.2. Outcome of screening

The main purpose of screening is to reduce the disease-specific mortality. Therefore, the primary indicator of effect is the observed disease-specific mortality compared with the expected mortality in the absence of screening, best expressed in terms of absolute risk difference or its reciprocal, the number needed to screen. In addition, several alternative end points can be used as a proxy. Table 1 shows a list of indicators used to establish effectiveness of cervical cancer screening ranked by decreasing level of evidence [13].

Studying cervical cancer mortality is particularly difficult because the certified cause of death often does not indicate the exact anatomical origin but rather is indicated as death from uterine cancer. An alternative end point can be all-cause mortality as has been advocated for breast cancer [14], but a significant effect on all-cause mortality is rarely demonstrable with screening. In cervical cancer screening, in which precursors are detected and treated, reduction in cervical cancer incidence, is a convincing end point, but reaching this outcome requires hundreds of thousands of women to monitor over many years. CIN3 as a direct precursor of invasive cancer is an acceptable proxy outcome of effectiveness [15]. The increased detection of CIN2+ or CIN3+ is clinically not so relevant as they rarely progress to cancer [16], leading to overtreatment. Consequently, outcomes 6 and 7 in Table 1 should not be targeted by a screening strategy.

1.1.3. Screening for low-prevalent diseases

Contradictory to most diagnostic studies, in screening, the prevalence of disease, especially for cancer, is typically low. This has an impact on the predictive values. Sensitivity is an indicator of the proportion of detected and missed prevalent predisease and determines the effectiveness. A very high specificity is needed to minimize the number of false-positive test cases. However, a high specificity can still be associated with high absolute numbers of false-positive test results (and thus anxiety, costs, and additional procedures in a lot of people) in case of low prevalence, for