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Editorial

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The pseudo-high-risk prevention strategy

Key Messages

- A fundamental failure of high-risk prevention strategies is their inability to prevent disease in the large part of the population at a relatively small average risk and from which most cases of diseases originate.
- The development of individual predictive medicine and the widening of high-risk categories for numerous (chronic) conditions lead to the application of pseudo-high-risk prevention strategies.
- Widening the criteria justifying individual preventive interventions and the related pseudo-high-risk strategies lead to treating, individually, ever healthier and larger strata of the population.
- The pseudo-high-risk prevention strategies raise similar problems compared with high-risk strategies, however on a larger scale and without any of the benefit of population-based strategies.

Some 30 years ago, the strengths and weaknesses of population-based and high-risk prevention strategies were brilliantly delineated by Geoffrey Rose in several seminal publications (Table 1).[1,2] His work had major implications not only for epidemiology and public health but also for clinical medicine. In particular, Rose demonstrated the fundamental failure of high-risk prevention strategies, that is, by missing a large number of preventable cases.[1] Indeed, since most cases of diseases do not originate among individuals within the highest risk category, the high-risk prevention strategies fail to prevent diseases in the numerous individuals at a small but non-optimal risk and from whom originates a large, if the not the largest, number of cases (Figure 1).

For Rose, this failure of high-risk prevention strategies was a strong argument in favour of population-based prevention strategies which are designed 'to control the determinants of incidence, to lower the mean level of risk factors, [and] to shift the whole distribution of exposure in a favourable direction'[1] and, hence, to reduce the risk in all segments of the population. That was however not an argument to target a larger number of individuals for individualized high-risk prevention strategies.

From this viewpoint, we argue that the development of individual predictive medicine and the widening of high-risk categories for numerous (chronic) conditions are fundamentally at odds with Rose's arguments and lead to the application of pseudo-high-risk prevention strategies.

High-risk vs population-based prevention strategies

Population-based prevention strategies aim to shift the whole distribution of risk factors toward ideal values (Table 1).[1,2] Their rational is based notably on the continuum in the relation between the level of many risk factors and the absolute risk of disease (Figure 1). They are relevant because, at a population level, most cases of diseases occur in individuals with risk factors not in the highest risk category of diseases. More precisely, notably for cardiovascular diseases, most cases occur in individuals with levels of risk factors around the population average, where most people are found if risk factors are normally distributed.

Population-based strategies require mass (structural) interventions reaching the entire population and targeting the determinant of average risk.[3,4] One advantage is that

Table 1. Principles, strengths and weaknesses of each preventive strategy (adapted from Rose 1985[1] and Rose 1992[2])

Principle	Population-based	High-risk	Pseudo-high-risk
	Shift the whole risk distribution toward lower risk values	Identify and treat individuals at the highest risk of disease	Identify and treat individuals at intermediate and high risk of disease
Global efficacy	Radical	Palliative and temporary	Palliative and temporary
Potential benefit for populations	Large	Small	Small
Potential benefit for individuals	Small	Large	Large for some, small for many
Behaviourally appropriate	Yes	No	No
Motivation for patients and physicians	Small	Large	Large
Balance risk/benefit	Worrisome if the intervention causes some harms	Good unless the intervention causes major harms	Good for some, worrisome for many
Issues of thresholds definition, risk stratification and screening/diagnostic tests	No	Yes	Yes

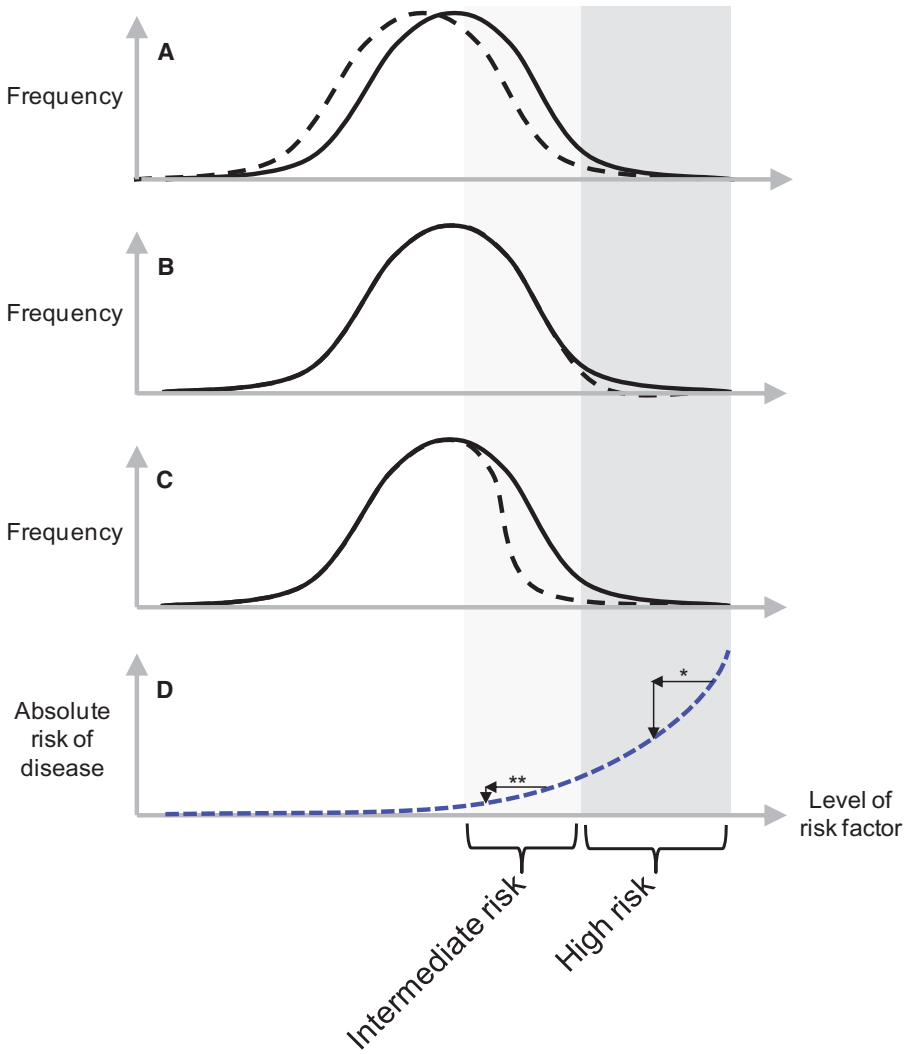

Figure 1. A) Population-based prevention strategies aim at shifting the whole distribution of risk factors toward lower values; B) High-risk prevention strategies aim at treating the individuals at the highest risk in the population; C) Pseudo-high-risk strategies aim at treating the individuals at intermediate and high risk in the population; D) The line shows the log-linear relationship often observed between a risk factor and the absolute risk of the disease.[10] A change in the level of risk factor for individuals within the high-risk range (*) is associated with a substantial change in the absolute risk of disease. By contrast, a similar change in the level of risk factor for individuals within the intermediate-risk range (**) is associated with a small change in the absolute risk of disease.

they do not require screening and individual diagnostic tests or any stratification methods to estimate risk. Nevertheless, as the individual benefit is often small, the risk of the intervention has to be minimal for the population-based strategies to have a favourable benefit/harm ratio.[4]

High-risk prevention strategies consist in the identification and treatment of individuals at the highest risk of disease (Table 1 and Figure 1).[1] One difficulty of these strategies is that they require tools to identify these individuals by appropriate screening and diagnostic tests and by stratification methods. Hence, resources have to be devoted to the assessment of risk.[4] High-risk strategies are the standard approach for clinicians and necessitate the participation of individuals. It can be however very hard even for high-risk individuals to make appropriate behaviour changes, especially if the environment is not optimal to do so and, if treated, to adhere to medications, especially to prevent a hypothetical and remote chronic condition.

Principles, strengths and weaknesses of both types of prevention strategies are listed in Table 1 and have been discussed extensively.[4–7]

Absolute risk prediction and individual predictive medicine

A specificity of high-risk strategies is that they require accurate methods and valid data, first to predict the absolute risk of future disease and second, to discriminate with confidence the individuals having a high probability of disease from those having a low probability of disease.[3] However, accurate prediction is very difficult, especially for chronic conditions. Indeed, chronic conditions such as cardiovascular diseases or cancers are characterized by a long preclinical period, with a slow pathological process over many decades, leading eventually to the clinically apparent disease. This process is complex, affected by numerous factors and dynamic: it does not always show regular progression and can be interrupted, if not reversed.

Despite this complexity, during the preclinical period it is possible to identify early risk markers of disease, which are either true early forms of the disease (e.g. precancerous lesions), surrogates (e.g. arterial stiffness) or merely (causal or non-causal) risk factors (e.g. blood pressure). Prediction tools to estimate the absolute risk of disease are based on the identification of these markers and on the design of appropriate algorithms to estimate risk. These tools are highly heterogeneous in their conception and are used in different settings: some are based on self-reported measures, others on clinical information and others on highly detailed biological information, such as genetic information.[8,9] They are the constitutive elements of the ever growing field of individual predictive medicine or personalized medicine. In an ideal setting, these tools should be able to discriminate future cases from non-cases, they should be calibrated on the absolute risk of the targeted population and they should help reclassify individuals in the proper risk strata. Not all these tools are focused on individual risk assessment and, in several specific clinical situations, some are useful.

However, most of the existing prediction tools are incapable predicting the absolute risk for instance of cardiovascular diseases at an individual level. Although they can estimate with accuracy the probability of having a disease at the population or group level, they cannot identify which individuals will actually develop the disease.[10,11] Research in personalized (e.g. omics-based) medicine may improve individualized prediction and increase discriminative power.[8,12] There are nevertheless limits to forecasting in personalized medicine which, at the moment, has delivered much less than expected.[12,13]

Although this difficulty of prediction at individual level is expected based on epidemiological evidence (notably due to the low discrimination power of most risk markers, the misleading inference to individuals of observations true at the group or population level, and the confusion between causes and risk factors),[3] there is a strong resistance to acknowledge it, nurturing an ever-ending quest to improve individualized prediction to a increasing share of the population and leading eventually to what we call pseudo-high-risk prevention strategies.

The pseudo-high-risk prevention strategy

Many clinicians are frustrated with high-risk prevention strategies because the numerous cases emerging from lower risk strata are not targeted and treated. Furthermore, clinicians would like to act earlier to prevent patients becoming at high risk of disease. This is a form of primordial prevention of disease, applied at a clinical and individual level.[14–16] Pharmaceutical companies are also keen to widen the criteria, to have more people eligible for treatment. Hence, there is tendency to widen the strata of people requiring individual intervention by targeting individuals at intermediate-risk (Figure 1).

This widening is at the core of pseudo-high risk prevention strategies. It is justified by the absence of self-evident or 'natural' thresholds to define high-risk status. Indeed, in many cases, there is a continuum in the relation between risk factor and the absolute risk of disease. However, in many cases, the relation is log-linear.[17] Therefore, for an identical absolute reduction in the risk factor, the resulting absolute risk of disease reduction will be much smaller for individuals within the intermediate-risk strata than within the high-risk strata (Figure 1, panel D). Consequently, interventions targeting patients at intermediate risk will have a relatively small (absolute) benefit.

There are numerous recent examples of widening criteria to define conditions requiring an individualized intervention. Hence, in 2003, the Seventh US Joint National Committee Guidelines defined 'pre-hypertension' for blood pressure between 130 and 139/85 and 89 mmHg, considered as a precursor of hypertension:[18] 40% of men and 23% of women in the USA have pre-hypertension, in addition to the 27% of men and women who have hypertension. Targeting all these persons for individualized treatment and follow-up is a huge burden for the healthcare system. Treatment of individuals with pre-hypertension could delay the occurrence of hypertension, but there is no proof that it would have any true health benefit such as a reduction of cardiovascular diseases.

More recently, a relative low absolute cardiovascular risk threshold was recommended to prescribe statins, resulting in 49% of US adults between the age of 45 and 75 becoming eligible for treatment.[19] However, it was shown that the US risk prediction algorithm overestimated the absolute risk.[20] Further, these new recommendations put many primary prevention patients on statin therapy where there is little trial evidence, and some patients for which trial evidence exists would not be eligible.[19]

Another example is pre-diabetes. The diagnosis of this condition aims to identify individuals at risk of diabetes and to reduce its occurrence. Pre-diabetes implies a condition which progresses toward diabetes, although probably less than half of individuals with pre-diabetes will develop diabetes later in life.[21] Furthermore, there is no evidence that treatment (either through lifestyle intervention or medication) of pre-diabetes improves any health outcomes, besides delaying the occurrence of diabetes. Lowering the blood glucose threshold to define hyperglycaemic disorders requiring personalized interventions such as pre-diabetes can lead to overdiagnosis,[21,22] which occurs when individuals are diagnosed with a condition for which there is no intervention improving substantially the prognosis.[23,24]

Contrasting with these examples, it is worth mentioning the 'polypill' prevention strategy which is a special case of high-risk strategies for the prevention of cardiovascular diseases.[10] The idea is to treat with a combination of various drugs (notably antihypertensive and statins) all individuals aged 55 years and over or with a personal history of cardiovascular diseases. The major difference with usual high-risk prevention strategy is the extreme simplification of the identification and risk stratification processes. Hence, it spares resources used for risk assessment and stratification, and potentially greatly simplifies healthcare delivery.[25] Further, the polypill strategy makes treatment culturally more appropriate since all individuals 55 years old and over would be treated. Hence, taking drug treatment for the prevention of cardiovascular diseases would become a normal health behaviour, which would facilitate the long-term adherence, as theorized by Rose for other health behaviours. Such strategy should however not be considered as a pseudo-high-risk prevention strategy.

Conclusion

Widening the criteria justifying individual preventive interventions and the related pseudo-high-risk strategies lead to treat, individually, ever healthier and larger strata of the population. If the treatments offered are the same as those in high-risk individuals, the benefit/harm balance of treating these people will be automatically less favourable. The pseudo-high-risk prevention strategies raise similar problems compared with high-risk strategies, however on a larger scale, and without any of the benefit of population-based strategies. We have also argued that their strategies have limited potential to improve individualized prevention and are unable to reduce the incidence of disease at a population level since they are not targeting determinants of average risk.

One driver of pseudo-high-risk prevention strategies is the fact that individual-focused interventions are easier to test in randomized controlled trials and hence easier to implement on the basis of strength of evidence compared with population-based intervention. If we want to limit the use of pseudo-high-risk prevention strategies, more research and stronger evidence are needed for the implementation of population-based strategies.

Finally, Rose argued that both high-risk and population-based strategies should be applied as they are mutually supportive, not rivals.[2] However, the pseudo-high-risk strategies are bound to absorb large resources because of the individual risk assessment and follow-up for a large share of the population. As such, these preventive strategies compete with other more efficient preventive interventions, which, in a time of healthcare cost containment and in low resources settings, is highly problematic.

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