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Time to revisit Geoffrey Rose: strategies for prevention in the genomic era?

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ABSTRACT

Geoffrey Rose, in his article "*Sick individuals and sick populations*" highlighted the need to distinguish between prevention for populations and prevention for high risk individuals. In this article we revisit some of these concepts in light of the burgeoning literature on "personalised medicine" and of findings from our investigations into personalised cancer prevention as part of an EU research gene-environment study on hormone related cancers, the Collaborative Oncological Gene-environment Study (COGS). We suggest that Rose's high risk strategy may be modified by segmenting the population by risk (in our example genetic risk) into a number of individual strata, to each of which differential interventions may be applied. We call this "stratified prevention", and argue that such an approach will lead to consequential advantages in efficiency, effectiveness and harm minimisation.

Key words: Geoffrey Rose; High risk prevention; Population prevention; Stratified prevention; Polygenic risk

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INTRODUCTION

Over 25 years ago, Geoffrey Rose published his paper "*Sick Individuals and Sick Populations*" (1) in which he highlighted the need to distinguish between disease prevention for populations and disease prevention for high risk individuals. In this article we revisit some of these concepts in light of increasing knowledge about the molecular basis of disease risk. We use as a case study our experience on an EU research programme into genetic variants as risk factors for breast cancer. Building on our work on breast cancer prevention we make some general remarks about how best to conceive stratified prevention programmes within Rose's framework.

Geoffrey Rose - two approaches to disease prevention

In his classic paper, Rose (1) highlighted two approaches to disease prevention: the individual and the population-based approach. The first aimed to identify those individuals at "*high risk*" and, either to control the level of exposure to a causal agent for that

individual or to provide an intervention that conferred "*some individual protection*" (1). Rose stated that this high risk strategy implied the segregation "*of a minority with special problems [at high risk of developing disease] from a majority who are regarded as normal and not needing attention*" (1). Rose's second approach focused on identifying the proximal and underlying causes of disease and altering the whole distribution of risk at a population level by removing or reducing the exposure or providing a generalised intervention that conferred protection.

Rose noted that the effectiveness of the individual "high risk" approach depended on the extent to which a particular risk in the population was confined to this identifiable minority. He commented that such a targeted approach would not be likely to be effective in population terms for a common disease with complex underlying factors. He went on to articulate a number of advantages and disadvantages to the two different approaches. He argued that preventive interventions, targeted at those individuals at highest risk, were the "*traditional and natural medical approach to prevention*" (1). The prevention offered would be appropriate for each individual, improving motivation and compliance on both the patient and clinician sides. It would be expected to be more cost-effective with a more favourable benefit to risk ratio in the high risk group of individuals. However, disadvantages of this approach would include the costs and difficulties in identifying "high risk" individuals and the potential for stigmatisation or medicalisation of individuals who had hitherto regarded themselves as well.

Population prevention worked, Rose argued, by trying to reduce the risk across the whole population through the "*traditional 'public health' form*" where structural or environmental change is implemented that affects the entire population and shifts the whole background of exposure in a favourable risk-reducing direction (1). Acting at a population level will produce greater gains by preventing disease in the larger number of individuals (even at smaller risk) rather than focusing on the smaller number of individuals at high risk. However, under this strategy, both the individual and the clinician may have poor motivation to participate because the risk of disease for an individual will be low. Rose spoke of the "*prevention paradox*" because the benefit to each individual will be extremely low even though the consequence will be of significant benefit to the population as a whole (2).

Rose acknowledged that, under, the population approach, many individuals have to change their behaviour or receive some intervention in order for a much smaller number to benefit. This led him to emphasise the importance of minimising harm arising from the intervention. He distinguished two forms of "*mass prevention strategy*". The first, he considered to be the "*removal of an unnatural factor and the restoration of 'biological normality'*" (2). For example, in coronary heart disease prevention Rose suggested that measures would include giving up smoking, reducing saturated fat intake or increasing physical activity. The second type of measure consisted in adding some "unnatural factor" in the hope of conferring protection. This could include all forms of long-term medication, such as the current use of statins to reduce cholesterol levels, or dietary interventions, such as the use of folic acid fortification to prevent neural tube defects. Rose argued that, for such mass interventions "*long-term safety cannot be assured, and quite possibly harm might outweigh benefit. For such measures as these the required level of evidence, both of benefit and (particularly) of safety, must be far more stringent*" (2).

The rise of genomics

It is now more than 25 years since Rose's ground-breaking epidemiological analyses of the different approaches to prevention (1, 2). Major scientific advances in the science of genomics have taken place in that time and, in particular, there is a much greater understanding of the factors that underlie disease at a molecular level. The question arises, however, whether his ideas are still relevant, how they should be applied and whether prevention programmes can still learn from his analysis.

With the completion of the Human Genome Project in 2003 (3), scientists and clinicians have been provided with unprecedented amounts of new knowledge with which to try to understand and manage health and disease. A major goal at the onset of the Project was to facilitate the identification of inherited genetic variants that influenced the risk of human disease. In 1991, Francis Collins predicted that "*the information derived from the Genome Project will…likely transform medicine in the*

21st century into a preventive mode, where genetic predispositions are identified and treated before the onset of illness rather than after illness is under way" (4). Single gene "high risk" disorders such as familial adenomatous polyposis (FAP), which is a hereditary form of bowel cancer, provide an example where genetic testing now allows more refined intervention, by identifying individuals with the specific underlying mutation and in this case offering colonoscopy and colectomy in early adolescence before bowel polyps become cancerous. For this genetic condition the penetrance is high (i.e. the occurrence of the disease phenotype is highly likely for an individual with the disease mutation) and the identification of a disease mutation can be used to predict future disease.

The last decade has also seen the contribution of genome-wide association studies to improvements in the understanding of biological mechanisms and genetic susceptibility underlying many common complex diseases. But despite genomic discoveries related to many human diseases thus far (5-7), the use of known common susceptibility variants in risk profiles has resulted in poor discrimination between those who will and those who will not develop common complex diseases (8). A recent editorial by Di Angelantonio and Butterworth (9), for example, stated that currently available evidence would not support the clinical use of genetic risk prediction for primary or secondary prevention of common forms of cardiovascular disease.

Genomic advances have thus massively increased understanding of disease causation and, for all common chronic disorders it is recognised that disease arises from a combination of genetic and environmental factors. Increasingly, we also understand that common chronic disorders are heterogeneous conditions, comprising a number of different subsets identifiable at molecular level. In many conditions there are single gene subsets that lead to high risk of disease, often at a young age.

The question then arises how we should interpret Rose's prevention approaches in the light of this new genomic knowledge and whether the differentiation of "high risk" and "population" approaches should now be modified. We examine this below in the context of breast cancer, drawing on findings from a European Commission FP7 project known as Collaborative Oncological Gene-environment Study (COGS) (10).

PREVENTION IN BREAST CANCER

Environmental and genetic risk factors

Breast cancer is not only the most common cancer amongst women worldwide but is also the leading cause of cancer-related mortality (11). The broad consensus from the literature is that a range of lifestyle risk factors are associated with the condition as well as other exposures related to reproduction. Risk is increased by obesity, higher alcohol intake, smoking, particularly before birth of first child, as well as by the use of oral contraceptive pills and hormone replacement therapy, especially when used over age 50 years. Reproductive factors include some which are difficult to modify, such as early menarche, late menopause and increased age at first childbirth; breast-feeding has a protective effect as does the number of pregnancies experienced.

Most breast cancers occur in women with no family history. Fewer than 5% of all cases of breast cancer can be attributed to highly-penetrant, deleterious mutations in one of the known breast cancer susceptibility genes (*BRCA1, BRCA2 and TP53*). The lifetime risk for developing breast cancer is 40% to 80% for women who are *BRCA1* carriers and 30% to 60% for women who are *BRCA2* carriers – the individual risks are likely to be modified by other inherited genetic variation and lifestyle and environmental factors (12).

For the common complex forms of breast cancer, genome-wide association studies have identified many risk alleles although the increase in risk conferred by each is small (usually a per-allele relative risk of less than 1.5). The most current estimate by Michailidou et al. (13) is that the polygenic risk based on 67 common genetic susceptibility variants explains approximately 14% of the genetic component of breast cancer risk. Although clinical utility of individual variants in predicting future risk for an individual is low, Pharoah et al. (14) showed that the combination of multiple risk alleles can lead to a distribution of risk in the population that is sufficiently wide to be clinically useful allowing differential targeting of preventive strategies according to risk strata.

Prevention approaches in breast cancer

The example of breast cancer shows that genomic information adds significantly and in a qualitatively different way to our knowledge

of risk for this common disease – but how does this map across to Rose's prevention strategies and does his consideration of 'population' and 'high risk' approaches help in the development of appropriate programmes?

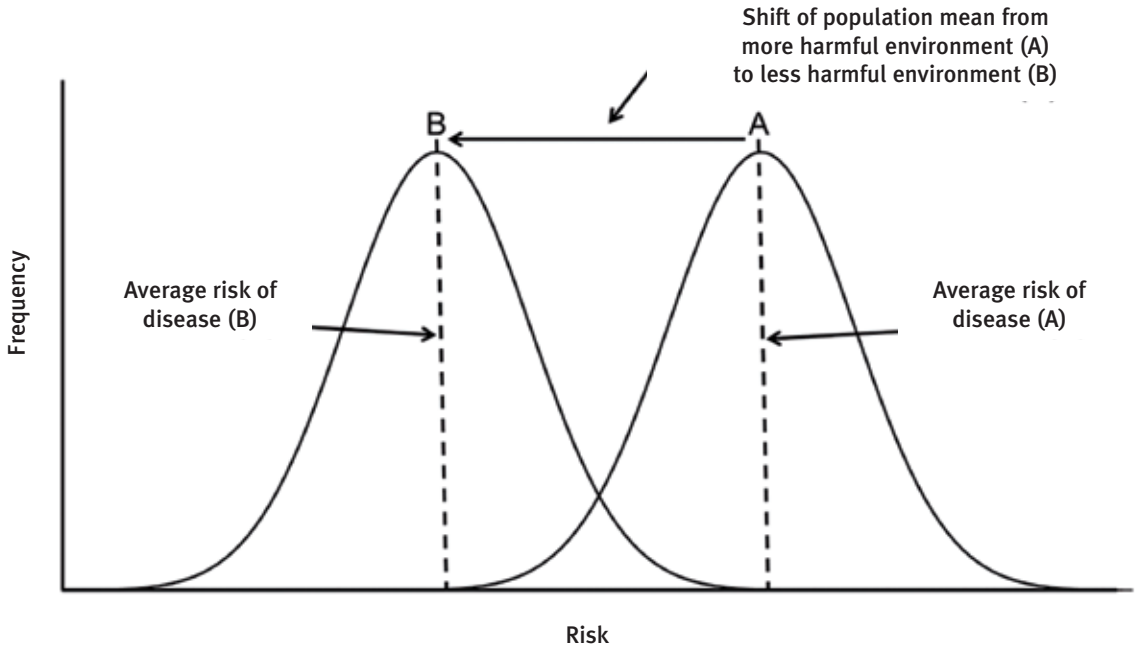
The population prevention approaches can be quite simply dealt with. Such programmes constitute those general health promotion programmes through which an environment is created that reduces propensity within the population for lifestyles associated with risk. Programmes that reduce average calorie or alcohol consumption, increase physical activity or even influence age at childbirth or breast-feeding at a population level clearly fall within this category. Conceptually, their effect is to reduce average risk within the normally distributed population – essentially to move the entire distribution from a more harmful environment (Environment A) to a less harmful environment (Environment B) (Figure 1).

It is clear that intervention in the "single gene" subsets of breast cancer – for example those with BRCA1/2 mutations who have an extremely high risk of disease – constitutes one form of what would undoubtedly be characterised as an example of Rose's high risk prevention strategy. Identification of such individuals would allow specific interventions. Because most have no family history of the disease (15), they would only be identified by the use of cascade testing or by testing those ethnic groups where the genetic variants are known to be particularly prevalent, such as Ashkenazi Jews (16, 17). Substantial benefit can accrue to those individuals who are known mutation carriers if recommendations are put in place for management. These include earlier start to mammography, the use of MRI as a more sensitive modality for screening, chemoprevention in the form of a selective oestrogen receptor modulator such as tamoxifen or raloxifene, or the use of risk-reducing surgery (18). Conversely, disadvantages according to Rose may then be the cost of identification strategies, the risk of stigmatisation and medicalisation of these individuals and, at a public health level, the relatively small effect this may have on the overall morbidity and mortality from breast cancer in the population.

Similarly there should be little debate about those individuals at one end of the population distribution who have been "dealt a hand" of susceptibility variants that puts them at a relatively higher risk than the general

FIG. 1

ROSE'S POPULATION PREVENTION STRATEGY WHERE THE AVERAGE RISK WITHIN A NORMALLY DISTRIBUTED POPULATION IS REDUCED FROM A MORE HARMFUL ENVIRONMENT (A) TO A LESS HARMFUL ENVIRONMENT (B)



population average. It is likely that, if it were possible to identify them, they should be considered to be a high risk group akin to those with raised cholesterol or blood pressure, as in Rose's own examples. However, the more interesting and more challenging question is how we conceptualise the situation in which risk is stratified across the whole population and differentiated preventive programmes are provided to each stratum that is effective, cost-effective, and minimises the prevention of harm.

We believe this approach to prevention follows on from the greater understanding about the heterogeneity of populations that has been provided by all the scientific work downstream of the Human Genome Project, and by the set of social changes that emphasise the importance of individual autonomy and which have led to changes in the practice of clinical medicine (19, 20). What we discuss below is a concrete example of such thinking in the context of public health practice.

Stratified prevention: a conceptual analysis and the example of COGS

A COGS work package, led by the Foundation for Genomic and Population Health in Cambridge (PHG Foundation), used modelling to investigate the possibility that a standard public health intervention such as breast screening could be applied differentially to each population stratum with a potentially more efficient outcome (14, 19). Pashayan and Pharoah (21) provided evidence through modelling work, in which they compared the number of individuals eligible for screening and the number of cases potentially detectable by screening between a population undergoing screening based on age alone (such as the current UK NHS Breast Screening Programme) and a population undergoing stratified screening based on age and polygenic risk profile. They found that stratified screening strategies based on age and genetic risk would potentially improve the efficiency and benefit-harm ratio of the screening programme. Using a 10-year absolute risk at 2.5% or greater, a personalised screening programme aimed at women aged 35-79 would result in 24% fewer women being screened with only 14% fewer cases being detected. Importantly, because of a reduction in overall number of screening episodes, stratified screening would reduce the number of false positives and the adverse consequences of unnecessary biopsies or other surgery.

How should this approach of stratified prevention be best conceptualised in Rose's classification? We suggest that it represents a "third way", one that optimises the potential of preventive interventions across the population as a whole, whilst minimising the harms; and in that sense akin to what Rose was trying to achieve through population prevention strategies. But at heart, even though applicable to the entire population rather than just to those individuals at the distant high risk end of the distribution, we believe that it is an approach more closely attuned to Rose's high risk prevention strategy. The essence of Rose's high risk approach is the measurement of risk, and its use to separate one group from another. Rose's examples categorised the population into two groups – those at "high risk" and all others (Figure 2a). The stratified prevention approach relies in the same way on the measurement of risk, but uses this to stratify and categorise populations into multiple groups (Figure 2b). Rose's examples only intervened in the high risk group; the stratified prevention approach allows different interventions in the different groups. In the mammographic example given above, stratification suggests that it is rational that entry to the mammographic screening programme should start at different ages dependent on the absolute risk of disease over a ten year period as ascertained by genetic variants.

Another aspect that places the stratified prevention approach within Rose's high risk paradigm, even though it is a strategy directed at the entire population or sub-population, is that it has specific recommendations for each of the population strata. The intervention is not applied equally to the entire population under the normal distribution, but differentially, depending on where an individual is within and under that population curve. Moving from Environment A to Environment B (see Figure 1) in Rose's population paradigm reduces the average incidence of disease, but the extent to which it affects the risk of each individual will be specific to that individual, and it is possible to conceive of a situation where the risk of disease in an individual is increased in a population paradigm that decreases population disease risk. This may still happen under stratified prevention, but a well thought out programme should bring greater benefit at the individual level than Rose's population approach.

FIG. 2a

ROSE'S HIGH RISK PREVENTION STRATEGY WHERE RISK IS MEASURED AND USED TO SEPARATE ONE GROUP ("HIGH RISK") FROM ANOTHER ("NORMAL")

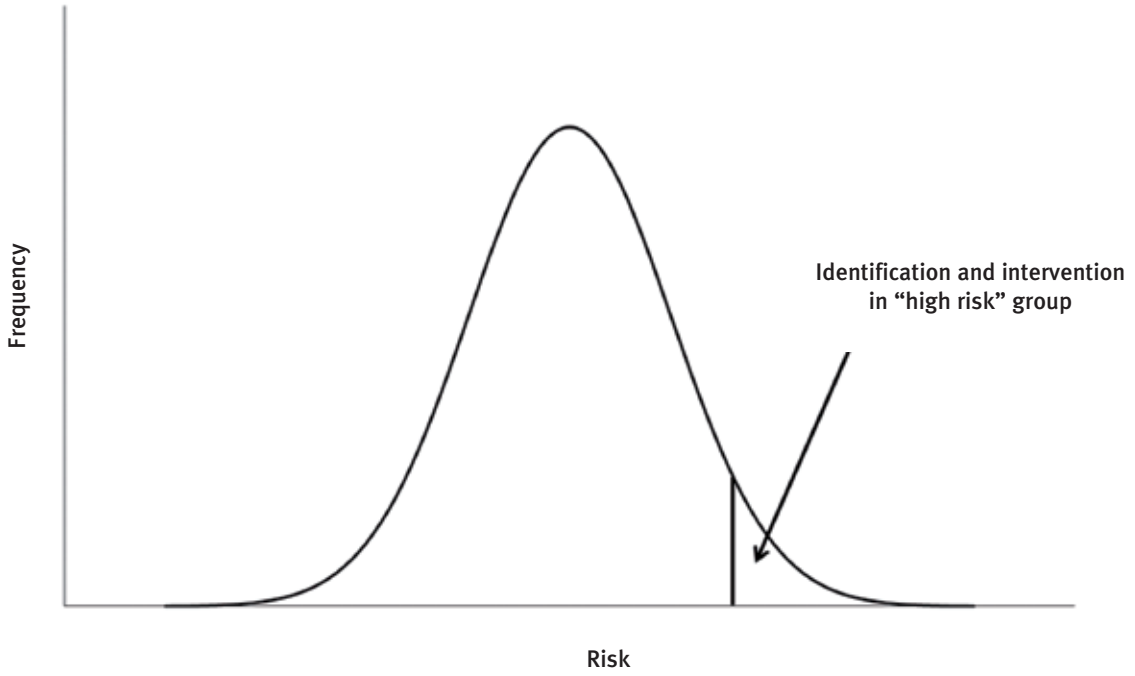
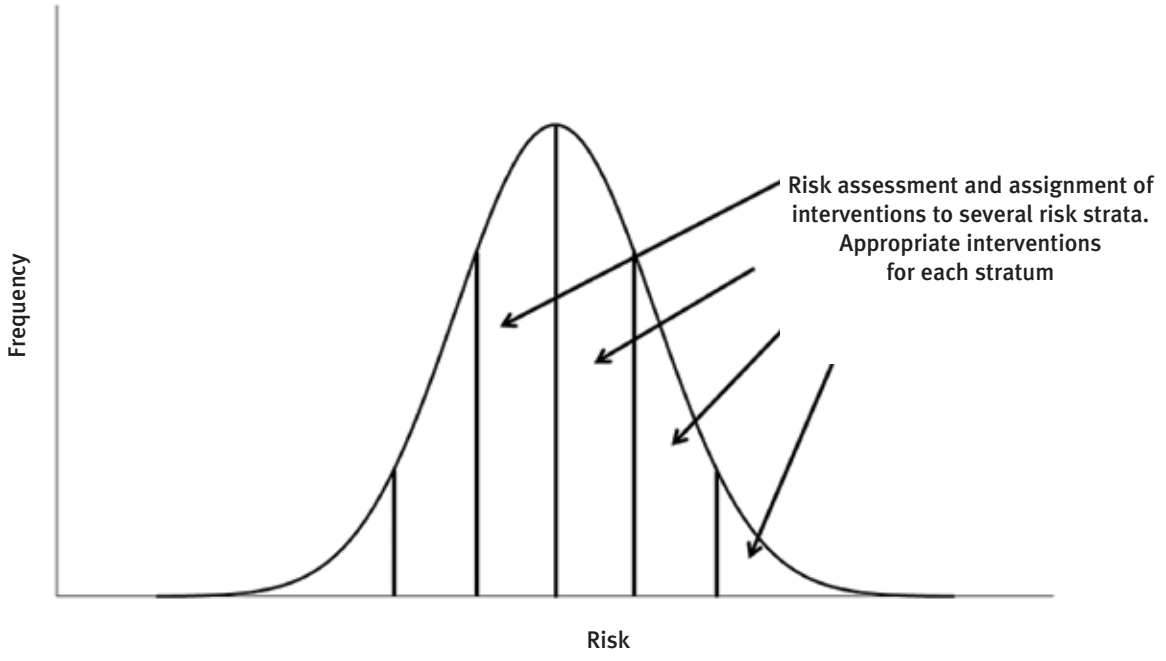


FIG. 2b

THE "STRATIFIED PREVENTION" STRATEGY ALLOWS CATEGORISATION OF THE POPULATION INTO MULTIPLE GROUPS WITH DIFFERENT INTERVENTIONS APPLIED IN THE DIFFERENT GROUPS



We also wish to emphasise that our approach and comments concern the measurement, identification and stratification of risk, and not just genetic risk per se. The measurement of risk may be made using non-genetic biomarkers or through risk scores that take into account multiple determinants including age, sex, genetic and environmental factors. Rose's examples of cholesterol or blood pressure as risk factors show this clearly (2). Although Rose did not do so in his examples, it is entirely possible to stratify and to provide differential interventions across the whole of the normal distribution by reference to these non-genetic risk factors. Genetic risk factors do however have an advantage for prevention over intermediate markers such as cholesterol or blood pressure. These are in effect phenotypic markers and a raised level will only emerge after a period of time. Genetic factors are present from birth, so theoretically it should be possible to identify groups at risk of developing high blood pressure or high cholesterol (and thus risk of heart disease) at an earlier age and before these secondary risk factors have had time to develop.

Although we are enthusiastic about the strength of risk stratification as a means of optimising prevention, it is an approach not entirely free of problems. Complex organisational, ethical, legal and social issues will inevitably arise by taking such an approach particularly where genetic testing is involved. Some of these may be resolved by considering this as a stratified prevention approach aimed at an entire population or sub-population. COGS stakeholder workshops, for example, identified possible problems related to public acceptability, complexity and concerns about possible discrimination (22) that may be mitigated by this approach. With regard to public acceptability, the COGS workshops raised the basic question of whether women would think it fair that the level of mammography screening offered was determined, at least in part, by underlying genetic factors. Under a stratified population approach it would be emphasised that all women would receive the same offer of risk assessment on the basis of which their eligibility to a particular screening pathway would be decided.

Stratified prevention is more complex as it involves an additional step of risk assessment followed by the offer of differential prevention interventions. Concerns were expressed by COGS stakeholders, particularly those responsible for current breast screening programmes, that risk assessment would be complex and that it may be hard for professionals to communicate individualised risk scores and to tailor them to recommendations for a specific breast screening schedule. Equally it may be difficult for women to understand and act upon nuanced differences in risk. Different risk assessments and recommendations may serve only to confuse, leading to loss of faith and disengagement with the programme. Under the stratified prevention approach the messages to women would be streamlined and simplified. At the outset, women would be informed and give consent to participation in the programme as a whole package. Following risk assessment they would be assigned to a screening schedule without a further discussion of their own personal risk score or options for mammography.

Finally, it was envisaged that a stratified prevention programme might give rise to fears of discrimination in areas such as employment or insurance. Consideration of the stratified prevention programme as an entity means that people would not be segregated into high risk groups, but simply described as higher, medium and lower risk within the 'normal' population. Thus fears of turning people into patients and, in turn, women's fears that they may experience discrimination in areas such as employment or insurance might be expected to be reduced; susceptibility would become more normalised, with individuals understanding that genetic variation would probably mean that they were higher risk for some diseases and lower for others.

CONCLUSIONS

Rose in an era of genomics and personalised prevention

Increasing scientific knowledge and new technologies in genomics have enabled greater understanding of disease at a molecular level. This has led to developments in clinical practice, broadly termed personalised or stratified medicine, where therapy is tailored more precisely to disease in the individual (23, 24). At the level of causation it is now clear that many common chronic diseases are heterogeneous with relatively rare high risk subsets caused by highly-penetrant mutations. These will

require separate approaches to prevention. Rose's approaches to common disease prevention were built on the understanding of the normal distribution of risk, which we now know arises, at least in part from the distribution of a large number of low risk variants that confer susceptibility to disease. It is appropriate to target the entire population with general "natural" disease prevention messages. However, for programmes that have potential for harm, such as mammography or preventive drug treatments, ensuring that benefit outweighs harm means that the type and intensity of intervention should be tailored according to risk.

We have now shown for breast cancer that assessment of risk using a set of susceptibility variants can be used to stratify the whole population, rather than just singling out the high risk group, with the intention of tailoring interventions to risk for all strata of the population. In this refinement, we suggest that a modification of Geoffrey Rose's "high risk" stratagem, one that we term "stratified prevention", may be used with consequential advantages in efficiency, effectiveness and harm minimisation. However, to put such strategies in place, it will be necessary for professionals to understand the importance of dealing with the population and its strata as a whole, and for people to understand and accept the basis on which such programmes are offered.

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