Published in final edited form as:

Per Med. 2012 June ; 9(4): 451–455. doi:10.2217/pme.12.40.

Population-based screening in the era of genomics

Nora Pashayan^{1,*} and Paul Pharoah²

¹ University College London, Centre of Applied Health Research, 1-19 Torrington Place, London WC1E 6BT

² University of Cambridge, Departments of Oncology and of Public Health & Primary Care, 2 Worts Causeway, Cambridge CB1 8RN pp10001@medschl.cam.ac.uk

Summary

To date, risk profiles based on the known common susceptibility variants have limited value in predicting risk of disease but they could be used for risk stratification in prevention programmes at population level. We illustrate the potential utility of polygenic risk stratification using the case of population-based screening for prostate and breast cancer. We compared the number of individuals eligible for screening and the number of cases potentially detectable by screening in a population undergoing screening based on age alone with a population undergoing stratified screening based on age and polygenic risk profile. Stratified screening strategy based on age and genetic risk would potentially improve the efficiency of screening programmes and reduce their adverse consequences. Organisational, ethical, legal and social issues need to be addressed before stratified screening programmes could be implemented.

Keywords

Polygenic risk; stratified screening; prostate cancer; breast cancer

Introduction

The continuing progress of the genome-wide association studies in identifying common genetic variants associated with the risk of common complex diseases has raised expectations of genetic profiling for personalised medicine. Thereby, preventative and therapeutic interventions for complex diseases would be tailored to individuals based on their genetic profiles. However, to date, risk-profiles based on the known common susceptibility variants discriminate poorly between individuals who will develop the disease of interest and those who will not [1]. This has led some investigators to conclude that polygenic profiling has limited clinical utility for risk prediction and individualised prevention of complex diseases such as type 2 diabetes [2;3], coronary heart disease [4], breast cancer [5-7], and prostate cancer [8;9]. However, discrimination is not the only measure of utility of a risk prediction model. In disease prevention, the aim is to stratify risk rather than to discriminate events [10]. By stratifying the population according to genetic risk alone or in addition to traditional disease risk factors such as age, standard public health

*Correspondence to Department of Epidemiology and Public Health Centre of Applied Health Research University College London 1-19 Torrington Place, London, WC1E 6BT Tel: +44 20 3108 3255; Fax: +44 20 7813 0280 n.pashayan@ucl.ac.uk.

Financial & competing interests disclosure The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

interventions could be applied differentially to each population strata with potentially more efficient outcome [5]. In this paper, we illustrate the potential utility of polygenic risk stratification at population level using the case of population-based screening for prostate and breast cancer [11;12].

Polygenic risk stratification for prostate and breast cancer screening

We compared the number of individuals eligible for screening and the number of cases potentially detectable by screening of two screening strategies - standard screening with eligibility based on age and stratified screening with eligibility based on a 10-year absolute risk of being diagnosed with cancer. The absolute risk was dependent on age and polygenic risk profile and equivalent to the risk threshold for eligibility in the age-based screening.

At any locus an individual can carry zero, one or two risk alleles. For example in prostate cancer with thirty-one risk loci, the number of risk alleles that an individual can carry ranges from zero to 62, representing 3^{31} unique combinations of alleles. Each different combination of risk alleles is associated with a different risk, and occurs at a different frequency in the population. The risk conferred by each of these loci appears to be allele-dose-dependent with multiplicative effect on the relative risk scale. Under the multiplicative model the distribution of polygenic risk in the population at birth follows the normal distribution when relative risk is plotted on a logarithmic scale. The normal distribution is defined by its mean and its variance or spread [13]. The variance of the distribution of polygenic risk is derived from the published risk allele frequencies and per allele relative risk [5;6]. The mean relative risk in the population at birth is set equal to unity. The distribution of relative risk among cases is also log-normal with the same variance as the population, but with a larger mean - the cases are on average at a higher prior risk than the population [13]. Given the variance and mean of the distribution of the log-normal relative risk distribution, the percentile rank associated with a given polygenic relative risk (or age-conditional absolute risk) threshold in the population or in cases can be calculated [11].

In case of prostate cancer, our estimates were based on the published 31 common susceptibility variants, which confer polygenic variance of 0.38 and explain approximately 24% of the genetic component of prostate cancer risk. We calculated the age-conditional absolute risk of being diagnosed with prostate cancer in the general population of men in England. We compared an hypothetical screening strategy based on age alone in which men are eligible for screening from age 55 (10-year absolute risk of being diagnosed with prostate cancer of 2% or greater), with a stratified screening strategy in which men 45-79 years and at a 2% 10-year absolute risk that is age-and polygenic risk-dependent are eligible for screening. Under the age-based approach, 63% of men aged 45 to 79 would be eligible for screening with 96% of the cases occurring in the screened population, that is, potentially screen-detectable. Under the stratified screening approach, 53% of men would be eligible for screening with 93% of the cases being potentially screen-detectable (Figure 1). Thus 16% fewer men would be eligible for screening at a cost of 3% fewer potentially screen-detectable cases. The efficiency of stratified screening will improve as more susceptibility variants are known [11]. Further variants are expected to be identified by the ongoing Collaborative Oncological Gene-environment Study (COGS) [101]. In an hypothetical best-case scenario analysis, assuming all possible susceptibility variants were known (assuming familial risk ratio of 2.20, then the predicted polygenic variance would be 1.58 [13;14]), 35% of men 45-79 would be eligible for screening while potentially detecting 90% of the cases (Figure 2) [11].

We applied similar approach to screening for breast cancer. We compared the UK National Health Service breast screening programme which offers screening to women aged 47 to 73

(10-year absolute risk of being diagnosed with breast cancer of 2.5% or greater) with a stratified screening strategy in which women 35-79 years and at a 2.5% absolute risk that is age- and polygenic risk-dependent are eligible for screening. The polygenic risk was estimated based on the published 18 common susceptibility variants, which confer polygenic variance of 0.12 and explain approximately 8% of the genetic component of breast cancer risk. Compared to the existing age-based breast screening programme (age 47-73: 10-year absolute risk of 2.5%), stratified screening of women 35-79 at the same risk threshold would result in 7% fewer women being eligible for screening and potentially detecting the same number of cases [11].

Figures 3a and 3b show that stratification based on absolute risk that is dependent on age and polygenic risk-profile reclassifies individuals into different risk groups, whereby some cancers that would have been detected under age-based screening will not be detected by stratified screening and other cancers that would be detected under stratified screening will not be detected by age-based screening. Such reclassification may improve the benefits and reduce some of the harms associated with screening. Prostate and breast cancer detected in younger individuals may tend to behave more aggressively [15;16]. Detecting prostate or breast cancer among younger individuals at high risk may improve the prognosis of these individuals. If polygenic low risk is associated with indolent, and possibly overdiagnosed cancer, then not detecting cancer among individuals at low risk, may potentially reduce the harms associated with overdiagnosis and overtreatment.

Stratified screening may confer additional benefits. A reduction in the number of individuals offered screening may reduce the number of false positive screens, with a reduction in the harms associated with a false positive test and the benefit of saving further resources on diagnostic tests. However, to estimate the true benefits of stratified screening, we need to understand whether and how tumour subtypes, screening test sensitivity, the natural history of cancer, and the probability of overdiagnosis vary by polygenic risk-profile. Further evidence from empirical data is needed.

While under an age-based screening strategy, all individuals within the age range will be eligible for screening, under a stratified screening strategy, individuals will be invited to screening at different ages based on their absolute risk level. For example in the case of screening for breast cancer, instead of inviting all women 47 to 73 years of age, 6%, 43% and 72% of women aged 40, 47 and 73 years, respectively would be invited to screening. Thus, the number of repeat screens and consequently the associated cost of screening over a lifetime will vary between individuals.

Challenges

A screening programme becomes viable if it does more good than harm at a reasonable cost [17]. Under stratified screening strategy, there is additional cost of offering genetic test for risk profiling and potential savings from repeat screening and diagnostic work-up of false positives. Our preliminary findings of cost-effectiveness analysis, using screening for prostate cancer as an example, showed that the cost per screening round would be lower for stratified screening compared to age-based screening, except if the cost of genetic profiling is added to the costs of the first round of screening. With further reductions in genotyping costs and increase in the number of known susceptibility variants, stratified screening would become cost-effective compared to age-based screening.

In addition to considering the effectiveness and the cost-effectiveness of stratified screening programmes, there are additional organisational, ethical, legal and social considerations before a risk tailored screening can be translated into policy and practice. It is not known how the public and the professionals will respond to genetic testing. Would it be acceptable

to health professionals, policy makers, and the public to have eligibility for screening based on absolute risk that is dependent on genetic profile in addition to age and possibly other environmental and lifestyle risk factors? Would it be acceptable to offer more sensitive and more expensive screening technology, such as MRI instead of mammography for screening for breast cancer, to those at high risk? How would the workforce be trained to understand genetic profiles and to communicate effectively the test results and the management options to the patients? A major organisational challenge will be to incorporate the advances of the rapidly evolving fields of genomics and the changes in environmental and lifestyle risk factors over an individual's lifetime into a dynamic risk estimation tool. How would the professionals organising the screening programmes and the public react to changing absolute risk levels?

Conclusion and Future Direction

Polygenic profiling based on the currently known common susceptibility variants for breast cancer or prostate cancer cannot determine who should receive risky or irreversible preventative interventions such as mastectomy or prostatectomy, but it can identify subsets of women or men who might benefit from earlier lower-risk interventions, such as screening. There are challenges and opportunities with incorporating genomic information into prevention programmes at population level. Concerted efforts from policy makers, healthcare professionals, healthcare managers, and researchers are needed to prepare for the advent of personalised screening.

Acknowledgments

NP is Cancer Research UK Clinician Scientist Fellow. The research leading to these results has received funding from the European Community Seventh Framework Programme under grant agreement 223175 (HEALTH-F2-2009-223175).

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Executive summary

Introduction

- Risk profiles based on the known common susceptibility variants have limited utility in risk prediction at individual level but they could be used for risk stratification in prevention programmes at population level

Polygenic risk stratification for prostate and breast cancer screening

- Stratified screening with eligibility for screening based on absolute risk based on age and polygenic risk and equivalent to the risk threshold for eligibility based on age alone could reduce the number of people eligible for screening while potentially detecting the majority of cancers identified through a standard age-based screening programme

Challenges

- Organisational, ethical, legal and social issues need to be addressed before stratified screening programmes could be implemented

Conclusion

- Stratified screening based on age and polygenic risk profile could improve the efficiency of screening programmes

Figure1.

Age-based vs. stratified screening: Proportion of the population of men 45-79 years and of cases of prostate cancer occurring in this population, England 2002-2006

Screening based on age alone in men aged 55-79 (10-year absolute risk 2.0% or greater) vs. screening men aged 45-79 with 2.0% 10-year absolute risk that is age-and polygenic risk-dependent

Of men 45-79 years, 63% are aged 55 years or above and 53% are at 10-year absolute risk of 2% or greater. 3% of men 45-79 years are younger than 55 years but have 10-year absolute risk of 2% or greater. Of all prostate cancers detected in men 45-79 years, 96% are in men aged 55 years or above and 93% are at 10-year absolute risk of 2% or greater. 1% of the cancers are in men younger than 55 years but have 10-year absolute risk of 2% or greater.

Figure 2.

Compared to age-based screening (age 55-79), the change in proportion of individuals eligible for stratified screening (age 45-79 at 10-year absolute risk of 2% or greater) with increase in the proportion of known susceptibility variants

* The 31 alleles explain 24% of the familial risk for prostate cancer

Figure 3. Reclassification

A. Eligibility to screening: Population of 100 men, 45-79 years, by age group and risk threshold (i), that would be eligible for screening based on age (ii) and based on age and polygenic risk (iii)

B. Potentially screen-detectable cases: Population of 100 men, 45-79 years, with prostate cancer by age group and risk threshold (i), that would be detectable by screening based on age (ii) and based on age and polygenic risk (iii)