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Personalized screening for cancers: should we consider polygenic profiling?

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Summary

Polygenic profiling and risk stratification for population-based screening for cancer improve the efficiency of the screening programs. Translation of genomics into personalized screening programs requires evidence from empirical research on the balance of benefits and harms of personalized screening, and engagement with the public, professionals and policy makers.

Keywords

Polygenic profiling; personalized screening; cancer

Conventionally, population-based screening programs for cancer use age to define the target population. All screening programs have the potential to do harm through false-positive findings, overdiagnosis and overtreatment. Advances in genomics allow moving from the conventional 'one-size-fits-all' to more personalized or risk-stratified screening approach. By stratifying the population into several groups according to genetic risk alone or combined with traditional disease risk factors (such as age and family history), screening could be offered differentially to each population stratum [(1)]. This would improve the efficiency of a screening program [(2,3)] and potentially improve the balance of benefits and harms of screening.

Recently, the Collaborative Oncological Gene-environment Study (COGS) identified 74 new common susceptibility loci associated with three hormone related cancers – breast, ovarian and prostate cancers, nearly doubling the number of known susceptibility loci associated with these cancers[(4)]. Taking into account the new loci, the estimated proportion of familial risk explained by all known loci with common susceptibility alleles (a total of 76 susceptibility alleles for breast cancer, 12 for ovarian cancer, and 77 for prostate cancer) is around 15% for breast cancer[(5)] , 4% for ovarian cancer[(6)], and 31% for prostate cancer[(7)].

As individual susceptibility alleles confer a modest increase in disease risk, then the predictive utility of a genetic test based on a single susceptibility allele is poor. Assuming log-additive model of interaction between loci, the susceptibility alleles can be combined into a polygenic risk profile that can be used for risk prediction. Under the log-additive

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model the distribution of polygenic risk in the population at birth and among the cases follows the normal distribution when relative risk is plotted on a logarithmic scale [8]. The discriminative accuracy of risk profiles can be measured by the area under the receiver operator characteristic curve (AUC_{-ROC}). AUC_{-ROC} is the probability that a test correctly identifies an individual who will develop the disease from a pair of whom one will be affected and one will remain unaffected. AUC_{-ROC} values range from 0.5 (total lack of discrimination) to 1.0 (perfect discrimination) [9].

Polygenic profiling in population-based screening programs

The polygenic risk profile based on the known susceptibility loci for breast cancer has AUC_{-ROC} of 0.63 and of 0.68 for prostate cancer [10]. As such these profiles yet are limited in predicting breast or prostate cancer for any given individual. However, these profiles would be useful for risk stratification in prevention programs for high-risk individuals and for populations [1].

For breast cancer, the log-relative risk distribution of the polygenic profile has a polygenic variance of 0.22, and compared to the population average the estimated relative risks at the 95th and 99th percentiles are 2.4 and 3.2, respectively [5]. Thus, polygenic profiling can identify small proportion of the population at clinically meaningful level of risk. For prostate cancer, the log-relative risk distribution of the polygenic profile has a polygenic variance of 0.43 and compared to the population average the estimated relative risks at the 90th and 99th percentiles are 2.7 and 4.7, respectively [7]. For comparison, the latter risk estimate is similar to that conferred by deleterious mutations in *BRCA2* [11], and such mutation carriers are undergoing targeted screening as part of an ongoing multi-national prostate cancer targeted screening trial, the IMPACT (Identification of Men with a genetic predisposition to ProstAte Cancer) study [7].

The potential utility of polygenic risk stratification in prevention programs at population level can be illustrated by using the case of population-based screening for breast and prostate cancer [3,12]. The UK National Health Service breast screening program is currently offered to women aged 47 to 73 years. Eligibility for the breast screening program can be considered to be based on a risk threshold, with risk currently determined only by age. This age based criterion for eligibility for screening is suboptimal as many women under the age for screening will develop breast cancer and most women above the age for screening will not develop cancer. Alternatively, identical absolute risk threshold for screening could be determined by a combination of age and polygenic risk profile. Using this approach some women under 47 years of age who are at above average genetic risk would be eligible for the screening program, whereas others who are older than 47 with a low genetic risk profile would not be eligible. The age of entry to the screening program will vary between individuals depending on their absolute risk levels. Compared with existing age-based screening program (age 47 to 73 years: 10-year absolute risk of being diagnosed with breast cancer of 2.5 percent or greater), personalized screening of women aged 35 to 79 years and at a 2.5 percent absolute risk that is age- and polygenic risk- dependent would be expected to result in 24 percent fewer women being eligible for screening whilst potentially detecting three percent fewer cases through screening [13].

Similarly with prostate cancer, compared with hypothetical screening program with eligibility based on age alone (aged 55-79 years: 10-year absolute risk of being diagnosed with prostate cancer of 2.0 percent or greater), personalized screening for men aged 45-79 years at the same risk threshold, 19 percent fewer men would be eligible for screening at a cost of four percent fewer potentially screen-detected cases [13].

The advantages of personalized screening include improving the efficiency of screening programs, detecting cancer in younger individuals who tend to have more aggressive forms of the disease, and reducing harms from false positive findings through screening fewer individuals [3]. With polygenic profiling and risk stratification, a subgroup of the population at low risk of cancer may receive no screening or screening at lower frequency. Such tailoring screening strategies to different risk groups may in turn improve the balance between benefits and harms of screening. The efficiency of personalized screening will further improve as more susceptibility loci are identified [3] and as additional information are incorporated into the risk score such as family history and other risk factors (for example mammographic density, reproductive history, lifestyle factors, etc.) [9,7,10]. However, the implementation of a risk stratified screening program is much more complex than a program with eligibility based on age alone [14,15].

Future perspective

Many questions need to be addressed before such personalized screening program becomes a standard practice. A critical research question is if and how the natural history of cancer varies by polygenic risk. There is yet no empirical evidence that incorporating polygenic profiling into a screening program will assist in detection of life-threatening cancers as opposed to indolent, possibly overdiagnosed cancers and will reduce cancer-specific mortality. The effectiveness of personalized screening strategy would ideally be addressed by randomized screening trials. Alternatively, comparative effectiveness studies [16] and pragmatic service evaluations [13] could provide supportive evidence.

Pragmatic questions remain on how to develop a dynamic risk score that incorporates the advances of the rapidly evolving field of genomics and the changes over time in individuals' non-genetic risk factors. Decision modeling could be used to explore the optimum screening strategy (covering screening frequency, screening test modality for different risk strata and the age range of eligibility for screening) and to compare the cost-effectiveness of personalized screening program to that of age-based screening.

It is important to explore whether genetic testing for stratification and eligibility for screening would be acceptable to the professionals and to the public, and how the public will perceive not or less frequently offering of screening to subgroup of the population at low risk of cancer.

Conclusion

So far the findings of the model-based estimates on the utility of polygenic profiling in population-based screening programs are promising. However, empirical evidence and engagement of the scientific community, health professionals, policy makers, experts in ethical and legal matters, and the public are needed to integrate advances in genomics into prevention programs at population level.

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