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Review

Can we really predict risk of cancer?☆

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ABSTRACT

Background: Growing awareness of the potential to predict a person's future risk of cancer has resulted in the development of numerous algorithms. Such algorithms aim to improve the ability of policy makers, doctors and patients to make rational decisions about behaviour modification or surveillance, with the expectation that this activity will lead to overall benefit. There remains debate however, about whether accurate risk prediction is achievable for most cancers. *Methods*: We conducted a brief narrative review of the literature regarding the history and challenges of risk prediction, highlighting our own recent experiences in developing tools for oesophageal adenocarcinoma. *Results and conclusions*: While tools for predicting future risk of cardiovascular outcomes have been translated successfully to clinical practice, the experience with cancer risk prediction has been mixed. Models have now been developed and validated for predicting risk of melanoma and cancers of the breast, colo-rectum, lung, liver, oesophagus and prostate, and while several of these have adequate performance at the population-level, none to date have adequate discrimination for predicting risk in individual patients. Challenges of individual risk prediction for cancer are many, and include long latency, multiple risk factors of mostly small effect, and incomplete knowledge of the causal pathways.

Clinical decision-making is generally based on estimating average risks within population subgroups and applying the same strategy for all within these groups. However, doctors want to know which diseases are most likely to affect their individual patients. Equally important, a patient wants to know if they have higher than average risk of certain diseases. If doctors can tailor prevention and treatment strategies for a patient based on their absolute risk for a disease, derived from the individual's specific characteristics (e.g., a panel of factors including age, sex, body mass index, and diet), there is potential for better clinical outcomes [1]. This is the aim of the term 'personalized medicine'.

To fully realize personalized medicine, the scientific community has synthesized information about established risk factors (clinical, environmental and genetic) for specific diseases into statistical models for risk prediction [2–4]. These models use information on multiple risk factors to estimate absolute risk. Risk models are generally developed by selecting the most important panel of predictive factors from among a larger list of candidate risk factors. Each predictor is then assigned a relative weight in a combined risk score [2,4]. Individual risk profiles can then be generated and used to identify those at high risk of having (diagnosis) or developing (prognosis) a particular disease. The models have various applications, including use in development of health policy, education, clinical decision-making, and designing future research (e.g., establishing eligibility criteria for intervention and screening trials) [5]. They are not however intended to replace doctors' clinical decision-making, but rather allow for more objective estimates of risk and uniform decision-making across different centers [6].

Risk prediction first received attention in the cardiovascular literature. One of the most widely validated and used prediction tools is the Framingham Risk Score (FRS) [7]. The FRS was designed to predict 10-year absolute risk for coronary heart disease. Absolute risk assessment charts based on the FRS and subsequent risk scores [8–12] are now included with many cardiovascular disease prevention guidelines [13–20]. Absolute risk estimates are used to guide the management of high-risk patients for cardiovascular disease and have improved the efficacy of medical interventions. The overall aim is to see their use translated into lower incidence and mortality from cardiovascular disease. However, decades after first being recommended, use of the absolute risk assessment charts in clinical practice tends to be highly variable. There remain many barriers to overcome (e.g., time constraints, over simplification of risk assessment, and overmedication) before they are routinely used [21–24].

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The first risk prediction model for cancer was described by Gail et al. in 1989 [25]. The Gail breast cancer model was developed using data from a nested case-control study (the Breast Cancer Detection and Demonstration Project) and predicted risk of developing invasive or in situ breast cancer in a defined age interval. The model was modified in 1999 to predict absolute 5-year risks for invasive breast cancer only [26]. The Gail breast cancer models included terms for age, hormonal or reproductive history, previous history of breast disease, and family history. Investigators have since further modified the original Gail model by adding modifiable risk factors (e.g., body mass index), terms for risk biomarkers (e.g., breast density) and multiple genetic variants, and by developing racial and ethnic specific models [27–29].

The National Cancer Institute (NCI) recognizes risk prediction as an "area of extraordinary opportunity" [30] and cancer risk prediction models are increasingly common in the medical literature. Population-based models have now been developed and validated for predicting risk of colorectal cancer [31], melanoma [32–36], lung cancer [37–41], liver cancer [42,43], and prostate cancer [44,45]. Many have associated online risk calculators available on the NCI's website (http://epi.grants.cancer.gov/cancer_risk_prediction/). More and more of these traditional models (i.e., those with only clinical and epidemiologic risk factors) are being modified to incorporate biologic and genetic data to estimate cancer risk more accurately.

It is difficult however to measure the value of these models. While most claim statistically significant results, few models have translated into clinically useful tools. Before being used clinically, a prediction model must be shown to provide accurate and generalisable risk predictions. The accuracy and generalisability of a model is assessed using measures of discrimination (how it performs at the individual-level) and calibration (population-level) [2,4]. These should be assessed in a similar, but external population to that in which the model was developed [3]. However, it is not always possible to find a suitable external validation dataset, and thus, models continue to be validated within the development dataset using various techniques (e.g., bootstrapping, and cross-validation) [2,3]. Several breast cancer models are currently used in clinical practice. In the United States, absolute risk estimates derived from the Gail model are used to identify high-risk women for mammography screening [46] and interventions trials [47]. However, while well calibrated at the population-level, the breast cancer models lack adequate discrimination in predicting risk for individuals [27,28,48].

We recently developed a model to estimate absolute risk for esophageal adenocarcinoma (EAC) [49]. EAC is a relatively rare cancer but is the fastest rising cancer in Western populations [50,51] and has poor survival [52]. EAC has a number of clearly established risk factors with reasonably large effect sizes (male sex, white ethnicity, reflux, obesity, and tobacco smoking) and thus ought to lend nicely to risk prediction [53]. However, despite the identification of 'high-risk phenotypes', it remains the case that very few people with one or more of these factors develop EAC. For instance, the absolute 5-year risk for EAC among obese, white, 50-year-old males with reflux remains only 0.04% [49], and more than 40% of EAC patients do not report reflux symptoms at diagnosis [54]. It comes as no surprise then that our model had only moderate discriminatory accuracy when internally validated. That is, it failed to effectively differentiate between those who will develop EAC and those who will not. Why are we seeing this time and again for these cancer risk prediction models?

Like other cancers, there are a number of issues as to why we may not be able to estimate EAC risk accurately at the individual level. Firstly, the primary risk factors for EAC are common in the population (for example, up to 20% of the adult population in Western countries suffer from weekly reflux symptoms [55], and approximately 30% are obese [56,57] and 20% are current smokers [58,59]) and are therefore prevalent in individuals who will not develop the disease. Secondly, while the relative risks for these factors are consistent across populations, and statistically significantly associated with EAC risk, the effects are typically modest (relative risks < 5) [60]. As a general rule of thumb, risk factors require relative risks greater than 10 to be good predictors of individual risk, although this does not guarantee high discriminatory accuracy [61,62]. Whilst knowledge of these factors helps advance our understanding of disease mechanisms, these risk factors alone do not accurately discriminate those who will develop EAC from those who will not. Thirdly, most cancers have long latent periods and arise in individuals with risk close to the population average. Therefore, identifying high-risk groups for EAC on the basis of a probability threshold (e.g., using 5-year absolute risks) with high sensitivity is difficult.

For rare cancers such as EAC, it may not be cost-effective to use risk prediction models in clinical practice. For example, even predictors with high sensitivity and specificity can still have low positive predictive values for rare diseases. That is, the number of people who actually develop cancer as a proportion of those predicted to do so will be low. As such, even if we had predictors with high discriminatory power (i.e., the test can correctly classify most people as 'affected' or 'not affected'), most people exposed to the risks of further investigation or treatment will not see any benefit. Therefore, such a model appears well suited for population prevention strategies, but may not be able to identify individuals at high (or low) risk in a clinically meaningful and cost-effective way.

With extensive research efforts already spent trying to improve current cancer models, is it possible to improve their clinical utility and move towards personalized medicine? Genetic risk profiling, in particular the addition of genetic variants to existing cancer risk models (as well as gene $\times$ gene and gene $\times$ environment interaction terms), has been proposed as a solution to increase discriminatory ability. However, it has been shown that, even when alleles with modest effect sizes are combined, the addition of genetic variants to these models has added only modestly to discrimination [29,63]. Thus, integrating genetic risk profiles to traditional models does not appreciably improve performance, at least with current knowledge [64]. Perhaps there are other risk factors (with high relative risks) not yet identified that, if added to existing cancer model, might add substantially to predictive ability over and above currently used risk factors. This seems unlikely for most cancers.

One of the major lessons that we have learnt from risk prediction is that our knowledge of disease pathways is imperfect. Assuming we had a validated cancer risk prediction model and before widespread implementation, we need robust external validation, and of course, we need evidence that these tools actually improve patient outcomes when used clinically. Such evidence is best sourced from randomized trials, which are not without challenges. The goal of personalized medicine, at least in terms of predicting risks for the purposes of targeted prevention, may therefore be illusory. Recent experience with cancer risk prediction adds a layer of complexity to the 'prevention paradox' described by Geoffrey Rose more than 30 years ago, in which he made the observation that the bulk of disease arises in people with low risk [65]. The most effective strategies might be to target prevention at the entire population, and then put efforts into better diagnosis and better treatment for those who do develop illness.

Conflict of interest

None declared.

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