Opinion on moderate/low cancer genetic risk markers in medical practice

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The search for genetic markers associated with low or moderate risk for different disorders has been applied for various multifactorial diseases to date, among them psychiatric, neurological and cardiological diseases and various types of cancer. The approach is of high scientific importance as it may provide new insights into pathomechanisms and interactions between functional components of biological systems. This knowledge might be the basis for the development of new therapeutic targets and individualised prevention strategies.

Nevertheless, despite its importance for basic research, testing for low/moderate risk markers in routine diagnostics for accurate cancer risk prediction as well as prevention, surveillance, and treatment schemes does not seem feasible to us in the near future.

Our understanding of the genetic basis of complex diseases is still in its infancy and use of the data for prevention and treatment will probably require much more time and data than previously thought. At present, the identification of SNPs and other types of genetic variability precedes the clarification of their functional relevance by far. One promising exception might be the field of pharmacogenetics, where polymorphic variants play an increasing role in medical practice. Based on current knowledge, screening for low/moderate genetic risk markers in sporadic tumours seems to be of limited value in routine practice. This is also underscored by several guidelines and recommendations of medical associations such as the Statement on the Genetic Diagnosis of Factors that Predispose to Multifactorial Diseases of the German Society of Human Genetics. The major concerns considered from different perspectives can best be illustrated by comparison with the major gene approach.

Medical considerations

The most important concern relates to basic considerations. In monogenic hereditary cancer syndromes (e.g. hereditary breast cancer, HNPCC, FAP, etc.) you have a family history, a specific tumour spectrum, an evident mode of inheritance, etc. In these cases there is a defined (limited) number of persons affected with a defined, high tumour risk due to a highly penetrant mutation in a limited number of genes. Due to the high predictive power regarding disease manifestation, we consider that the search for genetic factors in these families is straightforward and helpful for predictive diagnostics, surveillance and therapy.

In sporadic cancer – or families with a certain unspecified clustering of tumours – many, if not numerous, low/moderate risk variants will contribute to cancer risk. Moreover, it is unknown to date whether the interaction of different markers is based on additive, multiplicative, or epistatic effects. Even if all potential risk factors were identified and correctly interpreted, the predictive value for a given individual would still be limited.

Although the heritability of common sporadic cancers seems to be a substantial burden (estimates range from 26 to 42%, for CRC e.g. around 35%), several studies agree that probably 60-90% of the common cancers can be explained by environmental factors. Evidence for the predominant influence of environmental factors comes from three directions: i) twin studies where the rate of concordance in monozygotic twins is generally less than 15%, ii) migration studies, iii) studies on the risk of a second primary cancer in paired organs.

Based on these observations it seems to be impossible to provide sufficient individual risk assessments on the basis of low/moderate genetic risk factors alone [1, 2].

Assuming an optimal situation, all identified low/moderate susceptibility variants together (e.g. an SNP-based “risk profile”) may represent an important risk factor beside e.g. environmental influences. However, if dozens or hundreds of low/moderate risk markers are known, a huge number of combinations and interactions of various markers is possible in a given individual,
leading to all imaginable degrees of risk values throughout the population (maybe comparable to a Gaussian normal curve of distribution). It will be very difficult to calculate and validate the tumour risk conferred by each potential combination of variants, delineate different risk groups (which might always be arbitrary in a flowing risk model), and to develop appropriate specific surveillance and prevention strategies for all different risk groups, in particular due to the low number of persons harbouring a certain risk combination as well as compliance problems. Moreover, the role of protective factors is difficult to assess, and the influence of environmental or other non-genetic factors is not considered at all by the low/moderate risk genetic approach. Nowadays, the risk identified by e.g. certain SNPs is just a statistical correlation that cannot adequately predict the individual risk.

Anyway, to validate and recommend individualised prevention/surveillance protocols based on those profiles, much longer term clinical studies on large numbers of patients are needed. Even in late onset monogenic disorders the identification of a highly penetrant mutation in a healthy carrier does not often allow accurate prediction of the course of future disease (time at onset, spectrum of symptoms, complications, etc), although we all realise that probably not all carriers need the same kind and intensity of surveillance.

Psychological and ethical considerations

Molecular genetic tests in hereditary cancer syndromes are applied to a target population that is aware of its high tumour risk due to family history. Therefore, ethical or psychosocial problems in this context are mostly controllable, assuming that genetic counselling is offered to the selected patients. Moreover, you have “real facts” to explain to them, and can provide a real help by predictive diagnostics and surveillance for persons at risk and identified mutation carriers. In contrast, the low/moderate cancer risk marker approach implies broad genetic screening of the general population (population screening) for polymorphic variants in different genes, since there is no other way to select the target population. Thus, practical application will exhibit all the problems typical for population screening: the people who might benefit are healthy, have no family history of tumours and are at (low) a priori life-time risk of developing any type of cancer. As most people including physicians are not familiar with the correct interpretation and communication of risk figures, the test results are prone to be misunderstood in both ways, a false positive or false negative, leading to unfounded concerns or unfounded reassurance. Since every person will carry a few risk factors, the whole population might feel some kind of illness or risk for something after being tested. It will be a challenge to provide adequate genetic counselling to the large number of tested individuals, and to explain the complex risk figures and the difference between statistical association and individual risk. As a consequence, low/moderate risk gene screening will create a lot of uncertainty and anxiety in the population.

If it is accepted that patients with a relatively small risk increase (compared to monogenic disorders) might benefit from some kind of prevention/surveillance or modifications of existing population screening programmes, respectively, serious compliance problems may occur. Even high risk groups (e.g. mutation carriers for hereditary tumour syndromes) often do not perform surveillance at the desired intensity; the acceptance of less intensive surveillance for moderate risk prevention might be worse. Also, the surveillance methods applied, e.g. in hereditary tumour syndromes, are not free of (serious) side effects and complications, and thus their recommendation and intensity must always be balanced against the level of potential benefit. The risk/benefit ratio will only be sufficient in patients with a certain degree of risk. As probably most surveillance recommendations (e.g. gastrointestinal endoscopy) for low/moderate risks are not validated adequately, over-protection of patients accompanied by unnecessary side effects might be the consequence. Partly, these problem might be more relevant in hereditary tumour diseases and other conditions where invasive techniques of surveillance are applied compared to diseases where prevention strategies are restricted to (harmless) changes in diet, etc.

Economic considerations

This aspect includes not only the costs of molecular diagnostics, but also the costs of clinical surveillance programmes that follow for a given combination of low risk markers. While the current, relatively high costs of molecular diagnostics are expected to decrease due to the introduction of new and cheaper technologies (e.g. multiplex analysis of different variants), the costs for genetic counselling and clinical management will largely increase. It seems reasonable that almost every individual will have at least a few low/moderate risk markers. This would result in an increasing number of clinical surveillance programmes. It is expected that our health systems will manage the costs for molecular diagnostics and surveillance that are actually applied to families with hereditary cancer syndromes, but it would probably be
substantially overloaded by the introduction of the low/moderate genetic risk approach in routine practice.

**Legal considerations**

If the low/moderate genetic risk marker approach were broadly introduced to clinical practice, it is expected that legal aspects would expand. For a general practitioner (and not only for them) it is extremely difficult to understand the proper meaning of the genetic test itself and of the clinical consequences resulting from the test results. In order to avoid getting into legal trouble, this approach may lead to over-prevention by surveillance for each individual once the screening is introduced to clinical practice. The appropriate level of informed consent and pre-test counselling as well as the group of health care professionals who should be allowed to offer and interpret the (population-based) genetic screening are completely unknown to date. In any case, the broad introduction of low/moderate genetic risk screening will require new structures in health care systems.

**Conclusions**

The search for moderate genetic risk factors in multifactorial disorders is of high scientific importance as it may uncover important pathophysiological pathways and lead to identification of markers or combinations of markers that confer a significantly increased (cancer) risk and thus may justify individualised modifications of existing surveillance and treatment protocols. Therefore, it is appropriate to continue this approach on a research basis. However, although identification of certain risk profiles in the future may contribute to individual risk calculation in addition to traditional risk factors, the current state of knowledge does not justify screening for low/moderate risk markers in clinical practice, mainly based on medical reasons, but also because of ethical, psychosocial, economic and legal reflections. Some of these considerations are of more general relevance, while others may change in the future and should be reconsidered as soon as new hard and convincing results are available.

**References**

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