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Coverage of the Genetic Background of Breast Cancer in the Polish Population

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Background

It is a known fact that cancer risk is influenced by both environmental and genetic factors. Parameters such as the kind and site of the tumour and family history depend on the proportion between both and the population determines to a great extent the characteristics of the genetic background. Here we focus on breast cancer in the Polish population.

Despite complex population dynamics in the last centuries, the Poles seem to be surprisingly homogeneous in their genetics. A sequence-based screening of BRCA1 positive patients showed just 9 polymorphisms of BRCA1, where 91% of individuals shared just 3 common founder mutations [1]. The result is consistent with other Slavic countries [2-4]. In contrast, a similar screening in neighbouring Germany revealed 77 distinct BRCA1 mutations, 18 of them shared by 68% of BRCA1 positive patients [5].

Highly penetrating mutations, such as those of BRCA1, are mostly detected in conspicuous family aggregations via genetic linkage studies. Therefore, they may be detected with the help of just a few families even in heterogeneous populations. However, the probability of finding a new highly penetrating gene for the Polish population seems rather low; mutations of BRCA1 and BRCA2 already cover ~70% of cases of strong familial aggregations of breast and ovarian cancers [1]. The advantage of genetically homogeneous populations relies instead on the increased power of finding medium- and low-risk markers via large association studies that would otherwise be blurred in more complex populations.

Results

To date several variants of 6 genes have been demonstrated to significantly increase breast cancer risk in the Polish population: BRCA1, BRCA2, CHEK2, NBS1, NOD2, P16 [1, 6-9]. They actually cover ~25% of early onset (<50 yrs) breast cancer cases (n=3000). Current investigations extend those 6 genes up to 9 (data in preparation) (Fig. 1). One of them, represented as X2, includes a common variant that improves the total coverage up to 80% in a pre-

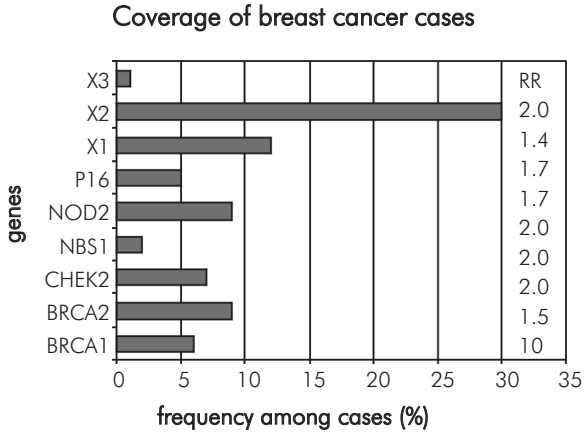

Fig. 1. Frequency of different genes with variants associated with breast cancer as covering a population of 3000 early onset (<50 yrs) breast cancer patients. Genes represented as X1-X3 are still subject of study and their values refer to estimations from preliminary data. Most of the genes represented include several disease-associated variants. The last column stands for the relative risk of each of them

liminary analysis: 700 cases out of 850 showed at least one disease-associated variant of the 9 analysed genes (Fig. 2).

Those values should drop for cases with onset at older ages as the cumulative exposure to external carcinogenic agents increases. Nevertheless, in familial aggregations of breast and ovarian cancer that percentage is expected to be higher since just BRCA1 and BRCA2 account already for almost 70% of cases. Both analyses have still to be performed.

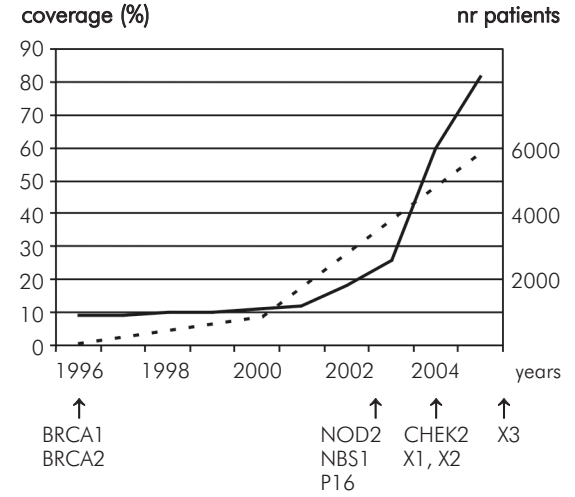

Fig. 2. Time sequence of the growth of the sample database (dashed line) in number of patients (note: the number of genotyped samples is actually 3500) and the improvement of the coverage of disease-associated genetic factors in the same population (continuous line). The percentage of coverage is based on estimations for different numbers of patients depending on the specific genes involved: 3000 patients for BRCA1, BRCA2, CHEK2, NBS1, NOD2 and P16; and 850 patients for those genes and the ones referred as X1, X2 and X3 (currently under study). The approximately onset of systematic analyses for the respective genes is indicated with an arrow and the gene's acronym

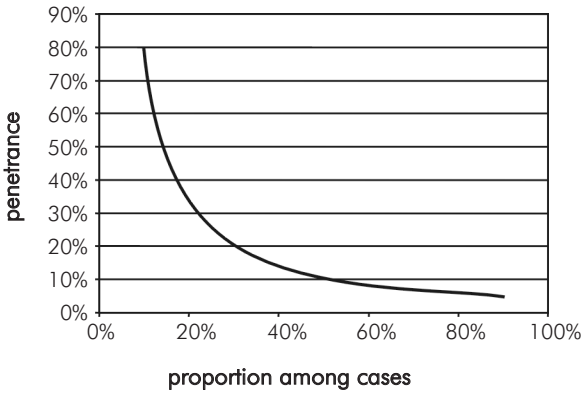

Fig. 3. Ideographic representation of the relationship between penetrance of the predisposing genetic factors and the proportion of the population of patients they are present in. Genes with highest penetrance are rather uncommon, in contrast to those with low penetrance, which can be very frequent. However, the interaction between different low penetrance factors may again increase the penetrance of the compound

Conclusions

The Polish population appears to be a useful group for detecting low-risk markers of cancer. It is large (~40m) and homogeneous enough to reach the statistical power necessary to detect small but still significant differences in cancer risk. Our actual knowledge of disease-associated genetic factors present in breast cancer cases is ~70% for familial aggregations and ~80% for early onset consecutive cases. Thanks to the parallel growth of the network country-wide for sample and data exchange and the genetic variants under analysis, we expect to approach 100% in the near future.

But even in such a scenario, the detection of a single predisposing genetic factor does not exclude the presence of additional ones. In fact, the current model predicts that the interplay between several genetic factors of low penetrance when analysed separately may increase the risk (either additively or synergically) to values comparable to much more penetrating ones (Fig. 3) [10]. Therefore, the search for new low-risk markers should continue even beyond the theoretical 100% of coverage, and bioinformatic analyses of the interplay among these factors should improve their application in clinical practice.

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