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Genetic contribution to all cancers: the first demonstration using the model of breast cancers from Poland stratified by age at diagnosis and tumour pathology

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Abstract The aim of the study is to verify the hypothesis that genetic polymorphisms are associated with the predisposition to all malignancies. Using as a model breast cancers from the homogenous Polish population (West Pomeranian region) after stratification of 977 patients by age at diagnosis (under 51 years and above 50 years) and by tumour pathology (ductal cancers—low and high grade, lobular cancers, ER-positive/negative) we tested this hypothesis. Altogether 20 different groups of breast cancer cases have been analyzed. The results were compared to a group of unaffected controls that were matched by age, sex, ethnicity and geographical location and originated from

families without cancers of any site among relatives. Molecular alterations selected for analyses included those which have been previously recognized as being associated with breast cancer predisposition. Statistically significant differences between the breast cancer cases and controls were observed in 19 of the 20 analyzed groups. Genetic changes were present in more than 90% of the breast cancer patients in 18 of 20 groups. The highest proportion of cases with constitutional changes—99.3% (139/140) was observed for lobular cancers. The number and type of genetic marker and/or the level of their association with the specific cancer predisposition was different between groups. Markers associated with majority of groups included: BRCA1, CHEK2, p53, TNRnTT, FGFRnAA, XPD

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CC/AA and XPD GG. Some markers appeared to be group specific and included polymorphisms in CDKN2A, CYP1B1, M3K nAA, and RS67.

Keywords Breast cancer · Genetic contribution to all cancers

Introduction

It is well recognized that a small percentage of common malignancies that include those of the breast, ovary or colon cancer are a result of constitutional mutations in genes such as BRCA1, BRCA2, MSH2, MLH1 and APC. Genetic predispositions for the majority of tumours, however, remains unknown but evidence is accumulating to suggest that low to moderate penetrance genes contribute to disease risk.

There are several different approaches that have been used to identify low to moderate genetic risk factors and currently the most popular is to perform genome-wide association studies on an appropriately large series of unselected cancer cases and unaffected matched controls [1]. These studies have focused on large multi-centre and multi-ethnic cohorts that have lead to the identification of genetic polymorphisms of moderate to low risk that appear to be common in the populations examined [2].

Since the aims of current research into the causes of malignancy is currently engaged in verifying the hypothesis that genetic constitutional changes contribute to the cancer predisposition in general, the use of genome-wide association studies for the identification of low to moderate genetic risk factors does, however, have some important limitations:

1. Pathological and/or clinical characteristics of cancers can be different depending on the associated moderate/low genetic risk markers [3–6]. Therefore, it is critical to use an appropriate cancer population that is stratified by age at diagnosis and tumour pathology.
2. As low to moderate risk markers occur with varying frequency in different ethnic groups the power to detect any association is compromised especially for low risk disease modifiers. Ideally, it is preferable to study large homogeneous populations to reduce population variance and increase the likelihood of identifying true genetic associations even when they are considered to be of low penetrance.

Taking the above into account we established an alternative strategy to efficiently identify panels of low-to-moderate genetic breast cancer risk markers using the following criteria:

- a. Consecutive breast cancer cases stratified into groups—by age at diagnosis and tumour pathology from homogeneous Polish population,

- b. Unaffected controls matched by age, sex, ethnicity and geographic location with negative cancer family histories
- c. Using single candidate markers (mutations/polymorphisms) known to be associated with increased genetic predisposition to breast cancers.

Employing the above criteria allowed us to identify a series of markers characteristic for 19 of 20 breast cancer groups that occur in more than 90% and almost 100% of patients in 18 out of the 20 breast cancer groups analyzed. The results provide evidence that there are a series of genetic polymorphisms that predispose to all breast cancer and suggest that other markers are likely to exist that are associated with all malignancies in general.

Materials and methods

Studies were performed on a series of 977 newly diagnosed consecutively collected breast cancer patients (participation rates above 95%) who underwent mastectomy at the Regional Oncology Hospital (Szczecin) in the years 2002, 2003, 2006 and 2007 or the University Hospital SPSK2 (years: 2002–2007), Szczecin, West-Pomerania, Poland.

Between the years 2000 and 2001 family doctors from the region in and around Szczecin collected cancer family history questionnaires from approximately 1.3 million inhabitants. Persons with a negative cancer family history were invited to participate in the project. A total of 1040 adult females accepted the invitation to participate and from these women the control population was created, which comprised 977 females matched for year of birth (± 2 years), ethnicity and location. The 977 pairs were classified into 20 different groups. Finally, the following groups were included for analysis:

1. All consecutive $n = 977$
2. Diagnosed under the age of 51 yrs $n = 310$
3. Diagnosed above the age of 50 yrs $n = 667$
4. Ductal, low grade (I and II degree by Bloom) $n = 401$
5. Ductal, high grade (III degree by Bloom) $n = 167$
6. Lobular $n = 140$
7. ER+ (estrogen receptor positive) $n = 508$
8. ER– (estrogen receptor negative) $n = 201$
9. Ductal, low grade and diagnosed above the age of 50 yrs $n = 266$
10. Ductal, high grade and diagnosed above the age of 50 yrs $n = 104$
11. ER+ and diagnosed above the age of 50 yrs $n = 334$
12. ER– and diagnosed above the age of 50 yrs $n = 118$
13. Ductal, low grade and diagnosed under the age of 51 yrs $n = 135$

14. Ductal, high grade and diagnosed under the age of 51 yrs $n = 63$
15. ER+ and diagnosed under the age of 51 yrs $n = 174$
16. ER– and diagnosed under the age of 51 yrs $n = 83$
17. Ductal, low grade and ER+ $n = 259$
18. Ductal, low grade and ER– $n = 55$
19. Ductal, high grade and ER+ $n = 76$
20. Ductal, high grade and ER– $n = 73$

All participants provided a blood sample from which DNA was extracted for analysis. Molecular studies included the analysis of the mutations/polymorphisms as described in Table 1. Experimental conditions to perform ASA, RFLP-PCRs, real time PCR and DNA sequencing have been reported previously (Table 1).

Genetic changes selected for analysis included alterations which have previously been shown to be associated with an increased risk of consecutive unselected breast cancers or of their sub-types.

Data analysis

In the first stage, BRCA1 mutation carriers were excluded. In order to find the other most optimal panels of markers, all samples were analyzed and then the marker selected based on the highest odds ration (OR) value in a comparison between cases and controls using Fischer's exact test. After the selection of markers all samples matching it were removed and then the process reiterated until the markers with $OR > 1$ and occurring in less than 90% of controls could be found.

Results

Statistically significant differences between cases and controls have been found for 19 of 20 analyzed groups (Tables 2–4) except of one small group ($n = 63$) of ductal, high grade, early onset cancers. Genetic changes were present in more than 90% of breast cancer patients in 18 of 20 groups except of ductal cancers ER (–) (Table 4). The highest proportion of cases with constitutional changes—99.3% (139/140) was observed for lobular cancers (Table 3). List of genetic markers and/or the level of their association with cancer predisposition reflected by their

Table 2 Frequency of identified panel of markers in all consecutive cancers and controls

Gene/marker	Cases (%)	Controls (%)
BRCA1	2.7% (26/977)	0% (0/977)
CKEK 2	11.9% (113/951)	6% (59/977)
p53	10.1% (85/838)	5.7% (52/918)
TNR	55.6% (419/753)	45.8% (397/866)
FGFR—GG	18.3% (61/334)	13.9% (65/469)
CDKN2A	7% (19/273)	5.4% (22/404)
XPD—GG	41% (104/254)	36.4% (139/382)
XPD—CC/AA	17.3% (26/150)	14% (34/243)
BRCA2	7.3% (9/124)	4.8% (10/209)
XPD—AA	20% (23/115)	18.6% (37/199)
Any marker	90.6% (885/977)	83.4% (815/977)
Statistical significance	$P = 3 \times 10^{-6}$	

Table 1 List of studied genes/changes

Marker	Gene	SNP or mutation	Variant used	Reference
BRCA1	BRCA1	C61G, 4153delA, 5382insC	Positive	[7, 8]
CHK2	CHK2	IVS+1G/A, I157T, 1100delC, del5395	Positive	[9, 10]
p53	P53	R72P	CC only	[11]
XPD-GG	XPD	D312N	GG only	[12]
XPD-AA	XPD	K751Q	AA only	[12]
XPD-CC/AA	XPD	K751Q/D312N	CC/AA only	[12]
CYP1B1	CYP1B1	R48G, A119S, V432L	Haplotype GG ⁴⁸ TT ¹¹⁹ CC ⁴³²	[13]
NOD2	NOD2	3020insC	Positive	[5, 14]
BRCA2	BRCA2	T1915M	Positive	[15]
CDKN2A (p16)	CDKN2A (p16)	A148T	Positive	[16]
FGFR2-nAA	FGFR2	Rs1219648,	AA excluded	[17]
FGFR2-GG	FGFR2	Rs1219648	Only GG	[17]
TNR-nTT	TNRC9	Rs3803662	TT excluded	[1, 18]
M3K-nAA	MAP3K	Rs889312	AA excluded	[1]
Rs67	–	Rs6983267	Only GG	[19]
FGFR2-nAA/TNR-nTT	Combined genotypes of FGFR2 and TNRC9			[1]

Table 3 Frequency of identified panel of markers in a group of lobular cancers and in controls

Gene/marker	Cases (%)	Controls (%)
BRCA1	0.7% (1/140)	0% (0/140)
CHEK 2	19.4% (27/139)	4.3% (6/140)
p53	10.7% (12/112)	6% (8/134)
BRCA2	9% (9/100)	4.8% (9/126)
FGFR—nAA	75.8% (69/91)	60% (72/120)
TNR	72.7% (16/22)	39.6% (19/48)
NOD 2	16.7% (1/6)	0% (0/29)
M3K—nAA	80% (4/5)	41.4% (12/29)
Any marker	99.30% (139/140)	87.90% (123/140)
Statistical significance	$P = 0.00073$	

Table 4 Frequency of identified panels of markers in different groups of breast cancers

Group	Cases (%)	Controls (%)	<i>P</i>
Consecutive	90.6% (885/977)	83.4% (815/977)	3×10^{-6}
Dgn < 51	91.0% (282/310)	81.9% (254/310)	0.0014
Dgn > 50	96.1% (641/667)	89.4% (596/667)	1×10^{-8}
Ductal, low grade	94.8% (380/401)	89.1% (357/401)	0.0041
Ductal, high grade	95.2% (159/167)	83.8% (140/167)	0.0010
Lobular	99.30% (139/140)	87.90% (123/140)	0.00073
ER (+)	96.3% (491/508)	90.0% (457/508)	2.4×10^{-5}
ER (−)	93.5% (188/201)	80.1% (161/201)	9.6×10^{-5}
Ductal, low grade, dgn > 50	96.2% (256/266)	88.0% (239/266)	0.0006
Ductal, high grade, dgn > 50	96.2 % (100/104)	86.5% (91/104)	0.0401
ER (+), dgn > 50	94.6% (316/334)	86.2% (288/334)	0.0003
ER (−), dgn > 50	96.6% (114/118)	82.2% (97/118)	0.0005
Ductal, low grade, dgn < 51	94.1% (127/135)	80.7% (109/135)	0.0015
Ductal, high grade, dgn < 51	96.8% (61/63)	88.9% (56/63)	0.1638
ER (+), dgn < 51	96.0% (167/174)	87.9% (153/174)	0.0097
ER (−), dgn < 51	92.8% (77/83)	78.3% (65/83)	0.0139
Ductal, low grade, ER (+)	96.1% (249/259)	90.0% (233/259)	0.0087
Ductal, low grade, ER (−)	81.8% (45/55)	58.2% (32/55)	0.0119
Ductal, high grade, ER (+)	98.7% (75/76)	84.2% (64/76)	0.0023
Ductal, high grade, ER (−)	84.9% (62/73)	61.6% (45/73)	0.0025

position on the list was different between groups. No single marker was identified as being associated with cancer in all groups except of BRCA1 mutations included on all lists by definition.

Markers associated with majority of groups include CHEK2, p53, TNRnTT, FGFRnAA, XPD CC/AA and XPD GG. Some markers were tightly associated with particular groups of patients for example CDKN2A with ductal cancers diagnosed under age of 51 years that were high grade and ER (+), CYP1B1 with ductal cancers of low grade and diagnosed under age of 51 years of age, M3K nAA with cancers diagnosed over age of 50 years and ER (−), RS67 with ductal cancers of high grade and diagnosed above the age of 50 years.

Supplementary data are presented in Tables 5–22 (see additional file to this manuscript).

Discussion

The report demonstrates for the first time that genetic components to malignancy appears to play a role in all cancers.

Evidence is presented of there being a series of low penetrant genetic polymorphisms that account for a proportion of disease risk observed in a series of breast cancer sub-types derived from the homogeneous Polish population. The data presented for breast cancer suggests that the approach utilized in this study would be applicable for the identification of low penetrance genetic risk factors in other malignancies.

The results presented appear not to reflect any major bias as the statistical significance clearly differentiates cases from controls in 19 of the 20 groups. Furthermore the selected genetic markers are present in more than 90% of cases in 18 of the 20 subgroups examined. Additionally, for all groups with at least 100 cases, patient/control pairs were divided randomly into two sub-groups with all results remaining consistent (data not shown). Additionally, the degree of accuracy of the registry used for this analysis belongs to one of the largest reported to date (>95% of consecutive cases, cancer free controls). It will be necessary to validate the results presented herein on additional collections of cases/controls, where similar population homogeneity can be expected.

The most significant results have been obtained for lobular cancers for which the genetic markers were represented in more than 99% of the cases. This may be related to the greater contribution of genetic factors in the development of this sub-type of breast cancer and, therefore, reflects a larger amount of constitutional change associated with this type of disease. For many years it has been suggested that the increased frequency of multifocal and bilateral disease are characteristic features of lobular cancer, which is consistent with features that are characteristic of breast cancers derived from patients with strong family histories of disease [20–22].

At present the current methodology for association studies is to employ platforms that utilize hundreds of thousands of SNPs (Illumina, Affymetrix) covering the whole genome. The alternative approach used genetic markers identified from studies of polymorphisms in candidate genes. The results of this study suggest that it might be appropriate to work with SNP platforms in two stages. For the first, platforms could be tailored to the study of functional changes within definitive genes. It appears that such an approach may be more economical and allows for easier data accumulation and a more rapid transfer into clinical use for the assessment of disease risk.

The data also demonstrates how much can be achieved if cancers are accurately stratified by clinical characteristics and/or pathology. Certainly, some genetic polymorphisms that are critical for the development of certain sub-types of cancer cannot be identified if association studies are limited to the analysis of consecutive unselected cases.

The results achieved in this study suggest that there are two major groups of genes:

1. Those that can be identified by analyses of consecutive unselected cases and represent a more general genetic risk factor;
2. Those that are more specific in nature since they appear to be determining factors for sub-types of disease which can only be identified after appropriate stratification.

Our data do not exclude the role of the environmental factors but suggest that they act effectively only on pre-disposed persons. The probability of being affected by cancer without any constitutional changes associated with disease predisposition seems to be extremely low. For example—only 3.9% of women with breast cancer diagnosed above the age of 50 years do not carry any of identifiable markers used in this study, it may be possible to categorize women aged above 50 years without any markers as having a breast cancer risk of more than 25 times less than someone with one or more markers.

Currently, except for rare situations when a person has great fears of being diagnosed with cancer, it is too early to use the described DNA examination as a diagnostic tool.

In the future, improvements in specificity and sensitivity of testing with more extensive panels of low to moderate cancer risk markers should allow for even more accurate assessment of risk. This could be achieved by adding additional molecular constitutional polymorphisms and by using the results of studies examining interactions between them or by ameliorating the statistical power due to increasing the numbers of cases and controls.

The results of this study suggest that after further improvements of testing with the use of low/moderate genetic cancer risk markers, DNA analysis will be the

initial starting point for prevention, surveillance and treatment schemes for all adults. At present, the major significance of the current findings is the proof of principle that there is no cancer without a genetic component.

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