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Low-risk Genes and Multi-organ Cancer Risk in the Polish Population

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There is continuing interest in identifying low-penetrance genes which are associated with increased susceptibility to common types of cancer. There are several approaches to this problem, including the use of chip-based single nucleotide polymorphism (SNP) arrays to interrogate a large number of genes simultaneously and pre-selecting candidate genes of interest. Candidate genes for cancers of a particular site may be selected because they are known to predispose to malignancies of other organs, or because they are mutated somatically in the cells from the cancer of interest. It is possible that missense variants of genes for which truncating mutations are clearly pathogenic may also be deleterious, but with reduced penetrance. In this situation the association may be overlooked unless large numbers of cancers are studied.

In our centre we performed population-based studies of common variants of three genes: a tumour-suppressor gene CDKN2A (OMIM 600160), NOD2 (OMIM 605956) involved in the chronic inflammation process, and CHEK2 (OMIM 604373) participating in the DNA damage response.

To determine whether CDKN2A common variant A148T may be associated with an increased risk of malignancies at different sites of origin we genotyped a series of 8,263 unselected cancer cases and compared the frequency of the change observed in this population to 3,000 controls in Poland. To establish the range of cancer types associated with three *CHEK2* mutations (VS2+1G → A, 1100delC, and I157T) we genotyped 4,008 unselected cases of cancer and 4,000 controls in Poland. In order to define the range of cancer phenotypes associated with the NOD2 3020insC mutation we examined 2,604 unselected invasive cancers of 12 different types and 1,910 controls from Poland.

Results

We showed an association between CDKN2A common variant and increased risk of malignant melanoma (OR=2.1), cancers of breast (under 50y, OR=1.5), lung (OR=2.0) and colon (OR=1.5) (table 1) [1-3].

We also found a positive association between common NOD2 variant and cancers of the colon (late-onset, OR=2.2), breast (early-onset breast cancer OR=1.9 and ductal breast cancer with an in situ component OR=2.1) and ovary (table 2) [4-7].

Positive associations with CHEK2 protein-truncating alleles were seen for cancers of the thyroid (OR=4.9), breast (OR=2.2) and prostate (OR=2.2). The missense variant I157T was associated with an increased risk of breast cancer (OR=1.4), colon cancer (OR=2.0), kidney cancer (OR=2.1), prostate cancer (OR=1.7) and thyroid cancer (OR=1.9) (table 3) [8].

Table 1. Association between A148T variants and selected types of cancer

	A148T		OR	95% Confidence Interval	p (adjusted p)
total controls (n=3000)	105 (3.5%) G/A				
bladder (n=223)	0 (0%) A/A	7 (3.1%) G/A	0.9	0.4105-1.945	0.7764 (n.s)
colon (n=724)	0 (0%) A/A	37 (5.1%) G/A	1.5	1.012-2.180	0.0423 (0.5499)
stomach (n=246)	0 (0%) A/A	8 (3.3%) G/A	0.9	0.4461-1.925	0.8384 (n.s)
larynx (n=396)	0 (0%) A/A	17 (4.3%) G/A	1.2	0.7326-2.088	0.4255 (n.s)
ovary (n=340)	0 (0%) A/A	12 (3.5%) G/A	1.0	0.5491-1.853	0.9777 (n.s)
lung (n=497)	0 (0%) A/A	34 (6.8%) G/A	2.0	1.358-3.018	0.0004 (0.0052)
prostate (n=348)	0 (0%) A/A	13 (3.7%) G/A	1.1	0.5946-1.925	0.8215 (n.s)
kidney (n=264)	0 (0%) A/A	6 (2.3%) G/A	0.6	0.2788-1.474	0.2915 (n.s)
thyroid (n=173)	0 (0%) A/A	3 (1.7%) G/A	0.5	0.1528-1.549	0.2129 (n.s)
non-Hodgkin Lymphoma (n=162)	0 (0%) A/A	6 (3.7%) G/A	1.1	0.4585-2.453	0.8909 (n.s)
breast (under 50y) (n=3318)	0 (0%) A/A	168 (5.1%) G/A	1.5	1.2764-1.832	0.002
melanoma (n=471)	0 (0%) A/A	33 (7%) G/A	2.1	1.387-3.111	0.0003
pancreas (n=210)	0 (0%) A/A	8 (3.8%) G/A	1.1	0.5246-2.273	0.8140 (n.s)

Table 2. Association of the NOD2 3020insC mutation and selected types of cancer

Site	Number tested	Number positive	Prevalence of 3020ins C (%)	Odds ratio	p-value
bladder	172	18	10.5	1.5	0.13
breast	462	37	8.0	1.1	0.62
with DCIS	126	18	14.3	2.1	0.009
without DCIS	336	19	5.7	0.76	0.30
colon	255	31	12.2	1.8	0.01
kidney	245	8	3.2	0.4	0.02
larynx	223	23	10.3	1.5	0.11
lung	258	30	11.6	1.7	0.03
melanoma	198	10	5.1	0.7	0.31
ovary	317	35	11.0	1.6	0.03
pancreas	127	6	4.7	0.6	0.37
prostate	298	17	5.7	0.76	0.40
stomach	213	20	9.4	1.3	0.27
thyroid	82	8	9.8	1.4	0.39
controls	1910	140	7.3		

Table 3. Association between CHEK2 variants and selected types of cancer

Site	No. tested	Number positive (prevalence), odds ratio, p-value			
		IVS2 + 1G>A	1100delC	Any truncating mutation	I157T
bladder	172	1 (0.6%) OR 1.2 p=0.7	0	1 (0.6%) OR 0.8 p=0.8	12 (7.0%) OR 1.5 p=0.3
breast	1017	11 (1.1%) OR 2.3 p=0.04	5 (0.5%) OR 2.0 p=0.3	16 (1.6%) OR 2.2 p=0.02	68 (6.7%) OR 1.4 p=0.02
colon	300	1 (0.3%) OR 0.7 p=0.9	2 (0.7%) OR 2.7 p=0.4	3 (1%) OR 1.4 p=0.8	28 (9.3%) OR 2.0 p=0.001
kidney	264	0	2 (0.8%) OR 2.7 p=0.5	2 (0.8%) OR 1.0 p=0.8	26 (9.8%) OR 2.1 p=0.0006
larynx	245	0	0	0	10 (4.1%) OR 0.8 p=0.7
lung	272	0	0	0	7 (2.6%) OR 0.5 p=0.1
melanoma	129	2 (1.5%) OR 3.3 p=0.3	1 (0.8%) OR 3.1 p=0.8	3 (2.3%) OR 3.2 p=0.1	6 (4.6%) OR 1.0 p=0.9
ovary	292	0	0	0	14 (4.8%) OR 1.0 p=0.9
prostate	690	8 (1.2%) OR 2.5 p=0.05	3 (0.4%) OR 1.7 p=0.2	11 (1.6%) OR 2.2 p=0.04	54 (7.8%) OR 1.7 p=0.002
stomach	241	4 (1.7%) OR 3.5 p=0.05	0	4 (2.1%) OR 2.3 p=0.2	13 (5.4%) OR 1.1 p=0.8
NHL	120	1 (0.8%) OR 1.8 p=0.9	0	1 (0.8%) OR 1.1 p=0.7	11 (9.2%) OR 2.0 p=0.05
pancreas	93	0	0	0	6 (6.4%) OR 1.4 p=0.6
thyroid	173	5 (2.9%) OR 6.2 p=0.0003	1 (0.6%) OR 2.3 p=0.9	6 (3.5%) OR 4.9 p=0.0006	15 (8.7%) OR 1.9 p=0.04
controls	4000	19 (0.475%)	10 (0.25%)	29 (0.725%)	193 (4.825%)

Conclusions

It seems that CDKN2A, NOD2 and CHEK2 are responsible for a wide range of cancer types.

We estimate that the mutations mentioned above are responsible for around 20% of malignancies occurring in the Polish population. According to our studies over 4 million people in Poland carry one of the mutations described above. We elaborated genetic tests for CDKN2A, NOD2 and CHEK2 aimed at reliable identification of persons with increased risk of developing cancers of the breast, ovary, lung, prostate, thyroid, colon, kidney and malignant melanoma.

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