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Irrelevance of CHEK2 variants to diagnosis of breast/ovarian cancer predisposition in Polish cohort

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Abstract *CHEK2* gen encodes cell cycle checkpoint kinase 2 that participates in the DNA repair pathway, cell cycle regulation and apoptosis. Mutations in *CHEK2* gene may result in kinase inactivation or reduce both catalytic activity and capability of binding other proteins. Some studies indicate that alterations in *CHEK2* gene confers increase the risk of breast cancer and some other malignancies, while the results of other studies are inconclusive. Thus the significance of *CHEK2* mutations in aetiology of breast cancer is still debatable. The aim of our study was to evaluate the relationship between the breast/ovarian cancer and *CHEK2* variants by: *i*) the analysis of the frequency of selected *CHEK2* variants in breast and ovarian cancer patients compared to the controls; *ii*) evaluation of relationships between the certain *CHEK2* variants and clinico-histopathological and pedigree data. The study was performed on 284 breast cancer patients, 113 ovarian cancer patients and 287 healthy women. We revealed the presence of 430T>C, del5395 and IVS2+1G>A variants but not 1100delC in individuals from both study and control groups. We did not observe significant differences between cancer patients and controls neither in regard to the frequency nor to the type of *CHEK2* variants. We discussed the potential application of *CHEK2* variants in the evaluation of breast and ovarian cancer predisposition.

Keywords Breast cancer · Cancer predisposition · *CHEK2* gene · Mutations · Ovarian cancer

Introduction

CHEK2 gene encodes cell cycle checkpoint kinase 2 that is regarded as a candidate tumor suppressor (Nevanlinna and

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Bartek 2006). CHEK2 participates in the DNA repair pathway, cell cycle regulation and apoptosis (Shieh et al. 2000). In response to DNA damage, CHEK2 is phosphorylated by ATM and ATR kinases. Active CHEK2 in turn phosphorylates p53 and BRCA1 (Brody 2002). Other substrates of kinase CHEK2 are the following: CDC25A, CDC25C phosphatases, PLK3 kinase and E2F1 transcription factor (Nevanlinna and Bartek 2006).

Mutations in *CHEK2* gene were detected for the first time among *TP53*-negative LFS (Li-Fraumenni syndrom) and LFS-variant families (Bell et al. 1999). A number of rare alterations in *CHEK2* which are defined as intermediate risk mutations, have been reported in breast cancer patients (Willems 2007; Turnbull and Rahman 2008). The more common mutations are the following: one missense variant (430T>C) and three truncating mutations (1100delC, IVS2+1G>A, del5395).

1100delC (c.1100delC/p.Thr367MetfsX15) disrupt the catalytic domain of CHEK2 resulting in an inactive kinase (Wu et al. 2001; Bell et al. 2007). In combined analysis of the ten case-control studies 1100delC was observed in 1.9% (201/10860) breast cancer cases and in 0.7% (64/9065) controls (*CHEK2* Breast Cancer Case-Control Consortium 2004). It was estimated that *CHEK2* 1100delC confers about two-fold increased breast cancer risk in women (*CHEK2* Breast Cancer Case-Control Consortium 2004). Nevertheless, the meta–analyses published by Weischer et al. (2008) showed that *CHEK2* 1100delC is an important breast cancer predisposition factor, increasing the risk by three- to five-fold. Studies carried out in Poland and neighboring countries shows that this mutation occurred in 0.0–5.2% breast cancer patients versus 0.0–0.92% in controls (Dufault et al. 2004; Kleibl et al. 2005; Rashid et al. 2005; Kwiatkowska et al. 2006; Cybulski et al. 2007a; Fedorova et al. 2007; Sokolenko et al. 2007; Suspitsin et al. 2009).

CHEK2 del5395 (originally described as del5567) has been observed by Walsh et al. (2006) in families with a high aggregation of breast and ovarian cancer. This mutation confers the deletion of two exons (9 and 10) (g.27417113_27422508del) and was detected in 0.9–1.3% of breast cancer cases while in 0.0–0.4% of controls (Walsh et al. 2006; Cybulski et al. 2006; Cybulski et al. 2007a).

Another *CHEK2* protein truncating mutation found in breast cancer patients is a splice-site mutation IVS2+1G>A (c.444+1G>A) (Cybulski et al. 2004b; Dufault et al. 2004). The estimated incidence of this alteration was 0.0–1.1% for breast cancer patients and 0.0–0.4% for controls (Dufault et al. 2004; Bogdanova et al. 2005; Cybulski et al. 2007a; Kleibl et al. 2008; Sokolenko et al. 2007).

Another recurrent *CHEK2* alteration found in breast cancer patients was missense variant 470T>C (c.470T>C/p.Ile157Thr) (Bell et al. 1999; Allinen et al. 2001; Schutte et al. 2003; Cybulski et al. 2004b; Friedrichsen et al. 2004; Kilpivaara et al. 2004; Bogdanova et al. 2005). In vitro studies showed that the *CHEK2* 470T>C variant encodes a protein with both reduced CDC25A catalytic activity and reduced capability of TP53 and BRCA1 binding (Falck et al. 2001a, b; Wu et al. 2001; Li et al. 2002; Bell et al. 2007). Kilpivaara et al. (2004) suggest that 470T>C variant may have negative effect on the pool of normal CHEK2 protein by formation of heterodimers with wild-type CHEK2. The occurrence of 470T>C variant was observed in 1.9–7.4% of cancer cases and in 0.6–4.8% of controls (Dufault et al. 2004; Kilpivaara et al. 2004; Bogdanova et al. 2005; Szymanska-Pasternak et al. 2006; Cybulski et al. 2007a; Kleibl et al. 2008). This variant confers lower risk of hereditary breast cancer than protein truncating mutation (Kilpivaara et al. 2004).

Another missense variant (1283C>T) associated with increased breast cancer risk was found in the Ashkenazi Jewish population (Shaag et al. 2005).

Summarizing, in some studies a strong correlation between specific *CHEK2* variants and breast cancer risk has been observed (*CHEK2* Breast Cancer Case-Control Consortium 2004; Dufault et al. 2004; Kilpivaara et al.

Table 1 Characteristics of breast and ovarian cancer patients

	Criteria	Number of cases
Breast cancer cases		
Family history of BrC and OvC	3 first-degree relatives	21
	2 first-degree relatives	64
	2 or more cases, but no specific pattern of inheritance	35
	One cancer	164
Histology	Ductal	156
	DCIS (Ductal carcinoma in situ)	26
	Medullary	7
	Lobular	33
	Tubular	7
	Other/advice	55
Ovary cancer cases		
Family history of BrC and OvC	3 first-degree relatives	4
	2 first-degree relatives	21
	2 or more cases, but no specific pattern of inheritance	11
	One cancer	*77*
Histology	Serosum	50
	Endometrioides	17
	Mucinosum	11
	Other/advice	35

2004; Bogdanova et al. 2005; Górski et al. 2005; Cybulski et al. 2007a; Weischer et al. 2008), contrary to others, where weak or no correlation was found (Allinen et al. 2001; Schutte et al. 2003; Friedrichsen et al. 2004; Kleibl et al. 2005, 2008; Rashid et al. 2005). It has been shown that mutations in *CHEK2* gene confers also a predisposition to some other malignancies like: prostate (Dong et al. 2003; Seppälä et al. 2003; Cybulski et al. 2004a, 2006), thyroid (Cybulski et al. 2004b), bladder (Złowocka et al. 2008) and colorectal cancer (Cybulski et al. 2004b, 2007b), as well as to sarcoma and brain tumors (Bell et al. 1999).

Since the results of studies on *CHEK2* mutations in aetiology of breast cancer conducted by many authors are inconclusive and the significance of *CHEK2* mutations in breast cancer risk is still debatable, the aim of our study was to search for the relationship between the breast/ovarian cancer and *CHEK2* variants by: *i*) the analysis of the frequency of selected *CHEK2* variants in breast and/or ovarian cancer patients negative for most common mutations in *BRCA1* and *BRCA2* genes in Polish population, comparing to the controls, *ii*) evaluation of relationships between the certain *CHEK2* variants and clinico-histopathological and pedigree data.

Materials and methods

The study was performed on DNA isolated from peripheral blood lymphocytes obtained from 284 breast and 113 ovarian cancer patients (altogether 397 women). Patients were unrelated and came from the south-west region of Poland (Lower Silesia). The group was characterized in respect to family history of cancer, tumor histology (see Table 1) age of onset of the diseases as well as the presence of most common mutations (in Poland) in *BRCA1* such as: 5382insC (c.5266dupC), 300T>G (c.181T>G), 4153delA (c.4034delA), 185delAG (c.68_69delAG) and *BRCA2* gene: 6174delT (c.5946delT). Individuals with mutations in either *BRCA1* or *BRCA2* genes were excluded from the analysis. The average age was 49±9 and 53±13 years for breast and ovarian study groups, respectively. The diagnosis of hereditary breast cancer (HBC) and hereditary breast/

Table 2 Frequency of *CHEK2* variants in controls and cases

Variant	Controls	BrC cases	OvC cases	All cases
All *CHEK2* mutation	21/287	28*/284	5/113	33*/397
	7.3%	9.9%	4.4%	8.3%
		p=0.28	p=0.29	p=0.63
		OR: 1.39	OR: 0.59	OR: 1.15
		95%CI: 0.76–2.54	95%CI: 0.20–1.71	95%CI: 0.66–2.01
430T>C	18/287	20/284	3/113	23/397
	6.3%	7.0%	2.6%	5.8%
		p=0.71	p=0.14	p=0.79
		OR: 1.33	OR:0.41	OR: 0.92
		95%CI: 0.57–2.23	95%CI: 0.09–1.87	95%CI: 0.48–1.75
IVS2+1G>A	2/287	3/284	1/113	4/397
	0.7%	1.1%	0.9%	1.0%
		p=0.65	p=0.84	p=0.67
		OR: 1.52	OR: 1.27	OR: 1.45
		95%CI: 0.25–9.32	95%CI: 0.11–14.44	95%CI: 0.26–8.14
del5395	1/287	6/284	1/113	7/397
	0.3%	2.1%	0.9%	1.8%
		p=0.055	p=0.49	p=0.09
		OR: 6.2	OR: 2.56	OR: 5.15
		95%CI: 0.36–104,83	95%CI: 0.15–43.84	95%CI: 0.39–68.19
1100delC	0/287	0/284	0/113	0/397
	0	0	0	0
All truncating mutations	3/287	7/284	2/113	11/397
	1.0%	2.5%	1.8%	2.8%
	–	p=0.20	p=0.56	p=0.12
		OR: 3.10	OR: 1.7	OR: 2.7
		95%CI: 0.72–13.43	95%CI: 0.27–10.66	95%CI: 0.67–10,89

* two mutations (430T>C; del5395) in one individual

Table 3 Frequencies of mutations in the *CHEK2* gene on the basis our study of literature

Mutation	Population / region	Group	Cases		Controls		p	References
			N	%	N	%		
470T>C	Poland	BrC OvC	20/284 3/113	7.0 2.6	18/287	6.3%	0.71 0.14	our study
	Poland	BrC (unselected) BrC (<51)	134/1978 207/3228	6.8 6.4	264/5496	4.8	0.001 0.002	Cybulski et al. 2007a
		BrC (all cases)	288/4454	6.5			0.0004	
	Poland	OvC	26/447	5.8	193/4000	4.8	0.4	Szymanska-Paternak et al. 2006
	Czech	BrC (unselected)	19/673	2.82	17/683	2.49	0.71	Kleibl et al. 2008
	Germany	BrC (unselected)	22/996	2.2	3/486	0.6	0.044	Bogdanova et al. 2005
	Germany	BrC (familial)	10/516	1.9	8/500	1.6	0.68	Dufault et al. 2004
	Belarus	BrC	24/424	5.7	4/307	1.3	0.005	Bogdanova et al. 2005
	Russia	OvC	9/77	(11.7)	7/150	(4.7)	0.06	Szymanska-Paternak et al. 2006
	Finland	BrC	77/1035	7.4	100/1885	5.3	0.021	Kilpivaara et al. 2004
	Finland	BrC	10/259	3.9	13/200	6.5	–	Allien et al. 2001
IVS2+1G>A	Poland	BrC OvC	3/284 1/113	1.1 0.9	2/287	0.7	0.65 0.84	our study
	Poland	BrC (unselected) BrC (<51)	21/1978 31/3228	1.1 1.0	22/5496	0.4	0.002 0.002	Cybulski et al. 2007a
		BrC all	43/4454	1.0			0.0008	
	Czech	BrC (unselected)	0/673	0.0	0/683	0.0	–	Kleibl et al. 2008
	Germany	BrC (unselected)	3/996	0.3	1/486	0.2	0.273	Bogdanova et al. 2005
	Germany	BrC (familial)	2/516	0.4	2/500	0.4	–	Dufault et al. 2004
	Belarus	BrC	4/424	0.9	0/307	0.0	–	Bogdanova et al. 2005
	Russia	BrC (hereditary)	2/302	0.7	–	–	–	Sokolenko et al. 2007
del5395	Poland	BrC OvC	6/284 1/113	2.1 0.9	1/287	0.3	0.055 0.49	our study
	Poland	BrC (unselected) BrC (<51)	19/1978 28/3228	1.0 0.9	24/5496	0.4	0.01 0.02	Cybulski et al. 2007a
		BrC all	39/4454	0.9			0.009	
	Czech, Slovakia	BrC (invasive)	8/631	1.3	0/367	0.0	0.03	Walsh et al. 2006
1100delC	Poland	BrC OvC	0/284 0/113	0 0	0/287	0.0	– –	our study
	Poland	BrC (unselected) BrC (<51)	10/1978 16/3228	0.6 0.5	12/5496	0.2	0.08 0.04	Cybulski et al. 2007a
		BrC all	20/4454	0.4			0.07	
	Eastern Poland Southern Poland	BrC BrC	3/487 1/296	0.6 0.3	– –	– –	– –	Kwiatkowska et al. 2006
	Western Poland	BrC	0/279	0.0	–	–	–	
	Poland	BrC (together)	4/1062	0.38	–	–	–	
	Czech	BrC (unselected) BrC (famililial, early)	3/688 1/358	0.44 0.28	2/730	0.27	0.67 0.99	Kleibl et al. 2005
	Germany	BrC Controls 2	5/613 –	0.82 –	6/651 0/600	0.92 0.0	– –	Rashid et al. 2005
	Germany	BrC (familial) BrC (bilateral)	8/516 0/103	1.55 0.0	6/1315	(0.46)	0.016 –	Dufault et al. 2004
	Russia	BrC (unilateral) BrC (bilateral)	14/660 8/155	2.1 5.2	– –	– –	– –	Chekmariova et al. 2006
		Controls (18–74)	–	–	1/448	0.2	–	
		Controls (75–96)	–	–	0/373	0.0	–	
	Russia	BrC (hereditary)	9/302	3.0	–	–	–	Sokolenko et al. 2007
	Russia	OvC	2/290	0.7	–	–	–	Suspitsin et al. 2009
	Russia	OvC	0/87	0.0	–	–		Fedorova et al. 2007

ovarian cancer (HBOC) was evaluated based on pedigree analysis (according to Berliner and Fay 2007; Lynch et al. 2003). HBCs/HBOCs were diagnosed in 136 breast cancer cases. The matched control group comprised of 287 healthy women coming from the same population, with no family history of cancer. The average age of the controls was 46± 18 years. DNA was isolated using commercial kit (Qiagen). Molecular analysis of three truncating mutations: 1100delC, del5395, IVS2+1G>A and one missense variant 470T>C were carried out by using PCR-RFLP and ASA-PCR, employing primers as previously described by Cybulski et al. (2004a, 2007a). The study design was accepted by Ethical Committee of Wroclaw Medical University. Analysis of the frequency of selected variants in the *CHEK2* gene in patients with breast and/or ovarian cancer in comparison to control group was assessed using the Fisher's exact test. Logistic regression was used to estimate odds ratios. Confidence interval was 0.95 and p-value of less than 0.05 was considered as significant. Statistical analysis of data was performed using StatSoft, Inc. (2005) STATISTICA, version 7.0.

Results

Molecular analysis revealed the presence of 430T>C, del5395 and IVS2+1G>A variants but not 1100delC in individuals from both study and control groups. In the group of ovarian cancer patients the occurrence of all *CHEK2* alterations was lower than in the control group, due to the relatively low incidence of missense variant (see Table 2). Therefore, ovarian cancer patients were excluded from further analysis. The frequency of all analyzed *CHEK2* variants was higher in breast cancer patients (9.9%) than in the controls (7.3%), however the difference was not statistically significant (p=0.28). We did not observe significant differences between cancer patients and controls neither in regard to the frequency nor to the type of *CHEK2* variants (see Table 2). The missense variant 430T>C was the most often observed alteration in both breast cancer patients (7.0%) and in control group (6.3%) (the result was not statistically significant p=0.71). The splice mutation IVS2+1G>A occured in 1.1 % of study in comparison to 0.7% of control groups (p=0.65), while del5395 was observed in 2.1% of cancer cases versus 0.34% of the controls (p=0.055). There were also no differences in the frequencies of *CHEK2* mutations between the hereditary and sporadic breast cancer patients.

The analysis of association between the clinico-histopathological characteristics of disease and *CHEK2* alterations revealed only an association between del5395 and breast cancer patients below/at 40-year-of-age (p= 0.043). Thus, further analysis was carried out for the whole breast cancer patients group versus controls. In the case of an odds ratio, the results were not statistically significant (the 95% confidence interval overlap 1.0), see Table 2.

Discussion

Despite the years of study, the importance of *CHEK2* variants in prediction of individual breast/ovarian cancer risk is still controversial. Our study revealed that in ovarian cancer patients the frequency of *CHEK2* mutations is lower than in control group. This observation supports the thesis of Nevanlinna and Bartek (2006) that the mutations in the *CHEK2* gene are not associated with increased risk of ovarian cancer.

Our observation pointed out the missense variant 430T>C as the most often observed alteration in both breast cancer patients (7.0%) and in control groups (6.3%), as well as the correlation between the incidence of the following *CHEK2* variants: del5395, and IVS2+1G>A are in agreement with the observations of other authors (Dufault et al. 2004; Bogdanova et al. 2005; Cybulski et al. 2007a; Kleibl et al. 2008). Nevertheless, all the correlations observed in our study have not been statistically significant.

Thus, when analyzing the results of present study in regard to still published data it can be noticed that our results are consistent with those, performed on groups similar in size to ours (see Table 3). The opposite results were obtained by authors studying a very large groups. They observed the strong correlation between certain *CHEK2* gene variants and breast cancer (*CHEK2* Breast Cancer Case-Control Consortium 2004; Dufault et al. 2004; Kilpivaara et al. 2004; Górski et al. 2005; Cybulski et al. 2007a; Weischer et al. 2008).

However, when discussing the potential inclusion of *CHEK2* variants into the cancer predisposition tests, two facts have to be taken into account: *i*) "any small difference, no matter how clinically unimportant, will be statistically significant (p<0.05) if the sample size is large enough" (Grunkemeier et al. 2009), *ii*) the presence of discussed above *CHEK2* variants in a substantial part of control group (what was observed in all still published studies) limits the possibility of their application in testing of breast cancer predisposition. Therefore, an employment of *CHEK2* variants in evaluation of cancer predisposition is doubtful.

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