RESEARCH ARTICLE

CHEK2 1100delC Variant and Breast Cancer Risk in Caucasians: A Meta-analysis Based on 25 Studies with 29,154 Cases and 37,064 Controls

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Abstract

Links between the CHEK2 1100delC heterozygote and breast cancer risk have been extensively explored. However, both positive and negative associations with this variant have been reported in individual studies. For a detailed assessment of the CHEK2 1100delC heterozygote and breast cancer risk, relevant studies published as recently as May 2012 were identified using PUBMED and EMBASE and selected using a priori defined criteria. The strength of the relationship between the CHEK2 1100delC variant and breast cancer risks was assessed by odds ratios (ORs) under the fixed effects model. A total of 29,154 cases and 37,064 controls from 25 case-control studies were identified in this meta-analysis. The CHEK2 1100delC heterozygote was more frequently detected in cases than in controls (1.34% versus 0.44%). A significant association was found between CHEK2 1100delC heterozygote and breast cancer risk (OR=2.75, 95% CI: [2.25, 3.36]). The ORs and CIs were 2.33 (95% CI: [1.79, 3.05]), 3.72 (95% CI: [2.61, 5.31]) and 2.78 (95% CI: [2.28, 3.39]) respectively in unselected, family, early-onset breast cancer subgroups. The CHEK2 1100delC variant could be a potential factor for increased breast cancer risk in Caucasians. However, more consideration is needed in order to apply it to allele screening or other clinical work.

Keywords: Breast cancer - CHEK2 - 1100delC variant - meta-analysis

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Introduction

Breast cancer is one of the most common cancers in the world. It negatively impacts women both physically and psychologically. After the BRCA1 and BRCA2 proteins were cloned and their association with family breast cancer was detected (Miki Y et al., 1994; Wooster R et al., 1995), greater emphasis was placed on the candidate gene of breast cancer. The cell cycle-checkpoint kinase 2 gene, or CHEK2, was widely researched as a strong candidate gene for breast cancer susceptibility (Vahteristo et al., 2002; Sodha et al., 2002; Offit et al., 2003; CHEK2 Breast Cancer Consortium, 2004; Dufault et al., 2004; Friedrichsen et al., 2004; Mateus Pereira et al., 2004; Baeyens et al., 2005; Kleibl et al., 2005; Rashid et al., 2005; Bernstein et al., 2006; Einarsdóttir et al., 2006; Cybulski et al., 2007; Weischer et al., 2007; Zhang et al., 2008; Fletcher et al., 2009; McInerney et al., 2010; Iniesta et al., 2010).

Initially, the CHEK2 1100delC variant was found in women suffering from breast cancer with familial Li-Fraumeni syndrome (Bell et al., 1999). A large study (Meijers-Heijboer et al., 2002) later found the same variant affecting familial breast cancer without the BRCA1 and BRCA2 mutations. In 2004, CHEK2-Breast Cancer Consortium did a collaborative analysis with 10 studies from 5 western countries, which involved 10 860 breast cancer cases and 9 065 controls (CHEK2 Breast Cancer Consortium, 2004). The Consortium found the frequency of CHEK2 1100delC to be 1.9% and 0.7% in cases and controls respectively, and confirmed that this gene variant could potentially increase the risk of breast cancer. And in 2008, another quantitative synthesis was done by Weischer et al. (2008). Combined with 16 studies, it showed that CHEK2 1100delC heterozygotes rate was 3- to 5-fold higher in breast cancer group than control group.

However, this widely discussed variant of CHEK2 – which seemed clearly associated with the predominance of breast cancer in western countries – was rarely detected in Asian populations, such as the Chinese (Song et al., 2006), Koreans (Choi, 2008), Japanese (Bell et al., 2007), Singaporeans (Lee and Ang, 2008), Malaysians (Thirthagiri et al., 2009) and South Indians (Rajkumar et al., 2003). With the influx of recent studies concerning these particular findings, a stricter meta-analysis with the recent data is necessary. Our research centers around a meta-analysis of the relationship between this variant of CHEK2 and breast cancer risk in various populations.

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Materials and Methods

Search strategy

To identify relevant studies, the terms "CHEK2" or "CHEK2 1100delC", and "breast cancer" or "breast neoplasm" were used in an electronic database search. PUBMED and EMBASE were the relevant databases used; Google Scholar was also used. References of the retrieved articles were also screened for relevant studies. This search strategy was performed iteratively up to and including 20 May 2012.

Selection criteria

Titles and abstracts of relevant studies were reviewed. The following criteria was used to identify relevant studies: (i) must be population-based or hospital-based; (ii) must be a case-control study; (iii) must provide the size of the samples, distribution of alleles, genotypes, or other critical information that would help to infer the results; (iv) must include the most recent or largest sample population; (v) the publication language was either in English or Chinese. Reviews, editorials, meeting abstracts, and commentaries were excluded from our analysis. We also excluded studies that did not detect the CHEK2 1100delC allele in both cases and controls (Rajkumar et al., 2003; Song et al., 2006; Bell et al., 2007; Choi, 2008; Lee and Ang, 2008; Thirthagiri et al., 2009).

Data extraction

Data were extracted independently by two reviewers (Yang Y. and Zhang F.). The following information was extracted from each article: first author, year of publication, country where each study was conducted, ethnicity of subjects, source of control group (population-based, hospital-based or mixed controls), matched factors of the control group, deviation from the Hardy-Weinberg Equilibrium (HWE) of the control group, case type (unselected, family and early-onset breast cancers), genotyping method, and the frequencies of genotypes in the case and control groups.

Statistical analyses

A crude odds ratio (OR) with a 95% confidence interval (CI) for alleles and genotypes was used to assess the strength of association between the CHEK2 1100delC heterozygote and breast cancer risks. The pooled ORs were performed for the allele contrast, additive genetic model, dominant genetic model, and recessive genetic model, respectively. The heterogeneity assumption was assessed by using the Cochran's χ^2-based Q statistic test and I-squared test. The heterogeneity was considered insignificant when $P>0.10$ and $I^2<50\%$. If the study lacked heterogeneity, the pooled OR estimate of each study was calculated using the fixed effects model. In other cases, the random effects model was used (Overton and Randall

Table 1. Characteristics of Studies Included in the Meta-analysis

Author or study name[a]	Year	Country[b]	source of the controls	Genotyping Method[c]	Cancer type	Case		Control	
						Total	H[d]	Total	H[d]
ABC	2004	UK	Hospital-based	Sequencing	Unselected	2886	35	3749	20
ABCFS	2004	Australia	population-based	Taqman	Early-onset	1474	10	736	1
Baeyens	2005	Belgium	Hospital-based	DHPLC	Mixed	178	4	100	0
Bernstein	2006	Canada, USA	Hospital-based	Sequencing	Family	2281	30	495	1
Cybulski	2007	Poland	Hospital-based	ASO- or RFLP-PCR	Mixed	4554	20	5496	12
Dufault	2004	Germany	Hospital-based	DHPLC	Family	516	8	1315	6
Einarsdottir	2006	Sweden	Hospital-based	Mass-array	Family	1509	19	1334	8
ERGO	2004	Netherlands	population-based	Sequencing	Unselected	79	2	460	6
Friedrichsen	2004	USA	population based	Sequencing	Early-onset	450	6	412	2
Hannover	2004	Germany	Hospital-based	Sequencing	Unselected	985	11	401	1
Heidelberg	2004	Germany	population-based	Sequencing	Unselected	601	2	650	1
Helsinki	2004	Finland	Hospital-based	Sequencing	Unselected	1035	21	1885	26
Kleibl	2005	Czech Republic	Hospital-based	DHPLC	Mixed	1046	4	730	2
Kuopio	2004	Finland	Hospital-based	Sequencing	Unselected	464	13	447	5
Mateus	2004	USA	Hospital-based	Taqman	Family	829	9	959	4
Mclnerney	2010	Ireland	Hospital-based	Taqman	Family	903	5	1016	1
Offit	2003	USA	Hospital-based	dHPLC,Sequencing	Unselected	300	3	1665	5
PROSPECT	2004	Netherlands	Hospital-based	Sequencing	Unselected	1066	35	265	0
Rashid	2005	Germany	Hospital-based	dHPLC	Mixed	770	8	417	2
RMOT	2004	Netherlands	Hospital-based	Sequencing	Unselected	1706	65	184	3
Sodha	2002	UK	Hospital-based	CSGE	Family	68	3	300	0
UKNCC	2004	UK	population-based	Taqman	Early-onset	564	7	288	1
Vahteristo	2002	Finland	Hospital-based	Sequencing	Family	507	28	942	13
Weischer	2007	Denmark	Hospital-based	Genescan	Unselected	1374	16	4633	22
Zhang	2008	Brazil, Pakistan, Filipino, Canada	Hospital-based	Sequencing	Mixed	3009	27	8185	22

[a]ABC, Anglian Breast Cancer Study; ABCFS, Australian Breast Cancer Case-Control Family Study; ERGO, Erasmus Rotterdam Health and the Elderly Study; PROSPECT, RMOT: The Rotterdam Medical Oncology Tumorbank; UKNCC, United Kingdom National Case-Control Studies; [b]UK, United kingdom; USA: United States of America; [c]DHPLC, denaturing high-performance liquid chromatography; ASO, allele-specific oligonucleotide; PCR, Polymerase Chain Reaction; RFLP, Restriction Fragment Length Polymorphism; [d]H, Heterozygosity

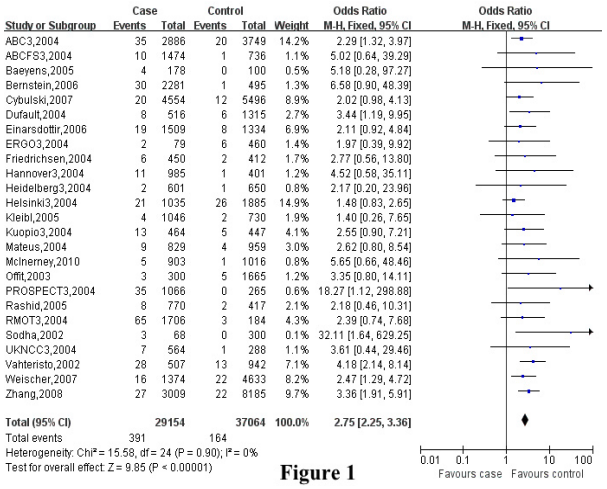

Figure 1

Figure 1. Forest Plot on Association Between CHEK2 1100delC Heterozygosity and Breast Cancer Risk

C, 1998). Stratification analyses by case type (unselected, family and early-onset breast cancers) were conducted to lower the heterogeneity and retrieve more precise data. The sensitivity analysis was conducted based on the leave-one-out sensitivity procedure. Possible publication bias was tested by the funnel plot.

All statistical tests were conducted with Cochrane Collaboration's Review Manager (Version 5.1). A P value of 0.05 for any test or model was considered to be statistically significant, except where otherwise specified. All statistical tests were two-sided.

Results

Eligible studies

After examining the data according to the eligibility criteria, a total of 25 studies from 16 publications were generated by the search strategy. As shown in Table 1, all of the studies were conducted in Europe, America or South America, with the exception of one study that was composed of mixed ethnicities across several countries (Zhang et al., 2008). These studies were all case-control studies; the majority of which were hospital-based controls that were matched for age and ethnicity. It should be noted that most studies did not specify whether the genotype distribution in the controls was deviated from the HWE or not. The genotype methods were almost sequencing or d-HPLC. All of 29,154 cases and 37,064 controls were involved in this meta-analysis.

Among the cases, 13,875 patients had unselected breast cancer, 7,945 patients had familial breast cancer and 5,802 patients had early-onset breast cancer. The remaining cases were categorized as unclassified.

In total, 391 patients were found with the CHEK2 1100delC heterozygote in 29,154 cases and 164 patients in 37,064 controls. The allele carrier rate was 1.34% and 0.44% in cases and controls, respectively. The allele frequency was approximately three times greater in cases as compared to controls.

Quantitative synthesis

Overall, the CHEK2 1100delC variant was more frequent in breast cancer patients. By using the fixed

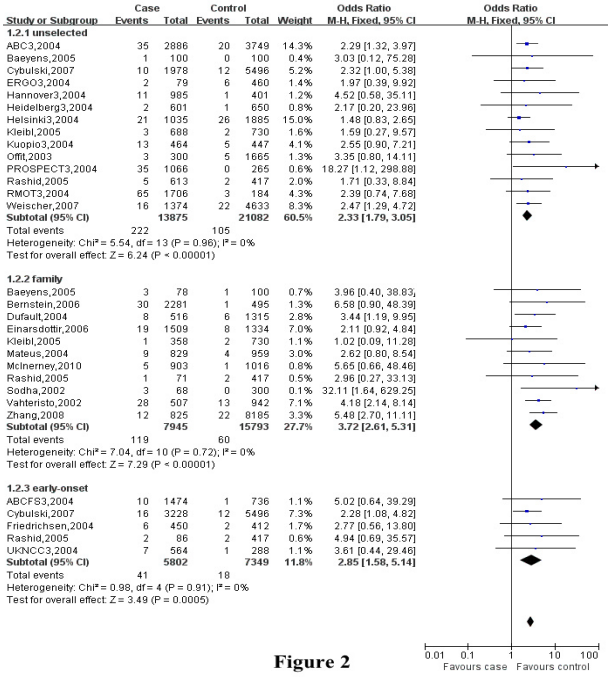

Figure 2

Figure 2. Forest Plot on Association of CHEK2 1100delC Heterozygosity with Unselected, Family and Early-onset Breast Cancer Risk

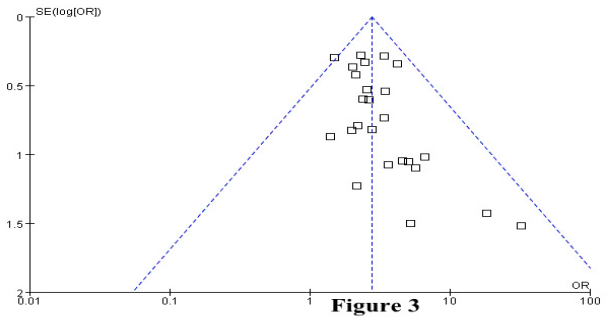

Figure 3

Figure 3. Funnel Plot Made Based on the Total Studies

effects model, the association between CHEK2 1100delC heterozygote and breast cancer was significant with OR 2.75 (95% CI: [2.25, 3.36]) (Figure 1). In the subgroup analysis, a significant correlation was also found in unselected, familial, early-onset breast cancer. The ORs and CIs were 2.33 (95% CI: [1.79, 3.05]), 3.72 (95% CI: [2.61, 5.31]) and 2.78 (95% CI: [2.28, 3.39]), respectively (Figure 2).

Sensitivity analysis

The sensitivity analysis was conducted by excluding certain studies, such as one that had none of the minor allele homozygous detected in the control group. We also did the sensitivity analysis by eliminating one study each time. Consequently, the results were not principally altered, although the I-square value for the heterogeneity was reduced in certain cases. This indicates that the results of the meta-analysis are statistically robust.

Publication bias

Funnel plots were performed to assess the publication bias. The shape of the funnel plot (Figure 3) did not reveal obvious asymmetry, indicating no obvious publication bias.

Discussion

According to the "World Cancer Report", the breast cancer is responsible for 22.9% of total cancers (excluding non-melanoma skin cancers) in women all over the world. It is estimated that 458,503 deaths were due to breast cancer in 2008 alone, which accounts for 13.7% of cancer deaths in women worldwide (World Cancer Report, 2008). Many candidate genes have been reported to be associated with breast cancer susceptibility, including CHEK2, BRCA1, BRCA2, TP53, CYP19, CASP8, XRCC3, PETN (Baig et al., 2011), and CTLA4 (Zhang et al., 2011). The CHEK2 gene, which encodes G2 checkpoint kinase, has been widely cited for its potential implications in breast cancer susceptibility. Among the various mutations of CHEK2 gene, the 1100delC mutation is the most studied and was first identified in familial Li-Fraumeni syndrome (Bell et al., 1999).

After our comprehensive analysis, we confirmed the results as the study done by Weischer et al (Weischer et al., 2008), that the variant of CHEK2 1100delC was significantly associated with breast cancer risk, particularly in familial breast cancer cases in non-Asian countries. The patients that carried the CHEK2 1100delC heterozygote could have increased breast cancer susceptibility.

However, our meta-analysis yielded a few significant differences. Although the rate of heterozygotes in cases and controls were similar, the ORs in the previous study were different. Our study found that the OR was 2.3 and 3.7 in unselected and familial breast cancer, respectively, which was lower than what was detected in the previous study as 2.7 and 4.8. And we did not agree with that it was a good clinical gene for individual woman seeking on the risk of breast cancer. Firstly, this variant heterozygote is very rare in the general population (0.44%). It also occurs at a very low frequency in familial breast cancer patients (1.50%). Furthermore, it is rarely found in Asians (Rajkumar et al., 2003; Song et al., 2006; Bell et al., 2007; Choi, 2008; Lee and Ang, 2008; Thirthagiri et al., 2009). Secondly, in the previous meta-analysis, the cumulative risk of breast cancer at 70 years of age was calculated based on another meta-analysis done in 2007, which estimated the cumulative risk of two other gene heterozygotes, BRCA1 and BRCA2 (Chen and Parmigiani, 2007). Their cumulative risk was found to be 37% while our study discovered the risk to be 29%. It was about half the risk in the BRCA1 (57%) and BRCA2 (49%). However, the frequency of BRCA1 and BRCA2 were 17.10% and 5.5%, respectively, in familial breast cancer (Shih et al., 2002), exactly higher than 0.75% of CHEK2 1100delC.

According to our study included more cases and more data, the results from our meta-analysis should be deemed as reliable and robust. In order to detect bias among the included studies, we did a sensitivity analysis and publication bias analysis. The heterogeneity was not significant in the total study analysis and subgroup analysis, with an I^2 value of lower than 50%. We did subgroup analyses based on the cancer type, unselected, familial and early-onset breast cancer. The OR was highest in familial breast cancer group. This indicates that the CHEK2 1100delC variant was more significant associated with familial breast cancer.

However, we did not conduct a subgroup analysis by ethnicity. In our meta-analysis, the data collected originates from western countries. Among one international study (Zhang et al., 2008), we did not use the data (including cases and controls) in Pakistan and Filipino which were Asian countries. Because the results in those two countries showed that no target variant was found in the cases and controls. Similar results were found for the CHEK2 gene in other studies conducted using Asian populations (Rajkumar et al., 2003; Song et al., 2006; Choi, 2008; Bell et al., 2007; Lee and Ang, 2008; Thirthagiri et al., 2009). Therefore, we excluded these studies in our meta-analysis. The CHEK2 gene was expressed differently in other ethnicities so further study is needed to confirm this conclusion.

We performed a strict meta-analysis on the relationship between CHEK2 1100delC variant and breast cancer risk and achieved robust results. However, a few limitations should be noted. Firstly, the controls were only population-based in several studies (CHEK2 Breast Cancer Consortium, 2004; Friedrichsen DM et al., 2004), while the remainder were hospital-based. This may not serve as an adequate representation of the general population. Secondly, the baseline controls and cases were matched only on a few common factors and our results were based on unadjusted estimates. A more precise analysis should be conducted based on the adjusted data involving more factors such as menstrual cycle, smoking status, and environmental factors. Thirdly, we did not conduct a subgroup analysis through the pathological classification of breast cancer or menstruation status, because this was not clearly defined in the original studies. Moreover, this meta-analysis did not consider the possibility of SNP-SNP or gene-gene interactions, or the possibility of linkage disequilibrium between polymorphisms. At lastly, more in-depth studies should be conducted to confirm the frequency of this variant in other populations around the world.

In conclusion, the present study evaluates the association between the CHEK2 1100delC variant and breast cancer risk in Caucasians. It is concluded that carriers of this heterozygote would be at increased risk of breast cancer, familial breast cancer in particular. However, further consideration would be necessary to apply these findings to a clinical setting, such as screening for the allele, and it is crucial to carry out a larger multi-center study to confirm the results.

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