*CHEK2*1100delC* and Risk of Malignant Melanoma: Danish and German Studies and Meta-Analysis

Maren Weischer[1,2], Ida M. Heerfordt[1], Stig E. Bojesen[1,2,3], Thomas Eigentler[4], Claus Garbe[4], Martin Röcken[4], Lisbet Rosenkrantz Hölmich[5], Henrik Schmidt[6], Helle Klyver[7], Lars Bastholt[8] and Børge G. Nordestgaard[1,2,3]

It is possible that reduced function of DNA repair and cell-cycle control genes increases the individual susceptibility to malignant melanoma. As CHEK2 is a cell-cycle master controller, we tested the hypothesis that heterozygosity for the frameshift alteration *CHEK2*1100delC* is associated with increased risk of malignant melanoma. First, we performed case–control studies of 1,152 Danish and 752 German individuals with malignant melanoma compared with 9,142 Danish and 3,718 German controls. Second, we performed a meta-analysis of *CHEK2*1100delC* and malignant melanoma, involving 2,619 cases and 17,481 controls. Third, we examined the risk of malignant melanoma associated with *CHEK2*1100delC* heterozygosity in an analysis stratified for sun exposure, as well as for subtype and location on the body. The odds ratios for malignant melanoma for *CHEK2*1100del* heterozygotes compared with those for noncarriers were 2.01 (95% confidence interval (CI), 1.03–3.91) in Danes, 1.42 (95% CI, 0.46–4.31) in Germans, and 1.79 (95% CI, 1.02–3.17) in Danes and Germans combined. In a meta-analysis, the odds ratio of malignant melanoma for *CHEK2*1100delC* heterozygotes compared with that for noncarriers was 1.81 (95% CI, 1.07–3.05). Stratifications did not alter these results. *CHEK2*1100delC* heterozygotes have a twofold risk of malignant melanoma compared with noncarriers.

Journal of Investigative Dermatology (2012) **132,** 299–303; doi:10.1038/jid.2011.303; published online 29 September 2011

INTRODUCTION

UV irradiation leads to three major classes of DNA lesions: cyclobutane pyrimidine dimers, pyrimidine 6–4 pyrimidone photoproducts, and their Dewar isomers (Rastogi *et al.*, 2010). These lesions cause a problem during DNA transcription and/or replication, wherein they block DNA replication forks leading to DNA double-strand breaks (Rastogi *et al.*, 2010). Furthermore, DNA double-strand breaks can also occur during repair of UV-induced single-strand breaks passing through base-excision repair (Vilenchik and Knudson, 2003). To protect genomic integrity, cells have over 150 DNA repair enzymes that identify and repair various types of DNA damage (Wood *et al.*, 2005; Branzei and Foiani, 2008). Among these is the nuclear CHEK2 protein, encoded by the *CHEK2* gene.

CHEK2 is involved in recognition of DNA double-strand breakage and in activation of downstream targets such as *p53 and BRCA1* causing cell-cycle arrest, DNA repair, and possibly apoptosis (Bartek and Lukas, 2003). CHEK2 is upregulated in response to UV exposure with peak levels of 4–8 hours following UV exposure (Yajima *et al.*, 2009), suggesting a key role of the protein in UV damage control. Although it is well recognized that individuals heterozygous for the nonfunctioning frameshift *CHEK2*1100delC* germline alteration have a two- to threefold increased risk of developing breast cancer (Vahteristo *et al.*, 2002; Schutte *et al.*, 2003; The CHEK2*1100delC Breast Cancer Association Consortium, 2004; Einarsdottir *et al.*, 2006; Cybulski *et al.*, 2007; Weischer *et al.*, 2007, 2008), only two studies have examined the association of *CHEK2*1100delC* heterozygosity with risk of malignant melanoma, with limited statistical power (Weischer *et al.*, 2007; Debniak *et al.*, 2008). Thus, more studies are needed to understand the role of *CHEK2*1100delC* in malignant melanoma.

We tested the hypothesis that *CHEK2*1100delC* heterozygosity is associated with increased risk of malignant melanoma. To do so, we first carried out case–control studies on 1,152 Danish and 752 German individuals with malignant melanoma compared with 9,142 Danish and 3,718 German controls. Second, we performed a meta-analysis

[1]*Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Copenhagen, Denmark;* [2]*Faculty of Health Science, University of Copenhagen, Copenhagen, Denmark;* [3]*The Copenhagen City Heart Study, Bispebjerg Hospital, Copenhagen University Hospital, Copenhagen, Denmark;* [4]*Department of Dermatology, Eberhard Karls University, Tübingen, Germany;* [5]*Department of Plastic Surgery, Herlev Hospital, Copenhagen University Hospital, Copenhagen, Denmark;* [6]*Department of Oncology, Aarhus University Hospital, Aarhus, Denmark;* [7]*Department of Plastic Surgery, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark and* [8]*Department of Oncology, Odense University Hospital, Odense, Denmark*

Correspondence: Børge G. Nordestgaard, Department of Clinical Biochemistry, Herlev University Hospital, Herlev Ringvej 75, Herlev DK-2730, Denmark. E-mail: brno@heh.regionh.dk

Abbreviations: CI, confidence interval; NA, not available; OR, odds ratio

Received 28 March 2011; revised 11 July 2011; accepted 14 July 2011; published online 29 September 2011

of *CHEK2*1100delC* and malignant melanoma, involving 2,619 cases and 17,481 controls. Third, we examined the risk of developing malignant melanoma associated with *CHEK2*1100delC* heterozygosity in analyses stratified for history of sun exposure and for location and subtype of the malignant melanoma, as individuals and locations on the body exposed to intermittent, as opposed to, chronic sun exposure have a higher likelihood of developing malignant melanoma (Caini *et al.*, 2009; Gerstenblith *et al.*, 2010; Newton-Bishop *et al.*, 2010), and as subtypes of malignant melanoma might differ in their molecular pathogenesis (Curtin *et al.*, 2005).

RESULTS

Case–control studies

We studied 1,152 unselected Danish and 752 unselected German patients with malignant melanoma and compared them with 9,142 Danish and 3,718 German controls (Table 1). The distribution of genotypes among the controls was in the Hardy–Weinberg equilibrium in both the nationalities (Danes $P = 0.81$ and Germans $P = 0.91$). Among cases, 11 were *CHEK2*1100delC* heterozygotes. Of these, six Danes and one German were women.

The odds ratios (ORs) for malignant melanoma among *CHEK2*1100delC* heterozygotes compared with noncarriers were 2.01 (95% confidence interval (CI): 1.03–3.91) in Danes, 1.41 (95% CI: 0.46–4.31) in Germans, and 1.79 (95% CI: 1.02–3.17) in Danes and Germans combined (Table 2; Danes vs. Germans: $P = 0.59$). Age and gender did not interact with *CHEK2*1100delC* heterozygosity on risk of malignant melanoma ($P = 0.84$ and $P = 0.82$; tested in Danes only).

*CHEK2*1100delC* heterozygosity was not associated with history of sun exposure and location and subtype of malignant melanoma (Supplementary Table S1 online).

Table 1. Characteristics of participants

	Danish		German	
	Cases	Controls	Cases	Controls[1]
Participants, *n*	1,152	9,142	752	3,718
*CHEK2*1100delC genotype*, n *(%)*				
Noncarriers	1,141 (99.0)	9,097 (99.5)	752 (99.5)	3,704 (99.6)
Heterozygotes	11 (1.0)	45 (0.5)	4 (0.5)	14 (0.4)
Homozygotes	0 (0)	0 (0)	0 (0)	0 (0)
Age, years				
Median (IQR)	54 (42–65)	60 (47–70)	55 (43–65)	NA
Women, %	54	55	50	NA
Ascertainment	Hospital	General population	Hospital	General population

Abbreviations: IQR, interquartile range; NA, not available.
[1]From references (Dufault *et al.*, 2004; The CHEK2*1100delC Breast Cancer Association Consortium, 2004; Rashid *et al.*, 2005; Scharrer *et al.*, 2010).

Meta-analysis

The characteristics of the 2,619 cases with malignant melanoma and the 17,481 controls in the four studies are listed in Table 3.

Using a fixed effect model, we found an aggregated OR for malignant melanoma of 1.81 (95% CI: 1.07–3.05) for *CHEK2*1100delC* heterozygotes compared with noncarriers (Figure 1). The funnel plot showed no evidence of publication bias. I^2-value was 0% (95% CI: 0–85) among studies, indicating no heterogeneity (Higgins *et al.*, 2003).

Stratified analysis

Supplementary Table S2 online shows age- and gender-adjusted ORs for malignant melanoma for *CHEK2*1100delC* heterozygotes compared with noncarriers stratified by history of sun exposure and location and subtype of malignant melanoma in Danes; this information was available for cases only and not for controls. Each stratum of cases was compared with the same group of 9,142 controls. We observed increased ORs of malignant melanoma associated with *CHEK2*1100delC* heterozygotes compared with noncarriers in all strata, although some estimates were not statistically significant (Supplementary Table S2 online).

DISCUSSION

In Danish and German case–control studies and in the meta-analysis, we found a twofold increased risk of malignant melanoma for individuals heterozygous for *CHEK2*1100delC* compared with noncarriers.

Mechanistically, it seems plausible that *CHEK2*1100delC* would increase the risk of malignant melanoma, because heterozygous individuals have an impaired ability to recognize and repair UV-induced DNA double-strand breaks (Bartek and Lukas, 2003; Rastogi *et al.*, 2010). As a consequence, damaged cells are allowed to proliferate, thereby increasing the risk of oncogenic transformation toward a malignant phenotype.

The twofold risk of malignant melanoma among *CHEK2*1100delC* heterozygotes compared with noncarriers is similar to that observed for polymorphisms in *MC1R*. *MC1R* encodes the melanocortin-1 receptor that is situated on the outside of melanocytes. A series of polymorphisms have been identified in *MC1R* that reduce response to stimulation of eumelanin production, causing melanocytes to

Table 2. Risk of malignant melanoma by *CHEK2*1100delC* heterozygosity

	Non-carriers	Heterozygotes		
	Cases/ controls	Cases/ controls	Odds ratio (95% CI)	*P*-value
All	1,889/12,801	15/59	1.79 (1.02–3.17)[1]	
Danes	1,141/9,097	11/45	2.01 (1.03–3.91)[2]	0.59
Germans	748/3,704	4/14	1.41 (0.46–4.31)[3]	

[1]Mantel–Haentzel statistics analysis adjusted for study weight.
[2]Logistic regression analysis adjusted for age at ascertainment and gender.
[3]Odds ratio calculated by χ^2-test.

Table 3. Characteristics of studies on *CHEK2*1100delC* heterozygosity and risk of malignant melanoma

	Overall				Heterozygotes							
	Cases		Controls		Cases		Controls					
Study	No.	(%)	No.	(%)	No.	(%)	No.	(%)	Study design	Case ascertainment	Genotyping method	Country
Weischer *et al.*, 2007	88	(98.9)	649	(99.5)	1	(1.1)	3	(0.5)	PR	GP	Genescan	Denmark
Debniak *et al.*, 2008	627	(99.7)	4,621	(99.8)	2	(0.3)	8	(0.2)	CC	Hospital	RFLP	Poland
Weischer, 2011	1,152	(99.0)	8,493	(99.5)	11	(1.0)	42	(0.5)	CC	Hospital	Taqman	Denmark
Weischer, 2011	752	(99.5)	3,718	(99.6)	4	(0.5)	14	(0.4)	CC	Hospital	Taqman	Germany

Abbreviations: CC, case–control study; GP, general population; PR, prospective cohort study; RFLP, restriction fragment length polymorphism.
Each control counted only once; Danish controls were split between reference (Weischer *et al.*, 2007) and present study (Weischer *et al.*, 2011).

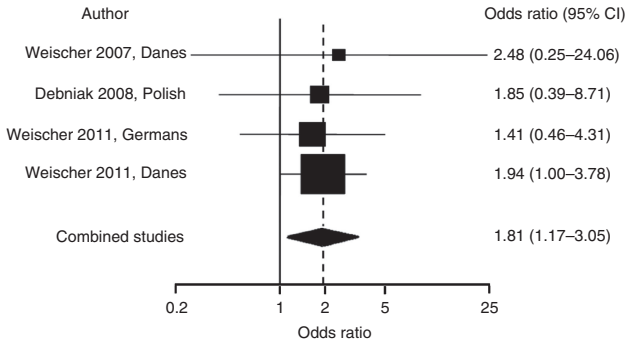

Figure 1. Meta-analysis of studies of *CHEK2*1100delC* heterozygosity and risk of malignant melanoma. Studies are adjusted for and ranked by increasing weight. Boxes indicate study weight, and horizontal lines indicate 95% confidence interval (CI). The aggregated fixed effect odds ratio (OR) is shown as a diamond. The perforated vertical line indicates the aggregated OR. To avoid counting the same controls twice, controls were divided between the Weischer *et al.*, 2007 and the present Danish case-control study (Weischer *et al.*, 2011) as shown in Table 3. Therefore, the OR of the Weischer *et al.* 2011 Danish case-control study differs slightly from that in Table 2.

produce mostly pheomelanin, which leads to lighter skin, hair, and eye color. A recent meta-analysis of non-red hair color and red hair color polymorphisms of *MC1R* reported aggregated ORs for malignant melanoma of 1.29 (95% CI, 1.10–1.51) and 2.44 (95% CI, 1.72–3.46; Williams *et al.*, 2011). The twofold risk of malignant melanoma in *CHEK2*1100delC* heterozygotes compared with noncarriers observed in this study is similar to the two- to threefold increased risk reported for breast cancer (The CHEK2*1100delC Breast Cancer Association Consortium, 2004; Weischer *et al.*, 2008).

As the majority of our cases had sporadic malignant melanoma, we did not test for *CDKN2A* mutations, as these are mostly found among individuals with familial history of the disease. At least 30 different functional mutations in *CDKN2A* have been reported (Orlow *et al.*, 2007). Their combined frequency is less than 1% in malignant melanoma patients not selected for familial history of disease, and even less in controls, limiting the possibility of identifying more than just a few individuals carrying the same variant (Orlow *et al.*, 2007). In addition, we did not examine mutations in pigmentation pathways, as these have been thoroughly examined by others (Landi *et al.*, 2006; Gudbjartsson *et al.*, 2008; Raimondi *et al.*, 2008; Gerstenblith *et al.*, 2010; Newton-Bishop and Gruis, 2010; Williams *et al.*, 2011).

Our study has several strengths. First, we studied both Danes and Germans and found similar results. Second, in a meta-analysis also including a Polish and an additional Danish study, the overall result was similar to that observed in the present two case–control studies. Finally, because of the fact that we reran the genotype test several times, we succeeded in genotyping 99.9% of all available participants. The limitations of our study include reduced statistical power in the stratified analyses and selection of German controls. These were found through literature searches and were chosen from four different studies. Thus, it is slightly concerning that the frequency of *CHEK2*1100delC* differed between the different control groups (Rashid *et al.*, 2005: 0.9 and 0%; Scharrer *et al.*, 2010: 0%; Dufualt *et al.*, 2004: 0.46%, and The CHEK2*1100delC Breast Cancer Association Consortium, 2004: 0.15% and 0.25%, respectively). In addition, for 502 controls, the gender was unknown; however, the remaining controls ($N=3,216$) were all women, which means that at least 86% of the German controls were female.

In conclusion, *CHEK2*1100delC* heterozygosity doubled the risk of malignant melanoma.

MATERIALS AND METHODS

Case–control studies

Study populations. *Cases*: Patients were recruited from the Department of Plastic Surgery, Herlev Hospital, Copenhagen University Hospital, Denmark ($n=469$); from the Department of Oncology, Aarhus University Hospital, Denmark ($n=361$); the Department of Plastic Surgery, Rigshospitalet, Copenhagen University Hospital, Denmark ($n=188$); the Department of Oncology, Odense University Hospital, Denmark ($n=134$); and from the Department of Dermatology, Eberhard Karls University, Tübingen, Germany ($n=752$). All patients were consecutively recruited from 2008 to 2010. On the day of the examination, the patients gave blood for DNA extraction and filled in questionnaires regarding their lifestyle and medical history. The questionnaire asked for information on sun exposure, requesting details about the number of childhood sunburns, number of vacations to sunny destinations within the last 10 years, and use of sunbeds within the last 10 years.

On the day of the examination, a physician counted nevi, diagnosed the presence or absence of solar keratosis, and noted the location of the malignant melanoma. The examining physicians were highly trained dermatologists, plastic surgeons, and oncologists. All participants gave written informed consent. Information on sun exposure was only available for cases. Confirmation of diagnosis of malignant melanoma for the Danish cases was obtained from The Danish Melanoma Group, a nationwide registry collecting prospective data on all Danish patients treated for malignant melanoma, including *in situ* lesions (www.melanoma.dk). Clinical and pathological data on the German patients were obtained from the electronic database of the Central Malignant Melanoma Registry, which is a German nationwide hospital-based registry.

Controls: Controls were selected from the Copenhagen City Heart Study, a prospective study of the general population initiated in 1976–1978 with follow-up examinations in 1981–1983, 1991–1994, and 2001–2003. The study included 9,244 participants who reflect the adult Danish population aged 20–80 + years. Although the study was named after its initial purpose, namely, to examine heart disease, participants were not selected according to disease status but were randomly chosen from the National Danish Civil Registration System and were invited to participate. On the day of the examination, participants filled in questionnaires, were physically examined, and gave blood for DNA analysis. Participants were monitored for development of malignant melanoma (International Classification of Disease 10 codes C43.0–C43.9) from 1 April 1968 to May 2009 (Bojesen *et al.*, 2003). Follow-up was 100% complete; that is, we did not lose track of even a single individual. Diagnoses of malignant melanoma were obtained from the Danish Cancer Registry, which identifies 98% of all cancers in Denmark (Storm *et al.*, 1997). A total of 9,142 participants who did not develop malignant melanoma during follow-up were included as controls. German controls were found in the literature through a computer-based search of PubMED using the keyword ''CHEK2'' and ''Germany''. We identified four studies with a total of 3,718 controls (Dufault *et al.*, 2004; The CHEK2*1100delC Breast Cancer Association Consortium, 2004; Rashid *et al.*, 2005; Scharrer *et al.*, 2010).

Meta-analysis

Search strategy and selection criteria. Cohort and case–control studies of *CHEK2*1100delC* and risk of malignant melanoma published before 1 February 2011 were identified through a computer-based search of PubMED, EMBASE, and Web of Science using the keywords ''CHEK2'', ''CHEK2*1100delC'', and ''CHK2''. This search identified seven studies (Cybulski *et al.*, 2004; Debniak *et al.*, 2004, 2008; Huang *et al.*, 2004; Thompson *et al.*, 2006; Cybulski, 2007; Weischer *et al.*, 2007). For cases, the inclusion criterion for this meta-analysis was a diagnosis of malignant melanoma, which could not be attributed to a known multicancer syndrome, and, for controls, the criterion was an absence of malignant melanoma. Both cases and controls were included only if they were of Northern or Eastern European descent and had *CHEK2*1100delC* genotype ascertained. We excluded five of the original seven identified studies (Cybulski *et al.*, 2004; Debniak *et al.*, 2004; Huang *et al.*, 2004; Thompson *et al.*, 2006; Cybulski, 2007). Studies were excluded if they were double publications (Cybulski *et al.*, 2004; Debniak *et al.*, 2004; Cybulski, 2007), if cases were ascertained on the background of another cancer (Thompson *et al.*, 2006), or if cases had malignant melanoma as part of a multicancer syndrome (Huang *et al.*, 2004). Cases and controls were counted only once. The Danish controls in the present paper have been presented previously (Weischer *et al.*, 2007); therefore, to avoid these controls being counted twice, controls were separated into two groups according to the number of cases in the present and previous study (Weischer *et al.*, 2007).

Data abstraction. From each study we extracted information on author names, year, study design, ascertainment of cases, genotyping method, nationality, and genotype frequency. For the paper by Weischer *et al.* (2007) we obtained information from the authors on the number of participants with malignant melanoma and the *CHEK2*1100delC* carrier status of participants, as these data were not provided in the original publication.

Genotyping. Leukocyte DNA was extracted from peripheral blood to amplify a 162-bp long fragment flanking the *CHEK2* gene by PCR using the forward primer 5′-GGCAGACTATGTTAATCTTTTTATTTTATGG-3′ and reverse primer 5′-CAAGAACTTCAGGCGCCAAGT-3′. *CHEK2*1100delC* carrier status was detected using a TaqMan-based assay (Applied Biosystems, Foster City, CA) using the following probes: wild-type allele 5′-VIC-TTTAGATTACTGATTTTGGGC-3′ and mutated allele 5′-FAM-TTAGATTATGATTTTGGGCAC-3′. In each run, two heterozygous samples were added as positive controls, one noncarrier was run as a negative control, and water was run as a non-template control. To reduce the number of no-calls to a minimum, two rounds of reruns were performed. We genotyped more than 99.9% of the participants. All identified heterozygotes were validated by DNA sequencing. The Danish and German controls were genotyped as described previously (The CHEK2*1100delC Breast Cancer Association Consortium, 2004; Dufault *et al.*, 2004; Rashid *et al.*, 2005; Weischer *et al.*, 2007; Scharrer *et al.*, 2010).

Statistical analyses

Case–control studies. We used the statistical software STATA (STATA/SE 11.1 for Windows, Stata Corp, College Station, TX). We examined Hardy–Weinberg equilibrium using the χ^2-test. Using logistic regression analysis, we calculated gender- and age-adjusted OR for the Danish participants. For the German participants we calculated an unadjusted OR using the χ^2-test. For Danes and Germans combined, we calculated a fixed-effect OR adjusted for study size using Mantel–Haentzel statistics (see below). To test whether the Danish-only and German-only ORs were significantly different, we used the *Z*-test described by Altman and Bland (2003). This test requires that the two estimates be independent, a requirement that we believe was fulfilled, as there was no overlap among cases or controls.

Meta-analysis. Odds ratios for *CHEK2*1100delC* heterozygotes compared with those for noncarriers were calculated as a fixed effect measure using Mantel–Haentzel statistics. In the fixed effect model, we assumed that all studies come from a common population and that the effect size is not significantly different among the different studies. The model was adjusted for study weight. We tested for publication bias graphically by using funnel plots, in which the

log(OR) is plotted against the standard error (log[OR]) to form a simple scatter plot. An asymmetric plot would indicate publication bias, but this was not observed. We tested for heterogeneity between studies using I^2 statistics.

Stratified analysis. We included Danish cases and controls with recorded histories on childhood sunburn, vacations to sunny destinations, use of sunbeds, solar keratosis, and malignant melanoma type and location. Participant numbers differ from the number of cases in Table 1 because of the lack of complete information or unknown status in questionnaires. Odds ratios were obtained by logistic regression adjusting for age, gender, and hospital.

Ethics

Participants gave written informed consent. Danish (KA-02152, KF-100.2039/91, KF-01-144/01) and German (376/2007O1) ethical committees approved the study. The Declaration of Helsinki Protocols was complied with.

Role of the funding organizations

The funding organizations had no role in designing or conducting the study, nor in collecting, managing, analyzing, or interpreting the data or in preparing, reviewing, or approving the manuscript.

CONFLICT OF INTEREST

The authors state no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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