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A Multicenter Study of Cancer Incidence in CHEK2 1100delC Mutation Carriers

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Abstract

The *CHEK2* 1100delC protein-truncating mutation has a carrier frequency of ~0.7% in Northern and Western European populations and confers an ~2-fold increased risk of breast cancer. It has also been suggested to increase risks of colorectal and prostate cancer, but its involvement with these or other types of cancer has not been confirmed. The incidence of cancer other than breast cancer in 11,116 individuals from 734 non-*BRCA1/2* breast cancer families from the United Kingdom, Germany, Netherlands, and the United States was compared with that predicted by population rates. Relative risks (RR) to carriers and noncarriers were estimated by maximum likelihood, via the expectation-maximization algorithm to allow for unknown genotypes. Sixty-seven families contained at least one tested *CHEK2* 1100delC mutation carrier. There was evidence of underreporting of cancers in male relatives (422 cancers observed, 860 expected) but not in females (322 observed, 335 expected); hence, we focused on cancer risks in female carriers. The risk of cancers other than breast cancer in female carriers was not significantly elevated, although a modest increase in risk could not be excluded (RR, 1.18; 95% confidence interval, 0.64-2.17). The carrier risk was not significantly raised for any individual cancer site, including colorectal cancer (RR, 1.60; 95% confidence interval, 0.54-4.71). However, between ages 20 to 50 years, the risks of colorectal and lung cancer were both higher in female carriers than noncarriers ($P = 0.041$ and 0.0001, respectively). There was no evidence of a higher prostate cancer risk in carriers than noncarriers ($P = 0.26$), although underreporting of male cancers limited our power to detect such a difference. Our results suggest that the risk of cancer associated with *CHEK2* 1100delC mutations is restricted to breast cancer, although we cannot rule out a small increase in overall cancer risk.

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Introduction

CHEK2 is a G_2 checkpoint kinase that plays a critical role in DNA repair. In mammalian cells, it is activated in response to ionizing radiation through phosphorylation by ATM, and its activation phosphorylates other key cell cycle proteins, including BRCA1 and p53 (reviewed in ref. 1). The role of *CHEK2* in breast cancer susceptibility was first suggested by the identification of a truncating mutation in exon 10 that abolishes CHEK2 kinase activity (1100delC) in three members of a family with Li-Fraumeni syndrome (2). Although this mutation is no longer thought to be involved in the Li-Fraumeni syndrome (3), it has since been shown to have a population carrier frequency of ~0.7% in Northern and Western European populations (with substantial heterogeneity) and to confer an ~2-fold increased risk of breast cancer to female heterozygous carriers (4-6). The highest frequencies have been reported in Finland and the Netherlands (1.3% and 0.99%, respectively), whereas only five carriers were seen among 1,665 healthy New Yorkers (4, 7). Reports of an association between *CHEK2* 1100delC mutations and prostate or colorectal cancer have not been confirmed, although there is some evidence that other variants within *CHEK2* may increase risk (8-12). In this study, we estimate the risks of all cancers other than breast cancer in carriers of the *CHEK2* 1100delC mutation using cancer incidence data from a cohort of 11,116 individuals from 734 breast cancer families, in which at least one person had been genotyped for this mutation.

Materials and Methods

Subjects

Seven hundred thirty-four families were ascertained through centers in the United Kingdom (236 families), the Netherlands (233 families), Germany (17 families), and the United States (248 families) based on breast cancer occurrence via clinical genetics clinics. Five hundred eighty-seven (80%) families had three or more members with breast cancer and 128 had two such members. The remaining 19 families were ascertained based on one early onset breast cancer (ages between 27 and 49 years at diagnosis). Each family had at least one member who had tested negative for *BRCA1* and *BRCA2* mutations and at least one member who had been tested for the *CHEK2* 1100delC mutation. Families were included whether a *CHEK2* 1100delC mutation was found, with the exception of 28 United Kingdom families, which were included as the only mutation-positive families to date from an ongoing series of breast cancer families, all of which had been routinely screened for *CHEK2* 1100delC. All studies were approved by local ethical committees or institutional review boards, and all individuals gave full informed consent.

Where necessary, pedigrees were pruned to include only those tested for *CHEK2* 1100delC, breast cancer cases diagnosed before age 60 years, male breast cancers at any age, and first-degree relatives of individuals in these categories. The 734 families contained 13,029 individuals, with a median of 16 individuals per family (interquartile range, 11-22). The largest family had 232 members. For each individual, ages at diagnosis of up to three cancers, other than breast cancer, were recorded, along with the type of cancer (International Classification of Diseases 9th revision code; ref. 13).

Mutation Testing of BRCA1, BRCA2, and CHEK2

We screened the full coding sequence and splice junctions of *BRCA1* and *BRCA2* for mutations in at least one individual from every family, either by using heteroduplex analysis (conformation-sensitive gel electrophoresis) or the protein truncation test for exons 10 and 11 of *BRCA2* and exon 11 of *BRCA1* and heteroduplex analysis for the remainder of the

coding sequence or by direct sequencing. In addition, we screened families from the Netherlands for the large genomic rearrangements known to be present in this population (14). We defined families as noncarriers of *BRCA1* or *BRCA2* mutations if they did not have a mutation clearly associated with breast cancer (such as a truncating mutation or one of the previously described pathogenic missense variants). The *CHEK2* 1100delC mutation was detected using PCR amplification of exon 10, application of PCR products to nylon filters, and hybridization under high stringency of ^{32}P-end-labeled oligonucleotides complementary to *CHEK2* 1100delC and the wild-type sequence. Oligonucleotides used for exon 10 amplification were designed such that the reverse primer had a base mismatch in the most 3′ nucleotide compared with sequences from nonfunctional copies; thus, the primers preferentially amplified the functional *CHEK2* on chromosome 22 rather than nonfunctional copies elsewhere in the genome. Positive results were confirmed by PCR reamplification from genomic DNA and direct forward and reverse sequencing of PCR product (5).

Estimating Carrier Probabilities

There were 115 tested *CHEK2* 1100delC mutation carriers and 1,209 noncarriers in the 734 families, with 67 families containing at least one carrier. The probability of carrying a *CHEK2* 1100delC mutation for the 11,705 untested family members was estimated based on their relationship to tested carriers and/or noncarriers and their personal and family history of breast cancer using the program MENDEL (15). Country-specific population incidence rates were taken from *Cancer in Five Continents*, volume VII (16). The population frequency of the *CHEK2* 1100delC allele was taken to be 0.00245, based on the frequency in 6,733 controls from the United Kingdom, the Netherlands, Germany, and Australia. For the purposes of these calculations, *CHEK2* 1100delC was assumed to confer a relative risk (RR) of female breast cancer of 2.34 (4). Male carriers were initially reported to have a 10-fold increased risk of breast cancer (5), but subsequent studies have failed to find any association between *CHEK2* mutations and male breast cancer (17-20). We assumed a male breast cancer RR equal to that for females to allow for a possible modest increase in risk (27 families included a male breast cancer).

Observed and Expected Cancer Incidence

We compared the observed and expected incidence of cancer in the cohort for 22 cancer sites as well as the incidence of cancer at any site other than the breast (excluding nonmelanoma skin cancers). Ovarian cancers were also excluded from the ‘all cancers’ category, as it is possible that the presence of ovarian cancer in a family could be a factor in their ascertainment, although it was not part of the formal criteria. On examination of the data, there seemed to be excesses of bone and liver cancers, particularly in females, in families with and without *CHEK2* 1100delC mutations. Some of these cancers may represent incorrectly coded breast cancer metastases, and so these two sites were also excluded from the ‘all cancers’ category.

Individuals born earlier than 1890 were excluded from the analysis. For cohort members without a breast cancer, entry into the cohort was taken to be at the later of their date of birth and January 1, 1960 because cancer records are not consistently available before this date. For those who had been diagnosed with breast cancer, entry was at the later of the date of breast cancer diagnosis or January 1, 1960. The follow-up period continued until the earliest of the (next) cancer diagnosis, age 80 years, last follow-up, or death. Anyone diagnosed with a non-breast cancer before his or her first breast cancer was excluded.

Expected numbers of cancers were estimated based on age, calendar period, and country-specific population incidence rates from the *Cancer in Five Continents* publications, volumes I to VIII (16, 21-27), using the program PYRS (28). RRs to mutation carriers and

noncarriers were estimated simultaneously by maximum likelihood, via the expectation-maximization algorithm, to allow for unmeasured genotypes as described previously (29). For prostate cancer, the significance of the ratio of the carrier RR to the noncarrier RR was tested using the Wald test, where the variance of the natural logarithm of this ratio was obtained from the variance-covariance matrix estimated using the expectation-maximization algorithm.

With these restrictions, 11,116 people contributed a total of 316,516 person-years to the cohort (median, 33.0 years per person; interquartile range, 20-40). Females comprised 50.6% of the cohort and 44.8% of the person-years. By country, 2,865 individuals came from the United Kingdom (78,616 person-years), 250 from Germany (6,268 person-years), 3762 from the United States (105,301 person-years), and 4,239 from the Netherlands (126,331 person-years).

Results

Among the cohort of 11,116 individuals, 442 cancers were reported in males [860 expected; standardized incidence ratio, 0.51; 95% confidence interval (95% CI), 0.47-0.56] and 322 in females (335 expected; standardized incidence ratio, 0.96; 95% CI, 0.86-1.07), excluding breast, ovarian, bone, liver, and nonmelanoma skin cancers. In view of the apparent underreporting of cancer among male family members, this report will focus on cancer risk in females, except where otherwise specified.

For the female ‘all cancers’, 4 were in known carriers (3.4 expected), 43 in noncarriers (30.9 expected), and 275 in untested women (301.1 expected). The estimated RR was 1.22 (95% CI, 0.66-2.26) in carriers and 0.95 (95% CI, 0.85-1.06) in noncarriers. Because the estimated risk in female noncarriers was close to that expected in the general population, the RRs presented in Table 1 are those estimated assuming the noncarrier RR is fixed at one (overall carrier RR, 1.18; 95% CI, 0.64-2.17). Although there was no statistically significant excess risk of cancer in female carriers, we cannot exclude a possible 2-fold increase in risk (i.e., of the same magnitude as that seen for breast cancer). Modest increased risks were seen at a range of sites, but none approached statistical significance. The risk of colorectal cancer to carriers, based on 73 female cases, was not significantly increased over that expected in the general population (carrier RR, 1.60; 95% CI, 0.54-4.71). Including the 58 cases in males did not substantially alter the estimate (RR, 1.51; 95% CI, 0.70-3.26).

Seventy-five prostate cancers were observed, compared with 135 expected, suggesting considerable underreporting of cancers at this site. However, there is no reason to believe that underreporting could be dependent on genotype. The ratio of the estimated carrier RR (1.42; 95% CI, 0.25-7.85) to the noncarrier RR (0.53; 95% CI, 0.52-0.68) was 2.68, although this difference was not significant ($P = 0.26$). Six of the reported prostate cancers were in *CHEK2* 1100delC-positive families.

Seventeen cancers were diagnosed in children or teenagers, nine in females (3.5 expected) and eight in males (4.4 expected). There was no evidence that male cancers were underreported in this age group; hence, both sexes were considered together. The reported cancers were one bone cancer, three connective tissue cancers, two melanomas, one cancer of the uterus, one of the cervix, four brain cancers, and five leukemias. Only two were in families with a *CHEK2* 1100delC mutation (a leukemia in a 13-year-old son of a carrier and a brain cancer in a 16-year-old sister of a carrier); hence, the RR estimates are imprecise. For all cancers, the carrier RR was 6.25 (95% CI, 0.37-105) with an estimated noncarrier RR of 1.99 (95% CI, 1.19-3.32).

Between the ages of 20 and 50 years, the risk of cancer seemed to be higher for both carriers and noncarriers in the cohort than in the general population (83 cancers other than brain, ovary, liver, bone, and nonmelanoma skin cancers were diagnosed in females in this age group; 49.3 expected). The estimated female carrier RR was 4.91 (95% CI, 2.11-11.40), with an estimated noncarrier RR of 1.54 (95% CI, 1.22-1.94), (ratio of carrier/noncarrier RRs, 3.2; $P = 0.008$); hence, the risks to carriers and noncarriers were estimated simultaneously (Table 1). The point estimates of the RRs were larger for carriers than for noncarriers for several sites, but the excess risk for carriers was only statistically significant for colorectal cancer and lung cancer ($P = 0.041$ and 0.0001 for the difference between the carrier and noncarrier RRs for colorectal cancer and lung cancer, respectively). Including males made little difference to the colorectal cancer carrier RR (carrier RR, 7.81; 95% CI, 2.23-27.3). The carrier RR for female lung cancer in this age group was much higher than that for noncarriers (Table 1), but this was based on just five cases, three of which occurred in *CHEK2* 1100delC-positive families. Of these, one was an obligate carrier, one was the sister of a carrier, and the third was the niece of a carrier who had a breast cancer at age 33 years, 4 years before her lung cancer. This observation may represent a true finding, but, given the number of cancer sites investigated, it may be a chance observation.

After the age of 50 years, there was an evidence of a deficit in reported cancers, both in carriers (RR, 0.56; 95% CI, 0.23-1.34) and noncarriers (RR, 0.83; 95% CI, 0.73-0.95).

Discussion

This cohort study has found no evidence for an overall increase in the risk of cancer other than breast cancer in female *CHEK2* 1100delC mutation carriers, although the 95% CI does not exclude a possible 2-fold increase in risk. Our findings support those of recent case-control studies that have also found no significant association between the *CHEK2* 1100delC mutation and non-breast cancers (8, 30-33). There was some evidence for an increase in the risk of cancer before the age of 50 years, although the only cancer sites for which this was statistically significant were lung and colorectal cancer. Eight of the 11 female cases and 6 of the 10 male cases of colorectal cancer before the age of 50 years came from the Netherlands center, including three cases from one family. This family has been published previously in the context of a possible association between *CHEK2* 1100delC and a combined hereditary breast and colorectal cancer phenotype, along with several of the other families analyzed here from the Netherlands (11). Reestimating the RRs without the Dutch families showed that there was no other evidence of an association between colorectal cancer and *CHEK2* 1100delC (noncarrier RR, 0.92; 95% CI, 0.14-6.16; carrier RR tends to zero). Other studies have also failed to find an association between *CHEK2* 1100delC and colorectal cancer (8, 10, 34) or multiple colorectal adenomas (35).

One strength of this study was that the large majority of the families were included irrespective of their *CHEK2* 1100delC carrier status (the remaining 28 carrier families were ascertained in an identical fashion and added to improve the power). The simultaneous estimation of RRs for carriers and noncarriers in these families relative to the general population allowed us to distinguish between effects attributable to the *CHEK2* 1100delC mutation and those due to other factors present in multiple-case breast cancer families (whether genetic or environmental) or artifacts of the methods of family ascertainment. For example, the overall risk of cancer in 20- to 50-year-old noncarriers was modestly, but statistically significantly, increased over that expected in the general population, but the magnitude of the increase was a third of that estimated for carriers ($P = 0.008$).

The apparent excess of childhood cancers is of interest, given that *CHEK2* 1100delC was first detected in a Li-Fraumeni syndrome family that included a childhood sarcoma (2).

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However, the number of cancers is small and the carrier RR was not significant when compared with the estimated noncarrier risk ($P = 0.42$). It is also possible that, influenced by that report, a few of the families in this study may have been tested for *CHEK2* 1100delC specifically because of the presence of a childhood cancer in a relative of a breast cancer patient; hence, these results should be viewed with caution. For example, the three childhood connective tissue cancers were all in mutation-negative families from the same center, each of which had only one breast cancer case (19 of the 734 families had just one breast cancer case). When the analysis was restricted to the 586 families with three or more breast cancer patients, the noncarrier risk under 20 years old was no longer significantly increased (noncarrier RR, 1.33; 95% CI, 0.69-2.59), but the point estimate of the carrier RR was higher (carrier RR, 9.97; 95% CI, 0.55-180; $P = 0.16$ for the difference between carrier and noncarrier RRs).

A limitation of this study was the reliance on family members' reports of cancer in their relatives. This should not have introduced differential bias because the pedigrees were collected before mutation testing, although inaccuracies in the reporting of some cancers could lead to underestimates of the true effect. Noncarrier RR estimates for women suggest that underreporting was not a major problem for female relatives. However, the extent of the underreporting for male relatives was such that it was not possible to obtain meaningful estimates of the risks to male carriers. Families were primarily collected for breast cancer research projects, and family members or research staff involved in taking the family histories may have not given equal attention to male and female relatives. We were therefore unable to confirm or refute reports of a possible association between *CHEK2* 1100delC and prostate cancer (8, 9, 12, 36).

Although the limitations of the available data prevent us from assessing cancer risks in male *CHEK2* 1100delC mutation carriers, we conclude that the excess risk to female carriers is largely confined to breast cancer, although modest risks of other cancers cannot be excluded.

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Table 1

Observed and expected numbers of cancers in female members of the cohort, with estimated carrier RRs

Cancer	Observed cancers	Expected cancers	Age 0-80 y	Age 20-50 y	
			Carrier RR* (95% CI)	Carrier RR (95% CI)	Noncarrier RR (95% CI)
Colorectal (153-154)	73	71.9	1.60 (0.54-4.71)	8.54 (2.12-34.4)	1.72 (0.89-3.31)
Lung (162)	34	43.8	1.62 (0.44-5.91)	20.8 (3.53-123)	0.46 (0.13-1.57)
Melanoma (172)	13	14.2	0.77 (0.016-38.0)	3.87 (0.066-228)	0.53 (0.17-1.64)
Uterus (180)	38	40.0	1.39 (0.24-8.09)	2.81 (0.47-16.9)	0.61 (0.37-1.00)
Kidney (189)	7	9.70	3.77 (0.28-51.6)	0	
Brain (191)	12	8.60	7.30 (0.70-75.8)	7.73 (0.14-439)	2.89 (1.29-6.50)
Thyroid (193)	8	6.71	3.83 (0.075-196)	9.55 (0.17-538)	1.95 (0.87-4.37)
Lymphoid and leukemia (200-209)	32	33.1	1.16 (0.14-9.77)	0	1.40 (0.50-3.97)
All excluding breast, ovarian, liver, bone, and nonmelanoma skin cancer	322	335	1.18 (0.64-2.17)	4.91 (2.11-11.4)	1.54 (1.22-1.94)

NOTE: Cancers shown are those for which the carrier RR estimate did not converge to zero.

*Estimated with noncarrier RR fixed at one.