The *CHEK2*1100delC* Allelic Variant and Risk of Breast Cancer: Screening Results from the Breast Cancer Family Registry

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Abstract

CHEK2, a serine-threonine kinase, is activated in response to agents, such as ionizing radiation, which induce DNA double-strand breaks. Activation of CHEK2 can result in cell cycle checkpoint arrest or apoptosis. One specific variant, *CHEK2*1100delC*, has been associated with an increased risk of breast cancer. In this population-based study, we screened 2,311 female breast cancer cases and 496 general population controls enrolled in the Ontario and Northern California Breast Cancer Family Registries for this variant (all controls were Canadian). Overall, 30 cases and one control carried the *1100delC* allele. In Ontario, the weighted mutation carrier frequency among cases and controls was 1.34% and 0.20%, respectively [odds ratio (OR), 6.65; 95% confidence interval (95% CI), 2.37-18.68]. In California, the weighted population mutation carrier frequency in cases was 0.40%. Across all cases, 1 of 524 non-Caucasians (0.19%) and 29 of 1,775 Caucasians (1.63%) were mutation carriers (OR, 0.12; 95% CI, 0.02-0.89). Among Caucasian cases >45 years age at diagnosis, carrier status was associated with history of benign breast disease (OR, 3.18; 95% CI, 1.30-7.80) and exposure to diagnostic ionizing radiation (excluding mammography; OR, 3.21; 95% CI, 1.13-9.14); compared with women without exposure to ionizing radiation, the association was strongest among women exposed >15 years before diagnosis (OR, 4.28; 95% CI, 1.50-12.20) and among those who received two or more chest X-rays (OR, 3.63; 95% CI, 1.25-10.52). These data supporting the biological relevance of CHEK2 in breast carcinogenesis suggest that further studies examining the joint roles of *CHEK2*1100delC* carrier status and radiation exposure may be warranted. (Cancer Epidemiol Biomarkers Prev 2006;15(2):348–52)

Introduction

Ionizing radiation is a known carcinogen in both animals and humans and has been implicated in breast carcinogenesis in particular. Exposure to ionizing radiation can cause a variety of types of damage to the DNA, of which the most serious are double-strand breaks. When unrepaired, DNA double-strand breaks can result in the loss of genetic material whereas incorrectly repaired double-strand breaks can result in damage ranging from localized mutations at the site of the original lesion to large-scale genomic rearrangements. The products of genes for which identified variants or mutations increase risk for breast cancer act predominantly within a common cellular pathway used by human cells to sense, signal, and repair such damage from DNA double-strand breaks (1). Stimulation of this pathway by exposure to ionizing radiation or other DNA double-strand break–inducing agents activates the ATM protein, a serine-threonine kinase, which phosphorylates a wide array of substrates including BRCA1 and CHEK2 (2, 3). Phosphorylation of CHEK2 on T68 is essential for its activation and all of its known functions. On activation, CHEK2 acquires the ability to carry out the following functions: (*a*) Activated CHEK2 regulates the S-phase cell cycle checkpoint, presumably by phosphorylating CDC25A (4, 5). (*b*) CHEK2 modulates p53 activity either by direct phosphorylation of p53 or by phosphorylation of murine double minute-2 and this interaction serves to both regulate the G_1-S cell cycle checkpoint and activate p53-dependent apoptotic pathways (6, 7). (*c*) CHEK2 also activates DNA damage–responsive, but p53-independent, apoptotic pathways through its phosphorylation of promyelocytic leukaemia protein and E2F1 (8, 9). (*d*) CHEK2 phosphorylates BRCA1 which may help to facilitate its role in DNA repair (10, 11). Thus, ATM and CHEK2 play key roles in the primary signaling pathway that controls cellular responses to double-strand breaks and both directly regulate the functions of BRCA1.

A genetic variant in the CHEK2 gene, *1100delC*, is predicted to result in the production of a truncated version of the CHEK2 protein. This variant has previously been associated with an increased risk of breast cancer. Although both positive and negative associations with this variant have been reported in individual studies, a recent pooling project, including 10,860 cases and 9,065 controls from 10 studies, observed an >2-fold risk of breast cancer associated with carrier status for *CHEK2*1100delC* [1.9% in cases versus 0.7% in controls; odds

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ratio (OR), 2.34; 95% confidence interval (95% CI), 1.72-3.20; $P < 0.0001$; ref. 12]. Given this elevated risk and the biochemical evidence suggesting the importance of CHEK2 in the cellular response to exposure to ionizing radiation, we sought to examine the association of the *CHEK2*1100delC* mutation and breast cancer risk among the population-based cases and controls enrolled at two sites of the Breast Cancer Family Registry (http://epi.grants.cancer.gov/CFR/).

Materials and Methods

Study Population. The female breast cancer cases and controls were obtained from the Northern California Family Registry and the Ontario Familial Breast Cancer Registry, two population-based registries of the Breast Cancer Family Registry (13). This study was limited to participants who provided blood samples and completed an epidemiologic questionnaire; 1,112 cases from California, 1,199 cases from Ontario, and 496 controls from Ontario.

Both sites used a two-stage sampling design to select cases. Newly diagnosed breast cancer cases were ascertained from the regional cancer registries in the San Francisco Bay area and Ontario, Canada. All cases who met the ''high-risk'' criteria (13) were invited to enroll in the Breast Cancer Family Registry; those who did not meet these criteria were selected through random sampling. In Ontario, controls were sampled from the general population using randomly selected residential telephone numbers. Controls recruited in California were not eligible for this study as DNA was unavailable. Participation rates varied by center and case status and are explained in detail by John et al. (13). Briefly, among cases, physician contact was obtained for 98% in Northern California and 91% in Ontario; eligibility was determined for 84% in Northern California and 65% in Ontario; questionnaire data were obtained by 78% in Northern California and 72% in Ontario; and a blood sample was provided by 64% in Northern California and 62% in Ontario. Among the 12,711 controls from households who were contacted through randomly selected telephone numbers, 38% had an eligible individual, of whom 64% completed the mailed questionnaire. Of the 676 eligible women who were asked to provide a blood sample, 62% ($n = 419$) did so.

Data and Biospecimen Collection. In California, cases provided information on family history of cancer through a structured questionnaire, administered by telephone, whereas other risk factor information was obtained through in-person interviews (13). In Ontario, information on family history of cancer and other risk factors was collected through mailed questionnaires. Using a common questionnaire, both sites gathered information on demographics, reproductive and past medical histories, treatment, and medical exposures. Information on age at first exposure and total number of exposures was ascertained for diagnostic radiation received to the chest (e.g., heart catheterization or scoliosis) and in the lower abdomen or pelvis. Questions pertaining to X-ray exposure from mammograms or therapeutic radiation were asked separately. A blood sample from all participants was collected and processed using a common protocol. All participants provided written informed consent before enrollment into the Breast Cancer Family Registry and the research protocols were approved by the respective Institutional Review Boards.

Genotyping. Genotyping for the *CHEK2*1l00delC* mutation was conducted using both primer extension and denaturing high-performance liquid chromatography. A fragment of *CHEK2* exon 10 containing position 1100 was amplified with PCR primers as previously described (14). The forward primer had two mismatches relative to a pseudogene sequence and the reverse primer had three consecutive mismatches at the 3′ end to increase specificity for the functional *CHEK2* gene. Primer extension was done with the AcycloPrime SNP Detection Kit (Perkin-Elmer Life Sciences, Boston MA) using a reverse extension primer according to standard protocols. The wild-type and mutant alleles were detected independently by fluorescence polarization using a standard plate reader, Victor^2 (Perkin-Elmer Life Sciences). All positive findings were confirmed by sequencing. Denaturing high-performance liquid chromatography was done on the WAVE platform (Transgenomic, Inc., Omaha, NE). *CHEK2* amplicons were injected under optimal conditions predicted based on the *CHEK2* sequence by the Wavemaker 4.1 software supplied by the manufacturer. Any variant chromatograms were verified by sequencing. All laboratory work was done blinded to case-control status. For quality control purposes, 10% of the samples were retested.

Statistical Methods. We used unconditional logistic regression to estimate age-adjusted ORs and 95% CIs. In addition, offsets for cases were set to the natural log of the sampling fraction and were included in all regression models to accommodate the two-stage sampling designs used in the two study sites (15). The population-based prevalence of the *CHEK2*1100delC* variant was estimated incorporating the population-specific sampling weight assigned to each case at each site. Case-control comparisons were restricted to participants from Ontario only (1,199 cases and 496 controls) whereas case-case comparisons to examine gene-environment interactions (16) were done for cases from both sites (1,112 from California and 1,199 from Ontario). All calculations were done using the Statistical Analysis System software.

Results

Among 2,311 cases screened, 30 harbored the *CHEK2*1100delC* variant (Table 1). Of the 1,199 Ontario cases, 18 carried the variant whereas only one of 496 controls was found to be a carrier—the estimated population-specific carrier frequency rate among the cases and controls was 1.34% and 0.20%, respectively (OR, 6.65; 95% CI, 2.37-18.68). Among cases from California, the estimated weighted carrier rate was 0.40%. Across both sites, there were 524 non-Caucasian cases, and of these, one carried the variant (non-Caucasian versus Caucasian cases: OR, 0.12; 95% CI, 0.02-0.85); among the Ontario controls, 19 were non-Caucasian, and of these, none harbored the variant. Because of this difference in carrier rates and the small number of non-Caucasian women in this study, all subsequent analyses were restricted to female Caucasian cases.

Adjusted ORs and 95% CIs for the association of *CHEK2*1100delC* carrier status and selected risk factors in cases only, both overall and stratified by age at diagnosis, are presented in Table 2. Across all age groups, *CHEK2*1100delC* carrier status was not associated with any risk factors, including family history of cancer. Although the Caucasian-only weighted carrier frequency rate was lower in California than the corresponding rate in Ontario, the difference was not statistically significant. However, among older cases, the odds of being a *CHEK2*1100delC* carrier were greater for those exposed to radiation through chest X-rays (excluding diagnostic mammograms; OR, 3.21; 95% CI, 1.13-9.14); risk was increased for women exposed ≥15 years before diagnosis (OR, 4.28; 95% CI, 1.50-12.20) and among those with two or more exposures (OR, 3.63; 95% CI, 1.25-10.52). The one carrier identified among the women diagnosed with breast cancer before age 45 had had a chest X-ray 5 to 9 years before her diagnosis. The number of women who had received therapeutic radiation to the chest and/or abdomen before diagnosis of breast cancer was too small to assess their independent effect. When combined with diagnostic X-rays, the association did not change substantially. We found no increase in the proportion of carriers among women who were young at the time of their first X-ray exposure (data not shown) or who had

Table 1. Characteristics of 2,807 female screened participants

Case/control status	Registry	Characteristic	*CHEK2*+ (*n*)	*CHEK2*− (*n*)	Weighted mutation carrier frequency* (%)
Cases	Canada	Caucasian†	18	1,121	1.40
		Non-Caucasian‡	0	48	N/A
		Race unknown	0	12	N/A
		All races	18	1,181	1.34
	California	Caucasian†	11	625	0.59
		Non-Caucasian‡	1	475	0.09
		Race unknown	0	0	N/A
		All races	12	1,100	0.40
Controls	Canada	Caucasian†	1	475	0.21
		Non-Caucasian§	0	19	N/A
		Race unknown	0	1	N/A
		All races	1	495	0.20

*The population-based prevalence of the *CHEK2*1100delC* variant was estimated incorporating the population-specific sampling weight assigned to each case at each site. N/A means not applicable.
†Included in subsequent analyses.
‡Female non-Caucasian cases included 18% blacks, 32% white Hispanics, 42% Asians, 6% other races, and 2% mixed races.
§Female non-Caucasian controls included 10% blacks, 32% Asians, and 58% other races.

a family history of cancer. Among the older cases, we observed an association of *CHEK2*1100delC* carrier status with history of benign breast disease (OR, 3.18; 95% CI, 1.30-7.80). Furthermore, there was a statistical association between history of benign breast disease and diagnostic X-rays ($P < 0.001$) as the same carriers were positive for both.

Discussion

Since the first observations that the variant in *CHEK2, 1100delC*, was associated with an increased risk of breast cancer, a number of studies, using different study designs, have examined the risk among various populations. Although not all studies have found a statistically significant association with breast cancer (17-24), the results reported by the large CHEK2 consortium pooling project that combined data from studies conducted in five countries provided strong evidence that *CHEK2*1100delC* is a breast cancer susceptibility allele that confers a modestly increased risk of breast cancer (12). The frequency of the variant was greater among the Ontario cases compared with the Ontario controls in our population-based series, 1.34% and 0.20% (OR, 6.65; 95% CI, 2.37-18.68). The number of controls screened, however, was relatively small and only one carrier was detected. Nevertheless, the increased risk is consistent with the results of the pooling project as well as other studies, including some that reported statistically nonsignificant elevations in risk (12, 14, 21, 25-30). Of particular relevance to our study are the similar frequencies observed in published population-based studies conducted in Western Washington (17), the United Kingdom (12), and the Netherlands (12), which, although based on smaller sample sizes (approximately half), found a higher proportion of carriers among cases compared with controls.

In our study, race was associated with carrier status. Among the non-Caucasian cases, who accounted for <20%, only 1 of 524 (0.19%) carried a *CHEK2*1100delC* allele compared with 29 of 1,775 (1.63%) among Caucasians. To our knowledge, the only published study in non-Caucasians found no carriers among 56 cases screened compared with 6 observed among 450 Caucasian cases (17). In our series, the population was drawn from multiple hospitals located in two countries. Because of the observed racial difference and the ethnic composition from the different sites, we restricted the association analyses to Caucasian women to minimize potential confounding by population admixture. As noted above, because no DNA samples were available from the California controls, all case/control comparisons were restricted to the Ontario women.

Unlike the findings from some prior studies, including the large CHEK2 Breast Cancer Case-Control Consortium pooling project (12, 26), we found no support for an association between carrier status and family history of breast cancer or age at diagnosis. This difference may be explained by the varying methods of case ascertainment in prior studies, particularly because most studies to date have been family based or included young women only. Our population-based series included a broad range of ages of probands, with 65% of our cases older than 45 years at diagnosis. Further, the proportion of cases with family history was smaller than that reported elsewhere, precluding our calculating reliable cumulative risk estimates such as that provided by other studies (12).

In the current study, the frequency of *CHEK2*1100delC* carriers was significantly elevated in two subsets: older cases with a history of benign breast disease and older cases reporting diagnostic X-rays to the chest (excluding diagnostic mammography). Both history of benign breast disease and low-dose radiation exposure have been independently reported to confer modestly increased risks for breast cancer (31). However, the biological significance of an association with carrier status is unclear, partially because information on age at breast biopsy was unavailable. It was therefore not possible to determine whether these were independent effects or whether there was a temporal relationship between the two factors. For example, we could not examine whether the association with benign breast disease was an artifact of older women receiving more biopsies or whether women who carry a *CHEK2*1100delC* allele were more likely to develop cystic breasts.

The association between breast cancer risk and low-dose radiation, such as that received from diagnostic X-rays, has been the subject of much debate; the weight of evidence from experimental and epidemiologic data does not suggest a threshold dose below which radiation exposure does not cause cancer (32). However, compared with higher doses, risks associated with low-dose radiation are likely to be lower and to decrease with decreasing dose of radiation (33). In our series, we observed that the odds of being a carrier were elevated among women receiving a greater number of nonmammographic diagnostic X-rays, especially among women with at least 15-year interval between last radiation exposure from X-ray examination and breast cancer diagnosis. Nevertheless, given the ambiguities associated with low-dose radiation, coupled with the observed association between breast biopsies and radiation exposure as described above, these results become complicated to interpret and it is not clear whether or not they truly reflect increased radiation sensitivity among carriers of the *CHEK2*1100delC* variant.

Given the prior reports of an association between carrier status for *ATM,* radiation exposure, and breast cancer risk (34, 35), it is of note that one woman in the current study

Table 2. Odds of *CHEK2*1100delC* positivity among female Caucasian cases by selected risk factors and stratified by age at diagnosis

Category	Variable	All ages		Ages <45		Ages 45+	
		No. positive/ total no.	OR (95% CI)*	No. positive/ total no.	OR (95% CI)*	No. positive/ total no.	OR (95% CI)*
Demographics	Study location						
	California	11/636	0.78 (0.36-1.66)	5/221	1.97 (0.52-7.41)	6/415	0.49 (0.19-1.30)
	Ontario	18/1,139	1.00	4/400	1.00	14/739	1.00
	Age at diagnosis (y)						
	<30	1/46	0.83 (0.11-6.36)				
	30-44	8/575	0.60 (0.26-1.41)				
	45-59	17/878	1.00				
	≥60	3/276	0.85 (0.25-2.92)				
	Education						
	Post high school	22/1,224	1.17 (0.49-2.76)	9/479	N/A	13/745	0.78 (0.31-1.98)
	High school or less	7/532	1.00	0/137		7/395	1.00
History of X-rays before breast cancer diagnosis	Had a diagnostic X-ray in chest area						
	Yes	10/454	1.77 (0.77-4.07)	1/147	0.38 (0.05-3.08)	9/307	3.21 (1.13-9.14)
	No	13/940	1.00	7/367	1.00	6/573	1.00
	Total no. diagnostic chest X-rays						
	≥2	8/298	2.19 (0.91-5.28)	1/104	0.60 (0.07-4.95)	7/194	3.63 (1.25-10.52)
	<2	14/1,022	1.00	7/396	1.00	7/626	1.00
	Time from diagnostic chest X-ray to diagnosis (y)						
	≥15	9/324	2.27 (0.95-5.40)	0/91	N/A	9/233	4.28 (1.50-12.20)
	<15	1/130	0.60 (0.08-4.60)	1/56 †	0.95 (0.12-7.90)	0/74	N/A
	No chest X-ray	13/940	1.00	7/367	1.00	6/573	1.00
	Had a diagnostic X-ray in chest or abdominal area						
	Yes	12/768	1.15 (0.49-2.69)	2/236	0.41 (0.08-2.05)	10/532	2.07 (0.64-6.66)
	No	10/668	1.00	6/284	1.00	4/384	1.00
	Total no. diagnostic chest or abdominal X-rays						
	≥2	9/457	1.56 (0.65-3.74)	2/146	0.85 (0.17-4.26)	7/311	2.14 (0.71-6.44)
	<2	12/872	1.00	6/350	1.00	6/522	1.00
Family history of breast cancer ‡	Any first-degree relative						
	Yes	11/592	0.81 (0.38-1.76)	2/154	0.73 (0.15-3.57)	9/438	0.84 (0.35-2.05)
	No	18/1,183	1.00	7/467	1.00	11/716	1.00
	Any second-degree relative						
	Yes	7/268	1.61 (0.62-4.21)	2/108	2.25 (0.31-16.16)	5/160	1.45 (0.48-4.40)
	No	11/871	1.00	2/292	1.00	9/579	1.00
	Any full sister						
	Yes	2/178	0.50 (0.12-2.16)	1/31	2.12 (0.26-17.52)	1/147	0.28 (0.04-2.09)
	No	27/1,597	1.00	8/590	1.00	19/1,007	1.00
	Mother						
	Yes	11/444	1.30 (0.61-2.80)	2/131	0.92 (0.19-4.46)	9/313	1.47 (0.60-3.59)
	No	18/1,331	1.00	7/490	1.00	11/841	1.00
Reproductive and medical history	Ever pregnant						
	Yes	25/1,447	1.21 (0.41-3.56)	6/469	0.64 (0.16-2.59)	19/1,008	2.74 (0.36-20.70)
	No	4/295	1.00	3/150	1.00	1/145	1.00
	Postmenopausal at date of diagnosis						
	Yes	9/656	0.68 (0.28-1.65)	0/24	N/A	9/632	0.72 (0.29-1.79)
	No	19/977	1.00	9/562		10/415	1.00
	History of biopsy diagnosed as benign breast disease						
	Yes	9/294	2.18 (0.97-4.89)	0/60	N/A	9/234	3.18 (1.30-7.80)
	No	20/1,481	1.00	9/561		11/920	1.00

*All ORs were adjusted for age and sampling method. N/A means not applicable.
†This positive case had a chest X-ray 5 to 9 years before cancer diagnosis.
‡Information on second-degree relatives was available for Ontario cases only.

was found to be heterozygous for both the *CHEK2*1100delC* variant and the very rare *ATM* variant *7271T>G* (V2424G). Heterozygosity for *7271T>G* has been associated with a greatly increased risk of breast cancer and cellular radiation sensitivity (36). This patient self-identified herself as ''other race.'' She was 51 years old at diagnosis with a personal history of benign breast disease and a family history of breast cancer (mother); however, she had never received radiation treatment or diagnostic X-rays. Given the relative infrequency of each of these variants, their co-occurrence here in a single subject was surprising. Although this observation is consistent with the known relationship of the products of the two genes, we could not assess whether the combination of variants enhances breast cancer risk based on a single observation. Functional studies of the cellular response to ionizing radiation in such doubly heterozygous individuals might help to resolve whether alleles at *ATM* and *CHEK2* may interact.[9]

[9] The results of the *ATM* screening of this same population of women are reported in a separate manuscript (J.L. Bernstein et al. Population-based estimates of breast cancer risks associated with the ATM gene variants 7271T>G and IVS10-6T>G from the Breast Cancer Family Registry, unpublished data).

In this study, we screened a large number of breast cancer cases for the *CHEK2*1100delC* variant and observed 30 carriers. Our results support the hypothesis that carrier status for *CHEK2*1100delC* is associated with increased breast cancer risk and suggest that this relationship may be modified by other factors, such as radiation exposure. With regard to potential risk modification by radiation exposure, our findings are statistically significant, consistent, and biologically plausible but should nevertheless be interpreted with caution—we cannot rule out the possibility of confounding from an unmeasured risk factor or the possibility of findings based on chance alone, given the relatively small number of carriers we have identified. To clarify the role of the *CHEK2*1100delC* variant in breast carcinogenesis, functional studies of the biochemical pathway affected by this variant as well as a general assessment of radiation hypersensitivity in carrier cell lines will be necessary. In addition, it will be important to replicate the findings from this study within a larger-scale study designed specifically to examine the joint effects of radiation exposure and genetic susceptibility on breast cancer risk.

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