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Cancer risks for other sites in addition to breast in *CHEK2* c.1100delC families



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ABSTRACT

Purpose: Female *CHEK2* c.1100delC heterozygotes are eligible for additional breast surveillance because of an increased breast cancer risk. Increased risks for other cancers have been reported. We studied whether *CHEK2* c.1100delC is associated with an increased risk for other cancers within these families.

Methods: Including 10,780 individuals from 609 families, we calculated standardized incidence rates (SIRs) and absolute excess risk (AER, per 10,000 person-years) by comparing first-reported cancer derived from the pedigrees with general Dutch population rates from 1970 onward. Attained-age analyses were performed for sites in which significant increased risks were found. Considering the study design, we primarily focused on cancer risk in women.

Results: We found significant increased risks of colorectal cancer (CRC; SIR = 1.43, 95% CI = 1.14–1.76; AER = 1.43) and hematological cancers (SIR = 1.32; 95% CI = 1.02–1.67; AER = 0.87). CRC was significantly more frequent from age 45 onward.

Conclusion: A significantly increased risk of CRC, and hematological cancers in women was found, starting at a younger age than expected. Currently, colorectal surveillance starts at age 45 in high-risk individuals. Our results suggest that some *CHEK2* c.1100delC families might benefit from this surveillance as well; however, further research is needed to determine who may profit from this additional colorectal surveillance.

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Introduction

Women with the *CHEK2* c.1100delC (p.Thr367fs) pathogenic variant (PV) have an increased risk to develop breast

cancer, which further increases in a familial breast cancer setting.¹ Approximately 1% of the general Dutch population is heterozygous for this PV, whereas it is detected in up to 5% of the counseled breast cancer families. In The

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Netherlands, diagnostic testing for *CHEK2* c.1100delC was implemented since 2014, and from 2018 onward, the complete *CHEK2* gene is sequenced. Based on family history and *CHEK2* c.1100delC status, a cumulative lifetime breast cancer risk is estimated.² This risk estimation guides recommendations on the age to start breast surveillance.

Currently, proven *CHEK2* c.1100delC heterozygotes do not receive cancer surveillance advice for sites other than the breast in The Netherlands. However, previous research has shown that c.1100delC confers an increased risk for other cancers. First, a Danish population study including 670 heterozygotes reported an increased risk for stomach cancer, renal cancer, sarcoma, and prostate cancer in heterozygotes compared with noncarriers.³ Second, a recent literature overview showed an increased risk of colorectal cancer and prostate cancer, suggesting that surveillance should be considered based on family history.⁴ Finally, association studies were conducted to evaluate if c.1100delC is more prevalent among patients with certain cancer types, although these studies are based on small numbers of heterozygotes.⁵⁻¹³ Therefore, our aim is to assess whether *CHEK2* c.1100delC relatives have an increased risk of cancer other than breast cancer.

Materials and Methods

Hereditary Breast, and Ovarian Cancer Research Netherlands (Hebion) study

As part of the nationwide Hebion study, all known *CHEK2* c.1100delC heterozygotes and homozygotes who were tested because of a familial increased risk of breast cancer and their tested relatives, were retrospectively selected and invited to participate between 2020 and 2022. Informed consent was signed by all participants, who also agreed to the use of (anonymized) pedigree information for research. From all Dutch clinical genetic centers, we were able to retrieve pedigrees from 794 participating *CHEK2* c.1100delC families.

Selection of pedigrees and relatives

Because the available pedigree information differed between families and centers, we harmonized the inclusion of relatives. Per family, we labeled the youngest known *CHEK2* c.1100delC-positive Hebion participant with breast cancer in the family as the index case. When PV status of the (grand) parents was known, we only used data from *CHEK2* c.1100delC-positive branches. However, if no further DNA testing was conducted within the families, we included both family branches because they have a likelihood of 50% of having this PV.

Families with homozygotes and families who carried other cancer-related (likely) PVs were excluded. All

CHEK2-unrelated branches were omitted (eg, partners of relatives and proven noncarriers and their children). Furthermore, we excluded families for which limited information was available and we were unable to impute years of birth (as a rule of thumb, at least 1 person per generation was needed with a known year of birth). Finally, we included all first-degree and second-degree relatives of the index case because the information provided on cancer diagnoses for more distant relatives was lacking or less reliable. Therefore, all relatives included have a priori chance of the *CHEK2* c.1100delC PV of 50% or 25%.

To estimate cancer risks, time at risk started January 1st, 1970 for those born before 1970 and at the date of birth for those born from 1970 onward because population data are available from 1970 to 2016. For the cancer diagnoses after 2016, the cancer incidences from 2016 were used. Time at risk ended at the date of diagnosis of a first primary cancer, at the date of death, at the date of last follow-up in family, or at age 80. In analyses for all cancers combined, survivors who developed multiple cancers were only counted once, and time at risk ended at the date of diagnosis of the first cancer. In site-specific analyses, individuals who developed multiple cancers contributed data regarding the cancer of interest, ignoring any preceding cancer diagnoses at another site. After exclusion, the analyzed cohort comprised 10,780 individuals from 609 *CHEK2* c.1100delC families, including 5696 women (52.8%) and 5084 men (47.2%; [Figure 1](#)). Of whom, 1056 (18.5%) women and 138 (2.7%) men are known heterozygotes. Furthermore, 3246 (57.0%) women and 3483 (68.5%) men had a 50% chance of being c.1100delC heterozygotes, and 1394 (24.5%) women and 1463 (28.8%) men had a 25% chance of being c.1100delC heterozygotes. Because of the design of the study, aimed at the inclusion of tested women and their families, we primarily focused on cancer risk in women. Cancer risks in men are presented in the [Supplemental Tables 1, 5-8](#).

Imputation of data

As year of birth was missing for 3601 relatives (33.4%), we imputed this variable based on the known years of birth in each generation of the family and the pedigree structure. The procedure was as follows: we assumed (1) 2-year intervals between siblings and (2) 25-year age difference between generations within each family. When there was uncertainty regarding the exact age of diagnosis, we decided to use the average age (eg, 42.5 for 40-45 years as reported in the pedigree) or the estimated age (eg, 62 for ± 62 years as reported in the pedigree). When broader range of age at diagnosis was given, we assigned the site- and sex-specific mean age for that group, eg, if a man was diagnosed with prostate cancer >60 years, we calculated the mean age for all men who were diagnosed with prostate cancer >60 years and assigned this value to that person.

Five of 9 centers were not able to provide any information on pathological confirmation of cancers at all. In total,

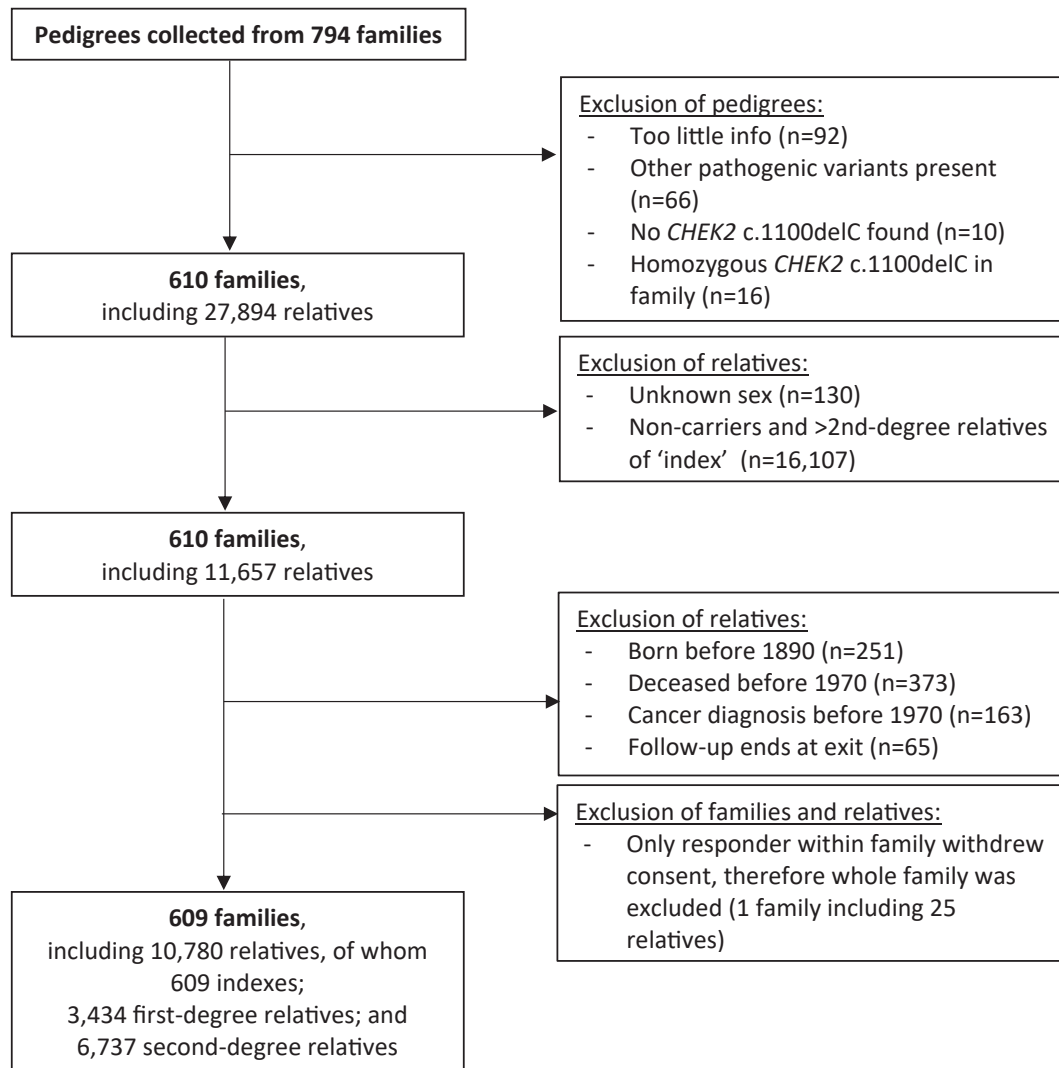


Figure 1 Flowchart of excluded families and relatives.

we had no pathological confirmation for 61.9% of the cancers. Therefore, we considered the possibility of metastatic disease instead of a primary cancer when multiple cancers within 1 person were reported. Frequent metastatic sites, such as liver, brain, lung, and bone, were reconsidered and excluded when we had no pathological confirmation of primary cancer status. For example, if a breast cancer patient had a second cancer in liver, brain, or bone without pathological confirmation, we assumed that this was a distant metastasis of breast cancer and removed this event. As a result, we removed liver cancer from 10 women and 3 men, brain cancer from 8 women and 5 men, lung cancer from 24 women and 26 men, and bone cancer from 7 women and 4 men.

In addition, when there were uncertainties regarding cancer type (eg, cervical cancer or endometrial cancer and subtypes of hematological cancers) we combined sites and provided an overview for those combined.

Statistical analyses

For all individuals, follow-up started January 1, 1970, or date of birth, whichever came last, and ended at the date of cancer diagnosis, date of death, date of last contact, last DNA test in the family, or at the age of 80 years, whichever came first. The calculation of the expected numbers of cancers was based on age-, sex-, and site-specific cancer incidence rates in the Dutch population, multiplied by the total corresponding number of person-years at risk in this analysis. From the observed and expected numbers of cancers, we used standard methods to compute the standardized incidence ratios (SIRs), the absolute excess risk (AER) per 10,000 person-years, and the corresponding 95% confidence intervals (CI).¹⁴ SIR was calculated by dividing the number of observed events by the number of expected events over the total person-years at risk. AER was calculated by subtracting the expected number of cases from the number

observed and dividing by person-years at risk (expressed per 10,000 person-years).

Analyses were done on (1) first-reported cancer only. Here, breast cancer risk was analyzed with and without the breast cancer indexes to adjust for the oversampling of breast cancer cases (testing bias), (2) site-specific analyses including all reported cancer, and (3) first-reported cancer in known heterozygotes and their first-degree relatives only. Attained-age analysis was conducted for sites where a significant elevated risk was found, except for liver, brain, bone, or lung cancer diagnoses because these likely represent metastatic rather than a primary disease.

Results

Cancer was reported for 1705 of 5696 women (29.9%) and 706 of 5086 men (13.9%). A detailed overview of all reported cancer sites is shown in [Table 1](#) and [Supplemental Table 1](#). [Table 2](#) provides an overview of the SIRs for the first-reported cancer site. Significant elevated risks were observed for all cancers in women (SIR = 2.36; 95% CI = 2.25-2.47). More specifically, increased risks were observed for breast cancer (SIR = 4.88; 95% CI = 4.62-5.16; AER = 53.8 in all women, SIR = 3.22; 95% CI = 3.00-3.45; AER = 32.5 when excluding breast cancer index from 489 families), liver cancer (SIR = 4.30; 95% CI = 1.97-8.16; AER = 0.3), colorectal

cancer (SIR = 1.43; 95% CI = 1.14-1.76; AER = 1.4) and hematological cancers (SIR = 1.32; 95% CI = 1.02-1.67; AER = 0.9). Similar results were found in site-specific analyses ([Supplemental Table 2](#)) and in the analysis on first-reported cancers in known heterozygotes and their first-degree female relatives only ([Supplemental Table 3](#)), except for a significant increased risk for renal cancer in women in our site-specific analysis (SIR = 1.99; 95% CI = 1.30-2.91; AER = 0.69).

The association of attained age with cancer risk was determined for breast, colorectal, and hematological cancers in women ([Table 3](#)). In general, breast cancer risk was significantly increased from age 25 onward, whereas colorectal cancer risk was increased from age 45 years onward. When assessing site-specific cancer risk, results were very similar. Furthermore, renal cancer risk in women was significantly increased between the age of 35 and 45 years ([Supplemental Table 4](#)).

In men, we found a significant lower overall cancer risk (SIR = 0.70; 95% CI = 0.65-0.75; AER = -17.9). Overall, we found similar risks as described in women, except for hematological cancers. In addition, risks of brain cancer (SIR = 2.51; 95% CI = 1.73-3.52; AER = 1.2) and bone cancer (SIR = 3.29; 95% CI = 1.21-7.15; AER = 0.2) were increased compared with the general population. Colorectal cancer risk was increased from age 55 onward ([Supplemental Tables 5-8](#)).

Table 1 Overview of all cancer diagnoses and pathological confirmed diagnoses observed in 609 *CHEK2* c.1100delC families, stratified by a priori chance of being a *CHEK2* c.1100delC heterozygote

Tumor Sites	Women (n = 5696)						
	Heterozygote (n = 1056)		50% Chance (n = 3246)		25% Chance (n = 1394)		
	Total	n	Pathological Confirmed, n (%)	n	Pathological Confirmed, n (%)	n	Pathological Confirmed, n (%)
Breast	1328	712	210 (29.7)	567	58 (10.3)	49	5 (10.2)
Vulva	5	-		5	0 (0)	-	
Cervix/uterus	47	10	3 (30.0)	36	2 (5.6)	1	0 (0)
Ovarian	42	14	3 (21.4)	27	1 (3.7)	1	0 (0)
Bladder	12	2	1 (50.0)	9	0 (0)	1	0 (0)
Kidney	26	7	3 (42.9)	13	0 (0)	6	0 (0)
Esophagus	8	1	0 (0)	7	0 (0)	-	
Stomach	15	2	0 (0)	8	0 (0)	5	0 (0)
Pancreatic	19	-		17	0 (0)	2	0 (0)
Liver	9	-		7	0 (0)	2	0 (0)
Gallbladder and bile ducts	3	-		3	0 (0)	-	
Colorectal	110	19	8 (42.1)	77	4 (5.2)	14	0 (0)
Hematological	67	9	2 (22.2)	49	5 (10.2)	9	0 (0)
Brain	15	2	0 (0)	9	0 (0)	4	0 (0)
Head and neck	10	1	1 (100.0)	8	0 (0)	1	0 (0)
Thyroid	6	2	0 (0)	4	0 (0)	-	
Lung	42	-		35	0 (0)	7	0 (0)
Bone	4	-		3	0 (0)	1	0 (0)
Sarcoma	8	4	3 (75.0)	4	0 (0)	-	
Melanoma	30	14	4 (28.6)	14	3 (21.4)	2	0 (0)
Unknown	28	0	-	27	0 (0)	2	0 (0)

Tumors were reported by the index, pathological confirmation of the tumors was registered only for a small portion of tumors in the pedigree.

Table 2 Observed number of cancers per site in women, the standardized incidence ratios and absolute excess risks for the first-reported cancer sites

Cancer Site	Women (186,745 Person-Years)				
	obs	exp	SIR	95% CI	AER
All malignancies	1705	723.9	2.36	2.25-2.47^c	52.5
Breast	1264	258.0	4.88	4.62-5.16 ^c	53.8
Without breast cancer index	794	246.5	3.22	3.00-3.45 ^c	32.5
Female genital organs, combined	77	90.2	0.85	0.67-1.07	-0.7
Vulva	5	4.1	1.23	0.40-2.87	0.1
Cervix/uterus	39	83.8	0.47	0.33-0.64 ^c	-2.4
Ovarian	33	33.2	0.99	0.68-1.40	-0.0
Urinary tract, combined	27	33.5	0.81	0.53-1.17	-0.4
Bladder	9	17.9	0.50	0.23-0.96 ^a	-0.5
Kidney	18	13.1	1.37	0.83-2.17	0.2
Digestive organs, combined	135	146.0	0.93	0.78-1.09	-0.6
Esophagus	5	5.9	0.85	0.27-1.97	-0.1
Stomach	11	15.5	0.71	0.35-1.27	-0.2
Pancreatic	18	15.1	1.19	0.71-1.88	0.2
Liver	9	2.1	4.30	1.97-8.16 ^c	0.3
Gallbladder and bile ducts	3	7.8	0.38	0.08-1.12	-0.3
Colorectal	89	62.2	1.43	1.14-1.76 ^b	1.4
Hematological cancers	67	50.7	1.32	1.02-1.67^a	0.9
Brain	15	8.7	1.73	0.97-2.85	0.3
Head and neck	9	13.7	0.66	0.30-1.24	-0.3
Thyroid	5	6.2	0.80	0.26-1.87	-0.1
Lung	42	54.8	0.77	0.55-1.04	-0.7
Bone	4	1.3	2.98	0.81-7.64	0.1
Sarcoma	8	4.7	1.71	0.74-3.36	0.2
Melanoma	24	31.8	0.75	0.48-1.12	-0.4
Unknown	28	21.0	1.34	0.89-1.93	0.4

SIR was calculated by dividing the number of observed events by the number of expected events over the total number of person-years at risk. AER was calculated by subtracting the expected number of cases from the number observed and dividing by person-years at risk (expressed per 10,000 person-years). Breast cancer analysis without BC-index was based on 168,418 person-years. When applicable, the combined sum of the reported organs within a system has been reported in bold.

AER, absolute excess risk; exp, expected; Obs, observed; SIR, standardized incidence ratios.

^aP value < .05.

^bP value < .01.

^cP value < .001.

Discussion

This is the largest study to date to investigate cancer risk for breast cancer and other cancers in *CHEK2* c.1100delC families using pedigree information. Contrary to a previous

Dutch study conducted in 67 *CHEK2* c.1100delC families,¹⁵ we found that colorectal, hematological, and liver cancers were more often found in women from these families than expected based on cancer incidence rates in the general population. Age at diagnosis for breast cancer and colorectal cancer in *CHEK2* c.1100delC relatives was younger than expected compared with the general population. Similar results were found in site-specific analysis, but additionally, an increased risk of renal cancer was found in women. However, when the analysis was restricted to known heterozygotes and their first-degree female relatives only, this increased risk of renal cancer was not replicated. Furthermore, while we showed a possible underreporting of cancer in men, we observed increased incidences for breast cancer, colorectal cancer, liver cancer, brain cancer, and bone cancer. In our analysis, we removed potential metastatic sites when reported as a later tumor diagnosis. We still found an increased risk of liver, bone, and brain cancer in men, and thus are unsure whether this association represents primary cancer or metastatic disease.

In this study, we found a 4- to 5-fold increased risk of breast cancer in women from *CHEK2* c.1100delC families compared with the general population. When removing the indexes with breast cancer, a 3.2-fold increased risk remained, which is in line with previous studies.¹⁶ Currently, the majority of the heterozygotes and their families are eligible for additional surveillance from age 40 years onward. However, we found a significant increased risk within these families from age 25 onward. This emphasizes the need for personalized breast cancer risk prediction and surveillance for these families.¹⁷ Also in men, we found a 4- to 5-fold increased breast cancer risk, which is in line with previous studies in which *CHEK2* c.1100delC was more often found in unselected male breast cancer patients.^{18,19}

Although results among previous studies varied,^{8,20-23} we found an increased risk of colorectal cancer in heterozygous *CHEK2* c.1100delC families compared with the general population. Attained-age analysis showed that the risk was higher than expected from the age of 45 years onward. In The Netherlands, additional colonoscopies are conducted every 5 years in individuals with an estimated lifetime risk above 10%. With a prevalence of 5% in the general Dutch population, and a SIR of 3.44 in 45 to 50 years old relatives found in these families, we expect that some *CHEK2* c.1100delC families might benefit from additional surveillance outside of the nationwide surveillance (fecal immunochemical test) starting at the age of 55. However, further research is needed to determine which individuals within these families may profit from additional colorectal surveillance.

We found an increased risk of hematological cancers in women, peaking between the ages 50 and 55 years. Although associations between hematological cancers and *CHEK2* variants have been described before,²⁴⁻²⁸ the number of patients with the *CHEK2* c.1100delC PV are small or

Table 3 Attained age at time of diagnosis for breast cancer, colorectal cancer, and hematological cancers as first-reported cancers within the *CHEK2* c.1100delC families, compared with the attained age in the general Dutch population

Attained Age	Breast Cancer					Breast Cancer (Without Hebon BC-Index)				
	obs	exp	SIR	95% CI	AER	obs	exp	SIR	95% CI	AER
25	27	1.4	19.94	13.14-29.01 ^c	18.2	13	1.6	11.22	5.97-19.18 ^c	10.0
30	64	4.7	13.58	10.46-17.34 ^c	41.3	24	4.0	6.01	3.85-8.94 ^c	16.5
35	127	10.8	11.74	9.79-13.97 ^c	80.4	61	6.3	6.53	5.00-8.39 ^c	41.3
40	163	19.1	8.54	7.28-9.96 ^c	101.3	80	16.7	4.80	3.80-5.97 ^c	50.4
45	187	29.8	6.28	5.41-7.25 ^c	116.4	105	26.9	3.91	3.20-4.73 ^c	63.3
50	251	33.8	7.42	6.53-8.39 ^c	177.2	167	31.5	5.30	4.53-6.17 ^c	117.1
55	163	32.2	5.06	4.31-5.90 ^c	115.8	111	30.8	3.60	2.96-4.34 ^c	73.6
60	84	34.6	2.43	1.94-3.01 ^c	48.2	62	33.7	1.84	1.41-2.36 ^c	28.2
65	67	35.3	1.90	1.47-2.41 ^c	34.5	50	34.9	1.43	1.06-1.89 ^c	16.7
70	64	32.6	1.97	1.51-2.51 ^c	39.4	57	32.4	1.76	1.33-2.28 ^c	31.0
75	65	25.1	2.59	2.00-3.30 ^c	55.5	63	25.1	2.51	1.93-3.21 ^c	52.9

Attained Age	Colorectal Cancer					Hematological Cancer				
	obs	exp	SIR	95% CI	AER	obs	exp	SIR	95% CI	AER
25	2	0.1	15.37	1.86-55.50 ^a	1.3	2	1.0	2.11	0.26-7.61	0.7
30	0	0.2	-	-	-0.2	0	1.1	0	-	-0.8
35	0	0.6	-	-	-0.4	3	1.4	2.15	0.44-6.28	1.1
40	2	1.2	1.65	0.20-5.94	0.6	5	1.8	2.78	0.90-6.49	2.3
45	7	2.0	3.44	1.38-7.08 ^b	3.7	6	2.5	2.44	0.90-5.32	2.6
50	5	3.6	1.38	0.45-3.213	1.1	15	3.4	4.41	2.47-7.27 ^c	9.5
55	9	5.6	1.60	0.73-3.03	3.0	9	4.3	2.09	0.96-3.97	4.2
60	34	8.2	4.17	2.89-5.83 ^c	25.2	6	5.8	1.04	0.38-2.26	0.2
65	11	10.7	1.03	0.51-1.84	0.3	7	7.2	0.97	0.39-1.99	-0.3
70	8	13.4	0.60	0.26-1.17	-6.8	4	9.0	0.45	0.12-1.14	-6.2
75	11	6.14	0.67	0.34-1.20	-7.4	7	10.2	0.69	0.28-1.41	-4.5

SIR was calculated by dividing the number of observed events by the number of expected events over the total number of person-years at risk. AER was calculated by subtracting the expected number of cases from the number observed and dividing by person-years at risk (expressed per 10,000 person-years). Six relatives were diagnosed with breast cancer before the age of 25, 1 relative (excluding the Hebon breast cancer index) was diagnosed with breast cancer before the age of 25, and 3 relatives were diagnosed with hematological cancers before the age of 25 and were therefore not included in this overview.

AER, absolute excess risk; exp, expected; Obs, observed; SIR, standardized incidence ratios.

^aP value < .05.

^bP value < .01.

^cP value < .001.

lacking. Therefore, further research using pathological confirmed hematological cancer patients could help shed light on this possible association.

In the site-specific analysis, we found a statistically significant increased risk of renal cancer in women, peaking between the ages 35 and 45. Previous studies also reported an increased risk of renal cancer.^{3,10,29} Although some studies focused on only women, others did not provide risks for men and women separately. This might be a consequence of *CHEK2* c.1100delC more often being tested in women than in men. Thus, the number of male heterozygotes in studies is relatively small. Furthermore, within our study, we predominantly had genetic status for women.

This study concerns a pedigree-based investigation that evaluated cancer risks for sites other than breast associated with *CHEK2* c.1100delC on a large scale. In The Netherlands, general population cancer (incidence rates) data are available from 1970 onward, allowing us to compare with national data for a long period of time. However, using pedigree information also has some limitations. First, as we collected data from clinical genetics

centers, we put together an enriched study population of *CHEK2* c.1100delC-associated breast cancer families and therefore might overestimate cancer risks. However, within our study, we checked for potential oversampling of families with increased risks of renal (I. van Beek, personal communication, November 30, 2023), prostate,³⁰⁻³² and colorectal cancer²⁰ because the association with these specific cancer types was studied in some centers before. However, we did not find evidence for an overrepresentation in our study because we made sure that these families were tested and counseled in the context of an increased risk of breast cancer. Therefore, we assume that there is no selection bias in the collection of these families.

Second, studies have shown that there is a multiplicative effect between family history and *CHEK2* c.1100delC on cancer occurrence.^{1,10,33-36} Because we selected families with a history of breast cancer, this may explain why we did not find an increased risk of other associated cancer sites, specifically male cancers, such as prostate cancer.^{3,37}

Third, there is a degree of uncertainty in the cancer types and in some dates of birth and diagnosis of relatives. We have

no pathological confirmation for 61.9% of the reported cancers, especially for (more) distant relatives. Furthermore, the exact year of birth was unknown for one third of the relatives, and year of diagnosis was unknown for 14% of the cancers. We carefully corrected for this by imputing missing dates and correcting for possible metastatic disease in the reported cancers per individual, however, some bias may be introduced. For example, while we assume that this was the best approach to ensure that we excluded metastatic disease, this approach may have resulted in an underestimation of these cancer site risks. Still, we found increased risks of liver, bone, and brain cancer within these families, it is unconfirmed whether these were primary cancers. This underlines the importance of availability of pathological confirmation of cancer sites to further study cancer risk for these sites within *CHEK2* c.1100delC families.

Fourth, although all included families tested positive for *CHEK2* c.1100delC, we cannot rule out that there are other PVs present within these families. Genetic testing changed over time. From 2014 until 2016, the breast cancer gene panel in The Netherlands included only *BRCA1*, *BRCA2*, and *CHEK2* c.1100delC. Since then, more genes were gradually added, including the complete *CHEK2* gene from 2018 onward. To date, the most frequently found *CHEK2* variant in The Netherlands is c.1100delC. Furthermore, once an index patient tested positive for a PV, healthy relatives were consequently invited to be (presymptomatic) tested only for that specific variant in most centers. In our study, 61.4% of the families were first tested for the c.1100delC before 2018 and were therefore likely only tested for this variant. Even though we excluded all families in which other cancer-associated genetic variants were found, we cannot guarantee that there are no other variants than *CHEK2* c.1100delC present within these families, although chances are small.

In conclusion, female relatives from *CHEK2* c.1100delC families have an increased cancer risk for other sites in addition to breast cancer, including colorectal and hematological cancers, starting at a younger age than expected in the general population. When analyzing all sites reported in addition to only the first reported cancers, we also found an increased risk for renal cancer. Our results suggest that some *CHEK2* families might benefit from colorectal cancer surveillance as well; however, further research is needed to determine which individuals may profit for additional colorectal surveillance.

Data Availability

We have established a cohort of which multiple layers of data allow for integrative analysis. The Hebon study collaborators will continue to collect data and include women from families with an increased risk of breast cancer and/or ovary cancer. We encourage collaborations with researchers, who can apply for data by submitting a proposal to Hebon (hebon@nki.nl). All proposals will be reviewed on scientific quality and methodology by the Hebon steering committee.

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Ethics Declaration

Hebon has a formal collaboration between all clinical genetics centers of the University medical centers and The Netherlands Cancer Institute. In addition, the updated Hebon study was approved by the institutional research board of The Netherlands Cancer Institute (19.221/IRBd19043) and medical ethical committee of the Maastricht UMC (11-4-089/2019-1388) and Erasmus MC (MEC-2011-471, amendment 2019). As part of the inclusion to the Hebon study, the women signed an (online) informed consent.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

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