

**Table 1 s. Characteristics of the studies and distribution of CHEK2\*1100delC genotype in breast cancer cases with two primary breast cancers and controls**

Study	Characteristics of cases with two primary breast cancers	Characteristics of controls	1100delC
BBC. Population-based, UK (12)	Ascertained through the English & Scottish Cancer Registries. 1 <sup>st</sup> primary dx <age 65 in 1971 or later <sup>1</sup> Age range: 26-65 Ethnicity: British Caucasian BRCA1/2 screened: No	i) Friends and non-blood relatives of cases N=160 ii) Cohort of healthy women participating in an RCT of mammographic screening. N=477 Age range: i) 24-81, ii) 46-52 Ethnicity: British Caucasian	Ca 11/583 (1.9%) Co i) 0/160 ii) 4/477 All 4/637 (0.6%) OR=3.04 (0.89-13.17)
ICR_FBC. Ascertained through cancer genetics clinics, UK (3)	Selected on FH of ≥1 affected relative with breast or ovarian cancer. Age range: 18-80 Ethnicity: 97% British Caucasian	Random sample from the 1958 Birth Cohort Collection. Females born in Britain between 01/01/1958 and 31/12/1958. Age range: All age 48	Ca 10/321 (3.1%) Co 6/1027 (0.6%) OR=5.47 (1.78-18.43)

	BRCA1/2 screened: 281/321	Ethnicity: British Caucasians	
HEBCS. Hospital-based, Helsinki, Finland (13)	i) Selected on FH of i) $\geq 2$ breast or ovarian cancers in 1 <sup>st</sup> or 2 <sup>nd</sup> degree relatives N=38 ii) $\geq 1$ breast or ovarian cancer in 1 <sup>st</sup> degree relatives N=41 ii) Additional cases not selected on FH N=65 Age range: 16-87 Ethnicity: Finnish Caucasian BRCA1/2 screened: 113/144	Healthy population controls from the Finnish Red Cross Blood Transfusion Service. Age range: 18-65 Ethnicity: Finnish Caucasian	Ca 10/144 (6.9%) Co 26/1885 (1.4%)  OR=5.34 (2.24-11.71)
Rotterdam. Ascertained through clinical genetics centre, Rotterdam, Southwest Netherlands. (2) & (14)	i) 112 cases with $\geq 2$ cases of female breast cancer in 1 <sup>st</sup> or 2 <sup>nd</sup> degree relatives, of which 1 $\geq$ case dx < age 60 ii) 33 additional bilateral cases, 28/33 dx age < 60 Age range: 23-81 Ethnicity: Caucasian BRCA1/2 screened: Yes	i) Spouses of individuals heterozygous for cystic fibrosis, ascertained through the clinical genetics centre Rotterdam, N=184 ii) Population based controls age > 55 years, N=460 iii) blood donors, N=265 Age range: N/A Ethnicity: 97% Caucasian	Ca 15/144 (10.4%) Co i) 3/184 ii) 6/460 iii) 0/265 All 9/909 (1.0%)  OR=11.62 (4.64-30.67)
ABCS. Hospital-based, Amsterdam & Leiden,	Majority (245/247) cases dx < age 50. Bilateral cases were those who developed a second primary > 1 year after the first primary.	Controls from Southwest Netherlands, as above <sup>3</sup>	Ca 15/247 (6.1%) Co i) 3/184 ii) 6/460

Netherlands (15) & (16)	Age range: 22-63 Ethnicity: 95% Caucasian BRCA1/2 screened: Yes <sup>2</sup>		iii) 0/265 All 9/909 (1.0%)  OR=6.47 (2.61-16.94)
HBBCS. Hospital-based, Hannover, Germany (17)	Cases received radiotherapy for breast cancer at Hannover Medical School Age range: 27-83 Ethnicity: Caucasian BRCA1/2 screened: Yes	Anonymous random blood donors at Hannover Medical School Age range: 18-68 Ethnicity: Caucasian	Ca 0/138 (0.0%) Co 1/500 (0.2%)  OR=0.0 (0.0 – 140.8)
St Petersburg. Hospital-based, St Petersburg, Russia (18)	Consecutive bilateral breast cancer cases dx at the NN Petrov Institute of Oncology between 1984-2004. Age range: 26-85 Ethnicity: Caucasian BRCA1/2 screened: Yes <sup>4</sup>	i) Healthy female blood donors N=356 ii) hospital controls from St Petersburg City Hospital N=92 iii) Elderly tumour free women from general hospitals in St Petersburg N=373 Age range: i) 18-54, ii) 55-74 iii)75-96 Ethnicity: Caucasian	Ca 8/145 (5.5%) Co i) 1/356 ii) 0/92 iii) 0/373 All 1/821 (0.1%)  OR=47.88 (6.30-2126.8)
i) GENICA. Population-based, Greater Bonn, Germany	i) GENICA study (N=17) ii) a cohort of cases diagnosed at the Städtisches Klinikum Karlsruhe (SKK) (N=89). Age range: 29-89	i) GENICA - population-based controls from Greater Bonn, North Rhine-Westphalia, Germany. Matched to cases by 5-year age groups and residency. N=724	Ca 2/106 (1.9%) Co i) 6/651 ii) 0/600 All 6/1251 (0.5%)

(19) (20)  ii) SKK. Hospital-based, Karlsruhe, Germany. (21)	Ethnicity: Caucasian  BRCA1/2 screened: No	ii) KORA - population-based controls from health survey in Augsburg, Bavaria, Germany. Matched to cases by 5-year age groups. N=600 Age range 24-80, Ethnicity: Caucasian	OR=3.99 (0.39-22.64)
Pooled data (Bilateral)			6.43 (4.33-9.56)

**Footnotes:** FH family history, dx diagnosed, N/A not available.

<sup>1</sup> 72/583 (12.3%) of the cases in the BBC were asynchronous ipsilateral cases whose second primary was registered as a new primary by the pathologist and the registry. The proportion of carriers of CHEK2\*1100delC in this group was 2/72 (2.8%) compared to 9/511 (1.8%) in bilateral cases from this study.

<sup>2</sup> Cases were screened for the BRCA1 & BRCA2 mutations found most frequently in the Dutch population (~70% of all BRCA mutations) (16).

<sup>3</sup> No independent controls were screened as part of the ABCS study. As both studies are based in Southwest Netherlands, the 909 controls from the Rotterdam study was used as a comparison group for the ABCS case series. The ABCS and Rotterdam data were analysed as a single study with 391 cases and 909 controls in the pooled analysis.

<sup>4</sup> Cases were screened for BRCA1 5382insC (26)