BRCA2 polymorphic stop codon K3326X and the risk of breast, prostate and ovarian cancers from the iCOGS collaborative study.

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ABSTRACT

Background: The K3326X variant in *BRCA2* (*BRCA2**c.9976A>T; p.Lys3326*; rs11571833) has been found to be associated with small increased risks of breast cancer and other cancers such as lung and upper aero-digestive tract in recent studies. However, it is not clear to what extent linkage disequilibrium with fully pathogenic mutations might account for this association. There is scant information about the effect of K3326X in other hormone-related cancers.

Methods: Using weighted logistic regression, we analyzed data from the large iCOGS study including 76,637 cancer cases and 83,796 controls to estimate the association of K3326X with breast, ovarian, and prostate cancer risks independent of known pathogenic variants. Using Cox proportional hazards modeling, we also examined the associations of K3326X with breast and ovarian cancer risks among 7,183 *BRCA1* variant carriers.

Results: The K3326X variant was associated with breast (OR=1.28; 95% CI: 1.17-1.40; $p=4.6x10^{-6}$) and invasive ovarian cancer (OR=1.26; 95% CI: 1.10-1.43; $p=4.0x10^{-3}$). These associations were stronger for serous ovarian cancer and for estrogen receptor-negative breast cancer (OR=1.46; 95%CI: 1.25-1.70; $p=3.7x10^{-5}$ and OR=1.50; 95% CI: 1.27-1.75; $p = 2.4x10^{-5}$, respectively). For *BRCA1* mutation carriers, there was a significant inverse association of the K3326X variant with risk of ovarian cancer but no association with breast cancer. No association with prostate cancer was observed.

Conclusions: Our study provides evidence that the K3326X variant is associated with risk of developing breast and ovarian cancers independent of other pathogenic variants in BRCA2. Further studies are needed to determine the biological mechanism of action responsible for these associations.

INTRODUCTION

Inheritance of a pathogenic variant in *BRCA2* is one of the strongest risk factors for breast and ovarian cancers [1-4]. Estimates of the cumulative risk by age 70 years in *BRCA2* variant carriers are 45% for breast cancer and 11% for ovarian cancer [5, 6]. *BRCA2* variants have also been shown to increase risk of prostate cancer [7-9], with the lifetime risk of prostate cancer in *BRCA2* variant carriers estimated in the range of 19% - 34% [9]. In some studies, carriers of *BRCA2* pathogenic variants also had increased risks of several other cancers, including pancreatic cancer [7, 8, 10, 11], stomach cancer, and malignant melanoma [7].

*BRCA*2*c.9976A>T; p.Lys3326*, hereafter referred to as K3326X, is a stop-gain variant in the coding region of *BRCA2*. It arises from a substitution of thymidine for adenine at nucleotide 9976 of the *BRCA2* coding sequence, and results in loss of the final 93 amino acids of the BRCA2 protein. This premature stop codon was first described in 1996 by Mazoyer et al. [12] who found a minor allele frequency of about 1% in the control population and no increased prevalence of this sequence variant in patients with breast cancer, although the study was small, with 462 controls and 513 cases. The K3326X variant has been identified through linkage disequilibrium (LD) in individuals with various types of cancers, either alone or in combination with known pathogenic variants in *BRCA2* [13-15]. Recent genome-wide association studies have identified the association between the K3326X variant and risk of squamous-cell lung cancer [16] and breast cancer [17] at genome-wide significance levels, with odds ratios of 2.47 ($P = 4.7x10^{-20}$) and 1.26 ($P = 4.9x10^{-8}$), respectively. Recently, a large pooled case-control study of cancers of the upper aero-digestive tract (UADT, including esophageal cancer) and the K3326X variant found that the K3326X variant was associated with UADT cancers (OR = 2.53;

95% CI: 1.89-3.38) [18] as well, with a particularly strong effect for esophageal cancer (OR = 3.30; $p = 3x10^{-4}$).

K3326X is in LD with the pathogenic variants *BRCA*2*c.6275_6276delTT (formerly reported as 6503-6504delTT) [12, 14] and *BRCA*2*c.9257-16T>C (formerly reported as IVS 24-17T>C) [19]. It is unclear therefore to what extent the association of the K3326X variant with cancer is due to its own functional impact or because it is in LD with other *BRCA2* pathogenic variants. In this study, we therefore analyzed the association of the *BRCA2* K3326X sequence variant with respect to risk of breast cancer independently from its association with known *BRCA2* pathogenic variants, and for the first time examined the association between K3326X and ovarian and prostate cancer. We further assessed whether K3326X is an independent modifier of breast, and ovarian cancer risk in *BRCA1* pathogenic variant carriers.

METHODS

This study used data from the four consortia within the Collaborative Oncological Gene-Environment Study (COGS): the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), the Breast Cancer Association Consortium (BCAC), the Ovarian Cancer Association Consortium (OCAC), and the PRostate cancer AssoCiation group To Investigate Cancer Associated aLterations in the genome (PRACTICAL). The COGS central focus was using data from high throughput genotyping of large epidemiological studies, with state-of-the-art analysis and mathematical models to combine data on genetic and environmental/life style risk factors [20]. Details on the numbers of participants in each consortium are shown in **Table 1**. To validate the effect of the *BRCA2* K3326X variant on ovarian cancer risk, we sequenced the *BRCA2* gene in an independent sample of ovarian cancer cases and controls.

Statistical methods:

Fisher's exact statistics were calculated to assess associations between the K3326X variant and known *BRCA2* pathogenic variants among study subjects in CIMBA. Using the datasets from the BCAC, OCAC, and PRACTICAL consortia, we evaluated the association of the *BRCA2* K3326X variant with risks of breast, invasive ovarian, and prostate cancer, respectively, through logistic regression models with adjustment for attained age, consortium study site, and principal components of population structure. To examine the hypothesis that K3326X is associated with breast and ovarian cancers independently from *BRCA2* pathogenic variants, we calculated and compared odds ratios using weighted logistic regression models (i.e., OR_w), described below, and odds ratios using un-weighted logistic regression models (i.e., OR) using Wald Z-statistics. Because of the lack of *BRCA2* status in the BCAC and OCAC datasets, to account for possible LD with *BRCA2* pathogenic variants, we developed a model using the CIMBA dataset to predict whether cases and controls were carriers of pathogenic *BRCA2* variants based on age at diagnosis (for cases) and age at interview (for controls) and carrier status at K3326X. We then used this model to predict the probability of not having a pathogenic *BRCA2* variant in the other datasets and used this as the weight in the logistic regression model. This weight allowed us to adjust for the contribution of each patient to the test statistics based on their probability of not having a pathogenic *BRCA2* variant. Details of the calculation of these weights are shown in the Appendix. The association of the K3326X variant with breast cancer risk by ER status, triple-negative status, and tumor morphology, specifically ductal and lobular, were estimated using a similar approach but restricting the case samples to ER+, ER-, triple-negative (ER, PR, and HER2 negative), ductal, and lobular, respectively. The association of the K3326X variant with ovarian cancer risk by histological subtypes of ovarian cancer, specifically

serous, mucinous, endometrioid, and clear cell, were estimated by restricting the case samples to these respective histologies. We also examined differences between the odds ratio estimates using Z-statistics to determine whether or not the magnitude of the associations between the K3326X variant and breast cancer risk were statistically different across breast and ovarian cancer subtypes. Using the datasets from the CIMBA consortium and Cox proportional hazards model, we examined the associations of the K3326X variant with breast and ovarian cancer risks for BRCA1 pathogenic variant carriers with censoring as defined in other CIMBA consortium analyses of data from the iCOGS study [21]. To account for the inclusion of multiple carriers from the same family, a robust variance approach clustering on family membership was used [22]. Statistical analyses were performed in R (version 2.14.2) [23]. All statistical tests were two sided.

Homology directed repair (HDR) assay:

The HDR assay for BRCA2 has been described previously by Guidugli et al (2013) [24]. Full-length Flag-BRCA2 wild-type and mutant expression constructs were co-transfected with an I-Sce1 expressing pcBASce plasmid into BRCA2 deficient V-C8 cells, stably expressing the DR-GFP reporter plasmid. HDR-dependent DNA double strand break was quantified by fluorescence-activated cell sorting (FACS) of GFP positive cells after 72 hours. Equivalent expression of wild-type and mutant BRCA2 proteins was confirmed by western blot analysis of anti-Flag-M2 (Sigma F1804) antibody immunoprecipitates from V-C8 cell lysates.

RESULTS

Table 2 shows the frequencies of the two most frequent *BRCA2* pathogenic variants (c.6275_6276delTT and c.4889C>G) among K3326X variant carriers in CIMBA. The

c.6275_6276delTT known pathogenic variant was identified in 233/306 K3326X variant carrier families carrying the K3326X variant and in 5/4795 K3326X variant non-carrier families, and c.4889C>G was observed in 9/306 K3326X variant positive families and 0/4795 K3326X variant non-carrier families. The list and frequency of all pathogenic variants in the *BRCA2* gene that co-occurred with the K3326X variant in CIMBA are shown in Supplemental Table 1. Within the BCAC dataset, among K3326X variant carriers, 1471 of 1490 individuals also harbored the *BRCA2**c.9257-16T>C variant, which was not considered pathogenic based on the low likelihood for splice site alteration [13]. Within the OCAC dataset, among K3326X variant carriers, all K3326X variant carriers also carried the *BRCA2**c.9257-16T>C variant. Within the independently sequenced set of ovarian cancer cases and controls, 2240 ovarian cancer cases and 1530 controls were included. Twenty-seven K3326X carriers were found in the controls compared to 48 in the cases (OR = 1.23 (95% CI: 0.7-2.0)) and three of these carriers (all cases) also carried the BRCA2*c.6275_6276delTT pathogenic variant. Functional analyses showed that the K3326X variant had only a slight reduction in DNA repair compared to wild-type and significantly different compared to the known pathogenic BRCA2 variants.

Association between the K3326X variant and breast cancer risk in BCAC and CIMBA:

Previous principal component analyses of these data derived six components used as adjustments for population structure in logistic regression models [17]. The analyses of K3326X and breast cancer are shown in Table 3. Of note, the odds ratios adjusted for potential LD with known pathogenic *BRCA2* variants were only slightly attenuated (e.g. from 1.31 to 1.28 for all invasive breast cancer). The weighted odds ratios were statistically different between ER- and ER+ breast cancer data subsets ($p = 0.03$) but not between triple negative and ER+ breast cancer data subsets ($p = 0.22$) (data not shown). There was no evidence that K3326X was associated

with lobular breast cancer (p = 0.69), but the sample size of lobular breast cancer cases among the K3326X variant carriers was relatively small (n = 67), and the association between K3326X and breast cancer was not statistically different between participants with ductal and lobular tumors (p = 0.13). No association with breast cancer risk for *BRCA1* pathogenic variant carriers was observed (HR = 1.00; 95% CI: 0.78, 1.29).

Association between the K3326X variant and ovarian cancer risk:

Previous principal component analyses derived five components used as adjustments for population structure in logistic regression models [25]. Adjusted weighted and unweighted ORs by histologic subtype of ovarian cancer are presented in Table 4. The K3326X variant was present in 323 of 14542 individuals (2.22%) with invasive ovarian cancer (OR = 1.29 (95% CI: 1.13, 1.46); OR_w = 1.26 (95% CI: 1.10-1.43)) compared to 1.78% of controls. A significant association of K3326X was observed with serous ovarian cancer (OR_w = 1.46; 95% CI: 1.25-1.70). However, little evidence was seen for an association of K3326X with non-serous ovarian cancer, although the sample size of such cancer cases among the K3326X variant carriers was small (n = 60). In contrast, among *BRCA1* carriers, a significant *decreased* risk for K3326X variant carriers versus non-carriers was observed (HR = 0.43; 95% CI: 0.22-0.84).

Association between the K3326X variant and prostate cancer risk:

Previous principal component analyses derived six components used as adjustments for population structure in logistic regression models [26]. The K3326X variant was present in 358 of 21,014 cases (1.70%) compared to 364 of 21,992 controls (1.66%) (OR = 0.92 (95% CI: 0.77-1.09); OR_w = 0.90 (95% CI: 0.76-1.07)). We estimated that this study had 87.6% power to detect

an odds ratio of 1.25 using a two-sided test, assuming that 1.7% of the population are K3326X carriers.

DISCUSSION

In this study, we confirmed that the *BRCA2* K3326X variant is associated with increased risk of breast cancer independent of additional *BRCA2* pathogenic variants and demonstrated an even stronger association with serous ovarian cancer. These results suggest a role for the K3326X variant in both breast and ovarian cancers etiology but not in prostate cancer etiology.

The prevalence of K3326X in control populations (1.7%) is consistent with the observed allele frequency of the K3326X variant in the European population reported by the International HapMap Consortium [27]. More recent data [Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: http://exac.broadinstitute.org) [accessed February, 2015)] found the variant in 609/33,749 (1.8%) non-Finnish European sequenced individuals and a carrier frequency of 2.4% in Finland. In our study, most K3326X carriers also carried the *BRCA2**c9257-16T>C variant, which is also consistent with previous studies [13, 19]. However, most individuals with *BRCA2* pathogenic variants do not carry the K3326X variant, with the exception of individuals with c.6275_6276delTT and c.4889C>G variants (**Table 2**).

The odds ratios obtained from unweighted logistic regression and weighted logistic regression were similar, suggesting that K3326X is associated with the risk of developing breast and ovarian cancers independently from *BRCA2* known pathogenic variants (**Table 3 and 4)**. The association of the K3326X variant with cancer risk was strongest in patients with triple negative breast and serous ovarian tumors (OR = 1.51 (95% CI: 1.18, 1.92) and 1.46 (95% CI: 1.25, 1.70), respectively). Our results, together with evidence of molecular commonalities

between triple negative breast and high-grade serous ovarian tumors [28], suggest a possible related etiology between these two tumor subtypes.

The K3326X variant was associated with the risk of ER- and triple-negative breast cancer by a greater magnitude than with the risk of ER+ breast cancer (**Table 3**). This association was more significant in participants with ER- than in those with ER+ tumors ($p = 0.03$). We did not detect a significant difference between the association of the K3326X variant in participants with triple negative and ER+ tumors ($p = 0.22$), but the number of participants carrying the K3326X variant among triple negative tumors was small ($n = 53$). ER negative and triple negative status has been linked to *BRCA1* variants but not *BRCA2* variants. *BRCA1*-related breast cancers are more likely to be ER- than are non-*BRCA1*-related breast cancers and *BRCA2*-related breast cancers [29, 30]. Most *BRCA1*-related breast cancers are also progesterone receptor (PR) and human epidermal growth factor receptor (HER) 2 negative (i.e. triple-negative) [29, 31-36]. Because of these findings, *BRCA1* tumors were hypothesized to have a different hormone-independent mechanism than *BRCA2* tumors [34]. Further studies are needed to understand the association of the K3326X variant on breast cancer risk in individuals with ER- and ER+ tumors.

Women carrying the K3326X variant had significantly higher risk of ovarian cancer. This association was shown in both the OCAC dataset and the full sequenced dataset; however, the independently sequenced set is too small to provide reliable odds ratio. The K3326X variant was significantly associated with risk of serous ovarian cancer but not mucinous, endometrioid, or clear cell ovarian cancer (**Table 4**). This finding is consistent with epidemiological and genetic data showing that serous tumors have a different etiology from other ovarian carcinomas [37-39]. It is of interest that the associations of K3326X with cancer risks were stronger in ER- breast cancer and in serous ovarian cancer, both of which are associated with *BRCA1* pathogenic

variants, while breast tumors of *BRCA2* pathogenic variants carriers tend to be ER+ breast cancers [34].

Our study also provides other interesting findings that warrant further investigation. First, the K3326X variant is associated with increased risks of breast and ovarian cancer in the general population; however, in *BRCA1* variant carriers, the K3326X variant is inversely associated with risk of ovarian cancer and not with risk of breast cancer. Second, our study found no association between the K3326X variant and prostate cancer risk, in contrast to the increased risk of prostate cancer in carriers of *BRCA2* pathogenic variants [44-47]. The difference between the risk associations of K3326X and known *BRCA2* pathogenic variants has been observed previously. Wang et al (2014) reported a more than two-fold increased squamous-cell lung carcinoma risk in K3326X variant carriers [16]; however, to date, there has been no evidence of any altered risk of lung cancer in families carrying *BRCA2* pathogenic variants [8, 40, 41]. Additional studies are required to analyze the discrepant risk associations of the K3326X variant and other known *BRCA2* pathogenic variants with prostate and lung cancer risks and whether the K3326X variant may have an association with cancer risk independent of other genes. In contrast to lung cancer, there have been some reports of carriers of *BRCA2* pathogenic variants having increased risk of some UADT cancers [40, 41].

We can only speculate about how K3326X might affect key functions of the BRCA2 protein. Fanconi anemia is an autosomal recessive disease characterized by cancer susceptibility, cellular hypersensitivity to DNA cross-linking agents, and other conditions [42]. *FANCD2* encodes the protein for Fanconi anemia group D2, and is monoubiquitinated in response to DNA damage [43]. Interaction of monoubiquitinated *FANCD2* and *BRCA2* is essential for activation of the homologous recombination activity of *RAD51*, an important enzyme involved in DNA

repair mechanisms, and for loading onto the damaged DNA [44-49]. Cells that express *BRCA2* protein lacking the C terminal exon 27 coding region do not show co-localization of *FANCD2*, *BRCA2*, and *RAD51* on chromatin [44, 49]; mice with deletions of exon 27 and *FANCD2* knockout mice had increased susceptibility to various types of cancers [50]. We hypothesize that the K3326X variant modifies breast and ovarian cancer risk by altering the C terminus of *BRCA2*, resulting in loss of the interaction between FANCD2 and BRCA2 and thus, inactivating *RAD51*. However, in the functional assay testing the ability of various *BRCA2* cell constructs to repair double-strand DNA breaks by homologous recombination, there was a slight reduction in DNA repair activity for the K3326X variant compared to the wild-type and quite distinct from the known pathogenic BRCA2 variants. Additional functional analyses on the K3326X variant are needed to demonstrate the role of the K3326X variant on the BRCA2 protein.

Our study is the largest study to date examining the association of the *BRCA2* K3326X variant and breast, ovarian, and prostate cancer risks. The large sample size and the use of weighted logistic regression models allowed us to estimate the underlying association of K3326X with cancer risk independent of known *BRCA2* pathogenic variants. A limitation of our analysis was the lack of *BRCA2* status in the BCAC and OCAC datasets resulting in our use of the CIMBA *BRCA2* dataset to calculate the probability of *BRCA2* in order to create weights for the logistic regression models. As shown in tables 3 and 4, the effect of LD between K3326X and two *BRCA2* pathogenic variants (i.e. c.6275_6276delTT and c.4889C>G) was quite small and did not materially change the results.

In conclusion, our study provides evidence that the *BRCA2**c.9976A>T (K3326X) variant contributes to the risk of developing breast and ovarian cancers. It remains open whether the underlying mechanism for this association is identical to that for lung and UADT cancers; it

is unlikely that this question can be resolved using genetic data alone. Additional functional studies will be needed to determine the biological mechanism of action of the K3326X variant in the diverse set of cancers associated with it.

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Table 1: Number of controls and breast cancer (BC), ovarian cancer (OC) and prostate cancer (PC) cases included in the analysis.

Study	**Included in the Analysis**
CIMBA (The Consortium of Investigators of Modifiers of BRCA1/2) **[51]**	- 7183 *BRCA1* mutation carriers, of which 1658 were unaffected, 2497 were breast cancer cases, 543 were ovarian cancer cases, and 267 had both breast and ovarian cancer. - 5101 *BRCA2* mutation carriers, of which 2183 were unaffected, 2538 were breast cancer cases, 240 were ovarian cancer cases, and 140 had both breast and ovarian cancer.
BCAC (Breast Cancer Association Consortium) **[52]**	41081 breast cancer cases and 38693 female controls
OCAC (Ovarian Cancer Association Consortium) **[53]**	14542 invasive ovarian cancer cases and 23111 female controls
PRACTICAL (Prostate cancer AssoCiation group To Investigate Cancer Associated aLterations in the genome) **[54]**	21014 prostate cancer cases and 21992 male controls

Table 2: Frequencies of the two most frequent *BRCA2* pathogenic variants that co-occurred with the K3326X common variant in CIMBA.

HGVS Nomenclature	***BRCA2* K3326X non-carriers**	***BRCA2* K3326X carriers**	
c.6275_6276delTT	5	233	$p < 0.001$[1]
c.4889C>G	0	9	$p < 0.001$[1]
Other *BRCA2* known pathogenic variants[2]	4790	64	Reference

[1]P-values from Fisher's exact tests calculated to assess the association between the K3326X variant and known *BRCA2* pathogenic variants. Each family in CIMBA was counted only once in this analysis.

[2]Listed in Supplementary Table 1.

Table 3: Association between *BRCA2* K3326X variant and risk of breast cancer by tumor subtypes; 38693 controls, of which 637 were K3326X carriers; Breast Cancer Association Consortium.

Subtypes	**Number of cases**	**Number of K3326X carriers in cases**	**OR (95% CI)[1]**	**P-values for OR**	**Weighted OR_w (95% CI)[1,2]**	**P-values for OR_w**
All invasive	41081	852	1.31 (1.20, 1.43)	$6.05x10^{-7}$	1.28 (1.17, 1.40)	$4.55x10^{-6}$
ER-	6441	158	1.54 (1.31, 1.79)	$5.07x10^{-6}$	1.50 (1.27, 1.75)	$2.44\ x10^{-5}$
ER+	24833	501	1.28 (1.15, 1.42)	$8.50x10^{-5}$	1.25 (1.13, 1.36)	$3.45x10^{-4}$
Triple Negative	2158	53	1.55 (1.22, 1.96)	$2.45x10^{-3}$	1.51 (1.18, 1.92)	$4.45x10^{-3}$
Ductal	21490	466	1.33 (1.20, 1.48)	$3.38x10^{-6}$	1.30 (1.17, 1.44)	$1.77x10^{-5}$
Lobular	3752	67	1.07 (0.87, 1.32)	0.57	1.05 (0.85, 1.29)	0.69

[1]Adjusted for attained age (at interview for controls and at diagnosis for cases), principal components of European population structure, and study site.

[2]Calculated using weighted logistic regression models. The weight applied for the i^{th} individual in the BCAC dataset is (1 - Probability of K3326X carriage and harboring known pathogenic variants in *BRCA2*)

Table 4: Association between *BRCA2* K3326X variant and risk of ovarian cancer by histological subtype; 23111 controls, of which 411 were K3326X variant carriers; Ovarian Cancer Association Consortium.

Subtype	**Number of cases[3]**	**Number of K3326X carriers in cases**	**OR (95% CI)[1]**	**P values for OR**	**Weighted OR_w (95% CI)[1,2]**	**P-values for OR_w**
All Invasive	14514	322	1.29 (1.13, 1.46)	$1.41x10^{-3}$	1.26 (1.10, 1.43)	$4.03x10^{-3}$
Serous	8360	210	1.50 (1.29, 1.74)	$9.21x10^{-6}$	1.46 (1.25, 1.70)	$3.66x10^{-5}$
Non-serous	4031	60	0.83 (0.65, 1.04)	0.18	0.81 (0.63, 1.02)	0.14
Mucinous	943	16	0.93 (0.59, 1.39)	0.79	0.91 (0.58, 1.37)	0.72
Endometrioid	2066	31	0.82 (0.59, 1.11)	0.31	0.81 (0.58, 1.09)	0.27
Clear Cell	1022	13	0.72 (0.44, 1.12)	0.26	0.71 (0.42, 1.10)	0.23

[1]Adjusted for attained age (at interview for controls and at diagnosis for cases), principal component of European population structure, and study site.

[2]Calculated using weighted logistic regression models. The weight applied for the k^{th} individual in the OCAC dataset is (1 - Probability of K3326X carriage and harboring known pathogenic variants in *BRCA2*)

[3]In total, 2129 cases did not have information on ovarian cancer histologic type.

APPENDIX

Calculated weights:

Probability of *BRCA2* pathogenic variant carriers also carrying the K3326X variant (i.e. P(K3326X|*BRCA2*)) was calculated using the following formula:

$$\mathrm{P}(\mathrm{K3326X}|BRCA2) = \frac{\#\ BRCA2\ carriers\ also\ harbor\ K3326X}{\#\ BRCA2\ carriers}$$

Applying the above formula to CIMBA dataset, we obtained P(K3326X|*BRCA2*) = 306/5101 = 0.060. Probability of K3326X variant carriers not harboring known pathogenic variants in *BRCA2* (i.e. P(K3326X| not *BRCA2*)) were calculated using the following formula:

$$\mathrm{P}(\mathrm{K3326X}|\mathrm{not}\ BRCA2) = \frac{\#\ BRCA2\ noncarriers\ harbor\ K3326X}{\#\ BRCA2\ noncarriers}$$

Applying the above formula to the BCAC control-only subset, we obtained P(K3326X| not *BRCA2*) = 637/38693 = 0.016. Applying the above formula to the OCAC control-only subset, we obtained P(K3326X| not *BRCA2*) = 408/23266 = 0.018. We assumed that probability of being a *BRCA2* carrier (i.e. P(*BRCA2*)) for each case and control in the BCAC and OCAC datasets was equal to the age-specific relative risk estimated by Antoniou et al (2003) based on a meta-analysis of *BRCA2* positive families identified through population-based studies of breast and ovarian cancer (Antoniou et al, 2003). Probability of K3326X carriers harboring known pathogenic variants of *BRCA2* was calculated using Bayes' theorem:

$$\mathrm{P}(BRCA2|\mathrm{K3326X})$$

$$= \frac{P(K3326X|BRCA2) * P(BRCA2)}{P(K3326X|BRCA2) * P(BRCA2) + P(K3326X|notBRCA2) * P(not\ BRCA2)}$$

The weight applied for the i[th] case in the BCAC dataset in the logistic regression model was:

$$\mathrm{w}_i = 1 - \mathrm{P}(BRCA2|\mathrm{K3326X})_i = 1 - \frac{0.060 * P(BRCA2)_i}{0.060 * P(BRCA2)_i + 0.016 * (1 - P(BRCA2)_i)}$$

The weight applied for the j[th] control in the BCAC dataset in the logistic regression model was:

$$\mathrm{w}_j = 1 - \mathrm{P}(BRCA2|\mathrm{K3326X})_j = 1 - \frac{0.940 * P(BRCA2)_j}{0.940 * P(BRCA2)_j + 0.016 * (1 - P(BRCA2)_j)}$$

The weight applied for the k[th] case in the OCAC dataset in the logistic regression model was:

$$\mathrm{w}_k = 1 - \mathrm{P}(BRCA2|\mathrm{K3326X})_k = 1 - \frac{0.060 * P(BRCA2)_k}{0.060 * P(BRCA2)_k + 0.018 * (1 - P(BRCA2)_k)}$$

The weight applied for the l[th] control in the OCAC dataset in the logistic regression model was:

$$\mathrm{w}_l = 1 - \mathrm{P}(BRCA2|\mathrm{K3326X})_l = 1 - \frac{0.940 * P(BRCA2)_l}{0.940 * P(BRCA2)_l + 0.018 * (1 - P(BRCA2)_l)}$$

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