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PRECLINICAL STUDY

Breast cancer risk in Chinese women with *BRCA1* or *BRCA2* mutations

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Abstract *BRCA1/2* mutations represent approximately 5 % of unselected Chinese women with breast cancer. However, the breast cancer risk of Chinese women with *BRCA1/2* mutations is unknown. Therefore, the aim of this study was to estimate the age-specific cumulative risk of breast cancer in Chinese women who carry a *BRCA1* or *BRCA2* mutation. Our study included 1816 unselected Chinese women with breast cancer and 5549 female first-degree relatives of these probands. All probands were screened for *BRCA1/2* mutation. The age-specific cumulative risks of *BRCA1/2* carriers were estimated using the kin-cohort study by comparing the history of breast cancer in first-degree female relatives of *BRCA1/2* carriers and non-carriers. Among the 1816 probands, 125 *BRCA1/2* pathogenic mutations were identified (70 in the *BRCA1* gene and 55 in the *BRCA2* gene). The incidence of breast cancer in the first-degree female relatives of *BRCA1/2* mutation carriers was significantly higher (3.7-fold and 4.4-fold for *BRCA1* and *BRCA2* mutation carriers, respectively) than in non-carriers. The estimated cumulative risks of breast cancer by age 70 years were 37.9 % [95 % confidence interval (CI) 24.1–54.4 %] for *BRCA1* mutation carriers and 36.5 % (95 % CI 26.7–51.8 %) for *BRCA2* mutation carriers, respectively. Our study suggests that the breast cancer risk of Chinese women with *BRCA1/2* mutations appears to be relatively high by the age of 70. Therefore, genetic counseling, enhanced surveillance, and individual preventive strategies should be provided for Chinese women who carry a *BRCA1/2* mutation.

Keywords *BRCA1* · *BRCA2* · Breast cancer risk · Chinese women

Introduction

Germline mutations in *BRCA1/2* confer a high risk of breast cancer and are associated with an early-onset of breast cancer [1–3]. It is well documented that Caucasian women who carry a pathogenic *BRCA1* or *BRCA2* mutation may have a 57–65 % or 45–49 % risk to development of breast cancer by age 70 years [4, 5]. However, the life-time risk of breast cancer varies between populations [4–22]. Some studies showed that women from the Ashkenazi Jewish and Icelandic descent who carry a *BRCA1/2* mutation have a breast cancer risk as high as 70 % by age 70 [11, 14, 17], whereas the breast cancer risk for *BRCA1/2* mutation carriers is only 35–49 % in women from Australia, the UK, and Korea [10, 22]. The discrepancies in breast cancer risk are owing to different populations or using different study methods. China has a lower incidence of breast cancer than western countries [23]. The prevalence of *BRCA1/2* germline mutations in Chinese women with familial breast cancer was around 10–15 % [24–26] which is comparable to 15–20 % in Caucasian women [27]. However, the spectrum of *BRCA1/2* mutations in Chinese women is different to that of Caucasian women [15, 24, 26, 28, 29]. Approximately, 50 % of *BRCA1/2* mutations in Chinese women were not reported in Caucasian women [24–26]. One recent study suggested that breast and ovarian cancer risks vary by type and location of

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BRCA1/2 mutations [30]. Therefore, the breast cancer risk in Chinese women with *BRCA1/2* mutations might be different when compared with Caucasian women. To our knowledge, no study has reported the breast cancer risk of Chinese *BRCA1* and *BRCA2* mutation carriers to date. Therefore, the aim of this study was to investigate the breast cancer risk in Chinese women who carry a *BRCA1* or *BRCA2* germline mutation.

Materials and methods

Study participants

A total of 4420 consecutive women diagnosed with breast cancer by pathology were tested for germline mutations throughout the *BRCA1* and *BRCA2* genes at the Breast Center, Peking University Cancer Hospital between January 2007 and December 2012. Approximately, 95.8 % of the women with breast cancer in this cohort are Chinese Han and reside in China. The hospital-based study was unselected for age of diagnosis and family history of cancer. Of these 4420 women, family history of cancer was obtained from 1821 patients. The remaining patients either refused to comply or could not be reached by telephone. This study was approved by the Research and Ethics Committee of Peking University Cancer Hospital. Written consent was obtained from all participants.

Data collection

Patient data were collected from medical records as described elsewhere [7], including nationality, age, vital status, and site of any cancer. During the telephone interview, the current age or age at death, and site of any cancer were ascertained for all female first-degree relatives of the participants, including parents, siblings, and children. Participants were also asked to list second- and third-degree relatives who had any history of cancer. If more than one family member was enrolled in the study, only the first individual for whom *BRCA* status was genotyped and was defined as proband. No relative was included more than once. A total of 1816 families from 1821 participants were created. The age of breast cancer for the 1816 probands was from 22 to 93 years. The 1816 probands provided information for 5549 first-degree female relatives, including 1679 mothers, 2614 sisters, and 1256 daughters. Participants were unaware of their mutation status at the time of interview.

BRCA1 and *BRCA2* analysis

BRCA1/2 pathogenic mutations were identified by direct DNA sequencing as described elsewhere [26]. We screened the entire coding regions and exon–intron boundaries of *BRCA1* and *BRCA2* for the familial, early-onset (breast cancer diagnosed at and before the age of 40 without family history of breast cancer), and triple-negative breast cancer patients; the remaining sporadic breast cancer patients were screened for *BRCA1/2* mutations in 4–19 recurrent mutations. All fragments were sequenced using the BigDye Terminator Cycle Sequencing Kit and ABI 3730 automated sequencer (Applied Biosystems, Foster City, CA). Each mutation was confirmed in duplicate. Mutations that lead to a truncated protein or have being reported previously as disease-associated are considered to be pathogenic.

Statistical analysis

Differences between ages at diagnosis of breast cancer in mutation carriers and non-carriers were compared using the Student's *t* test. Relative risks (RRs) of breast cancer in first-degree female relatives of *BRCA1/2* mutations carriers were estimated by comparing the breast cancer incidence in first-degree female relatives of non-carriers. The cumulative incidence of breast cancer in different *BRCA* status groups of first-degree female relatives was estimated using Kaplan–Meier survival analyses. The breast cancer risk among female carriers of *BRCA1* and *BRCA2* mutations was estimated using the kin-cohort design [7, 12, 31–38]. All statistical tests were two-sided. A P value of less than 0.05 was considered to be statistical significance.

Results

In this cohort of 1816 unselected Chinese women with breast cancer, a total of 125 *BRCA1/2* pathogenic mutations were identified (6.9 %) (70 in *BRCA1* and 55 in *BRCA2*). Approximately, 42 % of *BRCA1/2* mutations in this cohort were novel and had not previously been reported in the Breast Cancer Information Core database. *BRCA1/2* mutation carriers diagnosed with breast cancer were significantly younger than non-carriers (mean age, *BRCA1/2* vs non-carriers, 44.5 vs 51.4 years, $P < 0.001$). *BRCA1/2* mutation carriers were more likely to have a family history of breast cancers than non-carriers. Information about 5549 first-degree female relatives in this cohort of 1816 probands are available, and a total of 206 breast cancers occurred in these relatives, the breast cancer incidence in *BRCA1* mutation carriers, *BRCA2* mutation carriers, and non-carriers was 11.0, 12.7, and 3.2 %, respectively (Table 1). The risk of breast cancer in first-degree female relatives in the *BRCA1/2* mutation carriers was significantly higher than in relatives of non-carriers [*BRCA1* mutation carriers vs non-carriers, ratio of risk

Table 1 Distribution of breast cancer cases in first-degree female relatives of *BRCA1*, *BRCA2,* and non-carriers probands

	No. of breast cancer	RR (95 % CI)	*P*
First-degree female relative of *BRCA1* carriers ($N = 191$)	21 (11.0)	3.77 (2.34–6.09)	<0.001
First-degree female relative of *BRCA2* carriers ($N = 158$)	20 (12.7)	4.42 (2.70–7.25)	<0.001
First-degree female relative of non-carriers ($N = 5200$)	165 (3.2)	1 (Reference)	

RR: ratio of risk

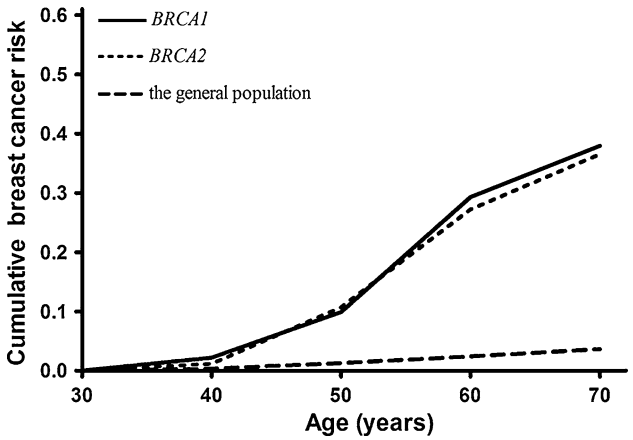

Fig. 1 Kin-cohort breast cancer cumulative risk estimates up to age 70 by genotype for *BRCA1/2*

(RR) = 3.77, 95 % CI 2.34–6.09, $P < 0.001$; *BRCA2* mutation carriers vs non-carriers, RR = 4.42, 95 % CI 2.70–7.25, $P < 0.001$] (Table 1).

The estimated cumulative risks of breast cancer by age 70 years were 37.9 % (95 % CI 24.1–54.4 %) for *BRCA1* mutation carriers and 36.5 % (95 % CI 26.7–51.8 %) for *BRCA2* mutation carriers, respectively (Fig. 1; Table 2). In the *BRCA1* mutation carriers, the estimated breast cancer risk was 2.2 % by age 40 years, 9.9 % by age 50 years, and 29.3 % by age 60 years, respectively. In the *BRCA2* carriers, the breast cancer risk was 1.2 % by age 40 years, 10.7 % by age 50 years, and 27.2 % by age 60 years, respectively (Table 2). We observed an increase of 19.4 % in the breast cancer risk from age 50 to 60 years for *BRCA1* mutation carriers and 19.5 % for *BRCA2* mutation carriers, respectively (Table 2). It is reported that breast cancer risk for the general population by age 70 years is 3.6 % in the Beijing area [39]; therefore, *BRCA1/2* mutation carriers may have a more than tenfold increased breast cancer risk compared with the general population by age 70 years.

Discussion

To our best knowledge, our study is the first to investigate the cumulative breast cancer risk in *BRCA1* and *BRCA2* carriers in Chinese women to date. Our study is a hospital-based study and comprised 1816 breast cancer probands (70 *BRCA1* mutations and 55 *BRCA2* mutations) and 5549 first-degree female relatives of these probands. Our results showed that the estimated cumulative breast cancer risks in *BRCA1* and *BRCA2* mutation carriers by age 70 years were 37.9 and 36.5 % for Chinese women, respectively. Our findings suggested that the cumulative risk of breast cancer in *BRCA1/2* mutation carriers is dramatically higher (approximately tenfold) than that in general population in Chinese women. These findings are in agreement with those of previous studies in other ethnic groups [1, 4–9, 40].

The breast cancer risk of *BRCA1/2* mutation carriers appears to vary among populations. The cumulative risk of breast cancer in *BRCA1/2* mutation carriers in Chinese women in this study was lower than that in Caucasian women [4, 5]. The differences in the breast cancer risk in different populations may be due to several reasons. First, the spectrum of *BRCA1/2* mutations is different between the Chinese women and Caucasian women, our current study indicated that approximately 42 % of *BRCA1/2* have Chinese-specific mutations that are not found in Caucasian women, this differences may influence the breast cancer risk [30]; second, study methods may lead to different results, our study is a relatively large cohort hospital-based study drawn from a consecutive series of breast cancer patients, although it is not a population study. The breast cancer risk appears to be lower in population- or hospital-

Table 2 Age-specific cumulative risks for breast cancer in *BRCA1/2* mutation carriers as obtained by a kin-cohort analysis

BRCA status	Breast cancer risk (%) (95 % CI)			
	By age 40	By age 50	By age 60	By age 70
BRCA1	2.2 (0–4.4)	9.9 (3.3–17.2)	29.3 (17.6–47.1)	37.9 (24.1–54.4)
BRCA2	1.2 (0–3.1)	10.7 (9.6–16.9)	27.2 (19.0–38.5)	36.5 (26.7–51.8)
BRCA	1.7 (0–3.2)	10.3 (6.2–16.3)	28.4 (19.3–34.5)	37.4 (33.3–43.4)

based studies compared with that of selected high-risk patients (i.e., multiple breast cancer in the families) [11, 14, 17, 41]. The cumulative risks of breast cancer associated with *BRCA1* or *BRCA2* mutations by 70 years were 87 and 84 % in high-risk Caucasian families (four or more breast cancer cases) [8, 42]; in contrast, the cumulative risks of breast cancer *BRCA1* or *BRCA2* mutation carriers are 57–65 % and 45–49 %, respectively, when the studies are conducted in the general populations in the Caucasian women [4, 5]. Third, other modified factors may affect the risk, including both genetic and environment factors [43].

Despite these population differences, we found that the risk of breast cancer to age 70 years in Chinese women with a *BRCA1/2* mutation was similar to the risk observed in Korean women (*BRCA1*, 38 vs 49 %; *BRCA2*, 37 vs 35 %) [22]. It suggested that Chinese and Korean women may have similar genetic background and life-style factors.

The breast cancer risk in *BRCA1/2* mutation carriers of the present study rose rapidly from age 40 years to age 50 years (9.9 % for *BRCA1*, 7.7 % for *BRCA2*), and dramatically increased from age 50 to 60 years (19.4 % for *BRCA1*, 19.5 % for *BRCA2*). Interestingly, van der Kolk et al. [44] also observed a high cancer incidence at older age in *BRCA1/2* families in northern Netherlands.

Women with a high breast cancer risk (i.e., *BRCA1/2* mutation carriers) should undergo enhanced surveillance or risk-reducing mastectomy [45]. Recent studies suggested that performing a prophylactic mastectomy remarkably decreases the breast cancer risk for *BRCA1/2* mutation carriers (more than 90 %) and also reduces the mortality [45–48]. Our study indicated that the breast cancer risk for *BRCA1/2* mutation carriers in Chinese women to age 70 years was approximately 37 %, the magnitude of breast cancer risk reaches the threshold of prophylactic mastectomy in many studies [49, 50].

In summary, this study suggests that cumulative breast cancer risks in *BRCA1* and *BRCA2* mutation carriers by age 70 years are 37.9 and 36.5 % in Chinese women. Based on these high risks of *BRCA1/2* mutation carriers, therefore, genetic counseling, individualized prevention, and even prophylactic mastectomy should be provided for Chinese women who carry *BRCA1/2* mutations.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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