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Original article:

OFFSPRING SEX RATIO AT BIRTH AND MATERNAL BREAST CANCER RISK: A CASE-CONTROL STUDY AND META-ANALYSIS OF LITERATURE

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ABSTRACT

To investigate whether offspring sex ratio at birth (SRB) was associated with maternal breast cancer risk, the present case-control study and a meta-analysis of literature were done. A total of 389 female breast cancer patients who had at least one offspring participated in the study. From general population 356 healthy female were selected as a control group. Control subjects were frequency matched with patients according to age and number of offspring. Among control group, 1324 offspring (666 males, 658 females) and within families of the breast cancer patients 1326 offspring (648 males, 678 females) were identified. There was no difference for SRB between breast cancer patients and control subjects ($P>0.05$). Meta-analysis was performed using 7 eligible studies. There was significant heterogeneity between studies ($P<0.05$). In overall the SRB was negatively associated with the maternal breast cancer risk (OR=0.95; 95 % CI: 0.92-0.99, P=0.02). Menopausal status of the patients was not associated with offspring SRB (P=0.07). Further researches are needed to determine the possible association between gender of offspring and maternal breast cancer risk.

Keywords: Breast cancer, case-control study, meta-analysis, risk, sex ratio

INTRODUCTION

It is well established that parity is a risk factor for breast cancer (Keinan-Boker et al., 2008; Enger et al., 1997). Higher number of full-term pregnancies is associated with a reduced breast cancer risk (Keinan-Boker et al., 2008). Childless women and women having children later in life are at an increased risk of developing breast cancer (Britt et al., 2007; Albrektsen et al., 1995a, b; Lambe et al., 1994). Some investigators found that the sex of the child should significantly affect the prognosis of a subsequent breast cancer (Juret et al., 1978; Janerich et al., 1980, 1994; Elwood and Coldman, 1981).

Sex hormones play an important role in the etiology of breast cancer (Enger et al., 1997). Estrogen has a marked effect on cell division by stimulating mitosis (Key, 1995; Trosis et al., 1998). On the other hand, substantial quantities of data have been supported the hypothesis that the mammalian offspring sex ratio at birth (SRB; male proportion) is partially controlled by the hormone levels of both parents around the time of conception (James, 1996, 2006a, b; Ansari-Lari et al., 2004; Saadat and Monzavi, 2008; Ansari-Lari and Tanideh, 2009).

The role of gender of children on risk of maternal breast cancer has received limited attention. Previous reports on the influence of offspring SRB on breast cancer risk have been conflicting (Olsson and Brandt, 1980; Albrektsen et al., 1995a, b, 2000; Olsen and Storm, 1998; Wohlfahrt and Melbye, 1999, 2000; Hsieh et al., 1999; Thalib and Hall,

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2006). These studies were performed in northern Europe: Denmark, Sweden and Norway. Because genetic and environmental risk factors of breast cancer might be different among populations (Saadat and Ansari-Lari, 2009; Hung et al., 2005; Saadat, 2006), and genetic alterations in high and low penetrance genes is associated with skewed offspring SRB in female breast cancer patients (de la Hoya et al., 2003; Domchek et al., 2005; Saadat and Saadat, 2010), the present case-control study was performed in Iran.

Some of the studies are limited by small sample sizes (Olsson and Brandt, 1980), so there is a role for meta-analysis in pooling data. In order to clarify the association between SRB and breast cancer risk, we carried out a meta-analysis using published data up to the January 2010, to obtain more precise estimates of risk.

MATERIALS AND METHODS

Case-control study

A total of 389 female breast cancer patients who had at least one offspring participated in the study. The patients were recruited from chemotherapy department of Nemazi Hospital in Shiraz, southern Iran. Because it is reported that parental age and birth orders have some effect on offspring SRB (Erickson, 1976), 356 healthy female from general population frequency matched with patients according to age and number of offspring, as a control group. The mean age of the patients and the controls was 47.8 ± 9.6 and 46.2 ± 10.1 years, respectively. The mean number of offspring in patients and controls was 3.6 ± 1.8 and 3.8 ± 2.1, respectively. All participants were Iranian (Persian) Muslims. Informed consent was obtained from all participants and the study was approved by the institutional review board at our department.

The association between SRB and risk of breast cancer was assessed by calculating the odds ratios (OR) and 95 % confidence interval (CI). An OR > 1.0 indicates an increase in the SRB and OR < 1.0 indicates a decrease in the ratio. Data analysis was performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) (version 11.5). A probability of $P < 0.05$ was considered a significant difference.

Meta-analysis study

Studies published up to January 2010 with information of offspring SRB and maternal breast cancer risk were identified using electronic databases, MEDLINE (National Library of Medicine, Washington, DC, USA), Scopus, EBSCOhost Research Databases, ProQuest, CAB Abstract, and SID (Scientific Information Database). Search terms were "breast cancer" and "sex ratio". The meta-analysis was limited to published articles in English language.

In overall 9 studies were identified (Olsson and Brandt, 1980; Albrektsen et al., 1995b, 2000; Olsen and Storm, 1998; Wohlfahrt and Melbye, 1999, 2000; Hsieh et al., 1999; Thalib and Hall, 2006, present study). Two articles (Albrektsen et al., 1995b; Wohlfahrt and Melbye, 2000) were not included in the analysis because they had overlapped with other two studies (Wohlfahrt and Melbye, 1999; Albrektsen et al., 2000). Articles selected for meta-analysis had no obvious overlap of cases with other studies.

For each study, the publication date, the country, where the study was conducted, and numbers of females and males offspring among cases and controls were abstracted. In some studies the numbers of offspring were estimated using data presented in tables of these articles.

To take into account the possibility of heterogeneity across the studies, a statistical test for heterogeneity was performed based on the Q statistic, in which a P-value greater than 0.05 suggested a lack of heterogeneity (DerSimonian and Laird, 1986). We carried out meta-analysis using a fixed-effects or a random-effects model. The fixed-effects method assumes no significant heterogeneity between the results of the individual studies being pooled, whereas, the random-effects method allows for such heterogeneity. The fixed-effects and random-effects methods were used by Mantel-

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Haenszel (Mantel and Haenszel, 1959) and DerSimonian and Laird methods (DerSimonian and Laird, 1986), respectively.

RESULTS AND DISCUSSION

Case-control study

Table 1 shows the sex of offspring among patients and controls. Among the control group, 1324 offspring (666 males, 658 females) were identified. The SRB in control group is similar with our previous report from Iran (Ansari-Lari and Saadat, 2002). We identified 1326 offspring (648 males, 678 females), within families of the breast cancer patients. There was no significant difference for offspring SRB between breast cancer patients and control subjects (OR=0.94, 95 % CI: 0.81-1.10, P=0.461). This finding confirmed our previous report (Saadat and Saadat, 2010) and is consistent with previous reports from Europe indicating no association between offspring SRB and risk of breast cancer (Olsen and Storm, 1998; Wohlfahrt and Melbye, 1999; Hsieh et al., 1999; Albrektsen et al., 2000; Thalib and Hall, 2006).

The subjects were stratified according to their menopause status (pre- and post-menopausal strata). In both strata, SRB was equal between patients and controls (for pre-menopause: OR=0.99, 95 % CI: 0.80-1.22, P=0.965; for post-menopause: OR=0.87, 95 % CI: 0.69-1.09, P=0.231). This is similar with some reports (Olsen and Storm, 1998; Hsieh et al., 1999; Wohlfahrt and Melbye, 1999; Albrektsen et al., 2000; Thalib and Hall, 2006) and is not in agreement with the study of Olsson and Brandt (1980). It should be noted that confounding is in theory possible, but as mentioned previously (Hsieh et al., 1999), none of the traditionally identified risk factors for breast cancer have been linked to the gender of the offspring.

Meta-analysis study

For meta-analysis 7 eligible studies in relation to SRB and breast cancer risk were identified (Table 2) (Olsson and Brandt, 1980; Olsen and Storm, 1998; Wohlfahrt and Melbye, 1999; Hsieh et al., 1999; Albrektsen et al., 2000; Thalib and Hall, 2006; present study).

Three studies reported the SRB in cases and controls (Olsen and Storm, 1998; Hsieh et al., 1999; present study). Including these studies, there was significant heterogeneity between the studies (Q=6.547, df=2, P<0.05). Considering the limited number of studies I failed to find the source of the heterogeneity. In overall the SRB was negatively associated with the maternal breast cancer risk (OR=0.95; 95 % CI: 0.92-0.99, P=0.02). This means that breast cancer patients had fewer sons in comparison with the control group.

Table 1: Association between offspring sex ratio at birth and breast cancer risk

Subjects	Males	Females	OR	95 % CI	P-value
All participants					
Controls	666	658	1.0	-	-
Cases	648	678	0.94	0.81-1.10	0.461
Pre-menopause participants					
Controls	391	408	1.0	-	-
Cases	310	325	0.99	0.80-1.22	0.965
Post-menopause participants					
Controls	275	250	1.0	-	-
Cases	338	353	0.87	0.69-1.09	0.231

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Table 2: Studies used in the meta-analysis

Study (year)	Place	All subjects				Pre-menopause		Post-menopause	
		Cases		Control		Cases		Cases	
		Males	Females	Males	Females	Males	Females	Males	Females
Olsson and Brandt (1980)	Sweden	139	155	-	-	91	62	48	93
Olsen and Storn (1998)	Denmark	2702	2511	10316	9709	-	-	-	-
Wohlfahrt and Melbye (1999)	Denmark	4789	4541	-	-	-	-	-	-
Hsieh et al. (1999)	Sweden	2986	2983	14041	12751	1055	1102	1931	1881
Alberkstsen et al. (2000)	Norway	5799	5468	-	-	1836	1729	3963	3739
Thalib and Hall (2006)	Sweden	3343	3054	-	-	1802	1736	1541	1318
Present study (2010)	Iran	648	678	666	658	310	325	338	353

In five studies the patients were stratified according to their age (Olsson and Brandt, 1980; Hsieh et al., 1999; Albrektsen et al., 2000; Thalib and Hall, 2006) or their menopause status (present study). The offspring SRB between these two subgroups were compared with each other. There was significant heterogeneity between the studies ($Q=23.97$, $df=4$, $P<0.05$). To find the source of heterogeneity, the study of Olsson and Brandt (1980) with small sample size was excluded. Heterogeneity between the studies dramatically decreased ($Q=3.823$, $df=3$, $P>0.05$). The menopausal status of patients was not associated with offspring SRB ($P=0.07$).

Previously it is reported that the offspring SRB in pre- and post-menopausal breast cancer patients is high and may be low as contrasted with controls, respectively (James, 2006b). The present finding, however, is not consistent with the James' report. It should be noted that James used the data of Olsson and Brandt (1980) and Thalib and Hall (2006) in his analysis. Small sample size in the study of Olsson and Brandt (1980) may be the reason for the discrepancy between the present finding and James' report.

Taken together the association between gender of offspring and susceptibility to breast cancer is still an open question. Further researches in this field are needed to determine the possible association between offspring SRB and risk of maternal breast cancer among pre- and post-menopause subjects.

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