Review Article

Role of Menopause and Early Menarche in Breast Cancer: A Meta-Analysis of Iranian Studies

Bibi Hajar Zahmatkesh,[1] Afsaneh Keramat,[2] Nasrinossadat Alavi,[3] Ahmad Khosravi,[2] and Reza Chaman[4,*]

[1]Student Research Committee, Department of Reproductive Health, Shahroud University of Medical Sciences, Shahroud, IR Iran
[2]Center for Health-Related Social and Behavioral Sciences Research, Shahroud University of Medical Sciences, Shahroud, IR Iran
[3]Breast Cancer Research Center, ACECR, Tehran, IR Iran
[4]Department of Community Medicine, School of Medicine, Yasuj University of Medical Sciences, Yasuj, IR Iran

[*]Corresponding author: Reza Chaman, Department of Community Medicine, School of Medicine, Yasuj University of Medical Sciences, Yasuj, IR Iran. Tel: +98-7433337239, Fax: +98-7433337250, E-mail: drchamanr@gmail.com

Abstract

Context: Various studies in Iran on the role of menopause and age at menarche in breast cancer reported different results.

Objectives: The current study aimed to estimate the overall odds ratio and explore the association between early menarche and menopause with breast cancer.

Data Sources: Scopus, Web of Science, PubMed, Google Scholar and Iranian databases such as Magiran and SID, breast cancer key journals (Asian pacific journal of cancer prevention, Iranian quarterly journal of breast) and conferences (international breast cancer congresses in Iran, annual breast cancer conferences and seminars in Iran) were searched from 2004 to 2014.

Study Selection: The observational studies in Iran that had reported the relationship between menopause and early menarche with breast cancer were searched. The exposure was menopause and early menarche and the outcome was breast cancer with pathological confirmation.

Data Extraction: Using strengthening the reporting of observational studies in epidemiology (STROBE) checklist, quality assessment of the articles and data extraction were performed separately by two authors.

Results: Of 4396 articles, 12 studies with a sample size of 27734, 11 studies with a sample size of 4039 and 20 studies with a sample size of 53417 were analyzed to estimate the overall odds ratio (OR) for early menarche and the standardized mean difference (SMD) of the average menarche age and overall OR of menopause, respectively. A significant relationship was observed between early menarche and breast cancer (OR = 1.57, 95% confidence interval (CI) = 1.05, 2.34). The mean menarche age in patients was also significantly lower than in healthy females (SMD = -0.087, 95%CI = -0.151, -0.02). Postmenopausal female had a higher risk for developing breast cancer; however, this relationship was not statistically significant (OR=1.35, 95%CI=0.98, 1.86).

Conclusions: Menopause and early menarche increase the odds of breast cancer. Therefore, breast cancer prevention and screening programs are needed to reduce the burden of this cancer and improve the quality of females' lives.

Keywords: Menarche, Menopause, Breast Neoplasm, Systematic Review

1. Context

Breast cancer is the most common type of cancer among females both in the developed and developing countries. The increased rate of breast cancer in the developing countries is attributed to the increased life expectancy, urbanization and westernization of lifestyle (1). According to the international agency for research on cancer (IARC), since 2008 the incidence and mortality of breast cancer increased by 20% and 14%, respectively. This type of cancer is the most common cause of cancer death among females accounted for 522,000 deaths in 2012 (2). Various risk factors for breast cancer are identified. However, no specific risk factor is identified for a large number of patients (3). Reproductive risk factors, old age at the first birth, use of oral contraceptive pills or hormone replacement therapy are among the most important risk factors for breast cancer (4). Recently, in a systematic review and meta-analysis, Narimanian et al. investigated the risk factors for breast cancer in the Eastern Mediterranean region and considered the early menarche as a risk factor for breast cancer. However, given the reported effect size (pooled odds ratio (OR) = 1.12, 95% confidence interval (CI) = 0.97, 1.28), no significant relationship was found. The selected studies were the ones published in English language, their full text were freely accessible and reporting OR and relative risk (5). However, Narimanian et al. (5) did not include Persian and cross-sectional studies in their review.

Various studies in Iran on the relationship between breast cancer and menopause and age at menarche reported different results. Thus, due to the aging population and the decreasing age of menarche in Iranian females and the role of these risk factors in breast cancer; the current study was conducted to determine overall estimates for these risk factors, in terms of OR. The main questions of the study were: "Is early menarche associated with risk of developing breast cancer in females?" "Is the risk of breast cancer in postmenopausal females higher than that of the premenopausal ones?"

2. Data Sources

The current meta-analysis aimed to determine all observational studies on the relationship between menopause, and age at menarche with breast cancer. All observational studies including cohort, case-control and cross-sectional studies on the relationship between these risk factors and breast cancer in Iran, published in Persian or English (from 2004 to 2014) were searched. To identify cancer synonyms, the medical subject headings (MeSH) was searched using the keywords of cancer, tumor, neoplasm, neoplasia, carcinoma, malignancy, malignant and benign. A combination of the above-mentioned words were used with OR and then the words Iran and breast were added to the search field using the operator AND.

The electronic databases of PubMed, Web of Science, Scopus (search date: 2015/05/11), Google Scholar and Iranian scientific electronic databases (search date: 2015/04/19) such as SID (in English and Persian languages) and Magiran (in Persian language) were searched. Moreover, the references of the selected articles and the abstracts of the articles presented at the international breast cancer congresses in Iran, annual breast cancer conferences and seminars in Iran, Iranian quarterly journal of breast disease (from the first issue to the end of March 2015), and the Asian pacific journal of cancer prevention from the first issue in 2004 to the end of 2014) were reviewed. To find the texts of the articles from the congresses, seminars and conferences, the corresponding authors were contracted. Moreover, the Irandoc data base was reviewed for thesis, but this database was incomplete. Therefore the authors tried to access the research project by requesting them from Iranian university libraries, but no response was received.

3. Study Selection

The observational studies (cohort, case-control and cross-sectional) on the relationship between age at menar-

che and menopause with breast cancer published in Persian and English from 2004 to 2014 were included in the study. The exposures included age at menarche $\leq$ 13 years and menopause in females. The studies conducted only on patients were excluded. There were no limitations in terms of age and race, and no comparison was made. Age at menarche is defined the age that first menstrual cycle happens in females. Menopause is also defined as an event in females' lives which occurs when menstrual periods stop permanently due to the cessation of ovarian activity. The desired outcome of this study was breast cancer (of any type), confirmed by the pathology report. Therefore, all types of breast cancer, regardless of their pathological features and tumors' stage, were included in this study. In all of the reviewed studies, controls were females without breast cancer. Two authors (Zahmatkesh and Khosravi) reviewed the obtained articles in terms of the inclusion criteria. The articles were not blind in terms of authors' names, journal's name and results. Any disagreement between the two authors was reviewed by the third author (Chaman). The strengthening the reporting of observational studies in epidemiology (STROBE) checklist was used to assess the risk of bias and to score the quality of studies, independently. Then the articles with a score $\geq$ 6 were selected. Some of the criteria of the STROBE checklist that were used to assess the articles were as follows: methods (setting, participants, variables, data sources/measurement, bias), results (main results) and discussion (limitation, generality). The study selection process is presented in the Figure 1.

4. Data Extraction

Two authors extracted the data of the included articles. The extracted variables included publication year, authors' name, type of the study, sample size, population age, age at menarche (the mean age at menarche and age groups for menarche), menopausal status, matching status, number of cases with breast cancer, and number of controls. The extracted data were transferred into the software, and the author was corresponded with in cases where lack of some data was encountered.

5. Measures of Exposure Effect and Data Analysis

No cohort study on the issue was available from Iran and only case-control and cross-sectional studies were obtained. Therefore, OR was selected as a criteria for the effect size. A meta-analysis with a 95%CI was used to obtain the combined effect size. The analysis was performed using the STATA 11.2 software (Stata Corporation, College Station, Texas, USA) and the results were reported using the
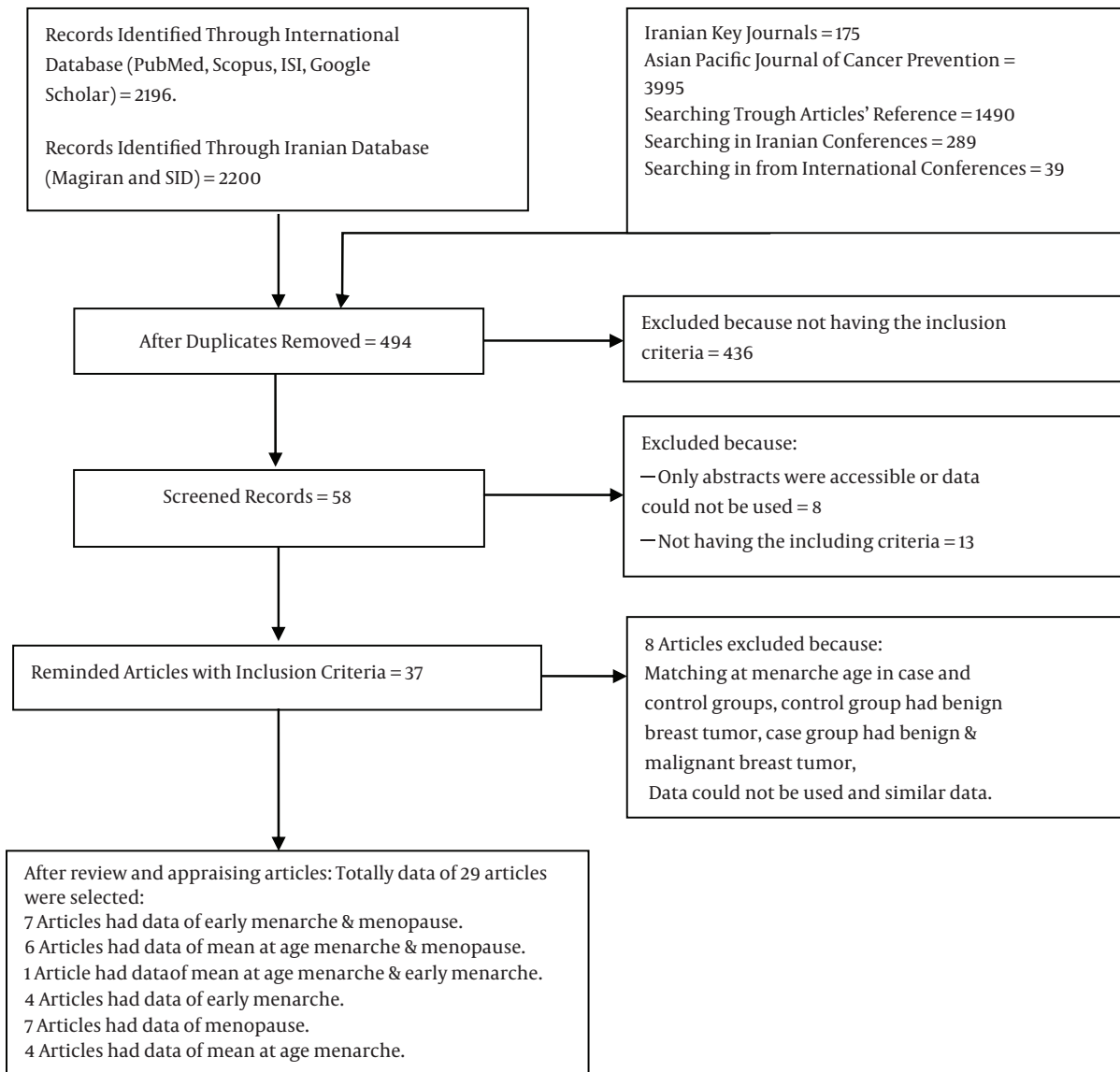
Figure 1. Flow Diagram of the Identification Process to Select Articles in the Review

random effects model. Statistical heterogeneity at a P value < 0.05 was determined using the Chi-square test. Within-study and between-study inconsistency or variation were estimated using the I^2 (6) and the Tau^2 (7) statistics respectively. The Begg and the Egger statistical tests were used to show the publication bias.

6. Results

6.1. Description of the Studies

A total of 4396 articles were obtained from the Iranian and international databases. Of these, 2200 and 2196 articles were from Iranian and international databases, respectively. After exclusion of duplicated articles and reviewing the titles and abstracts of the remained articles, 28 articles from the international databases and 22 from the Iranian databases remained.

Reviewing the titles of the articles presented at conferences held in Iran (i e, the 4th - 10th international breast cancer congresses in Iran as well as the 2th - 7th national breast cancer congresses in Iran) showed 289 relevant articles. However, after reviewing the abstracts, seven articles were added to the previous ones.

All issues of the Iranian quarterly journal of breast disease (up to the end of March 2015) were also reviewed, and four articles were relevant whose full texts had been obtained previously. Asian pacific journal of cancer prevention (from 2004 to 2014) was also reviewed and of the 3995 articles, ten were relevant, among which nine had been obtained previously and one new article was added to the list of the selected articles. Therefore, a total of 58 articles were included in the review but 50 articles were accessible with their full texts. About the other eight articles, the corresponding authors were emailed three times, but no response was received. As the data presented in these eight abstracts could not be used in the meta-analysis, they were excluded. The references of the articles whose full texts were accessible were also reviewed, and 51 articles were relevant that had been found in the previous search results. Therefore, 50 articles with accessible full texts were obtained and after review of full texts, 13 articles did not have the including criteria or data of menopause and age at menarche; therefore were excluded and 37 articles reminded.

Of the 37 reviewed articles, 32 articles reported the data of age at menarche, among which 14 articles presented the average age at menarche in the case and the control groups (8-21). In two articles, the case and the control groups had been matched in terms of the average age at menarche (19, 20), and in one article the control group had benign breast tumor (21), therefore the three later studies were excluded from the analysis. Finally, 11 articles included in the meta-analysis to estimate standard mean difference of menarche age.

To estimate pooled OR early menarche, of 37 articles, the article by Motamed et al. only reported the OR without CI (22), and the article by Dadashi et al. only reported the OR for early menarche without giving any definition of early menarche (23). Therefore these two articles were excluded from the analysis.

In 18 articles, the data of age at menarche were reported in terms of age groups (qualitatively) (18, 24-40). Three articles had similar data (24-26) and therefore only one of them was included in the analysis. Among these articles, one article reported the data of age at menarche both averagely and qualitatively.

According to the study by Mohsenzadeh-ledari et al. the average age at menarche of females in Iran was about 13 years (41). Therefore, the data of the articles were divided into $13 <$ and $13 \geq$ age groups. The data of three articles could not be used for meta-analysis. One article also had a wide confidence interval (27) and was excluded. Thus 12 articles included in meta-analysis to estimate the pooled OR of early menarche.

Of the 37 articles with full texts, 25 articles considered menopause as a risk factor for breast cancer in females. Two articles were excluded from the analysis since in one of them all subjects were aged ≤ 50 years (29) and in another article all females were aged over 50 years old (28). The data of three articles (24-26) were similar as they were resulted of a similar work. Therefore, only the data of one article (26) was included in the analysis. One article was excluded since the control group had benign breast tumor (21). Therefore 20 articles included in the meta-analysis to estimate pooled OR of menopause.

6.2. Association Between Early Menarche and Breast Cancer

The data of 12 case-control articles with a total sample size of 27704 individuals (case = 2020, control = 25684) were included in the meta-analysis to estimate the combined OR (Table 1) (18, 24, 30-36, 38-40).

The results showed that the odds of breast cancer was significantly higher in the females with menarche age $\leq$ 13 years than in those with higher menarche age (OR = 1.57, 95%CI = 1.05, 2.34) (Figure 2).

6.3. Comparison the Average Age at Menarche Between Breast Cancer Patients and Healthy Females

The data of 11 articles, which had the data of mean at menarche age, with a sample size of 4039 individuals, which had pointed out the average age at menarche, were included in the analysis (Table 2) (8-18). The standardized mean difference (SMD) of the age at menarche in the two groups (breast cancer patients and healthy females) indicated that the average age at menarche in the breast cancer group was significantly lower than that of the healthy females (SMD = -0.087, 95% CI = -0.15, -0.02) (Figure 3).

6.4. Association Between Menopause and Breast Cancer

Finally, twenty case-control studies with a sample size of 53417 were analyzed to estimate the OR (8, 9, 11, 13, 15, 17, 26, 27, 31, 33-37, 39, 40, 42-45). Of these, 17 studies were hospital-based and three were population-based (13, 27, 44).

The results of meta-analysis showed that menopause was a risk factor for breast cancer. In other words, the odds of breast cancer was higher in postmenopausal females than in premenopausal ones; however, this relationship was not statistically significant (OR = 1.36, 95%CI = 0.97, 1.91)

Table 1. Meta-Analysis Odds Ratio for Menarche Age ≤ 13 Years Old and Risk for Breast Cancer Using the Random Effects Method

Author	Year	Total Sample Size	Number of Cases	Number of Controls	OR	95% Confidence Interval	Weight, %
Hajian-Tilaki et al. (24)	2012	300	100	200	0.643	0.397, 1.042	8.66
Montazeri et al. (30)	2008	232	116	116	1.732	0.897, 3.346	7.81
Zare et al. (40)	2013	23440	98	23342	0.99	0.664, 1.475	9.02
Keihanian et al. (33)	2010	120	60	60	3	1.075, 8.37	6
Yavari et al. (39)	2005	599	298	301	1.262	0.852, 1.87	9.05
Tehranian et al. (38)	2010	624	312	312	4.017	2.769, 5.829	9.13
Tazhibi et al. (18)	2014	257	216	41	1.244	0.559, 2.769	7.1
Pourzand et al. (35)	2013	400	200	200	0.635	0.403, 1.003	8.78
Mahouri et al. (34)	2007	672	168	504	4.004	2.558, 6.267	8.81
Hosseinzadeh et al. (31)	2014	420	140	280	2.899	1.745, 4.817	8.55
Ghadiri et al. (32)	2013	353	174	179	1.328	0.816, 2.164	8.64
Saadat et al. (36)	2007	287	138	149	1.281	0.758, 2.166	8.46
Pooled OR			2020	25684	1.572	1.054, 2.344	100
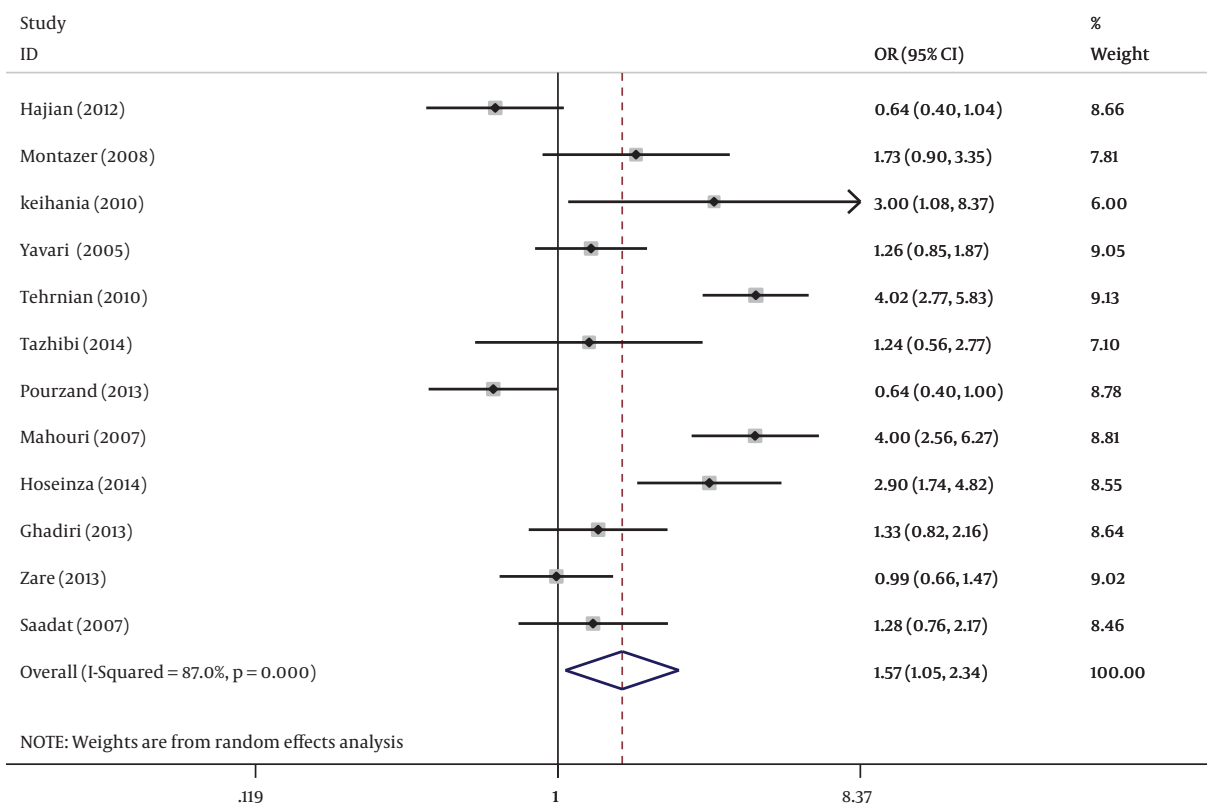
Figure 2. Forest Plot Diagram of the Relationship Between Age at Menarche ≤ 13 Years and Breast Cancer Using the Random Effects Method

(Table 3, Figure 4). In seven studies included in the meta-analysis (17, 26, 34, 37, 42, 43, 45), this relationship was in- verse and menopause was a protective factor, however, in five studies, this relationship was not statistically signifi-

Table 2. Meta-Analysis of the SMD of Age at Menarche in the Study Groups

Author	Year	Sample Size	SMD	95% Confidence Interval	Weight, %
Abbasi et al. (8)	2009	297	-0.207	-0.435, 0.021	8.1
Akbari et al. (9)	2010	801	-0.088	-0.227, 0.051	21.87
Azarshab and Bidgoli (10)	2014	176	-0.054	-0.365, 0.258	4.34
Bahadoran et al. (11)	2013	275	0.39	0.143, 0.638	6.86
Motie et al. (12)	2011	267	-0.218	-0.458, 0.023	7.28
Naieni et al. (13)	2007	750	-0.191	-0.343, -0.039	18.21
Nojomi et al. (14)	2004	580	-0.215	-0.401, -0.029	12.15
Sariri et al. (15)	2012	257	-0.038	-0.283, 0.207	7.05
Sharif Zadeh et al. (16)	2011	170	-0.134	-0.435, 0.167	4.65
Shokouhi et al. (17)	2008	209	0.129	-0.143, 0.4	5.71
Tazhibi et al. (18)	2014	257	0.091	-0.243, 0.425	3.78
Pooled SMD			-0.087	-0.151, -0.022	100

Abbreviation: SMD, standard mean difference.
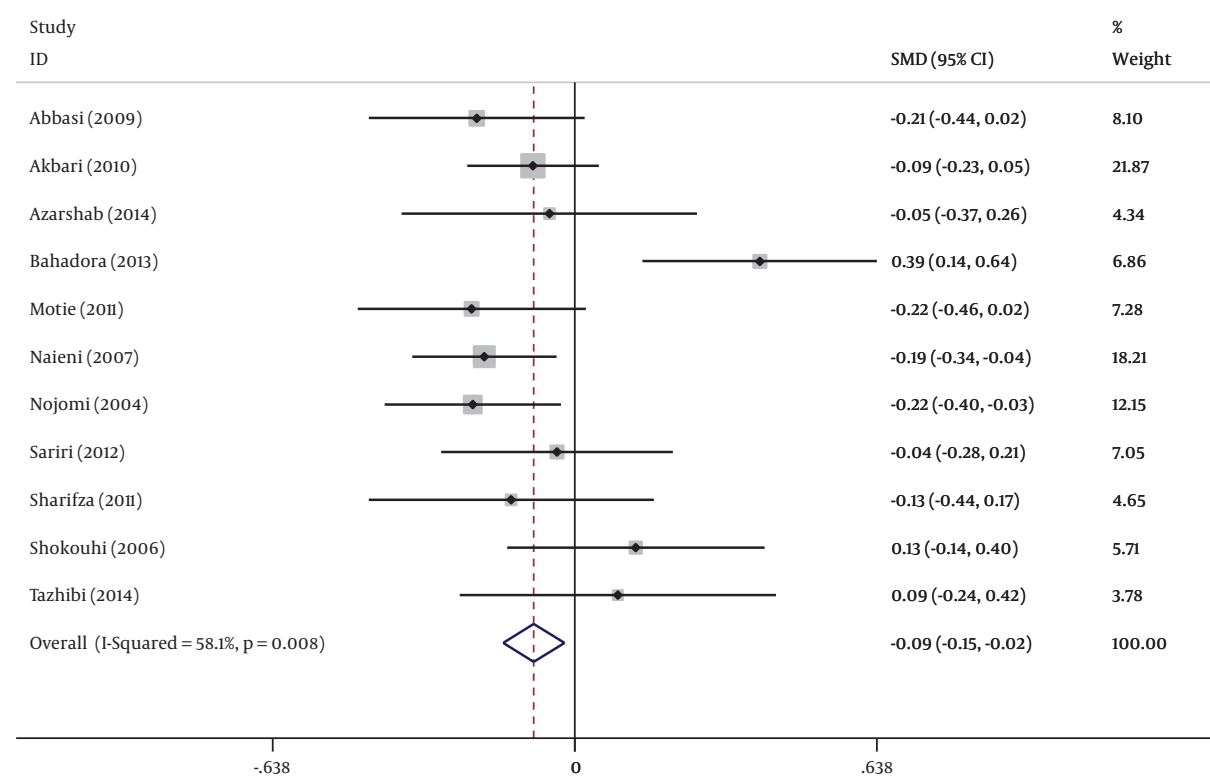
Figure 3. Forest Plot Diagram of the Difference Between Mean Age at Menarche Between Breast Cancer and Healthy Females

cant (17, 26, 34, 42, 45). On the other hand, 13 studies reported that menopause was associated with increased risk of breast cancer, however, in six articles this relationship was not statistically significant (9, 11, 27, 31, 35, 36).

Table 3. Meta-Analysis Results of Odds Ratio of Menopause Status on Breast Cancer Using the Random Effects Method

Study	Year	Sample Size	OR	95% Confidence Interval	Weight, %
Abbasi et al. (8)	2009	297	4.647	2.57, 8.399	4.89
Akbari et al. (9)	2010	801	1.104	0.831, 1.466	5.52
Besharat et al. (44)	2011	267	3.35	1.987, 5.649	5.06
Mobarakeh et al. (42)	2014	93	0.698	0.259, 1.883	3.86
Hajian et al. (26)	2013	300	0.755	0.466, 1.223	5.15
Hosseinzadeh et al. (31)	2014	420	1.476	0.982, 2.22	5.31
Keihanian et al. (33)	2010	120	3.237	1.529, 6.853	4.49
Lotfi et al. (27)	2008	140	1.494	0.762, 2.928	4.69
Mahouri et al. (34)	2007	672	0.946	0.667, 1.342	5.42
Naieni et al. (13)	2007	750	2.014	1.476, 2.749	5.48
Pourzand et al. (35)	2013	400	1.179	0.792, 1.754	5.33
Sariri et al. (15)	2012	257	4.697	2.741, 8.049	5.02
Shokouhi et al. (17)	2008	222	0.944	0.485, 1.838	4.71
Yavari et al. (39)	2005	600	2.991	2.106, 4.248	5.41
Zare et al. (40)	2013	35380	1.703	1.169, 2.481	5.37
Bahadoran et al. (11)	2013	275	1.019	0.612, 1.695	5.09
Saadat et al. (36)	2007	276	1.466	0.865, 2.486	5.05
Sepandi et al. (37)	2014	11850	0.317	0.237, 0.424	5.51
Rezaeian et al. (43)	2012	207	0.32	0.16, 0.637	4.65
Eftekhari et al. (45)	2009	90	0.796	0.312, 2.032	4
Pooled OR			1.36	0.968, 1.911	100

6.5. Heterogeneity and Publication Bias

To estimate the overall OR for the association of menarche age $\leq$ 13 years with breast cancer, between-study heterogeneity was measured using the Chi^2 and I^2 tests. Examining the risk factor of age at menarche $\geq$ 13 years showed that $Chi^2 = 84.38\%$, $P < 0.001$, $I^2 = 87\%$, and the difference among studies or $Tau^2 = 0.42$. Therefore, the results of the present study were heterogeneous. Of 12 analyzed studies, three reported an inverse relationship between menarche age $\leq$ 13 years and breast cancer, which was not significant (24, 35, 40). Five studies reported a direct relationship between menarche age $\leq$ 13 years and breast cancer, which was not significant (18, 30, 32, 36, 39). The four other studies reported a significant direct relationship between this risk factor and breast cancer.

To estimate the SMD of menarche age between patients with breast cancer and healthy females, the between-study heterogeneity was measured using the Chi^2 and I^2 tests. Examining the risk factor of age at menarche showed that $Chi^2 = 23.86\%$, $P < 0.009$, and $I^2 = 58.1\%$. Therefore, the heterogeneity of the present study was average. In three articles, the average age at menarche in the patients with breast cancer was higher than that of the healthy females (11, 17, 18). However, this difference was not statistically significant in the last two studies. In eight studies, the average age at menarche in the patients with breast cancer was lower than that of the healthy females, and in six studies this difference was not significant (8-10, 12, 15, 16)

To estimate the overall OR for the association of menopause and breast cancer, between-study heterogeneity was measured using the Chi^2 and I^2 tests. The results showed that the studies were heterogeneous, $Chi^2 = 210.66$, $P < 0.001$ and $I^2 = 91\%$. Therefore, there was extreme heterogeneity in the current study and $Tau^2 = 0.52$. After dividing the studies into subgroups based on the type of studies, the heterogeneity of hospital-based case-control studies did not change ($I^2 = 91\%$) and the heterogeneity of three population-based case-control studies changed ($I^2 = 50.7\%$). After using meta-regression for the variable of type of studies, the remaining I^2 was calculated as 90.48%, which indicated the existence of heterogeneity. Moreover, the adjusted R-squared was 2.44% which showed that the type of
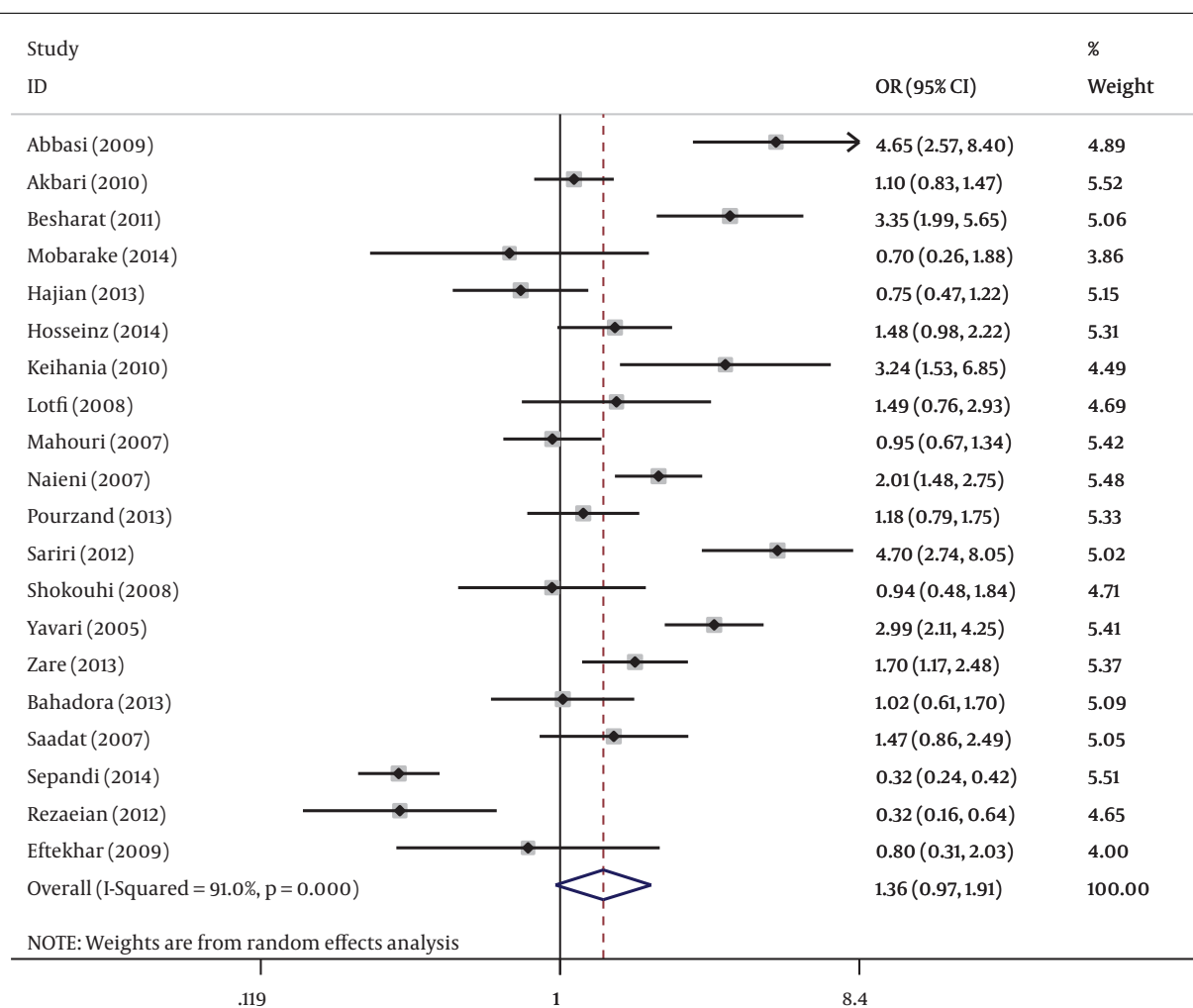
Figure 4. Forest Plot Diagram of the Relationship Between Menopause Status and Breast Cancer Using the Random Effects Method

studies play an insignificant role in heterogeneity (2.44%).

Publication bias was assessed using the Begg and the Egger tests. Results of the Begg and the Egger tests and the Egger test diagram showed lack of publication bias (Figure 5 - 7).

7. Discussion

Meta-analysis showed that menarche age ≤ 13 years increased the odds of breast cancer in Iranian females. This finding was consistent with that of a previous study by Sarmento de Almeida et al. (46). In a study by Namiranian et al. age at menarche less than 12 years was considered as a risk factor for breast cancer. However, the relationship was not statistically significant (5). The reason for the inconsistency might be due to the difference in the age at menarche and reviewed databases, examined areas and covering

Persian and English articles in the present study. In a systematic review, age at menarche ≥ 15 years was considered a protective factor against breast cancer, but menarche age < 13 years was not associated with breast cancer (47). The later study covered the studies published till 2011, and only used Cochrane and MEDLINE databases to search randomized controlled trials (RCTs), observational studies, systematic reviews and English meta-analyses. Moreover, females were in the age range of 40 - 49. On the contrary, the studies used in the present study were all case-control studies and there were no such limitations as age range for females. These differences were probably the reason for determining the age at menarche ≤ 13 years as the risk of breast cancer in the present study. A study by Besharat et al. showed that age at menarche < 13.37 years increased the risk of breast cancer in females by 1.3 times; however, it was
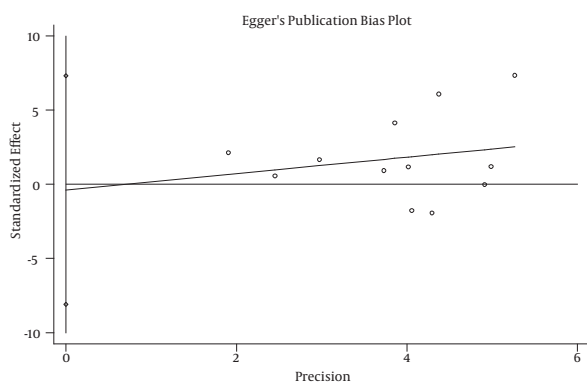
Figure 5. The Egger Test for the Publication Bias of the Relationship Between Menarche Age $\leq$ 13 Years and Breast Cancer
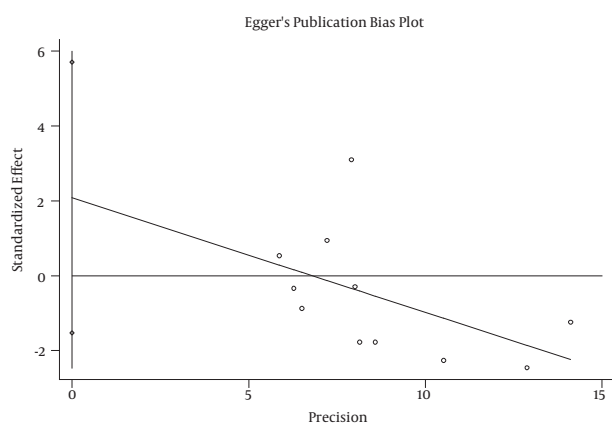

Figure 6. The Egger Test for the Publication Bias of the Difference in the Average Age at Menarche Between the Two Groups (Breast Cancer Patients And Healthy Females)
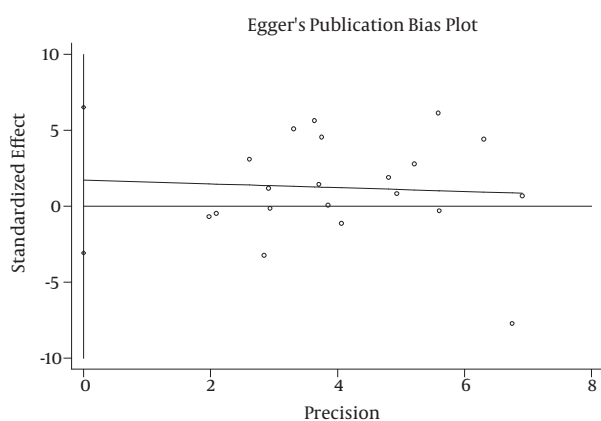

Figure 7. The Egger Test for the Publication Bias of the Relationship Between Menopause and Breast Cancer

not statistically significant (44). The low sample size of the study by Besharat et al. might be the reason for the difference between their results and the findings of the present study. Results of a study by Babita et al. were also consistent with those of the present study. They reported that females with age at menarche < 13 years were 3.7 times more likely to develop breast cancer, while the age at menarche > 15 was a protective factor for breast cancer (48).

The present study showed that the average age at menarche in females with breast cancer was significantly lower than that of healthy females. Consistently, a study by Beral et al. also showed that lower age at menarche increased the risk of breast cancer (49). However, Naieni et al. (13), Besharat et al. (44) Sharifzadeh et al. and Tazhibi et al. (16, 18) could not find any significant relationship between age at menarche and breast cancer. Such an inconsistency between these studies and the present study might be attributed to the low sample size and also selecting the controls from the neighbors of the patients in some of the aforementioned studies.

The results of meta-analysis showed that menopause was a risk factor for breast cancer. In other words, the risk of breast cancer was higher in postmenopausal females than in premenopausal ones. However, this relationship was not statistically significant. The results of the study by Sarmento de Almedia were also consistent with those of the current study (46). Bhadoria et al. in India reported that the risk for breast cancer in postmenopausal females was 2.5 times greater than in premenopausal females, and the difference was statistically significant (50). In another study by Ishida et al., menopause increased the risk of breast cancer by 2.65 times. However, the results of their study were different after adjustment of age, and menopause was considered a protective factor (51). Differences in race, lifestyle and methodology in studies might be the reason for differences in the results.

Limitation of this meta-analysis was lack of access to research projects and thesis related to the subject of the study. It was tried to access these documents by requesting from Iranian university libraries, but no response was received.

Given the decreasing trend in age of puberty and regional differences as well as the country's aging population, increase of menopausal females' population size and increasing prevalence of overweight and obesity in females, more research is needed on these risk factors.

In conclusion, early menarche and menopause increased the risk of breast cancer in Iranian females. Given the average age at menarche in Iranian females (about 13 years), decreasing trend in menarche age in Iranian females, increasing trend in incidence of breast cancer (52), increased life expectancy in females, and consequently in-

crease in the postmenopausal population, it is necessary to design breast cancer prevention and control programs more than ever.

Footnotes

References

1. World Health Organization . Breast cancer: prevention and control 2016. Available from: http://www.who.int/cancer/detection/breastcancer/en/.
2. International Agency for Research on Cancer . Latest world cancer statistics. Global cancer burden rises to 14.1 million new cases in 2012: Marked increase in breast cancers must be addressed 2013 2012. Available from: http://www.iarc.fr/en/media-centre/pr/2013/pdfs/pr223_E.pdf.
3. Canadian Cancer Society . Risk factors for breast cancer 2015. Available from: http://www.cancer.ca/en/cancer-information/cancer-type/breast/risks/?region=bc.
4. Lacey JJ, Kreimer AR, Buys SS, Marcus PM, Chang SC, Leitzmann MF, et al. Breast cancer epidemiology according to recognized breast cancer risk factors in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Cohort. *BMC Cancer.* 2009;**9**:84. doi: 10.1186/1471-2407-9-84. [PubMed: 19292893].
5. Namiranian N, Moradi-Lakeh M, Razavi-Ratki SK, Doayie M, Nojomi M. Risk factors of breast cancer in the Eastern Mediterranean Region: a systematic review and meta-analysis. *Asian Pac J Cancer Prev.* 2014;**15**(21):9535–41. [PubMed: 25422252].
6. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;**327**(7414):557–60. doi: 10.1136/bmj.327.7414.557. [PubMed: 12958120].
7. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. 5. Wiley Online Library; 2008.
8. Abbasi S, Azimi C, Othman F, Einollahi N, Dashti N, Nabatchian F, et al. Risk factors for breast cancer in Iranian women: a case-control study. *Int J Cancer Res.* 2009;**5**(1):1–11.
9. Akbari A, Hadi AR, Tabib AA, Majd AR, Razaghi Z, Esfahani MM, et al. Breast Cancer Risk Reduction by Parity and Breastfeeding, Islamic Perspective; A Case Control Study. *Iran J Cancer Prevent.* 2010;**3**(2):56–61.
10. Bidgoli SA, Azarshab H. Role of Vitamin D Deficiency and Lack of Sun Exposure in the Incidence of Premenopausal Breast Cancer: a Case Control Study in Sabzevar, Iran. *Asian Pac J Cancer Prevent.* 2014;**15**(8):3391–6.
11. Bahadoran Z, Karimi Z, Houshiar-rad A, Mirzayi HR, Rashidkhani B. Is dairy intake associated to breast cancer? A case control study of Iranian women. *Nutr Cancer.* 2013;**65**(8):1164–70. doi: 10.1080/01635581.2013.828083. [PubMed: 24066929].
12. Motie MR, Besharat S, Torkjazi R, Shojaa M, Besharat M, Keshtkar A, et al. Modifiable Risk of Breast Cancer in Northeast Iran: Hope for the Future. A Case-Control Study. *Breast Care (Basel).* 2011;**6**(6):453–6. doi: 10.1159/000335203. [PubMed: 22419899].
13. Naieni KH, Ardalan A, Mahmoodi M, Motevalian A, Yahyapoor Y, Yazdizadeh B. Risk factors of breast cancer in north of Iran: a case-control in Mazandaran Province. *Asian Pac J Cancer Prev.* 2007;**8**(3):395–8. [PubMed: 18159976].
14. Nojomi M, Mirfakhraee R, Hosseini N. Relationship between hormonal factors and breast cancer [in Persian]. *Hakim J.* 2004;**7**(1):19–25.
15. Sariri E, Kashanian M, Vahdat M, Yari S. Comparison of the dermatoglyphic characteristics of women with and without breast cancer. *Eur J Obstet Gynecol Reprod Biol.* 2012;**160**(2):201–4. doi: 10.1016/j.ejogrb.2011.11.001. [PubMed: 22119106].
16. Sharif Zadeh G, Hosseini M, Kermani T, Ataiee M, Akhbari SH. Breast cancer and the related factors: A case control study [in Persian]. *J Birjand Univ Med Sci.* 2011;**18**(3):191–9.
17. Shokoohi M, Keshavarz A, Majdzadeh S, Siassi F. The relationship between nutritional factors and breast cancer in women attending Imam Hospital [in Persian]. *J School Public Health Inst Public Health Res.* 2008;**5**(4):35–46.
18. Tazhibi M, Dehghani M, Babazadeh S, Makkarian F, Tabatabaeian M, Sadeghi M, et al. Hormonal and reproductive risk factors associated with breast cancer in Isfahan patients. *J Educ Health Promot.* 2014;**3**:69. doi: 10.4103/2277-9531.134818. [PubMed: 25077162].
19. Reyhani M, Fahami F, Mosharaf SH, Tarkesh N. The relationship between the amount of dairy products and animal proteins consumption and breast cancer in isfahani women [in Persian]. *J Zanjan Univ Med Sci.* 2012;**20**(81):45–54.
20. Ataollahi M, Sedighi S, Masoumi SZ. Nutritional and unhealthy behaviors in women with and without breast cancer. *Iran Red Crescent Med J.* 2014;**16**(9):ee19684. doi: 10.5812/ircmj.19684. [PubMed: 25593731].
21. Montazeri A, Jarvandi S, Ebrahimi M, Haghighat S, Ansari M. The role of depression in the development of breast cancer: analysis of registry data from a single institute. *Asian Pac J Cancer Prev.* 2004;**5**(3):316–9. [PubMed: 15373713].
22. Motamed N, Hadi N, Talei A. Assessment of some of the risk factors of breast cancer in women over 35 years in Shiraz [in Persian]. *J Zanjan Univ Med Sci Health Serv.* 2004;**12**(46):25–33.
23. Dadashi R, Shahpourian L, Hosseini Z, Motamednia L. Reoroductive factors related to cancer of the breast, before and after menopause; among women referring to health centers in Tehran, 2005. *Int J Fertil Steril.* 2010;**4**(1):85.
24. Hajian-Tilaki K, Kaveh-Ahangar T, Hajian-Tilaki E. Is educational level associated with breast cancer risk in Iranian women?. *Breast Cancer.* 2012;**19**(1):64–70. doi: 10.1007/s12282-011-0273-6. [PubMed: 21573750].

25. Hajian-Tilaki KO, Kaveh-Ahangar T. Reproductive factors associated with breast cancer risk in northern Iran. *Med Oncol.* 2011;**28**(2):441–6. doi: 10.1007/s12032-010-9498-z. [PubMed: 20364336].

26. Hajian K, Gholizadehpasha A, Bozorgzadeh S. Association of obesity and central obesity with breast cancer risk in pre- and postmenopausal women [in Persian]. *J Babol Univ Med Sci.* 2013;**15**(3):7–15.

27. Lotfi MH, Shobairi SCS. Breast cancer risk factors in an urban area of Yazd City-Iran, 2006. *Acta Medica Iranica.* 2008;**46**(3):253–7.

28. Ghiasvand R, Bahmanyar S, Zendehdel K, Tahmasebi S, Talei A, Adami HO, et al. Postmenopausal breast cancer in Iran; risk factors and their population attributable fractions. *BMC Cancer.* 2012;**12**:414. doi: 10.1186/1471-2407-12-414. [PubMed: 22992276].

29. Ghiasvand R, Maram ES, Tahmasebi S, Tabatabaee SH. Risk factors for breast cancer among young women in southern Iran. *Int J Cancer.* 2011;**129**(6):1443–9. doi: 10.1002/ijc.25748. [PubMed: 21064105].

30. Montazeri A, Sadighi J, Farzadi F, Maftoon F, Vahdaninia M, Ansari M, et al. Weight, height, body mass index and risk of breast cancer in postmenopausal women: a case-control study. *BMC Cancer.* 2008;**8**:278. doi: 10.1186/1471-2407-8-278. [PubMed: 18826621].

31. Hosseinzadeh M, Eivazi Ziaei J, Mahdavi N, Aghajari P, Vahidi M, Fateh A, et al. Risk factors for breast cancer in Iranian women: a hospital-based case-control study in tabriz, iran. *J Breast Cancer.* 2014;**17**(3):236–43. doi: 10.4048/jbc.2014.17.3.236. [PubMed: 25320621].

32. Ghadiri F, Iranpour N, Yunesian M, Shadlou Z, Kaviani A. Do the different reasons for lactation discontinuation have similar impact on future breast problems?. *Asian Pac J Cancer Prev.* 2013;**14**(10):6147–50. [PubMed: 24289543].

33. Keihanian S, Ghaffari F, Fotokian Z, Shoormig R, Saravi M. Risk factors of breast cancer in Ramsar and Tonekabon [in Persian]. *J Qazvin Univ Med Sci.* 2010;**14**(2):12–9.

34. Mahouri K, Dehghani Zahedani M, Zare S. Breast cancer risk factors in south of Islamic Republic of Iran: a case-control study. *East Mediterr Health J.* 2007;**13**(6):1265–73. [PubMed: 18341177].

35. Pourzand A, Farajkhah H, Azhough R, Fakhree MB. Breast Cancer Risk Factors among Women without Family History in North West of Iran. *Life Sci J.* 2013;**10**.

36. Saadat M, Kohan L, Omidvari S. Genetic polymorphisms of XRCC1 (codon 399) and susceptibility to breast cancer in Iranian women, a case-control study. *Breast Cancer Res Treat.* 2008;**111**(3):549–53. doi: 10.1007/s10549-007-9811-5. [PubMed: 17987379].

37. Sepandi M, Akrami M, Tabatabaee H, Rajaeefard A, Tahmasebi S, Angali KA, et al. Breast cancer risk factors in women participating in a breast screening program: a study on 11,850 Iranian females. *Asian Pac J Cancer Prev.* 2014;**15**(19):8499–502. [PubMed: 25339054].

38. Tehranian N, Shobeiri F, Pour FH, Hagizadeh E. Risk factors for breast cancer in Iranian women aged less than 40 years. *Asian Pac J Cancer Prev.* 2010;**11**(6):1723–5. [PubMed: 21338222].

39. Yavari P, Mosavizadeh M, Sadrol-Hefazi B, Mehrabi Y. Reproductive characteristics and the risk of breast cancer–a case-control study in Iran. *Asian Pac J Cancer Prev.* 2005;**6**(3):370–5. [PubMed: 16236002].

40. Zare N, Haem E, Lankarani KB, Heydari ST, Barooti E. Breast can-cer risk factors in a defined population: weighted logistic regression approach for rare events. *J Breast Cancer.* 2013;**16**(2):214–9. doi: 10.4048/jbc.2013.16.2.214. [PubMed: 23843856].

41. Mohsenzadeh-ledari F, Keramat A, Khosravi A. Systematic review and meta-analysis of mean age at menarche in Iranian girls. *Caspian J Reprod Med.* 2015;**1**(2):28–34.

42. Mobarakeh ZS, Mirzaei K, Hatmi N, Ebrahimi M, Dabiran S, Sotoudeh G. Dietary habits contributing to breast cancer risk among Iranian women. *Asian Pac J Cancer Prev.* 2014;**15**(21):9543–7. [PubMed: 25422253].

43. Rezaeiian F, Rashidkhani B, Mirzaei HR, Akbari E, Foroutan Ghaznavi M, Shadman Z, et al. Association between folate intake and breast cancer risk among Tehrani women: a case-control study [in Persian]. *Iran J Nutr Sci Food Technol.* 2012;**6**(4):21–32.

44. Besharat S, Motie MR, Besharat M, Roshandel G. Breast cancer risk factors in women of Golestan Province in Iran: A case-control study [in Persian]. *Iran J Obstetr Gynecol Infertil.* 2011;**13**(6):46–51.

45. Eftekhari MH, Moradi M. Assessment of energy and macronutrients intake in breast cancer patients [in Persian]. *Babol Univ Med Sci J.* 2009;**11**(3):60–6.

46. Sarmento de Almeida G, Leal Almeida LA, Rodrigues Araujo GM, Weller M. Reproductive risk factors differ among breast cancer patients and controls in a public hospital of Paraiba, northeast Brazil. *Asian Pac J Cancer Prev.* 2015;**16**(7):2959–65. [PubMed: 25854389].

47. Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. *Ann Intern Med.* 2012;**156**(9):635–48. doi: 10.7326/0003-4819-156-9-201205010-00006. [PubMed: 22547473].

48. Babita R, Kumar N, Karwasra RK, Singh M, Malik JS, Kaur A. Reproductive risk factors associated with breast carcinoma in a tertiary care hospital of north India: A case-control study. *Indian J Cancer.* 2014;**51**(3):251–5. doi: 10.4103/0019-509X.146759. [PubMed: 25494116].

49. Collaborative Group on Hormonal Factors in Breast C. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol.* 2012;**13**(11):1141–51. doi: 10.1016/S1470-2045(12)70425-4. [PubMed: 23084519].

50. Bhadoria AS, Kapil U, Sareen N, Singh P. Reproductive factors and breast cancer: a case-control study in tertiary care hospital of North India. *Indian J Cancer.* 2013;**50**(4):316–21. doi: 10.4103/0019-509X.123606. [PubMed: 24369207].

51. Ichida M, Kataoka A, Tsushima R, Taguchi T. No increase in breast cancer risk in Japanese women taking oral contraceptives: a case-control study investigating reproductive, menstrual and familial risk factors for breast cancer. *Asian Pac J Cancer Prev.* 2015;**16**(9):3685–90. [PubMed: 25987022].

52. Zahmatkesh B, Keramat A, Alavi N, Khosravi A, Kousha A, Motlagh AG, et al. Breast Cancer Trend in Iran from 2000 to 2009 and Prediction till 2020 using a Trend Analysis Method. *Asian Pac J Cancer Prev.* 2016;**17**(3):1493–8. [PubMed: 27039796].