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Breast Cancer Risk Factors in Iran: A Systematic Review & Meta-analysis

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Abstract:

To systematically investigate the epidemiology of breast cancer risk factors in Iran.

We performed a systematic search via PubMed, Scopus, Web of Science and Persian databases for identifying studies published on breast cancer risk factors up to March 2019. Meta-analyses were done for risk factors reported in more than one study. We calculated odds ratios (ORs) with corresponding 95% confidence intervals (CIs) using a fixed/random-effects models.

Thirty-nine studies entered into the meta-analysis. Pooling of ORs showed a significant harmful effect for risk factors including family history (OR: 1.80, 95%CI 1.47-2.12), HRT (OR: 5.48, 95%CI 0.84-1.74), ER positive (OR: 1.87, 95%CI 1.41-2.33), PR positive (OR: 1.84, 95%CI 1.38-2.29), stress condition (OR: 2.67, 95%CI 1.84-3.50), passive smokers (OR: 1.68, 95%CI 1.34-2.03), full-term pregnancy at age 30 (OR: 3.41, 95%CI 1.19-5.63), abortion (OR: 1.84, 95%CI 1.35-2.33), sweets consumption (OR: 1.71, 95%CI 1.32-2.11) and genotype Arg/Arg (crude OR: 1.59, 95%CI 1.07-2.10), whereas a significant protective effect for late menarche (OR: 0.58, 95%CI 0.32-0.83), nulliparity (OR: 0.68, 95%CI 0.39-0.96), 13 to 24 months of breastfeeding (OR: 0.68, 95%CI 0.46-0.90), daily exercise (OR: 0.59, 95%CI 0.44-0.73) and vegetable consumption (crude OR: 0.28, 95%CI 0.10-0.46).

This study suggest that factors such as family history, HRT, ER and PR positive status, stress condition, passive smokers, late full-term pregnancy, abortion, sweets consumption and genotype Arg/Arg might increase risk of breast cancer development, whereas late menarche, nulliparity, 13-24 months breastfeeding, daily exercise and vegetable consumption had an inverse association with breast cancer development.

Keywords: Breast Tumor, Mammary Neoplasm, Breast Carcinoma, Meta-analysis, Population at Risk

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Introduction:

Breast cancer is one of the most common health concerns throughout the world [1-4], which includes 30% of female cancers [5,6]. It is also known as the second cause of death in developed countries and the third leading cause of death in less developed countries [7-9]. Surprisingly, approximately 502000 women die due to breast cancer annually [10]. According to the World Health Organization (WHO) prediction, up to 2.3 million women will be diagnosed for breast cancer by 2050 [11,12].

In Iran, breast cancer has been identified as the most common cancer and also the fifth main cause of death among Iranian women [13,4]. The standardized incidence rate (ASR) is about 28 per 100,000 people, which has increased in recent years [14]. There are a variety of proven and controversial risk factors for breast cancer. The American Cancer Society has reported that only about a quarter of breast cancers are due to identified risk factors. These factors include aging, urban life, social class (upper-middle class), marital status (single), white race, history of ovarian cancer, early menstruation, post-menopause, history of breast cancer, history of breast fibrocystic, family history of breast, uterine and ovarian cancers, and history of radiation exposure. However, it seems that numerous factors have not yet identified [15].

According to the Iran, ageing, history of breast cancer, genetic modification, chest radiation therapy, diethylstilbestrol (DES) intervention, using hormonal replacement therapy (HRT), low levels of vitamin D, exposure to chemicals in cosmetics, diet, obesity [16], smoking [17], alcohol, fertility and hormonal factors, contraceptives, early menarche, late menopause, high age at first birth, absence of labor history, other malignancies such as ovarian and endometrial carcinoma, are all the most common reported risk factors for breast cancer [18,19].

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Considering the incidence and prevalence of breast cancer, the high cost of treating the disease, and the fact that the disease affects young women who are productive in social and socioeconomic settings (about 35 years of age and older) and in case of early diagnosis of this disease (screening by mammography), this disease is one of the most potent cancers, the importance of which is more pronounced [20-23].

Despite the relatively high rate of breast cancer in the country and the importance of the associated risk factors with this malignancy, there is no nationwide study in this regard according to our knowledge. Hence, we aimed to undertake a systematic review and meta-analysis focus on the epidemiology of breast cancer risk factors in Iran. We hope our findings could provide a comprehensive report and to be useful for future studies.

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Method:

Search Strategy

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline for study design, search protocol, screening and reporting. A systematic search was performed via international databases of PubMed, Scopus and Web of Science until 05 March 2019. Moreover, for finding Persian papers we used Google Scholar database and national databases of Scientific Information Database (SID), Iranmedex and Magiran. The search strategy included MeSH terms and free keywords as follows: ((Breast OR Mammary) AND (Cancer* OR Neoplasm* OR Tumor* OR Malignanc* OR Carcinoma*) AND ("Risk factor" OR "Risk factors" OR "Population at Risk" OR "Populations at Risk") AND AND Iran). Persian equivalent words were used for searching in national databases. There was no limitation about the date of publications in our search. Only human diagnostic studies on breast cancer were included.

Criteria study selection

Two group members (A.SH and K.HD) selected the papers independently and discussed to solve the disagreements. Studies met the following criteria included into meta-analysis: 1) studies were case-control or cohort; 2) studies included the risk factors of breast cancer patients in Iran; and 3) studies were considered the female breast cancer. Studies were excluded if they were: 1) conference abstracts, comments, letters, animal studies, reviews, case reports, ecological studies, cross-sectional studies, and in vitro studies; 2) duplicate publications; 3) insufficient for calculating of desired parameters, and 4) male breast cancer studies.

Data extraction & quality assessment

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Two researchers (Z.SH and K.HD) have independently evaluated the quality of studies and extracted data from included papers. The supervisor (R.AN) resolved any disagreements in this part. Data extraction checklist included the name of the first author, publication year, a region of study, number of patients, mean age, quantitative information of risk factors, clinicopathological features, and available correlations.

The Newcastle-Ottawa Scale (NOS) checklist was used to value the selected papers in relation to various aspects of the methodology and study process.

Data analysis

Statistical analysis was performed using STATA v.11 software. To assess the heterogeneities, we used the I-square (I^2) test. According to the studies heterogeneity, we pooled results using a fixed-effects or random-effects model as appropriate for heterogeneity more or less than 50%, respectively.

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Results

Study selection process

Our initial search through databases resulted in 562 papers. After excluding duplicated papers, remained papers screened using title and abstract. Finally, after eligibility assessment of 84 full texts, 41 studies entered into qualitative synthesis and finally, 39 studies entered into the meta-analysis. PRISMA flow diagram for the study selection process presented in Figure 1.

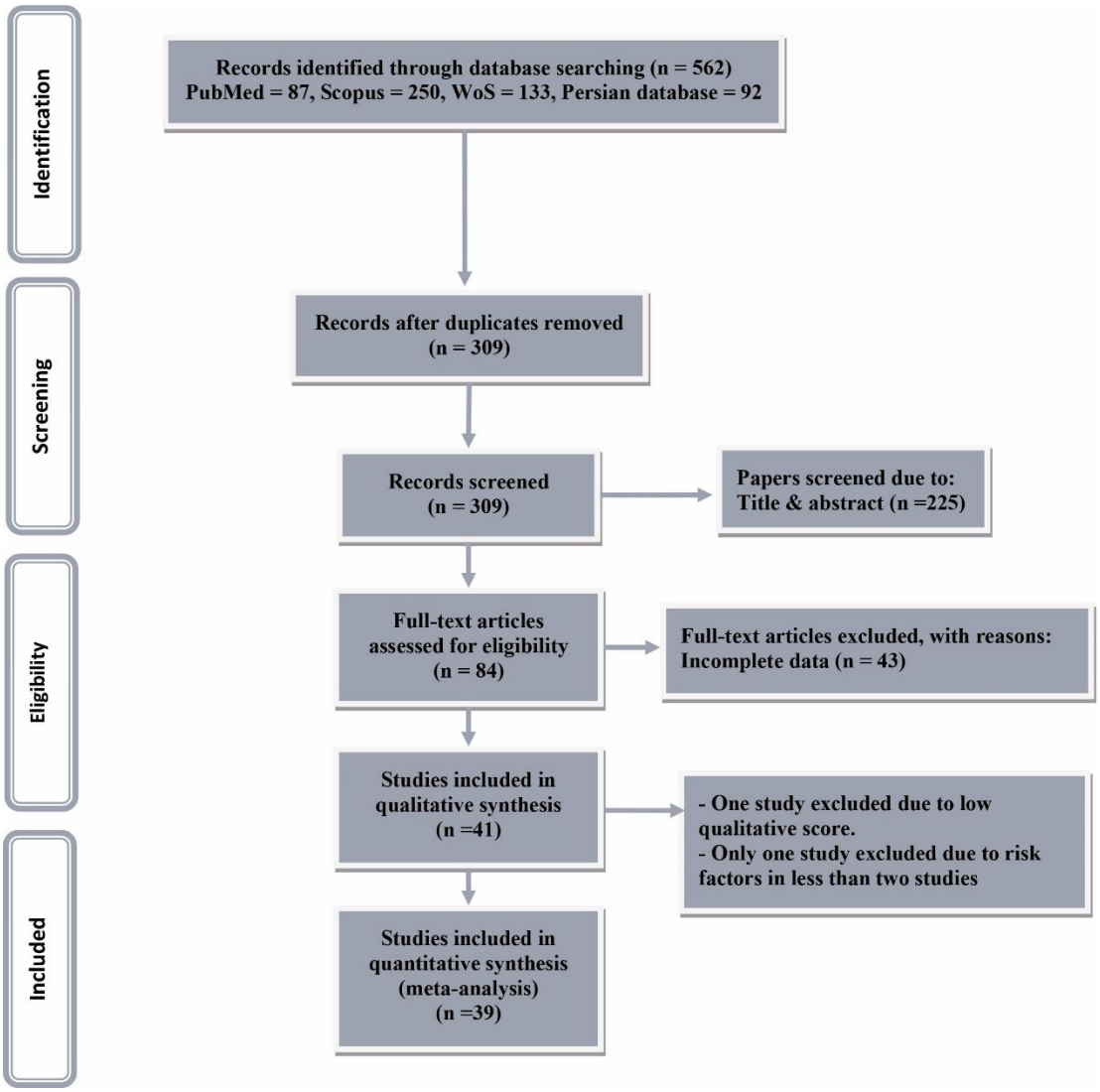

Fig. 1. PRISMA flowchart for study selection process

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Study characteristics

Out of 39 included studies, 35 studies were case-control and four of them were cross-sectional studies. The studies' sample size ranged from 93 to 25592 including 54347 participants. Nine studies were conducted in Tehran province, six in Fars, four in Mazandaran, four in Isfahan, three in East Azerbaijan, two in Guilan, two in Kermanshah, one in West Azerbaijan, one in Golestan, one in Yazd, one in Hormozgan, one in Khuzestan, and one in Razavi Khorasan. Moreover, one study was a joint study between Mazandaran and Guilan, and one study between Tehran and East Azerbaijan. Characteristics of studies entered into meta-analysis presented in Table 1.

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Table 1 Characteristics of studies entered into the meta-analysis

Author (Year)	Design	Region C/P	No. of Participants (Case/Control)	Total mean age (SD)	Case Mean age (SD)	Control Mean age (SD)	Risk Factors	Adjusted by
Ebrahimi *et al.* (2002) [24]	CC	Tehran C	535(286/249)	-	47.5(12.8)	44.2(13.2)	Age, Parity, FH, OCP, MeS, MaS, ES, Nulliparity, AFFTP	-
Pesaran *et al.* (2003) [25]	CC	Isfahan C	352(176/176)	-	49(11.3)	47(11.4)	FH	-
Montazeri *et al.* (2004) [26]	CC	Tehran C	729(243/486)	-	46.6(11.2)	45.5(10.1)	Age, FH, OCP, MeS, MeAS, MaS, ES, Depression, Hopelessness Quality of life, AFFTP, Anxiety, psychiatric medications	MeAS, FH, Depression and Hopelessness

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Yavari *et al.* (2005) [27]	CC	Tehran C	606(303/303)	-	48.8(9.8)	50.2(11.1)	FH, PBBD, OCP, MeS, MeAS, MaS, XE, ES, Parity, Abortion, BF	FH, PBBD, OCP, MeS, MeAS, MaS, XE, ES, Abortion, BF
Mahouri *et al.* (2007) [28]	CC	Bandar-Abbas C	672(168/504)	-	48.6(13.7)	48.4(13.6)	FH, PBBD, OCP, MeS, MaS, MeAS, Smoking, HRT, Nulliparity, Parity, Abortion, BF, AFFTP	-
Naieni *et al.* (2007) [29]	CC	Mazandaran P	750(250/500)	-	48.7(11.3)	48(11.4)	FH, PBBD, OCP, MeS, MeAS, Smoking, ES, BMI, Income, SS, BF, Parity, IM	Unclear adjustment
Lotfi *et al.* (2008) [30]	CC	Yazd C	160(80/80)	-	48.9(9.7)	49.1(9.8)	FH, OCP, MeS, MeAS, MaS, Occupation, XE,	Occupation, FH

							PhA, ES, BMI, BF, GS	
Kazemi *et al.* (2009) [31]	CC	Rasht &Tonekabon C	102(42/60)	-	-	-	TP53 Codon 72 Polymorphism	-
Ghiasvand *et al.* (2010) [32]	CC	Shiraz C	1042(521/521)	-	41.24	41.06	FH, OCP, MeAS, MaS, Occupation, ES, BMI, AFFTP, Parity, MA	Age, HP, Height, weight, BMI, OCP, BF. MeS, MeAS, ES, MaS
Hajian-tilaki and Kaveh-ahangar (2011) [33]	CC	Babol C	300(100/200)	-	51.2(9.6)	51.1(9.3)	MeS, MeAS, AFFTP, Parity, Abortion, BF	Parity
Hajian-tilaki (2011) [34]	CC	Babol C	300(100/200)	-	51.2(9.6)	51.1(9.3)	ES	Re, MeAS, Parity, Abortion, MeS, BF, OCP, FH, XE, Smoking, Exercise, BMI

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Motie *et al.* (2011) [35]	CC	Golestan P	267(134/133)	-	47.15(10.36)	42.96(11.93)	FH, XE, MaS, MeAS, PBBD, infertility	Unclear adjustment
Ghiasvand *et al.* (2012) [36]	CC	Shiraz C	986(493/493)	-	58.2(7.2)	58(7.4)	FH, OCP, MeAS, Occupation, ES, BMI	Age, Re
Sigaroodi *et al.* (2012) [37]	CC	Sari C	130(79/51)	-	47.77(12.55)	34.2(9.7)	Age, Human Papillomavirus	-
Ahmadinejad *et al.* (2013) [38]	CS	Tehran C	728(184/544)	48.1(8.6)	-	48.6(8.3)	Age, MeS, MaS, Smoking, Parity, AFFTP, BMI, Occupation, Diet	MeAS, Parity, AFD
Kaviani *et al.* (2013) [39]	CS	Tehran C	646	49.62(11.48)	-	-	ER, PR	Unclear adjustment
Pourzand *et al.* (2013) [40]	CC	Tabriz C	400(200/200)		50.05(11.47)	49.91(11.83)	GS, SS	-
Zare *et al.* (2013) [41]	CC	Tabriz & Tehran	25592(111/25481)	-	49.18(8.86)	46.65(9.4)	Age, FH, Occupation, OCP, MeS, MaS, HRT, ES, BMI, MA	Age, Occupation, ES, BMI, MeS, HRT, OCP

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Bidgoli and Azarshab (2014) [42]	CC	Sabzevar C	176(60/116)	-	36.45(7.02)	34.2(5.7)	SLE, SI, Diet	-
Hosseinzadeh *et al.* (2014) [43]	CC	Tabriz C	420(140/280)	-	47.6(10.7)	46.8(10.4)	FH, PBBD, OCP, MeAS, MeS, MaS, Smoking, PS, HRT, ES, BMI, Stress, Migration, Diet, Nulliparity, Abortion, BF, Infertility	MeS, BF, PBBD, MeAS, Parity, AFD, Abortion, OCP
Mobarakeh *et al.* (2014) [44]	CC	Tehran C	93(53/40)	-	40.02(10.01)	39.78(11.21)	BMI, Diet	Age, BMI, ES
Sepandi (2014) [45]	CC	Shiraz C	11850(197/11653)	-	49.4(8.7)	40.9(10.5)	FH, OCP, MeS, MeAS, MaS, Occupation, ES, BMI, Nulliparity, Parity, AFFTP	Age, MeAS, AFP, occupation, Parity, FH, BF, OCP
Tazhibi *et al.* (2014) [46]	CC	Isfahan P	257(216/41)	-	-	-	OCP, MeS, MaS, HRT	Occupation, Age, MaS,

								MeS, OCP, HRT
Salarabadi *et al.* (2015) [47]	CC	Kermanshah C	152(47/105)	-	-	-	Diet, SI	-
Tajaddini (2015) [48]	CC	Tabriz C	615(306/309)	-	46.4(10.2)	41.4(9.6)	Diet, SI	Age, MeS, Parity, BMI
Veisy *et al.* (2015) [49]	CC	West Azerbaijan P	194(111/830	-	47.6	46.5	OCP, MeAS, AFFTP	-
Ahmadnia *et al.* (2016) [50]	CC	Guilan P	450(225/225)	-	-	-	Diet	-
Jafari-Mehdiabad *et al.* (2016) [51]	CC	Isfahan P	296(98/198)	-	-	-	Mas, ES, BF, Income	-
Jafarinia *et al.* (2016) [52]	CC	Dezful C	340(170/170)	-	45.4(11)	45	FH, OCP, HRT, PhA, Stress, AFFTP, BF	ES, BF, Parity, MaS
Montazeri *et al.* (2016) [53]	CC	Tehran C/Tabriz C	975(432/543)	-	48.6(4.7)	40.6(10.7)	BF, MeAS, AFFTP	MeS, AFP, Age, BF
Dehghan *et al.* (2017) [54]	CC	Isfahan P	182(86/96)	-	52.88(11.92)	40.31(16.82)	Age, FH	FH, Occupation, MaS, Age, MeAS, MeS,

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								HRT, Abortion, BMI
Dianatinasab *et al.* (2017) [55]	CC	Shiraz C	1052(526/526)	-	47.8(10.58)	46.75(11.08)	FH, OCP, MeS, MaS, Smoking, PS, Occupation, XE, PhA, ES, Hysterectomy, Hair coloring, BMI, Stress, SQ, Parity, AFFTP, BF	MaS, AFD, Parity, Birth Spacing, BF, MeAS
Dianatinasab-2 *et al.* (2017) [56]	CS	Shiraz C	497	47.7(10.57)	-	-	Age, FH, Smoking, XE, PhA, Income, CD	-
Mirfarhadi *et al.* (2017) [57]	CS	Rasht C	232	42.82(10.23)	-	-	FH, MaS, ES, RR, IC, Income	-
Vahid *et al.* (2017) [58]	CC	Tehran C	293(145/148)	-	49.8(11.8)	48.5(11.9)	SI	Age, BMI, ES, Smoking, MeAS,

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								Occupation, MeS
Fararouei *et al.* (2018) [59]	CC	Shiraz C	1010(505/505)	-	41.78(10.56)	42.24(10.62)	FH, OCP, Smoking, PS, Occupation, PhA, ES, MA, Diet	Diet, PhA, ES, Occupation, PBBD, OCP, Smoking
Pouladi *et al.* (2018) [60]	CC	Tabriz C	303(143/160)	-	-	-	TP53 Codon 72 Polymorphism	-
Vahid *et al.* (2018) [61]	CC	Tehran C	293(145/148)	-	49.83(11.86)	48.54(12)	ER, PR	Age, ES, Exercise, BMI, Smoking, FH, MeAS, Parity, MaS, MeS, OCP, HRT
Marzbani *et al.* (2019) [62]	CC	Kermanshah C	620(212/408)	-	41.5(6.2)	39.5(7.1)	Age, MaS, ES, BMI, Diet, RR, IC, Occupation	Age, Sex, ES, BMI

C: City, P: Province, CC: Case-control, CS: Cross-sectional, FH: Familial history, OCP: Oral contraceptive pill, MeS: Menopause status, MaS: Marital status ES: Educational status, AFFTP: Age at first full-term pregnancy, HRT: Hormone replacement therapy, SLE: Sunlight exposure, SI: Supplement intake, XE: X-ray Exposure, PhA: physical activity CD: Chronic diseases, PS: Passive smoker, SQ: Sleep Quality, MeAS: Menarche age status, BF: Breastfeeding, IM: Irregular menstruation, PBBD: Previous benign breast disease, RR: Rural residency,

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Re: Residence area, IC: Insurance coverage, SS: Socioeconomic Status, GS: Genital surgery, OC: Ovary cancer, ER: Estrogen receptor, PR: Progesterone receptor, HP: history of pregnancy, AFD: age at the first delivery, MA: Marriage age

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Quality assessment

According to quality assessment using NOS checklist, 39 studies earned the minimum eligibility score and entered into the meta-analysis. It is remarkable that NOS modified checklist used for cross-sectional studies [63]. Only one paper excluded due to a low score. Summary of risk of bias presented in Fig. 2. for details see Additional file.

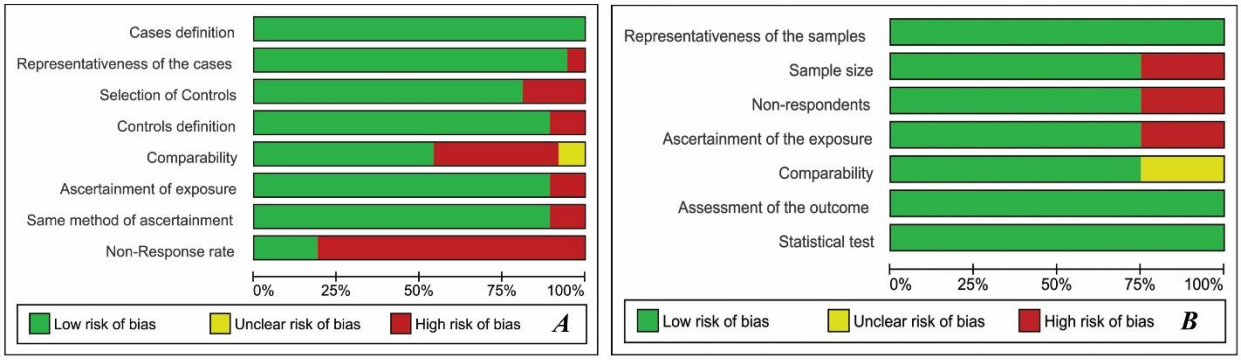

Fig. 2 Risk of bias summary. A: Case-control studies; B: Cross-sectional studies

Risk factors for breast cancer

According to included studies, over 20 risk factors were reported for breast cancer. The factors reported in only one study, which seems to be rare are as follows: High fat foods and dairy (e.g. milk, yogurt and cheese), Fast foods, Genital surgery, Hopelessness, Hair coloring, Human papillomavirus infection, Epstein–Barr virus infection, Ovarian cancer, Supplements of selenium, calcium, Vit B12 and Vit D.

The factors reported in more than one study are as follows: Age, Family history, Menarche age, Body mass index (BMI), Relationship status, Education Level, Stress conditions, Smoking status, Daily exercise, Hormone receptor status, Menopausal status, Hormone replacement therapy (HRT), Oral contraceptive, Birth giving status, Abortion status, Benign Breast Conditions, X-ray

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exposure, Breastfeeding duration, Dietary status (including sweets, egg, fish, and vegetables), Genotype status and Residency status.

Only clear well-known risk factors reported in two or more studies entered into the meta-analysis.

Individual-related risk factors (Table 2)

Age

Age was considered as a risk factor in four papers. The meta-analysis showed no significant difference between groups for breast cancer occurrence regarding age (OR: 1.04, 95%CI 0.97-1.11). A significant heterogeneity was observed (I^2=80.6%, P=0.023) (Additional file).

Family history

Eighteen studies reported on family history of breast cancer. The meta-analysis between two groups showed that the odds of breast cancer development was 1.80 times higher in subject with a family history of breast cancer (OR: 1.80, 95%CI 1.47-2.12). A modest heterogeneity was observed (I^2=24.3%, P=0.205) (Fig. 3).

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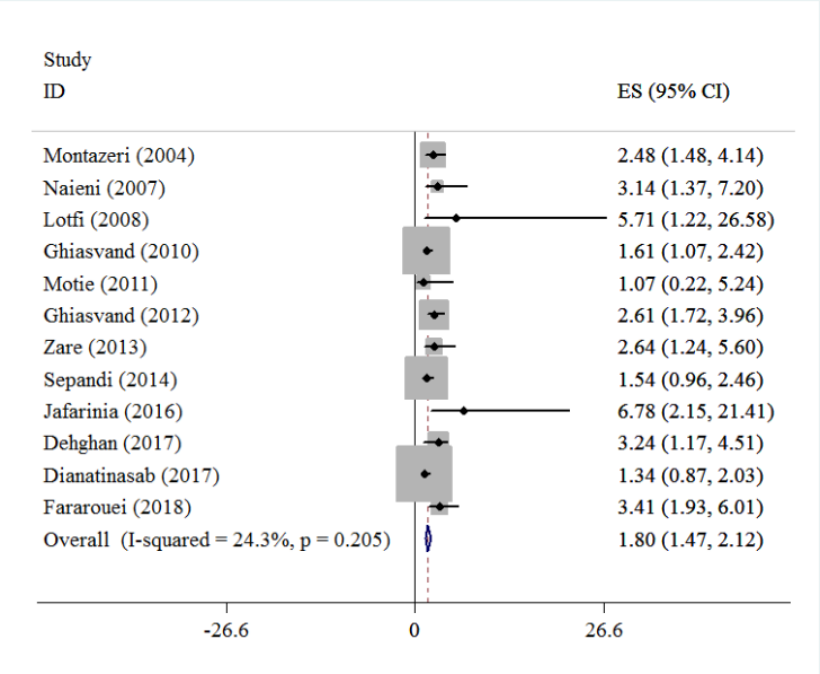

Fig 3 Forest plot for pooling adjusted odds ratio of family history

Menarche age

This factor was studied in Nine articles. The meta-analysis showed a significant protective effect for menarche age more than 15 (OR: 0.58, 95%CI 0.32-0.83). Moderate heterogeneity was observed in this regard (I^2=35.3%, P=0.201) (Fig. 4).

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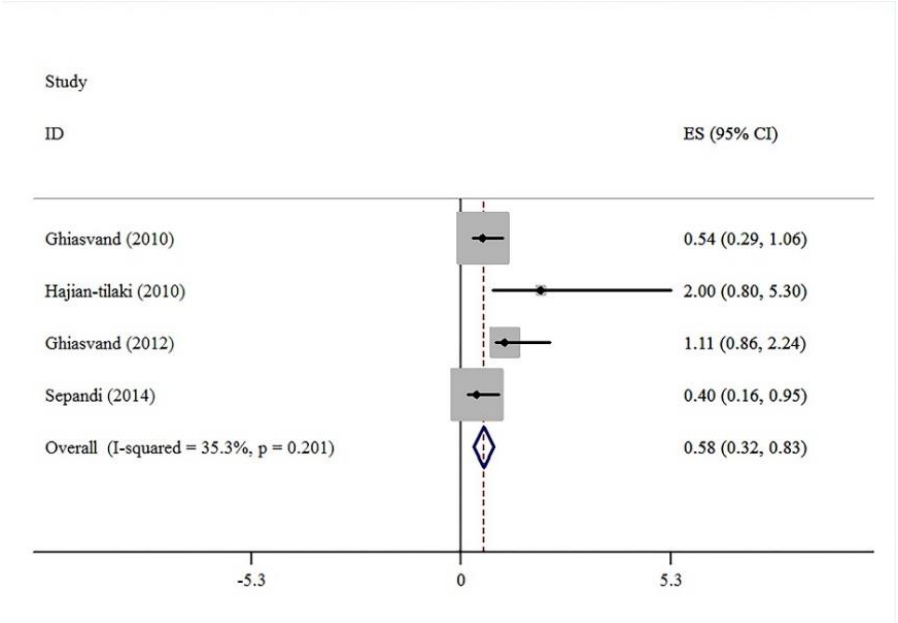

Fig. 4 Forest plot for pooling adjusted odds ratio of menarche age more than 15 years

Body mass index

BMI investigated in nine studies. The meta-analysis indicated no significant differences between groups for BMI status (OR: 1.04, 95%CI 0.99-1.09), BMI 25-29.9 (OR: 1.07, 95%CI 0.82-1.32) and BMI more than 30 (OR: 1.21, 95%CI 0.90-1.52) (Additional file).

Relationship status

Thirteen papers were studied relationship status. The meta-analysis, found that there were no significant differences between groups regarding single status (crude OR: 0.98, 95%CI 0.74-1.23), married status (crude OR: 0.64, 95%CI -0.25-1.54) and divorced status (crude OR: 1.15, 95%CI 0.87-1.43) (Additional file).

Education Level

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This factor was studied in 15 papers. According to meta-analysis, no significant differences were found for both basic education level (OR: 1.18, 95%CI 0.70-1.66) and academic education level (OR: 0.67, 95%CI 0.24-1.10) (Additional file).

Stress conditions

This factor was studied in three papers. The meta-analysis found a significantly higher chance of breast cancer occurrence in cases who experienced stressful conditions (OR: 2.67, 95%CI 1.84-3.50). No heterogeneity was observed (I^2=0.0%, P=0.384) (Fig. 5).

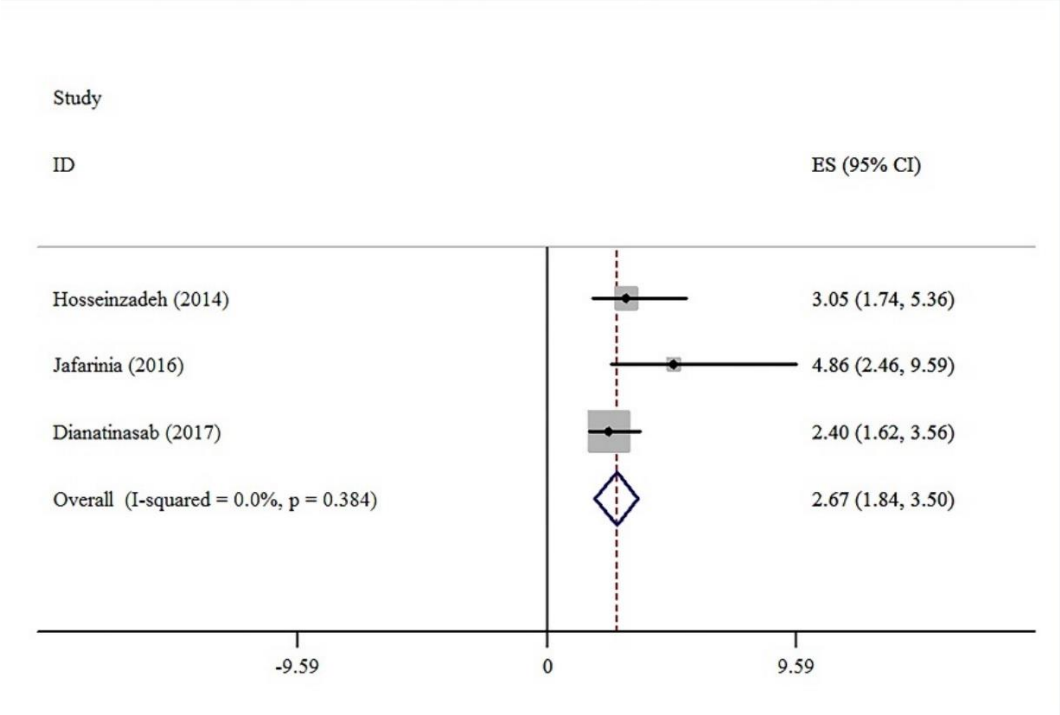

Fig. 5 Forest plot for pooling adjusted odds ratio of stress conditions experience

Smoking status

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Six papers studied this factor. The meta-analysis showed that the odds of breast cancer occurrence was 1.68 times higher in the passive smokers (OR: 1.68, 95%CI 1.34-2.03). However, no significant relationships were observed for active smokers (OR: 1.70, 95%CI 0.66-2.74) (Additional file).

Daily exercise

Three studies were included with this factor. The daily exercise showed a protective effect on the occurrence of breast cancer (OR: 0.59, 95%CI 0.44-0.73). No heterogeneity was observed (I^2=0.0%, P=0.678) (Additional file).

Hormone receptor status

Two studies were investigated ER and PR status. The meta-analysis showed a significant higher chance of breast cancer occurrence in both ER-positive subjects (OR: 1.87, 95%CI 1.41-2.33) and PR-positive subjects (OR: 1.84, 95%CI 1.38-2.29). No heterogeneity was observed (I^2=0.0%, P>0.05) (Additional file).

Menopausal status

Thirteen studies have investigated this factor. No significant relationships were observed between groups in this regard (OR: 1.29, 95%CI 0.84-1.74). High heterogeneity was observed (I^2=73.9%, P<0.0001) (Additional file).

Hormone replacement therapy

HRT was studied in five paper. The meta-analysis indicated that the odds of breast cancer occurrence was 5.48 time higher in the group with HRT history (OR: 5.48, 95%CI 0.84-1.74). No significant heterogeneity was observed (I^2=0.0%, P=0.509) (Fig. 6).

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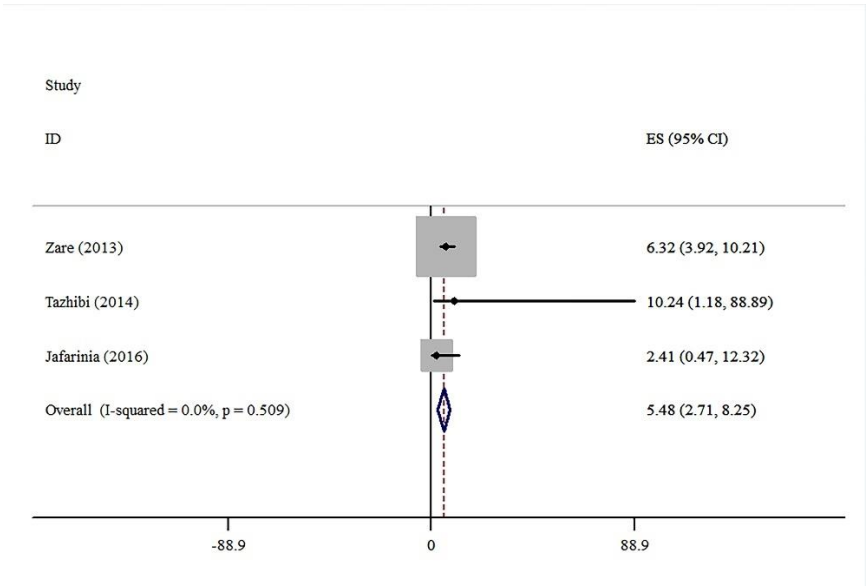

Fig. 6 Forest plot for pooling adjusted odds ratio of hormone replacement therapy

Oral contraceptive

History of OCP intake was discussed in 15 papers. The meta-analysis showed no significant differences between groups in this regard (OR: 1.17, 95%CI 0.77-1.57). High heterogeneity was observed (I^2=86.9%, P<0.0001) (Additional file).

Birth giving status

Age at first full-term pregnancy was considered in six studies. Meta-analysis showed a significant difference for age 20 to 24 (OR: 1.92, 95%CI 1.14-2.71) and age 30 (OR: 3.41, 95%CI 1.19-5.63) in this regard, but no substantial relationships were found for age 25 to 29 (OR: 1.55, 95%CI 0.82-2.29) (Additional file).

Six studies investigated the relation of nulliparity and chance of breast cancer development. The meta-analysis results indicated that this condition has an inverse relation with the occurrence of breast cancer (OR: 0.68, 95%CI 0.39-0.96) (Additional file).

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Moreover, five papers studied the history of abortion. A significant difference in odds was observed in the meta-analysis of two groups. Subjects with a history of abortion have a higher chance of breast cancer development (OR: 1.84, 95%CI 1.35-2.33). No significant heterogeneity was observed (I^2=0.0%, P=0.393) (Additional file).

Benign Breast Conditions

Data from five studies were combined for the meta-analysis of benign breast history as a risk factor to develop breast cancer. No significant difference was observed in this regard (crude OR: 1.24, 95%CI 0.82-1.67) (Additional file).

X-ray exposure

This factor was studied in four papers. No significant differences were observed regarding the history of x-rays exposure between cases and controls (OR: 1.02, 95%CI 0.19-1.86). A significant heterogeneity was observed (I^2=83.6%, P=0.002) (Additional file).

Breastfeeding duration

This factor investigated in seven studies. The meta-analysis revealed that 13 to 24 months of breastfeeding has an inverse association with breast cancer occurrence (OR: 0.68, 95%CI 0.46-0.90). No significant heterogeneity was observed (I^2=0.0%, P=0.624) (Additional file).

Dietary status

This factor was studied for egg, fish, sweets and vegetables. The meta-analysis revealed that egg (crude OR: 0.92, 95%CI -0.64-2.47) and fish (crude OR: 1.47, 95%CI 0.68-2.25) do not affect the chance of breast cancer occurrence significantly (Additional file). However, findings showed that the odds of developing breast cancer were higher in individuals with high sweets consumption

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(OR: 1.71, 95%CI 1.32-2.11) (Additional file) and lower in subjects with regular vegetable consumption (crude OR: 0.28, 95%CI 0.10-0.46) (Fig. 7).

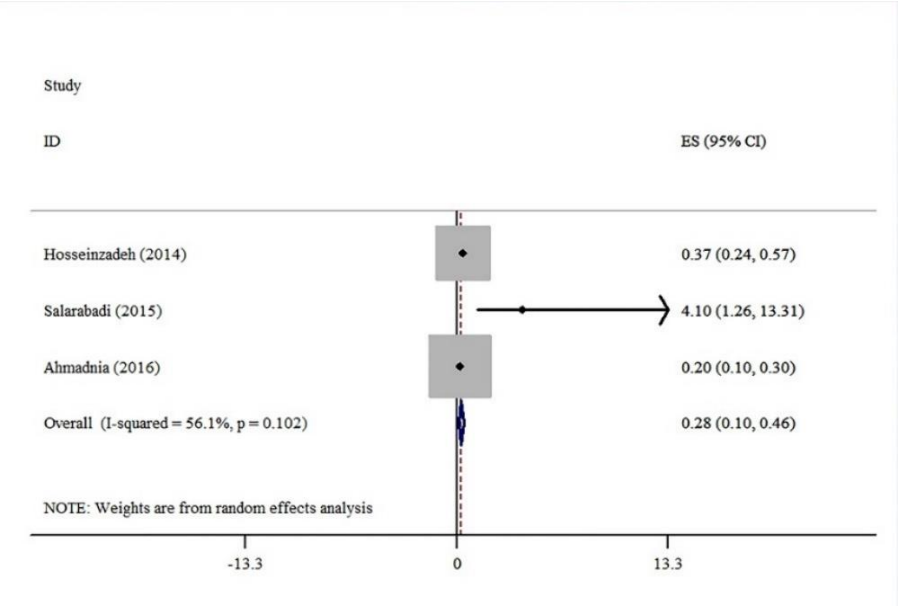

Fig. 7 Forest plot for pooling odds ratio of vegetable consumption

Genotype status

Two studies were investigated p53 codon 72 polymorphisms as a breast cancer risk factor. Although genotype Arg/Pro (crude OR: 0.69, 95%CI 0.37-1.00) was not related to the odds of breast cancer development, a significant higher chance found for genotype Arg/Arg (crude OR: 1.59, 95%CI 1.07-2.10) in this regard (Additional file).

Genital surgery

Genital surgery was considered in two studies. No significant differences were found regarding the history of genital surgery for breast cancer development (crude OR: 1.37, 95%CI 0.87-1.86) (Additional file).

Residency status

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Place of living was investigated in two studies. The meta-analysis delivered no significant difference between two groups with rural and urban residency status for breast cancer occurrence (crude OR: 1.37, 95%CI 0.87-1.86) (Additional file).

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Table 2 Summarized Pooled ORs of Considered Risk Factors

Risk Factor	Number of studies	I-squared; Crude, %	*P*-value; Crude	OR (95%CI); Crude	Number of studies	I-squared; Adjusted, %	*P*-value; Adjusted	OR (95%CI); Adjusted
Age	5	94.2	0.000	0.97 (0.92, 1.02)	2	80.6	0.023	1.04 (0.97, 1.11)
Family history	18	24.6	0.165	2.31 (1.95, 2.86)	12	24.3	0.205	1.80 (1.47, 2.12)
Menarche age status								
Unknown categorization	2	89.6	0.002	2.25 (-0.80, 5.30)	-	-	-	-
Less than 12 years	5	81.4	0.000	1.31 (0.23, 2.40)	-	-	-	-
Between 12 to 15 years	2	54.8	0.137	0.52 (0.26, 0.78)	2	77.3	0.036	0.55 (0.07, 1.03)
Less than 13 years	5	0.0	0.710	1.19 (0.94, 1.44)	-	-	-	-
Less than 14 years	5	38.6	0.164	0.91 (0.68, 1.15)	-	-	-	-
More than 15 years	5	75.5	0.003	0.81 (0.39, 1.23)	4	35.3	0.201	0.58 (0.32, 0.83)
Body mass index status								
Unknown categorization	3	65.3	0.056	1.02 (1.00, 1.05)	2	77.9	0.034	1.04 (0.99, 1.09)
Between 25-29.9	6	0.0	0.699	1.09 (0.91, 1.28)	3	0.0	0.766	1.07 (0.82, 1.32)
More than 30	5	0.0	0.433	1.15 (0.91, 1.39)	3	0.0	0.994	1.21 (0.90, 1.52)
Relationship status								
Single	11	13.6	0.315	0.98 (0.74, 1.23)	-	-	-	-
Married	2	0.0	0.678	0.64 (-0.25, 1.54)	-	-	-	-
Divorced	7	0.0	0.619	1.15 (0.87, 1.43)	-	-	-	-
Education Level								
Basic Education	14	75.5	0.000	1.23 (0.94, 1.51)	9	87.5	0.000	1.18 (0.70, 1.66)
Academic Education	12	71.4	0.000	1.21 (0.80, 1.62)	8	69.8	0.002	0.67 (0.24, 1.10)
Stress conditions	3	52.2	0.134	4.14 (2.51, 5.78)	3	0.0	0.384	2.67 (1.84, 3.50)
Smoking status								
Active Smoker	5	63.5	0.027	1.49 (0.89, 2.08)	3	66.3	0.051	1.70 (0.66, 2.74)
Passive Smoker	2	0.0	0.657	1.84 (1.43, 2.25)	3	0.0	0.442	1.68 (1.34, 2.03)
Daily exercise	4	73.5	0.010	0.40 (0.05, 0.75)	3	0.0	0.678	0.59 (0.44, 0.73)
Hormone receptor status								
Estrogen Receptor +	-	-	-	-	2	0.0	0.956	1.87 (1.41, 2.33)
Progesterone Receptor +	-	-	-	-	2	0.0	0.770	1.84 (1.38, 2.29)
Menopausal status	12	88.9	0.000	1.53 (1.06, 1.99)	9	73.9	0.000	1.29 (0.84, 1.74)
Hormone replacement therapy	4	61.9	0.049	1.80 (0.36, 3.23)	3	0.0	0.509	5.48 (2.71, 8.25)
Oral contraceptive	14	80.0	0.000	1.18 (0.93, 1.44)	10	86.9	0.000	1.17 (0.77, 1.57)
Age at first full-term pregnancy								

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20 to 24 years	3	68.0	0.044	1.48 (0.79, 2.17)	2	0.0	0.484	1.92 (1.14, 2.71)
25 to 29 years	5	0.0	0.560	1.40 (1.00, 1.80)	4	5.3	0.367	1.55 (0.82, 2.29)
30 years	5	0.0	0.758	2.23 (1.45, 3.01)	3	0.0	0.970	3.41 (1.19, 5.63)
Birth giving status								
Nulliparity	6	40.4	0.136	0.77 (0.55, 0.98)	3	28.0	0.249	0.68 (0.39, 0.96)
Abortion	5	86.9	0.000	1.25 (0.57, 1.93)	3	0.0	0.393	1.84 (1.35, 2.33)
Previous benign breast	5	0.0	0.672	1.24 (0.82, 1.67)	-	-	-	-
X-ray exposure	5	0.0	0.676	1.42 (1.18, 1.66)	3	83.6	0.002	1.02 (0.19, 1.86)
Breastfeeding duration								
Breastfeeding	3	0.0	0.526	0.58 (0.30, 0.85)	2	88.1	0.004	0.73 (0.14, 1.31)
1 to 12 months	3	40.0	0.189	0.95 (0.41, 1.49)	-	-	-	-
13 to 24 months	4	0.0	0.602	0.57 (0.42, 0.72)	2	0.0	0.624	0.68 (0.46, 0.90)
25 to 48 months	2	92.1	0.000	1.12 (-0.68, 2.92)	2	0.0	0.402	0.24 (-0.46, 0.94)
More than 49 months	-	-	-	-	2	0.0	0.410	0.10 (-0.25, 0.44)
Dietary status								
Egg	2	82.7	0.016	0.92 (-0.64, 2.47)	-	-	-	-
Fish	2	0.0	0.462	1.47 (0.68, 2.25)	-	-	-	-
Sweets	2	73.2	0.053	2.83 (1.38, 4.29)	2	0.0	0.391	2.21 (1.56, 2.87)
Vegetables	3	56.1	0.102	0.28 (0.10, 0.46)	-	-	-	-
Genotype status								
Arg/Arg	2	0.0	0.835	1.59 (1.07, 2.10)	-	-	-	-
Arg/Pro	2	0.0	0.824	0.69 (0.37, 1.00)	-	-	-	-
Genital surgery	2	0.0	0.325	2.23 (0.91, 3.55)	-	-	-	-
Residency status								
Rural	2	0.0	0.875	1.37 (0.87, 1.86)	-	-	-	-

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Discussion:

We undertook this systematic review and meta-analysis to identify the risk factors that contribute to the occurrence of female breast cancer in Iran. Out of 39 included papers, more than 60 factors were studied as breast cancer risk factors, of which only 27 factors entered into the meta-analysis. Out of these 27 risk factors, 11 factors including family history, HRT, ER and PR positive status, stress condition, passive smokers, late full-term pregnancy, abortion, sweets consumption and genotype Arg/Arg indicated to be significantly associated with a higher chance of breast cancer development. In contrast, five factors of late menarche, nulliparity, 13 to 24 months of breastfeeding, daily exercise and vegetable consumption, demonstrated to be protective factors in this regard. The other remaining risk factors were not associated with the development of breast cancer.

Family history of breast cancer was one of the associated risk factors for breast cancer development in our study. In one of the first meta-analysis on "*Family history and the risk of breast cancer*", Pharoah *et al.* [64] pooled estimate of relative risk (RR) indicated that the probability of breast cancer occurrence is higher in those individuals with a family history of this malignancy (RR: 1.9, 95%CI, 1.7-2.0). They also found that this probability is higher in the first-degree relatives, especially mother and sister (RR: 3.6, 95%CI 2.5-5.0). There are many other studies that reported the association of family history with the risk of breast cancer [65-67].

High levels of estrogen can increase the chance of breast cancer development through genotoxic stress induction and breast tissue mutations [68,69]. Therefore, receiving external estrogen through HRT may increase the risk of breast cancer development. In this regard, HRT users showed the highest chance of developing breast cancer in our meta-analysis (OR: 5.48, 95%CI 0.84-1.74), in

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consistent with several studies [70-72]. In contrast, study of Bae *et al.* reported no significant association in this regard among Korean Women [73].

The first systematic review on "*Adverse life-events and risk of breast cancer*"[74] indicated no significant relationships in this regard (OR: 0.8, 95%CI 0.96-1.06) and two other systematic reviews reported the same conclusion [75,76]. Our results were contrary to these studies, but was in the same line with the study of Lin *et al.* that demonstrated significant evidence for a positive relationship between life stressful events and risk of breast cancer (OR: 1.51, 95%CI 1.15-1.97, *P*=0.003) [77].

In our meta-analysis, although passive smokers were at higher risk of breast cancer development, no significant association was found for active smokers in this case. Our findings were in the same line with the systematic review of Chen *et al.* [78] among Chinese females, which implied that passive smokers were at higher risk of breast cancer development (OR: 1.62, 95%CI 1.39-1.85), but not active smokers (OR: 1.04, 95%CI 0.89-1.20). Moreover, some other studies reported a significant association between passive smoking and the risk of breast cancer [79-81].

In regard to the age at first full-term pregnancy, our results were in the same line with previous studies regarding the higher risk of breast cancer at age 30 or older ages [82,83]. For nulliparity condition, our study showed an inverse association with breast cancer development, which was in contrast with several previous reports [84,85].

Numerous investigators have studied the association of induced abortion and risk of breast cancer throughout the world. One of the oldest studies titled "*Induced abortion as a cancer risk factor*" discussed the induced abortion as a breast cancer risk factor [86]. Similarly, some meta-analysis also reported the same conclusions [87,88]. In this regard, our meta-analysis found that induced abortion was significantly associated with risk of breast cancer in Iranian women. Besides, the

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study of Deng *et al.* demonstrated that induced abortion might be associated with risk of breast cancer in parous women (OR: 1.11, 95%CI, 1.02-1.20, *P*=0.01), but not in nulliparous women (OR:1.02, 95%CI, 0.86-1.21, *P*=.85). In contrast, several studies arrived at contradictory conclusions [89,90].

The meta-analysis findings showed the significant association between sweet foods consumption and risk of breast cancer. Although we did not find a specific systematic review in this regard, several epidemiological studies in different regions reported the association of sweet foods consumption and risk of breast cancer [91-94]. For example, Tavani *et al.* performed a comprehensive case-control study in Italy and found a direct relationship between sweet foods consumption and risk of breast cancer development [94]. In fact, excessive sweets intake with a high glycemic index may cause insulin resistance as well as insulin-related growth factors as promoters of breast carcinogenesis. Moreover, ovarian steroid secretion including estrogens and androgens might be stimulated by insulin. Altogether, these processes end up in increased risk of breast cancer [95,96].

Previous studies have investigated the relationships of P53 codon 72 polymorphisms and risk of breast cancer development in different regions [97]. In this investigation, we found that the genotype Arg/Arg is associated with the development of breast cancer, which was in consistent with the study of Al-Qasem *et al.* among Saudi women, and in contrast with meta-analysis carried out by Ma *et al.* and Hou *et al.* studies [98,99].

Menarche age does not exactly match with the breast cancer onset. However, they are significantly correlated [100]. This meta-analysis demonstrated an inverse association between late menarche age and risk of breast cancer (OR: 0.58, 95%CI 0.32-0.83). Our findings were along the same

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direction with two other meta-analyses carried out by Li *et al*. [101] and Collaborative Group on Hormonal Factors in Breast Cancer [102].

We found that longer breastfeeding duration (13 to 24 months) plays a protective rule against breast cancer development, in consistent with numerous meta-analysis in various populations [103-106]. In this regard, according to one of the most comprehensive studies on "*Breast cancer and breastfeeding"* including 47 epidemiological studies in 30 countries, breast cancer development would be reduced by 42%, especially in developing countries because women in these countries usually have a long duration of breastfeeding throughout their lives [107]. In contrast, short breastfeeding duration, which is usual among women in developed countries with small family size, would contribute to a higher risk of breast cancer development in such countries [107].

The updated report "*Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*" in 2007, recommended physical activity as a protective factor against cancers, especially postmenopausal breast cancer [108]. It was also recommended by "*American Cancer Society Guidelines on nutrition and physical activity for cancer prevention*" [109]. Our findings also support this hypothesis as a preventive factor for breast cancer development. In fact, physical activities effect on the risk of cancers development through mechanisms such as metabolic, reproductive effects, hormonal, and immunity enhancement, etc. [110]. The comprehensive study of Moore *et al.* titled "*Association of Leisure-Time Physical Activity with Risk of 26 Types of Cancer in 1.44 Million Adults*" reported the significant association for high and low physical activity and lower risk of breast cancer (hazard ratio (HR): 0.9, 95% CI, 0.87-0.93).

The association between vegetables intake and risk of breast cancer was always controversial. Our results suggest a protective effect of vegetable consumption on risk of breast cancer. In the same

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direction, meta-analyses carried out by Liu *et al.*, Woo *et al.* and Aune *et al.* indicated a significant association between various types of vegetables and dietary fiber consumption and risk of breast cancer development [111-113]. In contrast, several systematic reviews and meta-analysis showed no significant relationships in this regard [114,115] and some others were controversial regarding the types of vegetables and its combination intake with fruits as well as breast cancer types [116,117].

According to the retrospective nature of the included studies, it is recommended to design some longitudinal cohort investigations in order to examine the accurate role of these risk factors in breast cancer development.

Conclusion:

Based on this systematic review and meta-analysis, factors including a family history of breast cancer, HRT, ER and PR positive status, the experience of stress condition, passive smokers, abortion, sweets consumption and genotype Arg/Arg, play a significant role in the development of breast cancer. In contrast, late menarche, nulliparity, long breastfeeding duration, regular physical activity and consumption of vegetables showed a significant inverse association with breast cancer occurrence.

Ethics approval

It is only remarkable that the protocol of this systematic review and meta-analysis registered in International Prospective Register of Systematic Reviews (PROSPERO) due to code CRD42019127382.

Conflict of interests

The authors declare that they have no conflict of interests.

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