RESEARCH ARTICLE

Risk Factors of Breast Cancer in the Eastern Mediterranean Region: A Systematic Review and Meta-Analysis

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Abstract

Background: Identifying risk factors of breast cancer is a key point for preventive strategies to reduce the incidence. The aim of current study was to determine most important risk factors for breast cancer in the Eastern Mediterranean Region (EMR) using a systematic review. Materials and Methods: PubMed, Scopus, Web of Science till August 24, 2012 and the reference lists of all included studies were searched. Analytic studies which had reported odds ratios (OR), relative risk (RR) or required data to calculate them were included. A total of 343 studies were critically appraised and finally 30 studies were meta-analyzed. Heterogeneity between the studies was assessed by I^2 and Cochran's Q. Egger's test was used to assess publication bias. Results: Twenty five case-control studies, one nested case-control and four cohort studies were included. The largest ORs were obtained for history of no live birth (2.25; 95%CI: 1.58-3.18), body mass index (BMI) more than 30 (2.21; 95%CI: 1.71-2.36), age at first pregnancy more than 30 years old (1.52; 95%CI: 1.30-1.77) and meat consumption more than three times per week (1.39; 95%CI: 1.03-1.87). The other important predictors were higher education and smoking as risk factors, physical activity and ovulatory stimulating medication as protective factors. Conclusions: The most important predictors of breast cancer in EMR were history of no live birth, BMI more than 30, age at first pregnancy more than 30 years old, physical inactivity and smoking. Almost all these risk factors are consistent with known risk factors for this cancer in other parts of the world.

Keywords: Breast cancer - Eastern Mediterranean Region - risk factors - systematic review

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Introduction

Breast cancer is the most common malignancy of women in the world (Minatoya et al., 2013). This cancer accounts about one fifth of all female malignancy. Breast cancer is the leading cause of death in high income countries and second leading cause in low and middle income countries (Jemal et al., 2011). This cancer is increasing in many developing countries (Yang et al., 2005)

The known most important determinant factors for breast cancer included: age, family history, genetics, personal history of breast cancer, radiation to chest/face before age 30, race/ethnicity, being overweight, pregnancy/breast feeding and menstrual history, using hormone replacement therapy (HRT), drinking alcohol, having dense breast, lack of exercise, and smoking (Das et al., 2012; Wafa et al., 2014).

The World Health Organization's (WHO) Eastern Mediterranean Region (EMR) covers a population of over 500 million, spread over a wide area of relative cultural and geographical similarity extending from Morocco to Afghanistan. The EMR includes 22 countries.

The population, cultures, religious, habits, and knowledge of women in EMR is different from the women lived in developed countries (Habibzadeh, 2012). Majority of women in this region knows little about screening methods of breast cancer. Differences in cultures, habits, and ethnicity affect on differences in marital age, pregnancy features, age of menarche, and other important risk factors of breast cancer in this region (Habibzadeh, 2012). In many countries (such as Iran, Tunisia, Pakistan) of this region the breast cancer diagnosis age is younger than other parts of the world (Shaukat, 2013; Bidgoli and Azarshab, 2014). Also, the stage of diagnosed breast cancer in some countries in this area is highest than the other regions which can be due to lack of knowledge about breast cancer screening (Harirchi, 2012).

Knowing about risk factors of breast cancer in EMR can help policy makers to plan preventive strategies to reduce the incidence of it. Findings of systematic reviews on risk factors of breast cancer in developed countries mostly cannot be useful and generalized to women in EMR. The aim of current study is to determine most

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important breast cancer risk factors in EMR by reviewing analytic studies by a systematic review and meta-analysis.

Materials and Methods

Data sources

We conducted a systematic search of all studies which evaluated breast cancer risk factors (except genetics) in EMR using PubMed database, Scopus, EMbase, and Web of Science up to August 24, 2012. The last updated search was done on July 21, 2014. The reference lists of all included studies were searched for further evidences too.

Search strategy

The search strategy was according problem, intervention, comparison, and outcome (PICO) characteristics: The women of EMR countries, risk factor and breast cancer. Table one shows the key words of our search based on medical subjects heading (Mesh).

Eligible studies

We included analytic studies if they had reported Odds Ratio (OR), Relative Risk (RR) or required data to calculate them with 95% confidence interval (CI). The search was restricted to English papers that published as full text. There was no age limitation. We excluded studies if they were reviews, letters, case reports, case series, cross sectionals and the studies that did not report obviously the population sources or the available data to calculate the OR and RR. Also any study on men was excluded too. Figure one depicts the selection process of studies included in the systematic review and meta-analysis.

Quality evaluation of articles and data extraction

Two independent investigators (NN and SKR) conducted data extraction using pre-specified inclusion and exclusion criteria. Discrepancies were resolved by discussion between reviewers and reaching to consensus and if required, senior investigator (MN) qualified the studies. The Newcastle-Ottawa scale as a tool for assessing case-control and cohort studies (Wells, 2000) was used to evaluate the quality of studies. Each study is judged on eight items, categorized into three groups: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively.

All of included studies (100%) fulfilled the key questions. Out of 30, just four studies fulfilled highest score (8 score out of 8). Finally, necessary information was extracted from each eligible study.

The extracted information included: first author name, the origin country, date of study, date of publication, sampled population, sample size, number of cases and controls, study design, reproductive, lifestyle, and socio-demographic risk factors of breast cancer. Selected life style factors contained body mass index, physical activity, smoking, alcohol consumption and dietary habits (especially meat consumption). The reproductive risk factors included age at first pregnancy, age at first menstruation, history of no live birth, induced abortion and nulliparity. Years of education was considered as a socio demographic risk factor.

Statistical analysis and synthesis of results

The OR with 95%CI was principle summary measure and if it was not presented in the individual study, OR with 95%CI was calculated by LaMorte-stat tool (Wayne and LaMorte, 2006) The reference cutoff for included risk factors were as follow: Body mass index between 25-30 (over weight) and more than 30 (obese), physical activity more than 5.5 hour/week/year, positive history of smoking (not considering pack/year), meat consumption more than three times per week, alcohol consumption (not considering standard unit of alcohol consumption per day), age at first menstruation less than 12 years old and age at first pregnancy more than 30 years old.

Heterogeneity between the studies was defined as $p<0.1$ or I^2 Index >50% using Cochran's Q and I^2 index respectively. I^2 Index was calculated as $100 \times$ (Cochrane Q - df)/Cochrane Q. In case of heterogeneity between the studies random-effect model was used in meta-analysis. If not, the fixed-effect model was done. Egger's linear regression test was used to indicate the publication bias ($P<0.05$ set as significant level). Meta-analysis was performed by the Stata statistical software (version 10, Stata Corporation, College Station, Texas, USA).

This study was approved by research and ethical committees of Tehran University of Medical Sciences.

Results

Search results

After removing 1034 duplicated records, 4314 studies were screened according title and abstract which 3971 were excluded and 343 studies were critically appraised. Finally, thirty (Aboudaoud, 1971; Henquin et al., 1994; Potashnik et al., 1999; Nustas et al., 2002; Alothaimeen et al., 2004; Gilani and Kamal, 2004; Yavari et al., 2005; Fakri et al., 2006; Lerner et al., 2006; Shaham et al., 2006; Faheem et al., 2007; Shema et al., 2007; Naieni et al., 2007; Mahouri et al., 2007; Katz et al., 2008; Peled et al., 2008; Montazeri et al., 2008; Saadat et al., 2008; Saleh et al., 2008; Ahmad et al., 2009; Calderon et al., 2009; Majid et al., 2009; Awatef et al., 2010; Abdulbari et al., 2010; Bidgoli et al., 2011; Ghiasvand et al., 2011; Hajian and Ahangar, 2011; Javed et al., 2011; Kloong et al., 2011; Tehranian et al., 2011) eligible studies included in the meta-analysis after quality assessment (Table 2 and Figure 1). Twenty five case-control studies, one nested case-control and four cohort studies were included.

Assessing publication bias

We used Egger's test to assess publication bias. The results of this test showed there were no publication biases for majority of reported risk factors ($p>0.05$). The results of Egger's test showed publication bias for history of using ovarian stimulation medication, age at first pregnancy, history of no live birth, education and age of menarche.

Table 3 illustrates pooled ORs for selected risk factors of breast cancer. Ten studies (Alothaimeen et al., 2004; Awatef et al., 2010; Abdulbari et al., 2010; Bidgoli et al., 2011; Ghiasvand et al., 2011;Gilani and Kamal,2004;

Table 1. PICO Characteristics MeSH Terms

Outcome	Intervention	Population
Breast Neoplasm	Risk	Kuwait*
Neoplasm, Breast	Risk Assessment	Lebanon*
Neoplasms, Breast	Risk Management	Libya
Tumors, Breast	Risk Reduction Behavior	Libyan Arab Jamahiriya*
Breast Tumors	Risk Sharing, Financial	morocco*
Breast Tumor	Risk Factors	Oman*
Tumor, Breast	Organs at Risk	Pakistan*
Mammary Carcinoma, Human	Risk Adjustment	Qatar*
Carcinoma, Human Mammary	Risk-Taking	Syrian Arab republic*
Carcinomas, Human Mammary	Behavioral Risk Factor Surveillance System	Sudan*
Human Mammary Carcinomas	Numbers Needed To Treat	Somalia*
Mammary Carcinomas, Human	Health Status Indicators	Saudi Arabia*
Human Mammary Carcinoma	Odds Ratio	south Sudan
Mammary Neoplasms, Human	Population Characteristics	Tunisia*
Human Mammary Neoplasm	RISK FACTOR	united Arab emirates*
Human Mammary Neoplasms	Predictor	Arabs*
Neoplasm, Human Mammary	Protective factor	Yemen*
Neoplasms, Human Mammary		middle east*
Mammary Neoplasm, Human		emro
Breast Cancer		Iran*
Cancer, Breast		Iraq*
Cancer of the Breast		Bahrain*
Cancer of the Breast		Israel*
breast gland cancer		afghan*
breast gland neoplasm		Palestine*
mamma cancer		Jordan*
mammary cancer		Djibouti*
mammary gland cancer		Egypt*
advanced breast cancer		Persia*
breast cancer recurrence		Bedouin*
		Transjordan*
		Aden*
		Republic of Yemen*
		south Yemen*
		Yemen democratic republic*
		yemen, northern*
		united Arab republic* orbyzantium*
		fertile crescent*
		near east*

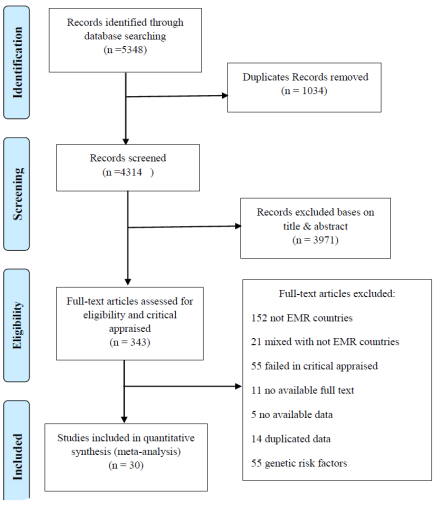

Figure 1. The Selection Process for the Studies Included in the Systematic Review-Meta Analysis

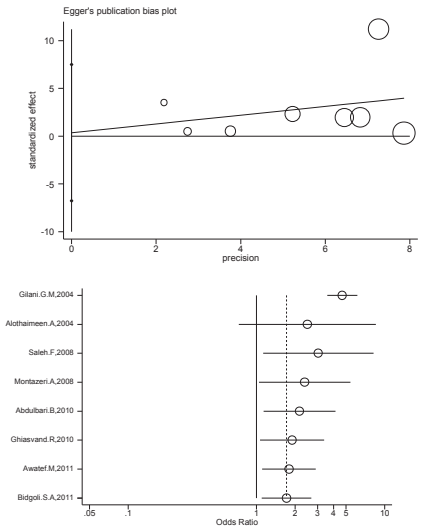

Figure 2. Cumulative Forest Plot of Breast Cancer and Body Mass Index (25-30)

Henquin et al., 1994; Lerner et al., 2006; Montazeri et al., 2008; Saleh et al., 2008) evaluated the association between BMI and breast cancer in EMR countries. Six studies had reported both cutoffs of 25-30 and more than 30 for BMI (Abdulbari et al., 2010; Bidgoli et al., 2011; Montazeri et al., 2008; Saleh et al., 2008; Ghiasvand et al., 2011; Gilani and Kamal, 2004). Two studies had assessed (Henquin et al., 1994; Lerner et al., 2006) a cutoff of more than 30 and other two studies a cutoff of 25-30 for BMI (Alothaimeen et al., 2004; Awatef et al., 2010)". . Just one of study categorized the results to pre and post-menopausal status. The pooled OR for BMI between 25 -30 versus lower than 25 was 1.71 [95%CI: 1.09-2.68], with low heterogeneity (I^2=22%; p=0.931) (Figure 2). For BMI more than 30 versus BMI lower than 25 the pooled

Table 2. Characteristics of Included Studies to Assess Risk Factors of Breast Cancer in EMR Countries

Author	Year	Study design	Sample size	Case	Control	Risk factor
A. Alothaimeen	2004	Case-control	997	499	498	BMI[1]
B. Abdulbari	2010	Case-control	508	167	341	BMI/Meat/ Smoking/education>12years
M. Awatef	2011	Case-control	800	400	400	PH.A[2]/BMI/menarche<12 years old/nulliparity/ first pregnancy>30 years old/education>12years/ no live birth
SA. Bidgoli	2011	Case-control	150	50	100	BMI/ Smoking/ nulparity
R.Ghiasvand	2010	Case-control	1042	521	521	BMI/ first pregnancy>30 years old,education>12years/ menarche<12years old/ nulparity
M.GH .Gilani	2004	Case-control	1494	498	996	BMI/abortion/ menarche<12years old/ first pregnancy>30 years old/ nulparity
K.Hajian-Tilaki	2012	Case-control	300	100	200	PH.A/ Smoking/ abortion/ menarche<12years old/ first pregnancy>30 years old/no live birth
N. Henquin	1994	Case-control	82	43	39	BMI
G. Lerner	2006	Nested case control	6015	61	120	BMI/ovarian stimulation medication/
A .Montazeri	2008	Case-control	232	116	116	BMI/nullparity/ menarche<12years old/ first pregnancy>30 years old/ education>12years/ no live birth
P. Nustas	2002	Case-control	200	100	100	PH.A
F. Saleh	2008	Case-control	100	50	50	BMI/PH.A/ Meat/Smoking/ education>12years/ Nulparity/menarche<12years old
S. Fakri	2006	Case-control	104	54	50	Smoking
M. Faheem	2007	Case-control	300	150	150	Smoking/ Nulparity/
S. Javed	2011	Case-control	200	100	100	Smoking/ first pregnancy>30 years old/ Nulparity/
K.H. Mahouri	2007	Case-control	672	168	504	Smoking/nulliparity/abortion/menarche<12years old/ first pregnancy>30 years old
M. Saadat	2008	Case-control	374	187	187	Smoking/Alcohol/ menarche<12years old
J. Shaham	2006	Case-control	739	326	413	Smoking/Meat/no live birth/ovarian stimulation medication
Kloong	2011	Cohort	1679	794	885	Alcohol/ education>12years
L. Shema	2007	Case-control	792	256	536	nulparity
N. Tehranian	2010	Case-control	624	312	312	Abortion/ menarche<12years old/ nulparity/
K. Naeini-Holakouie	2007	Case-control	750	250	500	Abortion/ education>12years
P. Yavari	2005	Case-control	606	303	303	Abortion/ menarche<12years old/ nulparity/ no live birth/first pregnancy>30 years old
R. Majid	2009	Case-control	550	296	254	Nulparity
D. Katz	2008	Nested cohort	7162	28	140	menarche<12years old/ first pregnancy>30 years old/ no live birth
S. Ahmad	2009	Case-control	1376	688	688	first pregnancy>30 years old
R. Peled	2008	Case- control	622	255	367	education>12years
KT. Abou- Daoud	1971	Case- control	212	72	140	first pregnancy>30 years old
G. Potashnik	1999	Cohort	1197	16	4	ovarian stimulation medication
R. Calderon-Margalit	2009	Historical cohort	15030	567	-	ovarian stimulation medication

1:BMI: body mass index; 2: PH.A: Physical activity

Table 3. Pooled Estimation of ORs Obtained from Meta-Analysis of Risk Factors of Breast Cancer in EMR

Risk factors	Included studies	Pooled Odds ratio	95% Confidence interval
Ovarian Stimulation Medication	4	0.86	0.81-0.91
First pregnancy>30 years old	11	1.52	1.30-1.77
Abortion	6	1.04	0.89-1.23
Nulliparity	13	0.94	0.88-1.01
No live birth	6	2.25	1.58-3.18
Education>12years	8	1.32	1.40-1.55
Menarche<12years old	11	1.12	0.97-1.28
Body Mass Index25-30	8	1.71	1.09-2.68
Body Mass Index >30	8	2.21	1.71-2.36
Physical Activity >5.5 h/w	4	0.32	0.27-038
Smoking	10	1.25	1.12-1.39
Meat consumption	3	1.39	1.03-1.87

OR was 2.21 (95%CI: 1.71-2.36), with low heterogeneity (I^2 =15%; p=0.99) (Figure 3).

Four studies (Nustas et al., 2002; Shaham et al., 2006; Awatef et al., 2010; Hajian and Ahangar, 2011) had evaluated the association between physical activity and breast cancer in EMR countries. The pooled OR using random model for physical activity more than 5.5 hour/ week/year versus no regular physical activity was 0.32

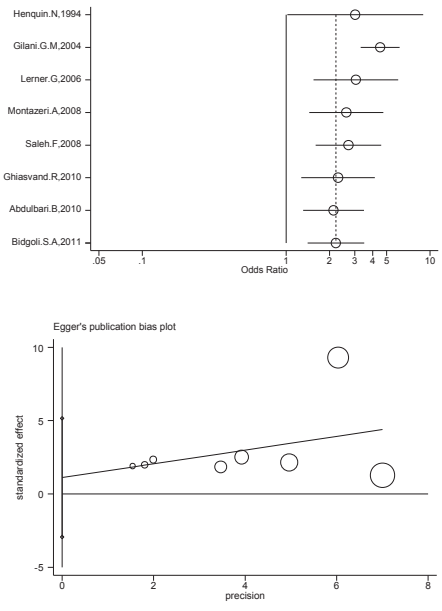

Figure 3. Cumulative Forest Plot of Breast Cancer and Body Mass Index More than 30

(95%CI: 0.27-0.38), with I^2=86% (p=0.003) (Figure 4).

Ten studies (Fakri et al., 2006; Shaham et al., 2006; Faheem et al., 2007; Mahouri et al., 2007; Saleh et al., 2008; Saadat et al., 2008; Abdulbari et al., 2010; Bidgoli et al., 2011; Hajian and Ahangar, 2011; Javed et al., 2011) had evaluated the association between smoking and breast cancer in EMR countries. Pooled OR using random model for smoking versus no smoking was 1.25 (95%CI: 1.12-1.39), with high heterogeneity (I^2=93%; p=0.003 (Figure 5).

Three studies (Shaham et al., 2006; Saleh et al., 2008; Abdulbari et al., 2010) had evaluated the association between meat consumption more than three times per week and breast cancer in EMR countries. The pooled OR for meat consumption more than three times per week versus less than three times was 1.39 (95%CI: 1.03-1.87), with no heterogeneity (I^2 =0%; p=0.99).

We just found two studies in which alcohol as a risk factor of breast cancer was assessed in EMR. Therefore, we did not calculate pooled odds ratio for alcohol consumption.

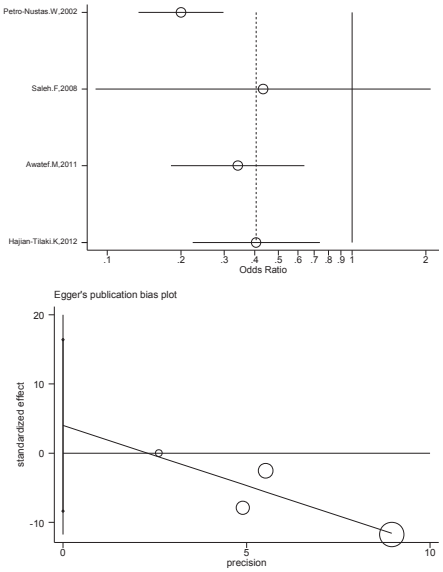

Figure 4. Cumulative Forest Plot of Breast Cancer and Physical Activity More than 5.5 h/w

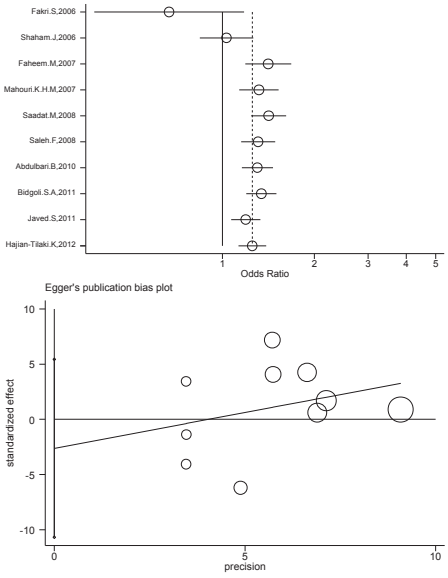

Figure 5. Cumulative Forest Plot of Breast Cancer and Smoking

Discussion

In this systematic review and meta-analysis we showed that obesity (BMI more than 30), over weight (BMI=25-30), meat consumption more than three times in a week, smoking, physical activity less than 5.5 h/w, first pregnancy more than 30 years old, not having live birth and education more than 12 years are the risk factors for breast cancer in women who live in EMRO. These findings are also supported by individual studies and other systematic reviews (Alothaimeen et al., 2004; Yavari et al., 2005; Saleh et al., 2008; Awatef et al., 2010).

Life style is one of the noteworthy risk factor for non-communicable diseases such as cancers, cardiovascular diseases and diabetes (Javed et al., 2011). Life style contains four major subgroups: diet, physical activity, tobacco abuse and risky behaviours. Changing of the Mediterranean diet to westernized diet in the EMR may be a basic breast cancer risk factor in EMR and this situation is recognised as transient period in epidemiological studies (Henquin et al., 1994; Ilic et al., 2013). Body mass index is noticeably associated with hormone receptor status and higher risk of oestrogen receptor (ER) positive breast cancer (Ghiasvand et al., 2011). As a limitation of studies on risk factor of breast cancer in EMR, obesity and overweight was not considered in post-menopausal and premenopausal separately. In the current systematic review we considered just meat consumption and did not evaluate other aspects of diet such as pattern of food preparation and storing the food in the individual studies.

Moving to industries world was limited the physical activity in people of developing countries. This situation gets worst by inadequate physical, environmental and political support and family restrictions for women in EMR. Several biologic mechanisms have supported the protective effect of physical activity on breast cancer such as endogenous sex steroid hormone production, effect on immune and antioxidant system (Abdulbari et al., 2010; Awatef et al., 2010; Kruk, 2014).

Increasing the proportion of smoker women in developing countries is an important point that was seen in developed countries in past decades (Bidgoli et al., 2011; Ilic et al., 2013). About 70% of deaths attributed to tobacco use are likely to happen in developing countries (Maziak et al., 2004). Association of smoking and breast cancer is shown in current study also has supported by International Agency for Research on Cancer (IARC) evaluation (IARC 2004). There were no evaluation of some smoking related variables such as current/ex-smoker, pack-year of smoking, alcohol confounding effect, and passive/active smoker in studies carried in EMR on breast cancer and smoking (Henquin et al., 1994; Bidgoli et al., 2011; Javed et al., 2011). Evaluation of alcohol consumption and breast cancer was restricted too. Also, there was not any consensus between founded (Saadat et al., 2008; Kloong et al., 2011). Therefore, it is necessary to do studies considering this issue in EMR. However systematic reviews carried out mostly in developed and developing countries have found a positive association

between alcohol consumption and breast cancer (Ellison et al., 2001; Collaborative group on Hormonal Factors in Breast cancer, 2002; Key et al., 2006; Ying et al., 2013) One explanation for lack of studies on alcohol consumption and breast cancer in EMR could be religious beliefs and culture of people in this region that could be a strong source of publication bias which is seen in other eastern studies too (Key et al., 2006). Our findings about reproductive factors and breast cancer are supported by individual studies (Das et al., 2012; Shaukat et al., 2013; Toleutay et al., 2013). But, the relation between years of education and age of first pregnancy should be considered by caution and confirmed in future studies.

The strength point of current study was assessing risk factors of most common cancer in women in a specified region (EMR). Systematic review of observational studies, especially on risk factors of non-communicable diseases, could help policy makers to plan the best approach for prevention of these common modern diseases. This study was unique according this issue. We tried to account most common risk factors of breast cancer in current study.

This systematic review has several limitations. Some limitations were about included individual studies. Majority of included studies were hospital based. This point could limit the generalizability of the findings to all women. Although, studies on risk factors of cancers usually carried out on hospital cases and this limitation is inevitable. The other limitation was about the details of studied risk factors in EMR investigations. Majority of these studies have not included some special aspects of life style risk factors such as special pattern of food preparing (for example, smoked food) or other type of tobacco consumption except cigarette smoking (for example, Bidi, chewing tobacco, betel nut, water pipe and snuff). Future studies with focusing on these aspects of risk factors recommended.

Finally, the most important limitation was about language of included studies. We considered language restriction to English; therefore, some relevant studies may be missed. Although, recently most investigators are interested in publishing their works in English journals that most of them indexed in searched databases in current study. However, this limitation could be account.

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