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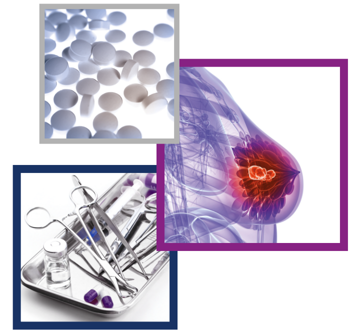
Breast Cancer Management



The pattern of breast cancer risk factors among Iranian women and predictors of class membership

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Aim: This study aimed to find subgroups of women on the basis of clustering of breast cancer risk factors. **Materials & methods:** The study was conducted in Shiraz between 2004 and 2013. In this cross-sectional study clinical breast examination, mammography or sonography, fine needle aspiration or biopsy and surgery in case of indications were performed for all participants. **Results:** Four latent classes were indentified among women with breast cancer; general population risk (65.7%), low risk (8.9%), moderate risk (20.5%) and high risk (4.9%). **Conclusion:** Focusing on education, age and the occupation of women may help in designing and executing effective programs to reduce the incidence of breast cancer among healthy women.

Plain language summary: This study aimed to investigate breast cancer in Iranian women by studying different factors that may increase the risk of getting breast cancer. We grouped the women into four different classes based on these risk factors. The results showed that most women, whether healthy or sick, had similar risk factors labeled 'general population risk'. Among healthy women, 15.4% were in the moderate and high risk groups, while among diseased women, 25.4% were in those same groups. We also found that breast cancer could be a significant risk for Iranian women due to a lower level of education and awareness. Our results demonstrate that it is essential to educate women about the risk factors for breast cancer. Focusing on education may help in designing and executing effective programs to reduce incidence of breast cancer among healthy women.

First draft submitted: 20 February 2023; Accepted for publication: 24 July 2023; Published online: 17 August 2023

Keywords: breast cancer • cluster • cross sectional • high risk • Iran • latent class analysis • low risk • moderate risk • risk factors • women

Breast cancer is the most common type of cancer and the leading cause of cancer death among women around the world [1,2]. With 1.7 million new cases annually, it accounts for 25% of all cancers among women [3]. Based on 2018 global cancer burden estimates (GLOBOCAN 2018), breast cancer incidence rates are fairly high in Australia, Western Europe and Northern Europe. However, the rate of this cancer is increasing much faster in Asia than in Western countries [4,5]. This rapid increase in incidence in developing countries may reflect cultural and socio-economic changes, such as delayed marriage and childbearing, having fewer children, increased obesity and lack of knowledge and awareness toward breast cancer [6].

While breast cancer is present worldwide, its prevalence, mortality and survival rates vary from region to region. . . , which can be due to the different lifestyle of individuals, the population structure of countries, as well as genetic and environmental factors [7]. For example, breast cancer accounts for 30 and 27% of all new cases

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of cancer in women in USA and Europe, respectively [8,9]. However, 44% of deaths and 39% of new cases of breast cancer take place in Asia [10]. China, the ranked populous country of Asia, accounts for 25% of overall deaths due to breast cancer, particularly in the younger population [11]. Also, 25% of new cases of breast cancer occur in India [10]. Iran is a multi-geographical, climatic, ethnic, regional and cultural country that makes Iranian people exposed to various risk factors for breast cancer [12]. Iranian women, who are one decade younger than their Western counterparts, have been reported to suffer from breast cancer, which is responsible for 24.4% of malignancies among them [13]. Metastatic breast cancer, also known as advanced or stage IV breast cancer, can spread to other organs in the body, such as bone, liver, lung and brain, thus early detection of the disease can lead to best improved prognosis and long-term survival of breast cancer patients [14]. Several factors, including premature menstruation, late-onset menopause, late age at first birth, breastfeeding period, socioeconomic status, smoking, low physical activity, obesity and high-fat diet have been associated with increased risk of breast cancer [3,15].

The cancer cluster is used extensively to determine the risk factors associated with breast cancer. The purpose of cancer cluster analysis is to identify potential unique subgroups of patients with specific behaviors and sensitivities as well as to determine the co-occurrence of these risk factors in order to detect the disease at early stages and promote health in a target population [16,17]. Latent class analysis (LCA) as a statistical modeling method, is used to detect heterogeneity in response patterns or clinical features of the classes in a population. This person-centered approach is also used in social and behavioral sciences [18]. Since the clustering of risk factors for breast cancer has not been previously investigated in Iran and also due to the uncertainty of epidemiological aspects of breast cancer among Iranian female patients [13]. The aim of this study was to explore the clustering of risk factors for breast cancer among female breast cancer patients versus healthy women in Iran through LCA analysis.

Materials & methods

Study design & setting

We conducted a large study based on the results of a breast cancer screening program in 11,860 women. referring to Shahid Motahhari breast clinic affiliated to Shiraz University of Medical Sciences between 2004 and 2013 in Iran. Women who participated in the screening program underwent a clinical breast examination. Then, they underwent mammography or sonography, fine needle aspiration or biopsy, and surgery in case of indications, depending on the physician's decision. All mammographic findings by radiologists and all demographic and clinical variables were documented by trained health workers.

Data collection

All women were interviewed in person by trained staff using a structured questionnaire to gather information regarding family history of breast cancer, height, weight, marital status, education level, age at menarche, occupation, parity, age, past use of oral contraceptives (OCP), age at the first pregnancy and lifetime breastfeeding. The validity and reliability of the questionnaire were confirmed in Iran [19]. Postoperative care and follow-up were provided to women with pathological confirmation of breast cancer at the Motahhari clinic.

The Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1391.S6422) has approved the study. Permission to conduct the study was obtained from this committee and all women had signed an informed consent form. In addition, all methods were performed in accordance with the Declaration of Helsinki.

Data analysis

A LCA model was used to detect the clustering of breast cancer risk factors among Iranian women using the disease status of participants as the grouping variable. According to this model, a number of observed variables were aggregated to represent a categorical latent variable. In order to select the best fitting model, we first calculated the G2, index. The likelihood ratio statistic G2 is used to check the fitted model. In fact, this statistic shows how well the fitted model matches the observed data has it. Additionally, the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were also calculated to identify the best model. For all these indices, lower values indicate better fit and more parsimony for the model. Item response probabilities of >0.5 were used to label each latent class and to describe the characteristics of each. Eight dichotomous observables (i.e., indicators) were selected for creating the subgroups. These indicators were: obesity, age of menarche, first pregnancy age, parity, OCP use, family history of breast cancer, breastfeeding and marital status. After finalizing the model, we entered the age, job (housekeeper/other jobs) status and education (uneducated/educated) of the participants as covariates in the LCA.

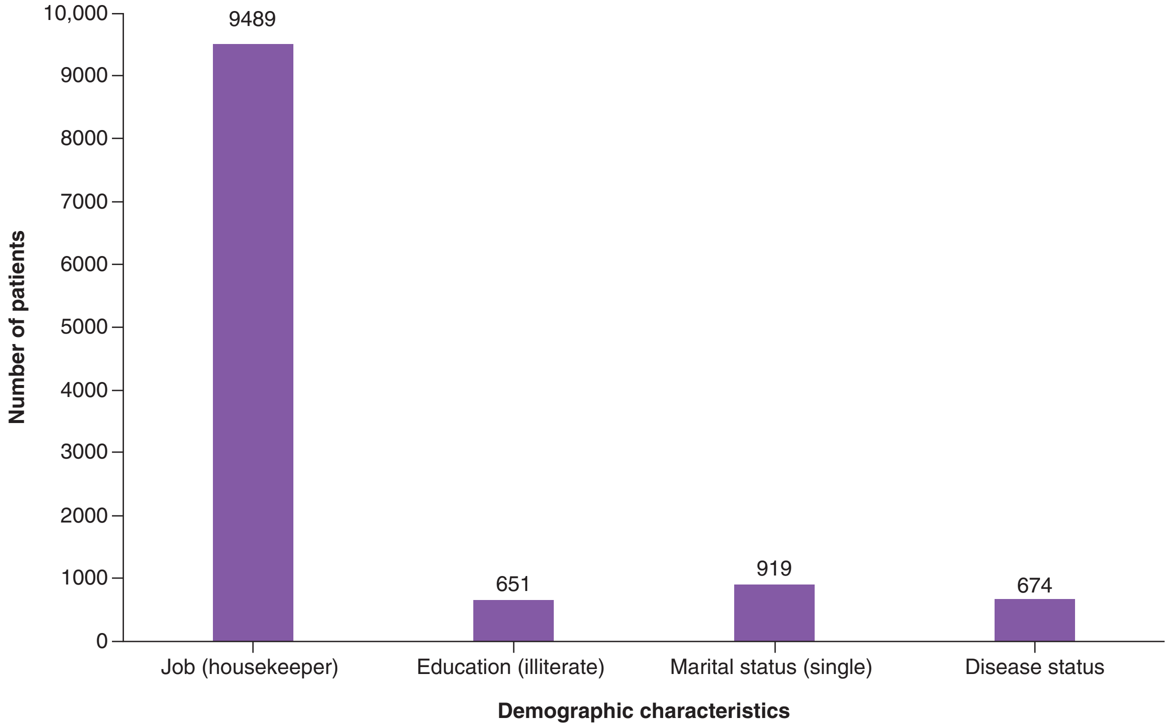

Figure 1. Demographic characteristics of study population.

Table 1. Prevalence of risk factors of breast cancer by disease status among Iranian women.

Items	Breast cancer, n (%)		p-value	Total (11,860), n (%)
	No (11,186)	Yes (674)		
Being obese (BMI >30)	2432 (21.7)	148 (22.0)	0.572	2580 (21.8)
Premature menstruation (under 12 years)	857 (7.7)	54 (8.0)	0.742	911 (7.7)
Late age at first pregnancy (up to 35 years)	103 (0.9)	6 (0.9)	0.935	109 (0.9)
Parity (don't have any children)	1626 (14.5)	161 (23.9)	<0.001	1787 (15.1)
Oral contraceptive use	6313 (56.4)	315 (46.7)	<0.001	6628 (55.9)
Family history of breast cancer	4146 (37.1)	194 (28.8)	<0.001	4340 (36.6)
Skipping breast feeding	1907 (17.0)	173 (25.7)	<0.001	2080 (17.5)
Marital status (being single)	823 (7.4)	96 (14.2)	<0.001	919 (7.7)

SPSS 16 was used to report the frequency of the observables, while PROC LCA in SAS 9.2 software was used for the LCA. In all analyses, a p-value < 0.05 was considered to be statistically significant.

Results

The mean age of participants was 41.12 ± 10.58 (41.18 among non-diseased and 40.25 among diseased women). Figure 1 indicates demographic characteristics of study population. Table 1 presents the participants status for each of the risk factors measured in this study and theirs relationship to disease status. This shows that the prevalence of OCP use was the highest among the all risk factors (56.4% in healthy women and 46.7% in diseased women). In total, 2580 (21.8%) participants were obese, while only 0.9% had a history of having higher age in the first pregnancy. This table shows that except obesity, premature menstruation and late age at first pregnancy, all of the risk factors studied had a significant relationship with disease status.

Eight binary variables (indicators) were utilized in the LCA. We attempted to fit the LCA models with classes ranging from 1 to 7, using disease status as the grouping variable. The different measures of model selection are shown in Table 2. For each model, we computed G2, AIC and BIC. Based on these model selection indices and the interpretability of the results, we concluded that a four-class model was the most appropriate for these women.

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Table 2. Comparison of LCA models with different latent classes based on model selection statistics.

Number of latent class	Number of parameters estimated	G^2	df	AIC	BIC	Maximum log-likelihood
1	16	14541.45	495	14573.45	14691.55	-39427.61
2	34	651.62	477	719.62	970.57	-32482.69
3	52	492.59	459	596.59	980.40	-32403.18
4	**70**	**174.91**	**441**	**314.91**	**831.57**	**-32244.33**
5	88	149.46	423	325.46	974.99	-32231.61
6	106	119.02	405	331.02	1113.40	-32216.39
7	124	93.08	387	341.08	1256.31	-32203.42

The final model has been bolded.
AIC: Akaike information criterion; BIC: Bayesian information criterion; df: degrees of freedom; LCA; Latent class analysis.

Table 3. The four latent classes model of risk factors of breast cancer among healthy women.

Healthy women	Latent class			
	General population risk	Low risk	Moderate risk	High risk
Latent class prevalence	0.836	0.009	0.076	0.078
Item-response probabilities				
Being obese (BMI >30)	0.247	0.222	0.193	0.160
Premature menstruation (under 12 years)	0.076	0.045	0.082	0.083
Late age at first pregnancy (up to 35 years)	0.000	**0.858**	0.016	0.000
Parity (don't have any children)	0.000	0.000	**0.879**	**0.999**
Oral contraceptive use	**0.647**	0.298	0.267	0.002
Family history of breast cancer	0.375	0.493	0.323	0.359
Skipping breast feeding	0.017	0.205	**0.993**	**1.00**
Marital status (being single)	0.000	0.000	0.011	**0.931**
Covariates	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Age ($p < 0.001$)	Reference	1.03 (1.01–1.05)	1.01 (0.99–1.02)	0.73 (0.71–0.75)
Job ($p < 0.001$)	Reference	0.09 (0.06–0.13)	0.21 (0.17–0.27)	0.07 (0.06–0.10)
Education ($p = 0.0002$)	Reference	0.39 (0.13–1.11)	0.23 (0.10–0.50)	2.03 (0.93–4.42)

The probability of a 'No' response can be calculated by subtracting the item-response probabilities shown above from 1.
Bold values show item-response probabilities >0.5 to facilitate interpretation.
OR: Odds ratio.

The LCA model for breast cancer risk factors in healthy women is presented in Table 3. This table include the latent class prevalence and item response probabilities. As can be seen in Table 3, among healthy women, the first (general population risk), second (low risk), third (moderate risk), and fourth (high risk) classes described 83.6, 0.9, 7.6 and 7.8% of healthy women. Table 4 shows the result of the LCA model for the breast cancer risk factors for women with breast cancer. Among these women, the prevalence of general population risk, low risk, moderate risk and high risk classes was 65.7, 8.9, 20.5 and 4.9%, respectively.

Tables 3 & 4 show that in the latent class 1 (general population risk) there was a similar pattern of breast cancer risk factors. In general population risk class, the probability of OCP use was high in healthy and diseased women. Among healthy women, in the low risk class, late age at first pregnancy had a high probability of occurring. Whereas, among diseased women in latent class 2 the probability of being obese was high. Similarly among healthy women, in latent class 3 parity and skipping breast feeding had high probability and in latent class 4 parity, skipping breast feeding and being single had high probability of being present. Among diseased women, the probability of parity, skipping breast feeding and being single was high in class 3. Also, the probability of parity, skipping breast cancer, and being single was high in class 4.

After identifying the optimal model (four-class model in this study) we conducted an LCA with covariates to detect the effect of predictors of latent class membership. Tables 3 & 4 show the odds ratio of each class to the first class associated with the age, occupation and education of the participants. This index compares the odds of membership in each class with the reference class (i.e. general population risk). As can be seen in Table 3, the odds of membership in latent classes 2 and 4 decreased significantly by age. Similarly, being housekeeper, decreased the

Table 4. The four latent classes model of risk factors of breast cancer among diseased women.

Diseased women	Latent class			
	General population risk	Low risk	Moderate risk	High risk
Latent class prevalence	0.657	0.089	0.205	0.049
Item-response probabilities				
Being obese (BMI >30)	0.220	**0.535**	0.140	0.122
Premature menstruation (under 12 years)	0.091	0.011	0.094	0.000
Late age at first pregnancy (up to 35 years)	0.000	0.083	0.007	0.000
Parity (don't have any children)	0.000	0.000	**0.998**	**0.681**
Oral contraceptive use	**0.628**	0.199	0.001	**0.757**
Family history of breast cancer	0.337	0.189	0.207	0.150
Skipping breast feeding	0.004	0.002	**0.998**	**0.991**
Marital status (being single)	0.000	0.000	**0.692**	0.000
Covariates	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Age ($p < 0.001$)	Reference	1.04 (0.98–1.09)	0.85 (0.83–0.89)	0.82 (0.78–0.87)
Job ($p < 0.001$)	Reference	0.25 (0.09–0.66)	0.10 (0.06–0.19)	0.41 (0.19–0.88)
Education ($p = 0.0002$)	Reference	1.58 (0.34–7.25)	4.35 (1.04–18.09)	10.60 (2.61–43.10)

The probability of a 'No' response can be calculated by subtracting the item-response probabilities shown above from 1.
Bold values show item-response probabilities >0.5 in bold to facilitate interpretation.
OR: Odds ratio.

odds of membership in latent classes 2, 3 and 4. Finally, being uneducated deceased the odds of membership in class 3 in healthy women. Table 4 shows that among diseased women, the odds of being in classes 3 and 4 significantly decreased by age. Also, being housekeeper decreased the odds of membership in classes 2, 3 and 4. On the other hand, being uneducated increased the odds of membership in classes 3 and 4 in comparison to the first class.

Discussion

The present study evaluated risk factors that are associated with the incidence of breast cancer in two groups of female patients with breast cancer and healthy women. According to the results of this study, four latent classes were identified for patients and healthy women. In this study, the majority of subjects in both groups fell under general population risk class. OCP use in general population risk class, and skipping breastfeeding and being single in moderate risk class, were more likely in both study groups.

However, the prevalence of general population risk class was much higher among healthy women compared with breast cancer patients. In general, the pattern of risk factors between the two groups was not different in class general population risk and low risk class, whereas, the pattern of risk factors was different between the two groups in class moderate risk and high risk. In class moderate risk, parity and skipping breastfeeding were more likely among healthy women. Whereas, except for these two being single was more likely to occur in breast cancer patients. In class high risk, parity, OCP use, and skipping breastfeeding were more likely to occur in breast cancer patients.

This is the first study to focus on clustering breast cancer risk factors using LCA approach in Iran, to the best of our knowledge. However, here we discuss a number of studies that used almost the same method used in our study. Lifestyle patterns in women with breast cancer were assessed using LCA. In this study, three latent classes were identified, including healthy behavior and diet pattern (Class 1), healthy behavior and unhealthy diet pattern (Class2), and unhealthy behavior and diet pattern (Class 3) [20]. Zhang *et al.* examined the relationship between body composition and risk of breast cancer in Chinese women, and identified four classes: Low Muscle Mass (Class 1), High Body Composition (Class 2), High Fat (Class 3) and Normal Body Composition (Class 4) [21].

The results of our study suggest that OCP use had important role in the clustering of breast cancer patients. This factor is highly likely to be present in latent class general population risk and high risk. Bethea *et al.* also showed that the use of OCP, particularly in the long run, was associated with an increased risk of breast cancer [22]. Breast cancer risk is higher when using OCPs due to estrogen levels being directly elevated and the role of progesterone in gaining weight indirectly [23]. Our study indicated that healthy women in class general population risk were also more likely to consume OCP. Therefore, it seems that this risk factor can also cause problems over time and co-occur with other risk factors in healthy women, leading to development of breast cancer in these individuals.

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We found an association between breast cancer and family history of this cancer. Previous studies have shown that family history of breast cancer is a well-established and significant risk factor associated with breast cancer [24,25]. Family members share common genes and genetic factors, which may explain the association between family history of breast cancer and the increased risk of breast cancer. These genetic factors constituted of mutations in genes, such as BRCA1 and BRCA2. Family members also have environments and lifestyles in common, which can increase the risk of breast cancer in women with a family history [26]. However, family history was not linked with the clustering of patients and healthy individuals, and probably the effects of other variables were more significant on the subgrouping of women in this study.

Increased parity can delay the development of breast cancer and inhibit the metastasis of the axillary lymph node (NLA) [27]. Breast cancer risk can be influenced by hormonal factors, such as estrogen and progesterone, and changes in these hormones can have a significant impact on protection against this cancer [28]. In an animal study, Yuri *et al.* found that exposure to estrogen and progesterone in animals during pregnancy protected breast tissue against cancer [29]. The results of the present study showed that parity was significantly associated with risk of development of breast cancer. In the pattern of risk factors, this variable also played an essential role in the classification of patients, as the probability of the occurrence of parity was high in two classes. However, it should be noted that among healthy women, parity was more likely to be a warning signal for developing risk factors for this cancer in healthy women in the moderate risk and semi moderate risk classes.

Our findings indicate that skipping of breastfeeding was related with development of breast cancer. This factor was also likely to occur in women with breast cancer in the moderate and high risk classes. One review study found that breastfeeding significantly reduced the risk of breast cancer in young women [30]. Breastfeeding period has been also shown to be associated with hormonal changes and changes in breast tissue, which may reduce the risk of breast cancer, reduce the menstrual cycle and ovulation timing through reproductive life, resulting in reduced exposure to rapid hormonal changes [31,32]. However, skipping breastfeeding was more likely in healthy women in the moderate risk and semi moderate risk classes, thus the co-occurrence of this variable with other risk factors can increase the risk of breast cancer. Probably, the interaction and simultaneous influence of several factors is required for the disease occurrence.

We discovered that being single was related to breast cancer. Many studies have proposed various reasons indicating married patients as a better prognosis of breast cancer. As such, these people generally have richer financial resources that support them to perform examinations earlier and more frequent. In addition, in married women, due to having more psychosocial support compared with singles, a better prognosis of the disease was observed, as reduced psychological support and stress is associated with tumor progression and immune deficiency [33,34]. In addition, single women may have poor health habits and behaviors. For example, a study founded that smoking and poor health examinations were more common in single women than in married women [35].

The results of our study showed that being uneducated significantly increases the odds of being in moderate risk and high risk classes in women with breast cancer. Gurdal *et al.* showed that women with university education performed better in breast self-examination and breast cancer prevention than women with low education [36]. In another study in Turkey, screening and breast exams increased with increasing levels of education in women [37]. In contrast to our findings, the results of a meta-analysis showed that higher levels of education could be associated with an increased risk of breast cancer due to the mediating role of alcohol consumption, age at menopause and hormone therapy [38]. Palme *et al.* believe that highly educated women are more likely to develop breast cancer, and the disease is therefore referred to as a welfare disease.

Based on these findings, we need more research in Iran.

We have shown that housekeepers are less likely to membership in moderate risk and high risk classes in women with breast cancer. A review study found that working at night was associated with breast cancer [39]. In Australia, there was no significant difference in the incidence of breast cancer in female employees compared with the general population [40].

Strengths & limitations

In this study, the large sample size ensures that the results are in some measure representative of all Iranian patients. Using the LCA approach as well, we were able to identify latent sub-groups of breast cancer risk factors. In addition, the present work had the following limitations: first, due to the cross-sectional design of the study, causality could not be assessed. Second, the study relied on self-report data; thus, underreporting of some risk factors was expected, even assuring the participants of the anonymity of the questionnaires. Future studies could use longitudinal or cohort designs to prevent similar limitations.

Conclusion

In this study, we reported the prevalence and pattern of risk factors of breast cancer by subgrouping a sample of Iranian women into four classes. Results of this study showed that the majority of healthy and diseased women fell under the latent class of general population risk. Among healthy women, 15.4% of them fell under moderate risk and high risk classes and among diseased women 25.4% were in moderate and high risk classes. Focusing on the education of women about risk factors of breast cancer and co-occurrence nature of them may be help in designing and executing effective programs to reduce incidence of breast cancer among healthy women.

Summary points

- The majority of healthy and diseased women fell under the latent class of general population risk.
- Four latent classes were identified and 4.9% of the women are in the fourth class with a high probability of parity and skipping breastfeeding for patient women.
- Four latent classes were identified for healthy women and 7.8% of the women are in the fourth class.
- The results of the present study showed among healthy women, 15.4% of them fell under moderate risk and high risk classes and among diseased women, 25.4% were in moderate and high risk classes.
- Older age (odds ratio [OR] = 0.82) was associated with high risk class.
- Being a housekeeper (OR = 0.41) was a protective factor for breast cancer.
- Being uneducated (OR = 10.60) was associated with high risk class.
- The results suggested focusing on the education of women to reduce the incidence of breast cancer among healthy women.

Author contributions

All authors contributed to the study conception and design. A Abbasi-Ghahramanaloo analyzed the data. M Sepandi, A Rezaian-zadeh, S Afrashteh, Y Alimohamadi and A Abbasi-Ghahramanaloo collected the data and wrote the manuscript. M Sepandi, Y Alimohamadi and S Afrashteh interpreted the data. All authors have read and approved the final manuscript.

Financial & competing interests disclosure

This research was supported by grant from Shiraz University of Medical Sciences. This university had no role in the study design, analysis, interpretation of the data, writing the manuscript, or the decision to submit the paper for publication. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1391.S6422). Permission to conduct the study was obtained from this committee. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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