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Impact of Age at Menarche on Breast Cancer: The Assessment of Recall Bias

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Abstract

Background: Our aim was to determine the association between age at menarche (AAM) and breast cancer adjusted for recall bias (misclassification) in AAM.

Methods: We have used data provided from a case-control study conducted in Iran from 2005 to 2009. The cases and controls were frequency matched based on 5-year age groups and region of residence. First, logistic regression was conducted to estimate the odds ratio (OR) and second, Bayesian analysis was applied to estimate the ORs adjusted for misclassification.

Results: The study was conducted on 880 cases and 998 controls. In the assumption of no correction for recall bias on self-reported AAM, the OR was 1.36 (95% Credible Interval (0.98, 1.90). Based on a sensitivity value = 71% and a specificity value = 81% (the indices about the ratio of true recall of AAM) for the case and control groups (as the first scenario), the AAM ≤ 12 years of age was associated with a lower OR for breast cancer by 1.23 (95% Credible Interval: 0.50, 3.13). In the other scenario, with consideration of 100% sensitivity and specificity of self- reported AAM in the case group, and 71% and 81% sensitivity and specificity of the item in the control group, the related OR between breast cancer and AAM was found increased to 2.96 (95% Credible Interval: 0.75, 7.66).

Conclusion: After adjustment for misclassification related to recall bias, this study provides evidence that the self-reported mode of AAM has a moderate impact on calculation of the OR.

Keywords: Bias, Breast cancer, Menarche, Misclassification

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Introduction

In medical sciences, measurement of many variables may be conducted with a degree of mistake.[1] In the traditional form of case-control design, often the exposure data related to early life time should be acquired through self-report, from which age at menarche (AAM) may be noted. The AAM is identified as one of the reproductive risk factors for breast cancer.[2-6] It is reported that the risk of breast cancer may be decreased by 10% per 2 years increase in AAM.[7]

In middle age, long time has passed to recall AAM correctly, which may potentially lead to recall bias or misclassification bias.[5,7] As this bias may have substantial impact on estimated measure of associations, the calculated measures of associations are prone to be misinterpreted.[8]

One of the objectives in epidemiological studies is to determine valid estimations. In order to achieve a valid estimation, a given study should be conducted based on appropriate approaches in design, implementation and analysis.[8,9] In some situations, like those studies with a case-control design, the bias is inevitable, so it should be under consideration in the process of data analysis. One of these biases is misclassification in the exposure variable.[8] There are many methods [1,9-15] to correct the impact of exposure misclassification on the estimated measures of associations. In some of these methods, like the Bayesian methods,[11,15] the prior distributions are used to calculate the corrected measures of associations.[11,15-18]

Considering the important role of AAM as a risk factor for breast cancer[3,6] and the qualitatively mentioned limitations related to the induced bias due to the misclassification in AAM in many previous studies,[2,19] we aimed to determine the association between AAM and breast cancer adjusted for misclassification related to recall bias in AAM quantitatively applying the Bayesian methods.

Materials and Methods

Study Design and Participants

We used data provided from a case-control study

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conducted in Shiraz, Iran from September 2005 to August 2009. The data on the reproductive risk factors for breast cancer were collected through interview with the cases from an outpatient breast clinic, where 80% of all the incident cases of breast cancer in the city are referred to. The cases were considered as breast cancer patients if they were histopathologically confirmed to be with breast cancer and were referred to the outpatient clinic for post-operative care.

After recruitment, all the participants were interviewed and assessed applying a structured questionnaire related to reproductive risk factors for the disease. This study included 880 cases and 998 controls. Ninety-six percent of the breast cancer patients were interviewed about 6 months after disease diagnosis. More details were presented in previously published studies.[3,13,15,20,21]

The respondents in the case and control groups were interviewed face to face by trained interviewers, who were not aware of the study targets. The interviews were conducted in a clinic for the case group and in a hospital for the control group. We excluded 92 women from the control group, as they refused to participate in the study. Eleven cases were also excluded due to living in cities far from the setting of the study. All the participants of the control group were selected from general urology surgery and the cardiovascular disease wards of a hospital and were frequency matched to the cases in terms of the 5-year age groups and place of residence. Controls were primarily selected from healthy female visitors accompanying patients referred to the Faghihi hospital for general surgery (60%), urology (24%) and cardiovascular (16%) diseases. At the time of interviews, the controls were asked about being with/without breast cancer, however, they had not undergone any examination. Cases were interviewed at their first time of treatment between September 2005 and December 2008. Controls were interviewed from May 2009 through August 2009. Interviews were conducted by two trained female nurses (one for cases and one for controls), and the time of interviews was similar for cases and controls. Height and weight were measured at the end of the interview. None of interviewers were aware of the study hypotheses.[3,20,21]

The studied variables included family history of breast cancer among first degree relatives (Yes/No), AAM ≤12 years and >12 years), menopause status (Yes/No for the control group and Happened before being diagnosed with breast cancer/Happened after being diagnosed with breast cancer for the case group), age at first pregnancy (<25 years, ≥25 years and nulliparous), and current body mass index (BMI: kg/m^2).

Statistical Analysis

Logistic regression analysis was conducted to estimate the odds ratio (OR) between the self-reported AAM and breast cancer adjusted for the covariates. In addition, Bayesian logistic regression analysis was applied to estimate the OR between the self-reported AAM and breast cancer. Then, OR was estimated considering the adjustment for misclassification in the self-reported AAM, and was compared to the OR found in the model without misclassification consideration.

The details of the applied Bayesian method have been explained previously[12,13,15,22] and in Supplementary file 1. Shortly, in the Bayesian analysis we used three models; the measurement, the exposure and the outcome models. In all the models, we needed to take the priors. The informative priors[15] were taken from previous literature (Table 1).[2,23-25] The priors in the outcome models were related to the ORs to determine the associations between the variables and breast cancer. Next, they were transformed into the normal distribution.[15,27,28] second kind of the applied priors were taken from the non-informative priors as applied by van Gelder et al[22]; the priors by normal distribution with mean 0 and variance 0.67. The priors in the exposure model were determined by normal distribution with the mean and variance equal to 0 and 1, respectively, as explained by MAcLehose et al[12] and Moradzadeh et al.[13] The priors in the measurement model were also obtained from the previous literature (Table 2). They were based on the accuracy of the self-reported AAM published by Cooper et al[28] In order to include the impact of potential misclassification in the self-reported AAM, the sensitivity and false positive rate (1-specificity) of the self-reported AAM were used with the hope to define the parameters in the Beta distribution.[13] The misclassification model was defined in Figure 1; based on the directed acyclic graph to show the associations between the study variables. As defined by Gustafson, there are non-differential and differential models for misclassification.[1] The self-reported

Table 1. Odds Ratios with 95% CIs for the Reproductive Factors in Relation to Breast Cancer Based on a Review of the Literature

Variable	OR (95% CI)
Self-reported age at menarche[23]	
>12	1
≤12	1.25 (0.83, 2.00)
Menopause status[a] [2]	
No (before)	1
Yes (after)	1.03 (1.02, 1.04)
Family history[b] [23]	
Yes	2.20 (1.60, 3.10)
No	1
Age at first pregnancy[24]	
<25 years	1
≥25 years and nulliparous	1.24 (1.00, 1.54)
Age (y)[25]	3.30 (0.20, 5.60)
BMI (kg/m^2)[24]	2.40 (1.65, 3.47)

[a] Yes/no for the control group and before/after of confirmed breast cancer for the case group.
[b] Family history of breast cancer in the first degree relatives.

Table 2. Prior Means, with 95% Prior Confidence Intervals, for the Sensitivity and Specificity of Misclassification of Self-reported Age at Menarche Based on Cooper et al[25]

Applied Approach for Misclassification	Women with Breast Cancer		Women without Breast Cancer	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Non-differential misclassification	0.71 (0.64, 0.78)	0.81 (0.78,0.84)	0.71 (0.64, 0.78)	0.81 (0.78,0.84)
Differential misclassification	1.00	1.00	0.71 (0.43, 0.72)	0.81 (0.99, 1.00)

AAM in the differential misclassification was dependent to the breast cancer. However, in the non-differential misclassification, this variable was independent from the breast cancer. In our study, we decided to relate the misclassification to the self-reported AAM according to both the non-differential and the differential models.

Finally, the three models were conducted to obtain the posterior ORs and the credible intervals adjusted for misclassification. For the analysis, we conducted the models with 10 000 burn-in and 30 000 iterations. Assessing convergence was conducted by density, auto correlation and history plots. The free R 3.5.1 and Open BUGS 3.2.3 soft-wares were applied for data analyses.

Results

The study included 880 respondents in the case and 998 respondents in the control group. 78 women (9%) in the case group and 60 women (6%) in the control group announced their AAM as ≤12 years. The mean age of the respondents was 49 years (standard deviation = 10.55, range 20-89 years). Table 3 shows the characteristics of the women who participated in this study.

In the logistic regression, the OR adjusted for potential confounders between breast cancer and AAM was 1.33 (95% CI: 0.92, 1.91) and in the Bayesian logistic regression analyses in the informative and non-informative priors they were 1.36 (95% credible interval: 0.98, 1.90) and 1.32 (95% credible interval: 0.92, 1.88), respectively. These analyses were conducted with no consideration to any misclassification in the AAM variable (Table 4).

When the components of misclassification were included in the analysis, we used a Bayesian logistic regression analysis to adjust the misclassification. According to the results from this step of analysis, AAM ≤12 years was associated with a lower odds for breast cancer [ORs for informative and non-informative priors of outcome model were 1.23 (95% credible interval: 0.50, 3.13) and 0.99 (95% credible interval: 0.20, 4.86)]. These findings were based on the sensitivity and the specificity values of

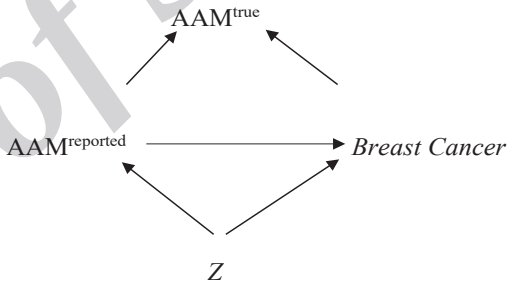

Figure 1. The directed acyclic graph to show the associations among the study variables (AAM^{reported}; Self-reported AAM and AAM^{true}; unobserved AAM that the participants may be failed to recall)

Table 3. Baseline Characteristics of the Study Participants

Variable	Case (n = 880)		Control (n = 998)		Univariate OR (95% CI)[b]
	No.	Percent[a]	No.	Percent[a]	
Age at Menarche					
≤12	78	8.86	60	6.01	1.52 (1.07, 2.16)
>12	802	91.14	938	93.99	1
Menopause status[c]					
No (before)	393	44.66	536	53.71	1
Yes (after)	487	55.34	462	46.29	1.44 (1.20, 1.72)
Family history					
Yes	190	21.59	92	9.22	2.71 (2.07, 3.54)
No	690	78.41	906	90.78	1
Age at the first pregnancy					
<25 years	612	69.55	831	83.27	1
≥25 years and nulliparous	268	30.45	167	16.73	2.18 (1.75, 2.71)
BMI (kg/m^2)					
Mean(SD)	27.60 (4.71)		27.06 (4.66)		1.03 (1.01, 1.05)

N, sample size, OR, odds ratio, CI, confidence interval, SD, standard deviation.
[a] The values are rounded to the nearest integer.
[b] The ORs are based on univariate analysis.
[c] Yes, no for control and before and after of confirmed breast cancer for case group.

71% and 81%, respectively, for both the case and control groups, therefore, we accounted for non-differential assumption for misclassification.

In the other scenario, we assumed that the recall of AAM was completely correct for the case group; i.e. the sensitivity and the specificity of the self- reported AAM were 100%. In contrast, the sensitivity and the specificity values in the control group were assumed to be 71% and 81%, respectively. Then, the related ORs between breast cancer and AAM in the informative and non-informative priors were increased to 2.96 (95% credible interval: 0.75, 7.66) and 1.09 (95% credible interval: 0.22, 4.95), respectively.

Discussion

Utilizing a model for correction of misclassification on the exposure variable (i.e. AAM), we showed that the association between AAM and breast cancer may be changed. Except where informative priors in differential misclassification were applied for the outcome model, we showed that the odds of breast cancer were reduced after correction for misclassification compared to the logistic regression estimation (i.e. without consideration of any correction for the misclassification). These ORs, however, were not statistically significant.

These findings add substantial information to the existing literature. Similar to our findings, in a previous study,[2] it was qualitatively indicated that the incorrect recall of AAM may lead to misclassification bias and consequently dilute the impact of AAM on breast cancer. Moreover, deep understanding on the reproductive characteristics, including early menarche, may be helpful in clarifying risk of breast cancer. This risk of breast cancer related to AAM may be due to duration of exposure to reproductive hormones.[2] Such issues are part of research priorities in the 21st century when women are at risk for early menarche and later menopause and have less desire to bear children.[2]

Several previous studies[19,29-31] have indicated that AAM was strongly associated with breast cancer, but almost all of them were prone to misclassification bias in AAM[32] due to measuring AAM based on self-reported data. In the present study, we sought to evaluate the impact of self-reported AAM on the odds of breast cancer and adjust the estimated OR for misclassification bias. In a cohort study, Bodicoat et al[7] showed a non-significant increase in breast cancer by AAM ≤12, considering that age at menarche was reported retrospectively at baseline (adjusted hazard ratio: 1.06 and CI 95%: 0.93, 1.21) and, therefore, induced misclassification bias. In some previous studies, the association between AAM and breast cancer was reported based on subtypes of tumors. Chung et al,[33] for instance, reported association between menarche age per year and breast cancer (OR: 0.92, 95% CI: 0.87, 0.97) which were similar to those found in our study.

Our findings were consistent with those found in previous studies emphasizing an association between AAM and breast cancer. However, none of the previous studies have reported the measure of associations adjusted for misclassification quantitatively. As a strength and novelty for our present study, we presented the association between AAM and breast cancer after adjustment for misclassification correction. Despite this strength, there may be some limitations in the present study. The first limitation of this study could be that we did not evaluate several known risk factors for breast cancer since their related data were not available in the dataset.[6] Such risk factors may include physical activity, endogenous biomarkers, alcohol consumption, and the consideration of different subtypes of breast cancer.[3,6,13] As the second limitation, we could not simultaneously adjust the misclassification for other self-reported covariates, including history of breastfeeding, oral contraceptive pills and family history of breast cancer in the first degree relatives because the relevant methods have not yet been developed.[34] Moreover, the impact of other types of bias (unmeasured confounding and selection bias) need to be examined in future validation studies. Another limitation is that it cannot demonstrate that AAM is independent from cardiovascular diseases; because the cardiovascular part has been one of the sources to select the control group. Though some studies have claimed attenuated association between AAM and cardiovascular diseases.[35] As information on the priors of measurement model was not available among the studied population, further studies are needed to obtain precise estimations.

In conclusion, our findings provide evidence that the self-reported AAM has moderate validity in calculating the measure of associations, including ORs, with breast cancer. In designing studies, there are available methods,

Table 4. Posterior Median of Odds Ratios and 95% Credible Intervals for Breast Cancer Associated with Self-Reported Age at menarche (Adjusted for Confounders) in Bayesian Model

Status	Measurement Model Priors	Outcome Model Priors	OR (95% Credible Interval)
Not adjusted for misclassification	--	According to Table 1	1.36 (0.98, 1.90)
		N(0, 0.67)	1.32 (0.92, 1.88)
Adjusted for misclassification	Non-differential misclassification[a]	According to Table 1	1.23 (0.50, 3.13)
		N(0, 0.67)	0.99 (0.20, 4.86)
	Differential misclassification[a]	According to Table 1	2.96 (0.75, 7.66)
		N(0, 0.67)	1.09 (0.22, 4.95)

[a] According to Table 2.

like proper data collection techniques, that may be used to increase the validity of the self-reported data. Such study designs are emphasized in health research, considering their possible impact on methodology and on the correct calculation of the measures while making clinical decisions. Our novel findings are informative in measuring the associations, adjusted for quantitative misclassification, between AAM and breast cancer.

Authors' Contribution

Study conception and design: RM, MM, RG, KH and TB. Data analysis: RM, MM, KH and TB. Data interpretation: RM, MM, RG, HN, KH AND TB. Drafting the manuscript: RM, MM, RG, TB, HN and KH. Critical revision of the manuscript: RM, MM, RG, TB, HN and KH.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

The ethics committee in Arak University of Medical Sciences, Research Ethics Board (Ethic code: IR.ARAKMU.REC.1394.381) was approved the study and informed consent was obtained from all the participants before recruitment.

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Supplementary Materials

Supplementary file 1 contains the details of the applied Bayesian method.

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