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Original Article

Socioeconomic Factors, Health Behavior and Late-Stage Diagnosis of Breast Cancer: Considering the Impact of Delay in Diagnosis

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Abstract

Purpose: Stage of cancer at diagnosis is one of the most important factors in the prognosis of the patients. Controlling for diagnostic delay, this study aimed to identify factors associated with the late-stage of breast cancer. ***Methods:*** From November 2014 to January 2017, required information on 497 patients who were newly diagnosed with breast cancer was obtained from patient's medical record. Logistic regression was used to measure the association between stage of cancer and the study variables. ***Results:*** The results suggested that only 18.3% of the patients were diagnosed at stage I. The rest were diagnosed at stage II (45.5%) or higher (36.2%). Among those with less or equal to 3 months diagnostic delay, age (OR=0.96, 95% confidence interval [CI]: 0.93 – 0.99), place of residency (OR Urban/rural=1.72, 95% CI: 1.42 – 1.93), income (OR high/low=0.27, 95%CI: 0.10 – 0.72), performing BSE (OR yes/no=0.51, 95% CI: 0.0.26 -0.98), smoking (OR yes/no =2.23, 95%CI: 1.37 – 3.62), history of chest X-ray (OR yes/no = 1.40, 95% CI: 1.16 – 1.98) and suffering from chronic diseases (OR yes/no =1.73, 95% CI: 1.36 – 5.48) and for those with a delay longer than 3 months, marriage age (OR=0.83, 95% CI: 0.73 – 0.94), income (OR high/low=0.07, 95% CI: 0.008 – 0.63), family history of BC (OR=3.82, 95% CI: 1.05 –5.05), daily exercise (OR<10/10-20=0.10, 95% CI: 0.01 – 0.67) and suffering from chronic diseases (OR yes/no =1.77, 95% CI: 1.73 – 5.07) were associated with the late stage of cancer. ***Conclusion:*** The study revealed that shortening the diagnosis delay can help patients to take medical treatments at the earlier stage and have better prognosis. It seems

that smokers or younger women and those with chronic conditions or a family history of breast cancer are better to take extra caution as they may have worse prognosis if diagnosed with cancer.

Key words: breast cancer; stage; diagnostic delay; behavioral factors; socioeconomic factors.

Background

Breast cancer is the most common type of cancer and is the first cause of death from cancer among women [1-3]. Several studies introduced tumor stage at diagnosis (TSD) as a strong predictor of patient's prognosis and survival [4]. Accordingly, diagnose of breast cancer at earlier stage comes with better response to treatment and better prognosis [2, 5]. For example, it is suggested that five-year survival rate among patients with breast cancer at early stage (85%) is much higher than those diagnosed at late stage (25%) [1]. As a result, identifying predicting factors of TSD can help in improving the survival of the patients. Several researchers investigated the association between socioeconomic and demographic factors and survival of the patients with breast cancer [6]. However, it is likely that the associated factors exert their effect via the delay time between starting the first disease related symptoms and diagnosis of the disease, known as diagnosis delay (DD) [7, 8]. It is important to notice that controlling for DD, TSD seems to represent the rate of progression of the tumor [2]. Despite the importance of the issue, current evidence about TSD and its predictive factors are still under serious debate [9]. Moreover it seems that the associations of the studied factors with tumor stage is changing between countries [10, 11]. Moreover, due to the tight association of diagnosis delay and stage of tumor [2, 4, 12], the solely effects of other potential associates are not adequately understood [9]. In other word, we don't know precisely if the associates of stage are exert their effect independently or via the duration of delay in diagnosis. In the present study, in a delay-stratified analysis the associations of a wide range of variables including socio-demographic and clinical factors with tumor stage of breast cancer are investigated. Doing so, it is possible to distinguish between DD intermediated and direct associations of the study variables.

Materials and Methods

Settings: In this study, the associations of tumor stage with demographic, socioeconomic and clinical characteristics of the patients were measured. In total, 497 newly diagnosed patients at Namazi hospital were

selected from November 2014 to January 2017. The hospital is located in Shiraz (the capital of Fars province) and provides medical services to patients from southern part of Iran. Patient's medical records were obtained from cancer registry database of Namazi hospital, the biggest and the most referred medical center, for other provinces in the southern part of Iran, including Fars, Khuzestan, Bushehr, Hormozgan and Kohgiluyeh & Boyer Ahmad for all types of diseases, including cancer [13].

Data collection: Face to face interview run by a trained nurse and patient's medical file were used to obtain required information. A subsample (50 patients) of the participants was selected to evaluate the reliability of an interview-administered questionnaire (using test-retest method) and interview procedures. Accordingly, the questioner's reliability was estimated to be adequate (Cronbach's alpha=0.86).

Based on the results of the pilot study, the timing, method and place of interview was finalized. Demographic information including age, education, income, marital status, number of children and place of residency was obtained via interview, which was conducted by a trained female nurse in a quiet and private place. Data on smoking, family history of breast cancer, and patient's health status including history of any chronic disease or previous breast problems as well as her knowledge about breast self-examination was also obtained during the interview. In addition, after a brief explanation, the first related symptom and the approximate date at which it was notified was reported by the patients at the middle part of the interview. Clinical data was collected via reviewing patient's medical records conducted by an experienced medical coder. The clinical data included, the type of tumor, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2), pre-neural (PN) invasion, lymph- vascular (LV) invasion and stage of the disease.

An experienced pathologist defined the stage of cancer based on tumor-node-metastasis category (TNM). Type of tumor was defined as ductal, lobular-medullary or unknown. In this study, stages I or II were defined as early stage and stages III or IV were considered as late or advanced stage [14]. The delay in diagnosis (DD) is defined as the time interval (day) between the self-reported date of onset of the first related symptom to the date at which pathology report was issued [2].

Inclusion and exclusion criteria: Only new cases with pathology reports were selected. As the result, participants with relapsed disease were excluded from the analysis. Finally, 497 cases were qualified to be included in the analysis.

Statistical analysis: As mentioned before, the stage of breast cancer was dichotomized into early (stages I or II) or late (stages III or IV) stages. Power analysis suggested that with such a sample size a significant level at 5% and 80% power, 50% difference in the risk of late stage diagnosis was detectable for those having a family history of the disease. For bivariate analysis, the unadjusted associations of all independent variables with the stage of cancer were measured using Chi-square test. Multivariable logistic regression was used to measure the adjusted associations between the study variables and stage of cancer. Stepwise selection strategy was applied to define the final logistic model [15]. The modeling procedure was started after collinearity between the independent variables was tested using variance inflation factor index (VIF). The cut point for VIF was set at 0.1. After variables in the model were defined, any significant interaction was also tested. Akaike information criterion (AIC) was used to compare models. To distinguish between direct or intermediated (via DD) causal effects of independent variables (i.e. age, education etc.) two major approaches were applied. First, the results of both univariate (unadjusted for DD or other covariates) and multivariate (adjusted for DD and all other covariates which remained in the model) analysis were used to define whether an associate is fully or partially affecting the stage of disease via DD or the variable is directly associated with stage of disease. A variable which is significantly associated with stage of disease in both uni and multivariate analysis considered to have (at least partially) direct effect on the outcome [16, 17]. Second, DD-stratified analysis was conducted to measure DD controlled associations of the explanatory variables and TSD. All statistical approaches were applied assuming a two-sided test based on a 5% level of type I error. STATA (version 12) was used to conduct the analysis.

Patients with literacy read and signed informed consent and verbal consent obtained from illiterate patients. Ethical approval was obtained from Shiraz University of Medical Sciences ethical committee.

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Results

Selected characteristics of the study subjects

In total, 497 women with breast cancer were selected for analysis. The distributions of study variables by the stage of breast cancer among participants are presented in table 1. The mean age of patients at diagnose was 47.7 (SD=10.57) with a range of 25 to 76 years. Only 18.3% of the patients were diagnosed at stage I. The rest were diagnosed at stages II (45.5%), III or IV (36.2%).

Univariable analysis

Table 1 presents the un-adjusted associations between the stage of breast cancer at diagnosis and study variables. Accordingly, among patients who were diagnosed at late-stage, 54 (30.0%) had at least a family member who were diagnosed with breast cancer, whereas, only 69 (21.8%) of patients at early stage reported a history of breast cancer among their family (p=0.04). Among patients at early stage, 170 (53.6%) were able to self-exam their breast (BSE), whereas, only 71 (39.4%) of patients at late stage were aware of BSE (p=0.002). Of the patients diagnosed at late stage, 101 (56.1%) had more than 3 month delay in diagnosis compare with 57 (18.0%) among those at early stage. (p<0.001). Among patients at late stage and early-stage of tumor, 129 (71.7%) and 134 (42.3%) were reported with LV invasion respectively (p<0.001). Also, PN invasion was reported in 110 (34.7%) of the patients who were diagnosed at early-stage compared with 79 (43.9%) among patients at late stage (p=0.03). Moreover, education (p=0.01), family income (p<0.001), smoking (p=0.001) and suffering from other chronic diseases (P<0.004) were associated to the stage of cancer. On the other hand, the status of age at diagnosis, place of residency, occupation, marital status, age at marriage, age at first delivery, history of breast problem, physical exercise, X-Ray history of patients, type of tumor, ER, FR and Her2 among those who experienced late stage of cancer did not differ significantly from that of those with early stage (p>0.05 for all).

Multivariable analysis

After controlling for the effects of delay time and other potential confounders, results from multivariable analysis suggested that, older age at diagnosis (OR=0.97, 95%CI: 0.94 – 0.99, P=0.02) and higher family income

(OR high/low =0.19, 95%CI: 0.06 – 0.58, p<0.001) are significant preventive factors of being diagnosed at late stage of breast cancer. As expected, longer delay in diagnosis was strongly associated with the late stage of disease on a daily basis (OR=1.05, 95%CI: 1.03 – 1.08, p<0.001). The risk of being diagnosed at late stage was also significantly increased with having other chronic diseases (OR yes/no =1.77, 95%CI: 1.73 – 5.07, p=0.03) or reporting a history of breast cancer among the relatives (OR yes/no =2.48, 95%CI: 1.04 – 3.62, p=0.04). Significant interactions between diagnosis delay with income (p=0.006) and suffering from other disease (0.04) were found.

Table 2 also shows the results of delay-stratified analysis using the same strategy used for the main model variable selection. Accordingly, among those with less or equal to 3 months diagnostic delay, age (OR=0.96, 95% CI: 0.93 – 0.99, p=0.03), place of residency (OR Urban/rural=1.72, 95% CI: 1.42 – 1.93, p=0.04), income (OR high/low=0.27, 95%CI: 0.10 – 0.72, p=0.009), ability of performing BSE (OR yes/no=0.51, 95% CI: 0.0.26 -0.98, p=0.04), smoking (OR yes/no =2.23, 95%CI: 1.37 – 3.62, p=0.001), history of chest X-ray (OR yes/no = 1.40, 95% CI: 1.16 – 1.98, p=0.04) and suffering from other chronic diseases (OR yes/no =1.73, 95% CI: 1.36 – 5.48, p=0.004) were directly associated with the stage of BC.

Among those with a delay longer than 3 months, age at marriage (OR=0.83, 95% CI: 0.73 – 0.94, p=0.005), income (OR high/low=0.07, 95% CI: 0.008 – 0.63, p=0.01), family history of BC (OR=3.82, 95% CI: 1.05 –5.05. p=0.04), daily exercise (OR<10/10-20=0.10, 95% CI: 0.01 – 0.67, p=0.01) and suffering from other chronic diseases (OR yes/no =1.77, 95% CI: 1.73 – 5.07, p=0.03) were associated with the stage of cancer.

Discussion

In the present study, more than a third of patients were diagnosed at late stage. The mean age at diagnosis of the patients was about 45 years of age which is in line with the latest report from the Iranian health minister at 2007, it is also in accordance to other Iranian studies which reported the mean age of patients at diagnosis of breast cancer [18, 19]. Other important factors which were directly associated with TSD were DD and suffering from other chronic diseases. Family income was the only factor which was reversely associated with TSD. As shown in the result section, longer delay in diagnosis is strongly associated with the late stage of disease. The results of several studies on the same subject are consistent with what was found by the present study [20]. The later stage of breast cancer among women with significant DD can possibly be associated to the fact that longer DD is associated with

longer time for progression of the disease. On the other hand, later stage of breast cancer among women with no DD may suggest more invasive or faster growing disease. In the present study, a significant number of the patients were aware of the method of breast self-examination and some reported to have checked their breasts for palpable masses regularly. Among those with no diagnostic delay, being aware of breast self-examination is inversely associated with the stage of cancer at the time of diagnosis. However, this association no longer exists when there is a diagnostic delay longer than 3 months. This finding is in accordance with what was reported by AK Hackshaw et al. [21].

The multivariate and DD-stratified analysis revealed an inverse association between age of those with no significant DD and the stage of breast cancer. This may indicate that those having breast cancer at younger age experience faster progression of the disease and, as a result, worse prognosis. This finding is in accordance with what was reported by Nixon [22] but in contrast with Arndt et al [23]. It worth noticing that in these studies the possible effect of DD on the association between age and TSD was not considered. In addition, only among those with no DD, smoking and X-Ray are significantly associated with TSD. The above results may suggest the contribution of the later factors on more invasive and faster progress of BC. Ecological studies suggested that women from low-and middle-income countries have a higher chance of being diagnosed at late stage [24].The association is also reported by Clegg et al who found an inverse association between income and stage of breast cancer among women [25]. Harper et al. suggested that difference in socioeconomic status in various geographic areas is the main determinant of the spatial differences in the stage of breast cancer [26]. These findings were interpreted as possible DD intermediatory effect on the association as women from higher socioeconomic status (higher education, being younger, and having better access to medical services) have faster response and shorter DD. However, the findings from current study suggest that among those with no DD, people with better socioeconomic status were diagnosed at lower TSD. This raises a question as what drives the association between socioeconomic status of women and TSD irrespective of DD.

Based on the results of the present study, there was no significant association between TSD and the marital status, a result which is supported by Mohaghegh et al, [27] but is in contrast to Shieh et al. who reported a significant association between TSD and the patient's marital status [20]. Obtaining an inverse association between age at marriage and stage of cancer among those with significant DD is not reported before and needs closer look in to it as

women married at younger age are predominantly from communities with lower socio-economic status and lower education. Among similar group, family history was associated with TSD.

In line with the results of a published study [28], analysis of data from those with no significant DD suggested that smoking is directly associated with TSD [28]. However, the association does not exist when studying participants with a significant TSD. Several studies reported smoking as an important risk factor for breast cancer and few suggested that smoker patients had worse prognosis [29, 30]. These findings may suggest smoking as a risk factor for not only breast cancer but also for more invasive types of the disease.

The association between suffering from other chronic diseases and the stage of cancer is another important finding of the present study. As shown in the result section, irrespective of diagnostic delay, women with a chronic condition were diagnosed at later stage. Yancik et al. suggested that several chronic diseases such as diabetes increase the risk of mortality among patients with advanced stage of breast cancer [31]. In addition, Neil et al. shown that obesity and insulin resistance are associated with poorer prognosis in early-stage of breast cancer [32]. Although it is suggested that women with other chronic diseases may relate their symptoms to their chronic condition and seek medical help later [10], the results of the present study suggested that the association is possibly independent of DD. With the same analogy for the association of smoking and TSD, chronic diseases may also make women unable to resist against tumor progression or cause more invasive types of the disease.

Results of the present study also suggested that, among those with no significant DD, women who live in rural areas had a higher chance of being diagnosed at late stage of breast cancer [33]. However, the association turned to be non-significant when considering those with DD. A significant association was also found between the self-reported history of chest X-ray and the stage of disease among those with no DD. Again this finding may suggest exposure to X-ray as a contributor to more invasive type or faster progression of breast cancer. Finally, no association was found between marital status as well as the number of children and TSD.

Strengths and Limitations

The present study used a wide range of variables that might influence the rate of progression of breast cancer. Recruiting participants who visited the biggest referral center in the southern part of Iran makes the results

generalizable to the population of the country. However, interpreting the results, the possibility of error in the self-reported information such as the date at which the first symptom was noticed is to be taken into account.

Conclusions

Although, this study was not able to measure any causal association between the outcome and other study variables, the results did introduce several potential causal actions which worth further research.

The results indicated that several important known risk factors of breast cancer are possibly also important in the rate of progression of the disease. As mentioned by some other researchers, delay in diagnose found to be an important predicting factor of the stage of breast cancer. As a result, shortening the diagnosis delay can help patients to take medical treatments at the earlier stage and have better prognosis. Although more studies are needed to confirm the results and explain the mechanism of action of the associated factors, it seems that smokers or younger women and those with chronic conditions or a family history of cancer are better to take extra caution as they may have worse prognosis if diagnosed with cancer.

Declarations

Abbreviations: BC= breast cancer, TSD= tumor stage at diagnosis, DD= diagnosis delay, MTN= metastases-tumor-node, BSE= breast self-examination, OR=odds ratio, 95% CI= 95% confidence interval, AIC= Akaike information criterion, LV invasion= lymph- vascular invasion, PN invasion= pre-neural invasion, ER= estrogen receptor, PR=progesterone receptor, Her2= human epidermal growth factor receptor 2

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Authors' contributions

MD contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MF contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MM contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MZ contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AZ and ND contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. All authors approve the final version that is submitted to the Journal of Clinical Breast Cancer. The corresponding author affirms the information mentioned here on behalf of research team and has been given the authority to modify the manuscript if requested by the journal's editorial team.

Conflict of interest

All members of the study declare that they have no conflicts of interest.

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Table1: Characteristics of the study participants and tumor stage at diagnosis (N= 497)

Characteristics	**Early stage** n (%)	**Late stage** n (%)	**Total (%)**	**P value***
Age				0.66
<40	81 (25.6)	55 (30.5)	136(27.4)	
40 – 50	107 (33.8)	59 (32.8)	166(33.4)	
50-60	87 (27.4)	45 (25.0)	132(26.5)	
>60	42 (13.2)	21 (11.7)	63(12.7)	
Place of residence				
Rural	60 (18.9)	47 (26.1)	107(21.5)	0.06
Urban	257 (81.1)	133 (73.9)	390(78.5)	
Education				
Primary or illiterate	114 (36.0)	71 (39.4)	185(37.2)	0.01
Middle school	50 (15.7)	42 (23.3)	92(18.5)	

High school	95 (30.0)	51 (28.4)	146(29.4)	
College	58 (18.3)	16 (8.9)	74(14.9)	
Family income				
Low	56 (17.7)	51 (28.3)	107(21.5)	<0.001
Moderate	103 (32.5)	69 (38.3)	172(34.6)	
High	158 (49.8)	60 (33.4)	218 (43.9)	
Occupation				
Housewife	235 (74.1)	141 (78.3)	376(75.7)	0.29
Employed	82 (25.9)	39 (21.7)	121(24.3)	
Marital status				
Ever married	293 (92.4)	166 (92.2)	459(92.4)	0.93
Never married	24 (7.6)	14 (7.8)	38(7.6)	
Age of marriage (y)				
< 20	172 (54.3)	100 (55.5)	272 (54.7)	
20-25	68 (21.4)	40 (22.2)	108 (21.7)	0.96
25-30	35 (11.0)	16 (8.9)	51 (10.3)	
>30	18 (5.7)	10 (5.6)	28 (5.6)	
Single	24 (7.6)	14 (7.8)	38 (7.7)	
Age at first childbirth				
<20	136 (42.9)	77 (42.8)	213 (42.9)	
20-30	111 (35.0)	59 (32.8)	170 (34.2)	0.92
>30	26 (8.2)	17 (9.4)	43 (8.6)	
Single or no child	44 (13.9)	27 (15.0)	71 (14.3)	
Family history of BC				
No	248 (78.2)	126 (70.0)	374 (75.3)	0.04
Yes	69 (21.8)	54 (30.0)	123 (24.7)	
History of breast problem				
No	263 (83.0)	148 (82.2)	411 (82.7)	0.83
Yes	54 (17.0)	32 (17.8)	86 (17.3)	
Aware of breast-exam				0.002

No	147 (46.4)	109 (60.6)	256(51.5)	
Yes	170 (53.6)	71 (39.4)	241(48.5)	
Daily exercise (min)				
< 10	193 (60.9)	117 (65.0)	310 (62.4)	0.31
10 – 20	22 (6.9)	16 (8.9)	38 (7.6)	
>20	102 (32.2)	47 (26.1)	149 (30.0)	
Smoking				
No	279 (88.0)	138 (76.7)	417(83.9)	0.001
Yes	38 (12.0)	42 (23.3)	80(16.1)	
X_ Ray history				
No	233 (73.5)	132 (73.3)	365(73.4)	0.96
Yes	84 (26.5)	48 (26.7)	132(26.6)	
Other Chronic disease				
No	207 (65.3)	94 (52.2)	301(60.6)	0.004
Yes	110 (34.7)	86 (47.8)	196(39.4)	
Delay in diagnosis (day)				
<15	117 (36.9)	9 (5.0)	126(25.4)	
15-30	84 (26.5)	29 (16.1)	113(22.7)	<0.001
31-90	59 (18.6)	41 (22.8)	100(20.1)	
>90	57 (18.0)	101 (56.1)	158(31.8)	
Type of tumor				
Ductal	289 (91.2)	167 (92.8)	456(91.8)	0.79
Lobular &medullary	16 (5.0)	8 (4.4)	24(4.8)	
†Unknown	12 (3.8)	5 (2.8)	17(3.4)	
PN invasion				
No	192 (60.6)	91 (50.5)	283 (56.9)	0.03
Yes	110 (34.7)	79 (43.9)	189 (38.1)	
†Unknown	15 (4.7)	10 (5.6)	25 (5.0)	
LV invasion				< 0.001

No	168 (53.0)	41 (22.8)	209 (42.0)	
Yes	134 (42.3)	129 (71.7)	263 (52.9)	
†Unknown	15 (4.7)	10 (5.5)	25 (5.1)	
ER				
Negative	82 (25.9)	37 (20.6)	119 (23.9)	0.18
Positive	205 (64.7)	125 (69.4)	330 (66.4)	
†Unknown	30 (9.4)	18 (10.0)	48 (9.7)	
PR				
Negative	86 (27.1)	45 (25.0)	131 (26.3)	0.62
Positive	201 (63.4)	117 (65.0)	318 (64.0)	
†Unknown	30 (9.5)	18 (10.0)	48 (9.7)	
Her 2				
Negative	175 (55.2)	105 (58.3)	280 (56.3)	0.55
Positive	111 (35.0)	59 (32.8)	170 (34.2)	
†Unknown	31 (9.8)	16 (8.9)	47 (9.5)	

333 *: Based on Chi-square test; †: not included in the analysis

334 Table 2: Delay-stratified associations of study variables with the stage of breast cancer

Variables	**≤3 month**		**>3 month**		**Overall**	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Age (year)	0.96 (0.93 – 0.99)	0.03	-	NI	0.97 (0.94 -0.99)	0.02
Age at marriage	-	NI	0.83 (0.73 – 0.94)	0.005		
Place of residence		0.04	-	NI	-	NI
Urban	1 (-)					
Rural	1.72 (1.42 – 1.93)					
Education	-	NI			-	NI
Primary and lower			1 (-)	-		
Middle school			3.06 (0.67 – 13.82)	0.14		

High school			3.22 (0.61 – 19.61)	0.16		
College			0.05 (0.001 – 5.21)	0.21		
Family income						
Low	1 (-)	-	1 (-)	-	1 (-)	-
Moderate	0.40 (0.15 – 1.04)	0.06	0.12 (0.01 – 0.89)	0.03	0.55 (0.28 – 1.07)	0.08
High	0.27 (0.10 – 0.72)	0.009	0.07 (0.008 – 0.63)	0.01	0.19 (0.06 – 0.58)	< 0.001
Family history of BC	-	NI				
No			1 (-)		1 (-)	
Yes			3.82 (1.05 –5.05)	0.04	2.48 (1.04 – 3.62)	0.04
Aware of breast-exam		0.04	-	NI	-	NI
No	1 (-)					
Yes	0.51 (0.26 -0.98)					
Daily exercise (minute)	-	NI			-	NI
< 10			1 (-)	-		
10 – 20			0.10 (0.01 – 0.67)	0.01		
>20			0.35 (0.10 – 1.24)	0.10		
Smoking		0.001	-			
No	1 (-)			1 (-)	-	0.08
Yes	2.23 (1.37 – 3.62)			1.64	0.92 – 2.93	
X_ Ray history		0.04	-	NI	-	NI
No	1 (-)					
Yes	1.40 (1.16 – 1.98)					
Suffering from Chronic diseases*		0.004		0.03		0.03
No	1 (-)		1 (-)		1 (-)	
Yes	1.73 (1.36 – 5.48)		1.77 (1.73 – 5.07)		1.77 (1.73 – 5.07)	
Delay in diagnosis (day)	-	NA	-	NA	1.05 (1.03 – 1.08)	< 0.001

NI=not included in the final model after stepwise variable selection; NA= not applicable, * diabetes, hypertension and cardio-vascular disease.