Do reproductive and hormonal risk factors for breast cancer associate with attendance at mammography screening?

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Title: Do reproductive and hormonal risk factors for breast cancer associate with attendance at mammography screening?

Short title: Risk factors and mammography screening attendance

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Abstract

Purpose To determine whether reproductive and hormonal risk factors for breast cancer associate with mammography attendance.

Methods We linked data from the Malmö Diet and Cancer Study to the Malmö mammography register (Sweden, 1992–2009). We analyzed 11,409 women (age 44–72) who were free of breast cancer at study entry and a total of 69,746 screening invitations. Generalized Estimating Equations were used to account for repeated measures within subjects. Models were adjusted for age and other sociodemographic factors.

Results In this study cohort, mammography screening attendance ranged from 87.6 to 94.5 % between calendar years, with an average attendance of 92 %. Higher attendance was found among women who had given birth to fewer than three children (ORs ranging between 1.15 and 1.37) and had used oral contraceptives (OC) within the last decade (OR = 1.22, 95 % CI 1.07–1.38) and for a longer period (OR = 1.13, 95 % CI 1.01–1.27). A lower odds of attendance was found among post-menopausal women (OR = 0.86, 95 % CI 0.77–0.96). Age \13 at menarche, age C30 at first childbirth, age C55 at menopause, age\20 at first OC use, nulliparity, breastfeeding, and hormone replacement therapy were not associated with mammography attendance.

Conclusion Reproductive and hormonal risk factors for breast cancer have little effect on mammography screening attendance. This may indicate a potential for under-screening of some women at higher risk.

Introduction

The public health impact of mammography screening programs depends on high attendance rates in general, but also on the regular screening of women at highest risk for breast cancer. Despite evidence that regular mammography screening can reduce breast cancer mortality by 20–50 % [1, 2], not all women attend screening, and the factors influencing mammography attendance are not well understood.

In general, there is a positive relationship between risk perception and mammography screening [3, 4]. In particular, older age and a family history of breast cancer are positively associated with greater screening attendance [3, 4]. In contrast, the relationship between reproductive and hormonal risk factors for breast cancer and mammography attendance is less clear. Such risk factors include age at menarche and menopause, lifetime number of menstrual periods, parity, breastfeeding, oral contraceptive use, and hormone therapy after menopause [5, 6]. Of the few studies to examine this question, only hormone therapy after menopause is consistently associated with greater mammography attendance [7–14]. Compared with family history and older age, which are well-established and well-known risk factors for breast cancer, it is possible that reproductive and hormonal risk factors for breast cancer are less well known by the general female public.

From the first pilot and trials starting in 1974, population-based outreach mammography screening for women over the age of 40 or 50 was gradually introduced throughout Sweden, and by 1997, a nationwide screening program had been implemented [15]. Coupled with the availability of population-based registers of vital statistics, we were able to prospectively follow a large cohort of women and study their patterns of mammography attendance in relation to risk factors at baseline. To do this, we linked data from the Malmö Diet and Cancer Study to the Malmö mammography register and examined whether pre-existing reproductive and hormonal risk factors for breast cancer were associated with greater mammography attendance over the subsequent two decades.

Methods

Design, setting, and population

In this community-based cohort study, we linked data from the *Malmö Diet and Cancer Study* (MDCS) to the *Malmö Mammographic Screening Register*. Data sources and sample selection are described below. This study was approved by the ethics committee at Lund University.

Data sources

The MDCS is a prospective cohort study, conducted in Malmö, a city in southern Sweden with a growing population of approximately 303,000 residents as of year 2011 [16]. The primary goal of the MDCS is to investigate the association between diet and different types of cancer. Recruitment started in 1991 and was predominantly done by postal invitation at random from the source population of Malmö residents born between 1926 and 1945. An additional 18.1 % of the respondents joined the study spontaneously as a result of the passive recruitment campaign, and recruitment was extended to some older and younger age groups in 1995. At the end of recruitment in the autumn of 1996, a total of 17,035 women had joined the study [17, 18]. At baseline, all participants completed a health questionnaire, which was reviewed for missing answers by a research assistant during the second study visit, a few weeks later.

The *Malmö Mammographic Screening Program* is an outreach mammography screening program that was established in Malmö, Sweden, in 1990. Invitations to attend mammography screening are mailed to all eligible female residents in intervals of 1.5–2 years, depending on their date of birth and breast density. Reminders are not used. The mammography register is continuously updated to ensure inclusion of all eligible women (all Swedish residents are assigned a unique 10-digit personal identification number that can be linked to central health and census registers). The screening register contains basic information on number of invitations, dates, attendance, and recall for each woman. The age groups invited have varied somewhat over the years due to changes in recommendations. Between 1990 and 1998, only women aged 50–69 were invited; however, in 1999, the upper age limit was extended to 74 years, and since 2009, the lower age limit decreased to 40 years. Two-view mammography and double reading of the mammograms is practiced.

Sample

For the purpose of this study, we selected women who completed the MDCS baseline questionnaire between February 17, 1992 and September 25, 1996 (second and third questionnaire versions) and who had been invited to the mammographic screening program in Malmö between baseline and end of follow-up (date of death, date of emigration from Sweden, date of breast cancer diagnosis, or December 31, 2009, whichever came first). Women who had been diagnosed with breast cancer before baseline were excluded. The sample flow chart in Fig. 1 describes the different steps of exclusion, resulting in a final sample of 11,409 individuals.

Measures and definitions

Outcome: screening attendance

The outcome variable of interest in this study is mammography screening attendance, and we used the individual mammography invitation as the unit of analysis. Among the 11,409 subjects included in the study sample, there were a total of 69,746 screening opportunities (invitations) during follow-up. Of these, 64,194 (92 %) resulted in attendance and 5,552 (8 %) resulted in non-attendance.

Reproductive and hormonal risk factors for breast cancer

Information on reproductive and hormonal risk factors was obtained from the baseline MDCS health questionnaire. We examined the following variables: *early menarche*, defined as first menstrual period before age 13 [11, 19]; *early menopause*, defined as last menstrual period before age 55 [5, 14]; *oral contraceptive* (OC) use, categorized as ever versus never, age at first OC use (<20 years vs. ≥20 years), recency of use (<10 years ago vs. ≥10 years ago), and total duration of use (<15 years vs. ≥15 years) [5, 20]; *parity*, categorized as nulliparous vs. parous, and according to number of childbirths (0, 1, 2 and 3?); and *age at first childbirth*, categorized as <30 years and ≥30 years [5, 11]. Among parous women, information on breastfeeding was collected for the first seven children. However, because of missing data for individual children, we were unable to reliably determine total duration of breastfeeding; therefore, we calculated duration of breastfeeding for the first child only; this variable had the most complete data. *Breastfeeding duration* was categorized as <8 months and ≥8 months. Women who had reached menopause were asked about use of *hormone replacement therapy* (HRT). HRT use among post- menopausal women was categorized as ever versus never, and duration of HRT use was categorized as short-term (<5 years) vs. long-term (≥5 years) [21].

Statistical analysis

Descriptive characteristics are reported as mean [standard deviation (SD)] or count (percent). We estimated odds ratios and 95 % CI for mammography attendance from binary Generalized Estimating Equation (GEE) models where adjustments are made for the correlation of repeated measures within subjects (with an autoregressive correlation structure). There were only repeated measures for the outcome variable and not for the exposure variables. We first conducted univariate analyses to determine the effects of the different risk factors for breast cancer on the odds of attendance. These effects were then adjusted by age and finally for age and sociodemographic factors, including education, employment status, and country of birth.

Sensitivity analyses

To evaluate the possibility of a differential effect over time, we examined associations with screening attendance in two nine-year intervals: 1992–2000 and 2001–2009.

Results

Of 17,035 women who completed the MCDS baseline questionnaire between 1992 and 1996, 13,649 received at least one invitation to attend the Malmö mammography screening clinic before December 31, 2009, and 11,409 met our inclusion criteria (**Fig. 1**). The distribution of the screening opportunities is presented in **Table 1**. The number of screening opportunities per woman ranged between one and twelve [mean = 6.1 (2.5)]. In individual calendar years, the mammography attendance rate ranged between 87.6 and 94.5 % (**Fig. 2**), with an overall attendance rate of 92 % for the entire follow-up period.

Sample characteristics are presented in **Table 2**. At baseline, women were an average of 54.9 years (range 44–72). Mean age at first screening opportunity was 56.7 years (range 45–75). Approximately two-thirds of women had not completed high school, two-thirds were employed, and 88.3 % were born in Sweden. In terms of occupational status (present or most recent position), 55.6 % were non-manual workers and 36.6 % were manual workers.

Relationship between risk factors and mammography attendance

Associations between risk factors and mammography attendance are presented in **Table 3**. The fully adjusted ORs were adjusted for age and other sociodemographic factors.

Higher attendance was found among women who had given birth to fewer than three children (ORs ranging between 1.15 and 1.37) and among women with more recent OC use (OR = 1.22, 95 % CI 1.07–1.38) and longer OC use (OR = 1.13, 95 % CI 1.01–1.27). Lower odds of attendance were found among post-menopausal women (OR = 0.86, 95 % CI 0.77–0.96) when adjusting for age and other sociodemographic factors. The associations between mammography attendance and early menarche, late menopause, nulliparity, older age at first childbirth, breast feeding, ever use of OCs, young age at first OC use, and use of hormone replacement therapy were not statistically significant.

Results were similar when we divided the screening period into two nine-year intervals (1992–2000 and 2001–2009), although there were some discrepancies. Late menopause, while positively associated with high attendance during the later time period (OR = 1.43, 95 % CI 1.08–1.89), was not significant during the earlier time period (OR = 0.98, 95 % CI 0.79–1.22). The association between early start of oral contraceptive use and high screening attendance was statistically significant during the earlier time period (OR = 0.74, 95 % CI 0.61–0.89), but not the later time period (OR = 0.98, 95 % CI 0.81–1.18). Both recent and longer use of OCs had a stronger positive effect on attendance between 2001 and 2009 compared to 1992–2000. Longer use of HRT had a significant negative effect on screening attendance in the second half of the study period (OR = 0.64, 95 % CI 0.46–0.89), but had no effect on attendance during the first half (OR = 0.94, 95 % CI 0.65–1.36).

Discussion

In this Swedish cohort of women who received regular invitations to attend mammography screening, few reproductive and hormonal risk factors for breast cancer predicted greater screening attendance. Higher odds of attendance were found among women who had used oral contraceptives within the last decade, had used OCs for a longer period of time, had given birth to fewer than three children, and who were pre-menopausal. However, the magnitudes of these associations were small (all ORs between 0.8 and 1.4), suggesting small clinical significance. As well, many established risk factors were not associated with greater screening, such as older age at first childbirth, nulliparity, or use of hormone replacement therapy. When the follow-up period was divided into two halves, there were some discrepancies indicating that there could have been some periodical effects on the results. However, these discrepancies pointed in different directions for different risk factors and their magnitudes were not large enough to warrant further stratification by time period.

Preferably, women at higher risk for breast cancer would be screened to a greater extent [22]. However, this was not apparent in our study. It is possible that many of the risk factors examined in our study were not so easily identified by women or that many lacked knowledge about them. Only one-third of women in our sample had completed high school, which may support this hypothesis. Alternatively, perhaps the presence of these risk factors did not cause women to feel vulnerable to breast cancer. While many studies show a positive relationship between risk perception and mammography screening [3, 4], others suggest that a greater perception of cancer risk could inhibit screening attendance because of heightened anxiety or feelings of helplessness about personal vulnerability [23, 24]. Both possibilities have implications for public health campaigns designed to increase screening attendance [3]. Unfortunately, our data sources did not contain information on women's knowledge or perceived risk, and therefore, we could not evaluate the direct effect of these factors on screening attendance. Finally, a woman's decision to attend screening may also be influenced by recommendations from her health practitioner who is more likely to advise women at greater risk to attend screening. In this study, however, screening invitations were automated and thus not specifically directed at a woman's risk profile.

Although nulliparity is a known risk factor for breast cancer, greater screening attendance was not associated with nulliparity or age at first childbirth; however, attendance was more likely among women who gave birth to fewer than three children compared with those who gave birth to three or more children. The literature shows a similar mixed picture, with many studies finding no effect of nulliparity on screening [10, 11, 14, 25, 26], a positive effect of parity [9, 12, 27], but less screening among women with more children [28–31]. Even though we controlled for sociodemographic factors, it is likely that a residual or unmeasured effect from sociodemographic or behavioral factors explains this association.

Our sample constituted of a selection of individuals with high screening attendance. The overall attendance rate of 92 % in this cohort is considerably higher than rates reported in earlier studies, which were closer to 65 % [32, 33]. Greater heterogeneity may exist in the source population with respect to the distribution of these risk factors and their relationship with attendance. This may explain the weak and/or absence of associations between risk factors and screening attendance, for example, between screening and HRT use, which is now a well-known risk factor for breast cancer and is consistently associated with mammography screening in other studies [7–9, 12, 13, 29, 30, 34]. As well, we did not have information on type of HRT or OC, nor the exact duration of use for each type. Similarly, other details concerning hormonal and reproductive risk factors for breast cancer were not measured to a preferable extent. In particular, information on breastfeeding was incomplete for many multi-parous women, and this may explain the lack of association between breastfeeding and screening attendance. Most importantly, we did not have information about breast cancer heredity or previous benign breast disease, which may be more commonly known risk factors and make women feel more vulnerable to breast cancer. To examine all these factors together would be of great interest in a future study.

Despite these limitations, our study has many strengths, including its large size (11,409 women and 69,746 screening invitations) and prospective follow-up of screening attendance. Information on risk factors was collected independently of mammography screening, which reduces the potential for recall bias. Further, while many studies rely on self-reported data on mammography attendance, we obtained this information from register data, which would minimize measurement error and misclassification. Finally, we were able to exclude women who had had breast cancer before baseline and therefore examine screening attendance prior to any breast cancer diagnosis, which would likely alter screening attendance.

In conclusion, our results suggest that reproductive and hormonal risk factors for breast cancer have little effect on subsequent mammography screening attendance. Weak or absent associations between risk factors and attendance may be partly explained by insufficient variation in attendance. Nonetheless, our results may indicate that some women at higher risk for breast cancer may be under-screened and that public health campaigns designed to optimize mammography screening may benefit from targeting screening referrals to women at greatest risk. However, the proportion of non-attendance was very small and our study did not account for other strong risk factors (e.g., family history, breast density, and biopsy history).

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Conflict of interest

The authors declare that they have no conflict of interest.

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Figure 1. Selection of Analytic Cohort

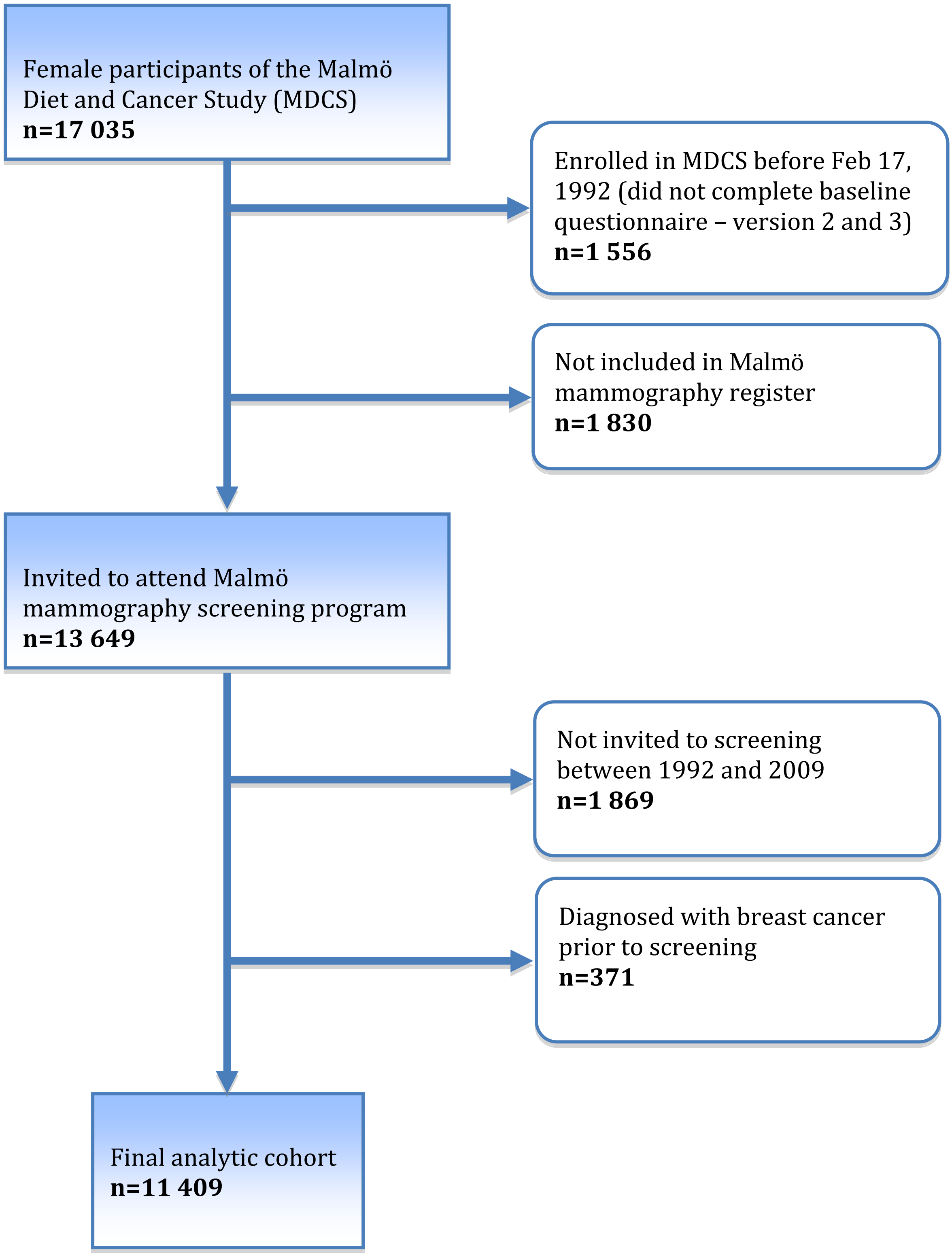

Figure 2. Annual Mammography Attendance Rate of Study Cohort (Malmö, Sweden, 1992-2009)

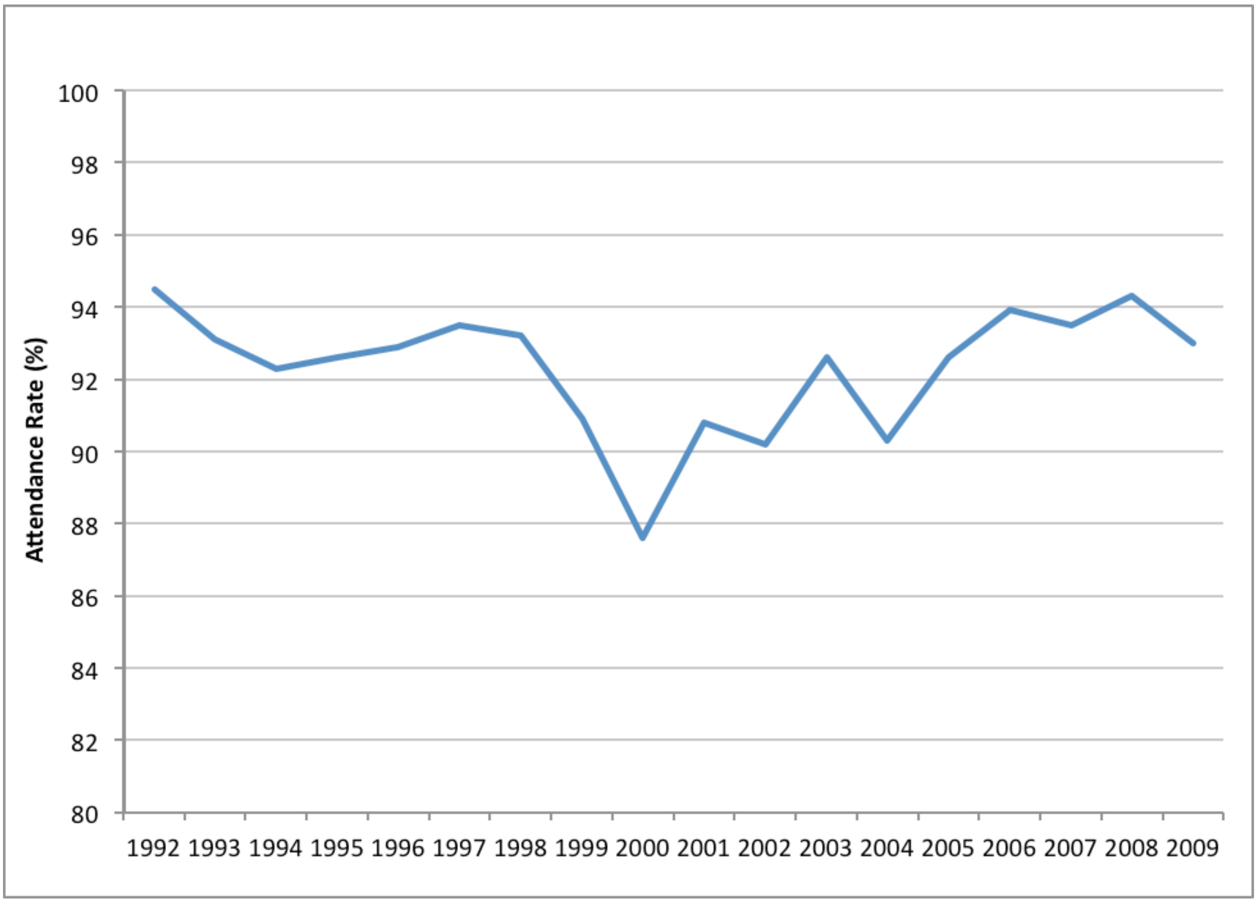

Table 1. Distribution of mammography screening invitations among women in study cohort (Malmö, Sweden, 1992-2009).

Number of invitations	**Frequency**	**Percent**
1	793	6.95
2	602	5.28
3	568	4.98
4	808	7.09
5	1,271	11.14
6	1,626	14.25
7	1,896	16.62
8	1,921	16.84
9	1,247	10.93
10	609	5.34
11	67	0.59
12	1	0.01
Total	11,409	100

Table 2. Sociodemographic characteristics of study sample (n=11,409) from the MDCS cohort (Malmö, Sweden, 1992-2009).

Sociodemographic variables	n (%)
Mean age at baseline (SD)	54.9 (6.7)
Mean age at 1st subsequent screening invitation (SD)	56.7 (6.4)
Age group (years)	
44-49	3,442 (30.2)
50-54	2,470 (21.6)
55-59	2,086 (18.3)
60-64	2,155 (18.9)
65-72	1,256 (11.0)
Education level	
High school or higher	3,717 (32.7)
Less than high school	7,665 (67.3)
Missing	27
Occupation (present or latest job)	
Self-employed/employer/farmer	885 (7.8)
Higher non-manual	741 (6.6)
Middle non-manual	2,049 (18.1)
Lower non-manual	3,489 (30.9)
Skilled manual	803 (7.1)
Unskilled manual	3,341 (29.5)
Missing	101
Employment status	
Employed	7,695 (67.6)
Not employed	3,681 (32.4)
Missing	33
Country of birth	
Sweden	10,066 (88.3)
Other	1,336 (11.7)
Missing	7

Table 3. Mammography screening attendance in relation to reproductive and hormonal risk factors for breast cancer (Malmö, Sweden, 1992-2009).

Risk factors	Subjects n=11,409	**Odds ratios for mammography attendance (95% CI)** Unadjusted	Age adjusted	Fully adjusted*
Age at menarche (yrs)				
<13	2,603 (23.0%)	1.00 (0.91-1.09)	1.02 (0.93-1.12)	1.04 (0.95-1.14)
≥13	8,728 (77.0%)	1.0	1.0	1.0
Missing	79			
Menopausal status				
Post-menopausal	7,615 (67.7%)	1.14 (1.05-1.23)	0.87 (0.78-0.97)	0.86 (0.77-0.96)
Pre-menopausal	3,630 (32.3%)	1.0	1.0	1.0
Missing	164			
Age at menopause (yrs)				
<55	6,944 (91.2%)	1.0	1.0	1.0
≥55	671 (8.8%)	1.21 (1.00-1.46)	1.11 (0.92-1.34)	1.13 (0.93-1.37)
Pre-menopausal or missing	3,794			
Parity				
Nulliparous	1,541 (13.5%)	1.07 (0.95-1.20)	1.07 (0.95-1.20)	1.08 (0.96-1.22)
Parous	9,845 (86.5%)	1.0	1.0	1.0
Missing	23			
Number of childbirths				
None	1,541 (13.5%)	1.29 (1.13-1.47)	1.31 (1.15-1.50)	1.30 (1.14-1.49)
One	2,365 (20.8%)	1.13 (1.01-1.27)	1.15 (1.03-1.29)	1.15 (1.03-1.29)
Two	4,848 (42.6%)	1.39 (1.26-1 53)	1.42 (1.29-1.57)	1.37 (1.24-1.51)
Three or more	2,632 (23.1%)	1.0	1.0	1.0
Missing	23			
Age at birth of first child (yrs)				
<30	8,521 (86.6%)	1.0	1.0	1.0
≥30	1,319 (13.4%)	1.02 (0.90-1.15)	1.03 (0.91-1.16)	1.09 (0.97-1.24)
Nulliparous or missing	1,569			

* Adjusted for age, education, employment status, and country of birth.

Table 3 continued		Odds ratios for mammography attendance (95% CI)		
Risk factors	Subjects n=11,409	Unadjusted	Age adjusted	Fully adjusted*
Breastfeeding				
Ever	8,978 (94.7%)	1.0	1.0	1.0
Never	506 (5.3%)	0.84 (0.70-1.02)	0.87 (0.72-1.05)	0.89 (0.73-1.07)
Nulliparous or missing	1,925			
Months breastfeeding 1st child				
<8 months	7,860 (83.9%)	1.09 (0.97-1.22)	1.11 (0.99-1.25)	1.07 (0.95-1.20)
≥8 months	1,511 (16.1%)	1.0	1.0	1.0
Nulliparous or missing	2,038			
Use of oral contraceptives (OC)				
Ever	6,290 (55.2%)	0.99 (0.91-1.07)	1.09 (1.00-1.19)	1.02 (0.94-1.12)
Never	5,112 (44.8%)	1.0	1.0	1.0
Missing	7			
Age at first OC-use				
<20 years	995 (16.1%)	0.82 (0.72-0.95)	0.92 (0.79-1.07)	0.89 (0.76-1.03)
≥20 years	5,189 (83.9%)	1.0	1.0	1.0
Never-user or missing	5,225			
Recent use of OC				
Yes (<10 years ago)	1,459 (24.1%)	1.24 (1.09-1.40)	1.25 (1.10-1.42)	1.22 (1.07-1.38)
No (≥10 years ago)	4,599 (75.9%)	1.0	1.0	1.0
Never-user or missing	5,351			
Duration of OC-use				
Shorter (<15 yrs)	4,311 (70.5%)	1.0	1.0	1.0
Longer (≥15 yrs)	1,807 (29.5%)	1.18 (1.05-1.33)	1.18 (1.05-1.32)	1.13 (1.01-1.27)
Never-user or missing	5,291			
Hormone replacement therapy				
Ever	1,303 (27.9%)	1.10 (0.97-1.25)	1.05 (0.92-1.29)	1.03 (0.90-1.18)
Never	3,363 (72.1%)	1.0	1.0	1.0

Pre-menopausal or missing	6,743			
Duration of HRT-use				
Shorter (<5 yrs)	780 (69.1%)	1.0	1.0	1.0
Longer (≥5 yrs)	348 (30.9%)	0.91 (0.71-1.16)	0.77 (0.58-1.02)	0.77 (0.58-1.02)
Pre-menopausal or missing	10,281			

* Adjusted for age, education, employment status, and country of birth.