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EPIDEMIOLOGY

# History of oral contraceptive use in breast cancer patients: impact on prognosis and endocrine treatment response

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**Abstract** The purpose was to study oral contraceptive (OC) use in relation to breast cancer events and endocrine treatment response in a prospective population-based cohort, because it is unclear whether history of OC use impacts on prognosis in breast cancer patients. Between 2002 and 2011, 994 primary breast cancer patients without preoperative treatment were enrolled in Lund, Sweden and followed until December 2012. History of OC use was obtained from preoperative questionnaires. Tumor characteristics, clinical data, and date of death were obtained from pathology reports, patient charts, and population registries. Among the 948 patients with invasive cancer and no metastasis detected on the post-operative screen, 74 % had ever used OCs. Patients were followed for up to nine years (median follow-up 3 years), and 100 breast cancer events were recorded. Ever OC use was not associated with prognosis, irrespective of duration. However, any OC use before age 20 was associated with a threefold increased risk for breast cancer events in patients <50 years but not in patients ≥50 years ($P_{\text{interaction}} = 0.009$). In patients ≥50 years with estrogen receptor positive tumors, previous OC use at any age was associated with a significantly decreased risk of breast cancer events among patients who received aromatase inhibitors compared to patients who never used OCs (adjusted HR 0.37: 95 % CI 0.15–0.87). OC use was not associated with tamoxifen-response. If confirmed, history of OC use may yield valuable prognostic and treatment predictive information in addition to currently used criteria.

**Keywords** Breast cancer · Oral contraceptives · Tumor characteristics · Prognosis · Treatment prediction · Endocrine therapy

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## Introduction

Although the relationship between oral contraceptive (OC) use and breast cancer incidence has been widely studied, few studies have investigated the relationship between OC use prior to the breast cancer diagnosis, tumor characteristics [1–5], and survival among breast cancer patients [4, 6–10]. The results have been inconsistent.

OCs are widely used in Sweden [11]. About 300 million women worldwide have used OCs, and the number is increasing [12]. Thus, it is of great importance to understand the full range of risks and benefits of their effect associated with their use. OCs were introduced on the Swedish market in 1964 [13, 14]. The first OCs were high-dose combined OCs (≥75 μg ethinylestradiol), and these were later replaced by low-dose OCs [15].

The breast is especially sensitive to hormonal stimuli, including OCs, between menarche and first full-term pregnancy [16]. For example, women who used OCs before age 20 or before their first child had an increased risk of

developing breast cancer at an early age, compared to women who started later or never used OCs [17, 18]. OC use has also been shown to have an impact on tumor characteristics and molecular subtypes of breast cancer, although results of previous studies have been contradictory [19–21].

Choice of adjuvant treatment is currently based on tumor characteristics and menopausal status [22]. Most patients with hormone receptor positive tumors are offered endocrine treatment, often either the selective estrogen receptor modulator tamoxifen (TAM) or aromatase inhibitors (AI). Some studies suggest that AIs are more effective than TAM in preventing relapse in postmenopausal women [23–25]. To our knowledge, there are no studies investigating whether prior OC use impacts on endocrine treatment response, and history of OC use is not considered when selecting the type of endocrine treatment.

The aim of this study was to determine whether history of OC use impacts on breast cancer prognosis and endocrine treatment response in breast cancer patients, and if so, whether any association was modified by age at first use, time since OC start or duration of use.

## Materials and methods

Patients diagnosed with primary breast cancer at Skåne University Hospital in Lund were invited to take part in an on-going prospective cohort study, which started in October 2002. One aim of the study was to explore non-genetic factors and their prognostic and predictive values. The study was approved by the Lund University Ethics Committee (LU75-02, LU37-08, LU658-09, LU58-12, LU379-12), and written informed consents were obtained from all participants.

This paper is based on a study population of 994 patients included between October 8, 2002 and December 31, 2011. Patients with treatment prior to surgery ($n = 51$) were not included since this could influence tumor characteristics. The flowchart in Fig. 1 shows the study population in the various analyses.

The patients were asked to fill-out a three-page preoperative questionnaire including questions on intake of medications during the last week, preoperative smoking and alcohol intake, reproductive history, use of hormonal contraception, and treatment for menopausal symptoms. A research nurse measured height, weight, hip and waist circumferences, and breast volume [26] prior to surgery. Patients also completed post-operative follow-up questionnaires including information on current treatment.

Information on ever use and current use of OCs was collected. Other information included starting age, duration of use before age 20, duration of use before the first child, and total duration of use. If the patient responded to the question about starting age with an interval, the mean value was entered, truncated to a full year. Duration of use was recorded in months; if an interval was reported, the mean value was entered. It was assumed that patients did not take OCs during pregnancy and the post-partum period. Some patients did not take a full-term pregnancy into account when providing duration of use, and provided inconsistent answers. For example, a patient reported an OC start age of 16 years, duration of use of 4 years prior to age 20, and a full-term pregnancy at age 18. In such cases, 12 months of use were deducted. In nulliparous women, all OC use was considered to be before the first child. Questions regarding OC use did not differentiate between combined OCs and OCs containing only progestin. Age 50 was used as a proxy variable for menopause, since usage of hormonal intrauterine device, hormone replacement therapy, and hysterectomy without oophorectomy made it difficult to determine the actual age at menopause. To examine the effect of use of OCs with different doses, a proxy variable was created. High-dose OCs disappeared from the Swedish market in 1974 [15], and 1974 was used as a cut-off between high- and low-dose OCs.

Information concerning type of surgery, sentinel node biopsy, axillary node dissection, and adjuvant treatment was obtained from clinical records and questionnaires. Information regarding treatment was registered up to the last follow-up or death. Treatment was administered according to the standard of care at Skåne University Hospital during the time the cohort was compiled, and not randomized. Tumor characteristics, i.e., TNM status, ER and PgR status, were collected from pathology reports. ER and PgR status was determined as previously described [27, 28]. Analyses of HER2 amplification were introduced in routine clinical practice as of November 2005. Analyses were conducted in patients <70 years with invasive tumors, with the method previously described [29]. HER2 status was available for 618 patients. Ki-67 were routinely analyzed first as of March 2009 and therefore not included in this study [30]. All tumors were analyzed at the department of pathology at Skåne University Hospital in Lund.

Information on events and deaths were obtained from patients' charts, pathology reports, and the Regional Tumor Registry. Information on date of death was obtained from the Swedish population register, which is virtually 100 % complete.

### Statistics

Data were analyzed using the IBM Statistical Package for Social Sciences (SPSS) version 19.0 (SPSS, Inc., Chicago, IL). Since several of the patient characteristics were not

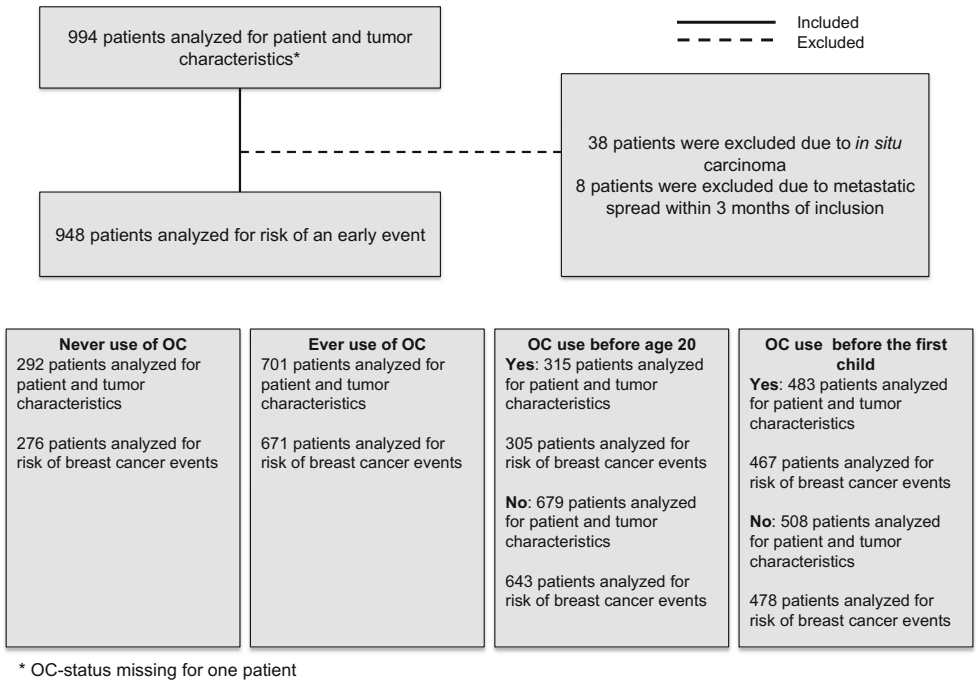


**Fig. 1** Flowchart of patients

normally distributed, the median and interquartile ranges are presented.

OC use was examined using different cut-off categories: ever use (yes/no), use before age 20 (yes/no), and use before the first child (yes/no). Patient and tumor characteristics were analyzed in relation to the different categories of reported OC use. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Waist to hip ratio (WHR) was calculated as waist circumference divided by hip circumference. TNM status included pathological, i.e., invasive tumor size [$\leq$20 mm, 21–50 mm, $\geq$51 mm, muscle or skin involvement, or $\geq$21 mm or muscle or skin involvement (yes/no)], pathological axillary lymph node involvement [0, 1–3, 4 + or axillary lymph node involvement (yes/no)], histological grade [I–III or grade III (yes/no)], and hormone receptor status [ER +/PgR + , ER +/PgR−, ER−/PgR−, ER−PgR + , ER +, and PgR +].

Pearson's Chi-squared test was used for analysis of categorical variables in relation to OC use, and Fisher's Exact Test was used when the expected number of patients was small. Since several of the continuous variables were not normally distributed, the Mann–Whitney *U* test was used for univariable analyses. The multivariable analyses variables that were not normally distributed were either transformed using the natural logarithm or categorized in the multivariable analyses.

A breast cancer event was defined as a local or regional recurrence, contralateral breast cancer, or distant metastasis. Risk of breast cancer events was calculated from time of inclusion until an event or last follow-up or death, prior to January 1st, 2013. Patients were censored at the time of death due to a non-breast cancer-related cause. Analyses of risk of breast cancer events were performed on 948 patients after exclusion of patients with carcinoma in situ (n = 38) or metastatic spread within three months of surgery ($n = 8$).

Kaplan–Meier was used for univariable analysis of risk of breast cancer events in relation to OC use. Adjusted hazard ratios (adjHR) with 95 % confidence intervals (CI) were obtained with Cox Regression. Adjustments were made for tumor characteristics: invasive tumor size $\geq$21 mm or skin or muscular involvement (yes/no), any axillary lymph node involvement (yes/no), histological grade III (yes/no), and positive ER-status (yes/no). Adjustments were also made for patient characteristics: age (continuous) and BMI $\geq$25 kg/m$^2$ (yes/no). In the analyses of risk of breast cancer events, age 50 and above and different categories of OC use were first analyzed as independent variables. Secondly, interaction variables (multiplicative) were created to analyze whether there were interactions between age 50 and above at diagnosis and timing of OC use.

A $P$ value of $<0.05$ was considered significant. All $P$ values were two-tailed. Nominal $P$ values without adjustment for multiple testing are presented.

## Results

### Patient characteristics in relation to history of OC use

Patient characteristics differed according to OC status, regardless of whether OC status was classified according to ever use, use before age 20, or use before the first full-term pregnancy, Table 1. In general, the patients who had used OCs were younger when diagnosed, taller, had a lower BMI, WHR, and breast volume, had more often given birth, were more often smokers, and abstained less often from alcohol.

### Tumor characteristics in relation to history of OC use

Most of the tumor characteristics did not differ significantly between the different categories of OC status, Table 2. Ever OC users had significantly smaller tumors. There was a significantly higher frequency of grade III tumors in patients with OCs use before age 20 or before the first child, compared to patients with later start or never use.

### Risk for early breast cancer events in relation to history of OC use

The patients were followed for up to nine years with a median follow-up time of 3.03 (interquartile range 1.93–5.23) years in the 948 patients with invasive cancer and no distant metastasis within 3 months of surgery. In total, 100 patients had a breast cancer event during the follow-up, 65 of these patients had distant metastases.

Ever OC use, OC use before the first child, or OC use before age 20 were not associated with overall risk of breast cancer events. In order to study whether previous OC use had differential impact on prognosis depending on menopausal status, the patients were stratified according to age 50 years. Seventy of the breast cancer events were observed in patients ≥50 years and 30 in the younger patients. There was no association with ever OC use or use before the first child and risk of breast cancer events in the patients ≥50 years. Among the patients <50 years, the results were similar with no significant association between ever OC use or use before the first child and risk of breast cancer events. However, OC use before age 20 was associated with a non-significantly decreased risk of breast cancer events (Log Rank, $P = 0.25$; adjHR 0.70: 95 % CI 0.33–1.46), among patients ≥50 years, while in younger patients, it was associated with a threefold higher risk of breast cancer events (Log Rank, $P = 0.049$; adjHR 3.26: 95 % CI 1.06–10.01; $P_{\text{interaction}} = 0.009$), see Fig. 2a, b and Table 3. Similarly, there was no association between distant metastases and OC use prior to age 20 among patients ≥50 years, and there was a significantly increased risk in younger patients (Log Rank $P = 0.018$; adjHR 8.74: 95 % CI 1.03–74.43; $P_{\text{interaction}} = 0.017$).

Overall, in patients with OC start 1974 or later, the risk of breast cancer events was approximately twofold (adjHR 2.13 95 % CI 1.21–3.74) compared to patients who started OCs prior to 1974 or never used OCs. Among the patients ≥50 years, OC start 1974 or later was associated with an increased risk of breast cancer events (adjHR 2.29 95 % CI 1.02–5.14) compared to patients who never used OCs, while there was no association between OC start prior to 1974 and increased risk of breast cancer events (adjHR 0.96 95 % CI 0.55–1.67). In patients <50 years, OC start 1974 or later was also associated with higher risk for breast cancer events than OC start prior to 1974. However, this was not significant due to the small number of patients with OC start prior to 1974 in this age group. The duration of OC use was not significantly associated with breast cancer events, neither in patients ≥50 years nor in the younger patients.

### Response to endocrine treatment in relation to history of OC use

The response to endocrine treatment, defined as risk of breast cancer events, was then investigated in relation to previous OC use. The association between OC use and endocrine treatment response to TAM or AIs was first analyzed among the 670 patients aged 50 years or older, with ER-positive tumors. There were 372 patients who received TAM-treatment, and 277 patients who received AI-treatment. OC use was not significantly associated with risk of breast cancer events among patients who received TAM-treatment (Log Rank $P = 0.46$; adjHR 0.82: 95 % CI 0.37–1.82), adjusted for tumor and patient characteristics, and AI-treatment, see Fig. 3a. However, OC use was associated with a significantly decreased risk of breast cancer events among patients who received AI-treatment (Log Rank $P = 0.041$; adjHR 0.37: 95 % CI 0.15–0.87) adjusted for tumor and patient characteristics, and TAM-treatment, see Fig. 3b.

In the 155 patients younger than 50 years with ER-positive tumors, there were 20 events. Nineteen out of these 20 events were observed in the patients who had previously used OCs. Further, there were only 12 of these 155 younger patients who had never used OCs. Taken together with the fact that AI-treatment is rarely prescribed to premenopausal patients, no further analyses on any potential effect modification by OCs with respect to response to TAM or AIs were conducted among the younger patients.

**Table 1** Patient characteristics in relation to history of OC use

| | All | Missing | Ever OC use | | | OC use before age 20 | | | OC use before the first child | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Median (IQR) or % | | Median (IQR) or % | | *P* value | Median (IQR) or % | | *P* value | Median (IQR) or % | | *P* value |
| | $n = 994$ | | Yes $n = 701$ | No $n = 292$ | | Yes $n = 315$ | No $n = 679$ | | Yes $n = 483$ | No $n = 508$ | |
| Age at diagnosis (years) | 61.1 (52.4–68.1) | 0 | 58.6 (50.0–65.2) | 67.7 (61.0–73.1) | <0.0001 | 51.6 (46.1–57.6) | 65.2 (59.6–70.5) | <0.0001 | 54.1 (47.6–60.5) | 66.5 (61.1–71.6) | <0.0001 |
| Year of birth | 1946 (1940–1955) | 0 | 1949 (1943–1957) | 1940 (1934–1946) | <0.0001 | 1956 (1950–1962) | 1942 (1937–1947) | <0.0001 | 1952 (1946–1960) | 1941 (1936–1945) | <0.0001 |
| Weight ( kgs) | 69.0 (61.5–78.0) | 21 | 69.0 (61.0–78.0) | 70.0 (62.0–79.0) | 0.46 | 69.0 (61.0–78.3) | 69.0 (61.9–78.0) | 0.96 | 68.4 (61.0–78.0) | 70.0 (62.0–78.3) | 0.39 |
| Height (m) | 1.65 (1.62–1.70) | 21 | 1.66 (1.62–1.70) | 1.64 (1.60–1.68) | <0.0001 | 1.67 (1.63–1.71) | 1.65 (1.61–1.69) | <0.0001 | 1.67 (1.63–1.72) | 1.64 (1.60–1.68) | <0.0001 |
| BMI (kgs/m$^{2)}$ | 25.1 (22.5–28.3) | 23 | 24.7 (22.3–27.9) | 25.8 (22.9–29.1) | 0.005 | 24.4 (22.2–27.7) | 25.3 (22.6–28.6) | 0.042 | 24.4 (22.0–27.7) | 25.7 (23.0–29.0) | <0.0001 |
| Waist–Hip ratio | 0.85 (0.81–0.90) | 31 | 0.85 (0.80–0.90) | 0.86 (0.81–0.91) | 0.073 | 0.85 (0.80–0.90) | 0.86 (0.81–0.90) | 0.045 | 0.85 (0.80–0.89) | 0.86 (0.81–0.91) | 0.001 |
| Total breast volume (mL*) | 1000 (650–1550) | 149 | 950 (620–1500) | 1100 (700–1600) | 0.004 | 850 (580–1450) | 1000 (700–1600) | 0.002 | 900 (600–1400) | 1050 (700–1600) | <0.0001 |
| Age at menarche (years) | 13 (12–14) | 6 | 13 (12–14) | 13 (13–14) | 0.001 | 13 (12–14) | 13 (13–14) | <0.0001 | 13 (12–14) | 13 (13–14) | <0.0001 |
| Parous (%) | 87.5 % | 1 | 89.0 % | 83.8 % | 0.025 | 91.4 % | 85.7 % | 0.011 | 84.1 % | 90.7 % | 0.002 |
| Parity | 2 (1–3) | 1 | 2 (1–3) | 2 (1–2) | 0.005 | 2 (2–3) | 2 (1–3) | 0.060 | 2 (1–2) | 2 (1–3) | 0.0002 |
| Age at first full–term pregnancy ( years**) | 25 (22–28) | 131 | 24 (22–28) | 25 (21–28) | 0.63 | 25 (22–28) | 25 (21–28) | 0.19 | 26 (24–29) | 23 (20–26) | <0.0001 |
| Current smoker (%) | 21.2 % | 2 | 23.4 % | 15.9 % | 0.008 | 27.3 % | 18.3 % | 0.001 | 23.6 % | 18.8 % | 0.063 |
| Alcohol abstainer (%) | 10.4 % | 3 | 8.0 % | 16.2 % | 0.0001 | 6.3 % | 12.3 % | 0.004 | 6.4 % | 14.3 % | <0.0001 |
| Ever treated for menopausal symptoms (%) | 44.7 % | 2 | 45.6 % | 42.1 % | 0.31 | 30.3 % | 51.3 % | <0.0001 | 37.1 % | 51.9 % | <0.0001 |
| Ever use of OC (%) | 70.6 % | 1 | 100 % | 0 % | | 100 % | 56.9 % | <0.0001 | 100 % | 42.4 % | <0.0001 |
| OC use before age 20, % | 31.7 % | 0 | 44.9 % | 0 % | <0.0001 | 100 % | 0 % | | 62.7 % | 2.4 % | <0.0001 |
| OC use before first child (%) | 48.7 % | 3 | 69.2 % | 0 % | <0.0001 | 96.2 % | 26.6 % | <0.0001 | 100 % | 0 % | |
| Duration of OC use (months) | 36 (0–120) | 15 | 72 (30–144) | 0 (0–0) | <0.0001 | 96 (54–168) | 4 (0–60) | <0.0001 | 84 (36–156) | 0 (0–36) | <0.0001 |

* Among patients without previous breast surgeries

** Among parous patients

*** Fisher's exact test

**Table 2** Tumor characteristics in relation to history of previous OC use

| | All | Ever OC use | | | OC use before age 20 | | | OC use before the first child | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Number and % | Number and % | | *P* value | Number and % | | *P* value | Number and % | | *P* value |
| | | Yes | No | | Yes | No | | Yes | No | |
| | $n = 994$ | $n = 701$ | $n = 292$ | | $n = 315$ | $n = 679$ | | $n = 483$ | $n = 508$ | |
| *Invasive tumor size* | | | | $P_{trend} = 0.013$ | | | $P_{trend} = 0.72$ | | | $P_{trend} = 0.74$ |
| In situ | 38 (3.8 %) | 26 (3.7 %) | 12 (4.1 %) | | 8 (2.5 %) | 30 (4.4 %) | | 14 (2.9 %) | 24 (4.7 %) | |
| 1–20 mm | 688 (69.2 %) | 504 (71.9 %) | 183 (62.7 %) | | 228 (72.4 %) | 460 (67.7 %) | | 346 (71.6 %) | 340 (66.9 %) | |
| 21–50 mm | 251 (25.3 %) | 161 (23.0 %) | 90 (30.8 %) | | 75 (23.8 %) | 176 (25.9 %) | | 115 (23.8 %) | 135 (26.6 %) | |
| 51 or larger | 15 (1.5 %) | 9 (1.3 %) | 6 (2.1 %) | | 3 (1.0 %) | 12 (1.8 %) | | 7 (1.4 %) | 8 (1.6 %) | |
| Muscle or skin involvement | 2 (0.2 %) | 1 (0.1 %) | 1 (0.3 %) | | 1 (0.3 %) | 1 (0.1 %) | | 1 (0.2 %) | 1 (0.2 %) | |
| Missing | 0 | 0 | 0 | | 0 | 0 | | 0 | 0 | |
| *No. of involved axillary lymph nodes* | | | | $P_{trend} = 0.70$ | | | $P_{trend} = 0.32$ | | | $P_{trend} = 0.42$ |
| 0 | 621 (62.6 %) | 436 (62.2 %) | 184 (63.4 %) | | 187 (59.4 %) | 434 (64.1 %) | | 294 (60.9 %) | 326 (64.4 %) | |
| 1–3 | 282 (28.4 %) | 201 (28.7 %) | 81 (27.9 %) | | 99 (31.5 %) | 183 (27.0 %) | | 147 (30.4 %) | 135 (26.7 %) | |
| 4+ | 89 (9.0 %) | 64 (9.1 %) | 25 (8.6 %) | | 29 (9.2 %) | 60 (8.9 %) | | 42 (8.7 %) | 45 (8.9 %) | |
| Missing | 2 | 0 | 2 | | 0 | 2 | | 0 | 2 | |
| *Histological grade* | | | | $P_{trend} = 0.47$ | | | $P_{trend} = 0.013$ | | | $P_{trend} = 0.11$ |
| I | 234 (23.8 %) | 168 (24.1 %) | 66 (23.0 %) | | 66 (21.0 %) | 168 (25.1 %) | | 111 (23.1 %) | 122 (24.4 %) | |
| II | 484 (49.2 %) | 330 (47.4 %) | 153 (53.3 %) | | 146 (46.5 %) | 338 (50.4 %) | | 225 (46.8 %) | 257 (51.4 %) | |
| III | 266 (27.0 %) | 198 (28.4 %) | 68 (23.7 %) | | 102 (32.5 %) | 164 (24.5 %) | | 145 (30.1 %) | 121 (24.2 %) | |
| Missing | 10 | 5 | 5 | | 1 | 9 | | 2 | 8 | |
| *Hormone receptor status* | | | | | | | | | | |
| ER+ PgR+ | 665 (69.2 %) | 463 (68.2 %) | 201 (71.5 %) | $P = 0.31$ | 210 (68.2 %) | 455 (69.7 %) | $P = 0.64$ | 325 (69.0 %) | 338 (69.4 %) | $P = 0.89$ |
| ER+ PgR− | 167 (17.4 %) | 120 (17.7 %) | 47 (16.7 %) | $P = 0.73$ | 52 (16.9 %) | 115 (17.6 %) | $P = 0.78$ | 81 (17.2 %) | 86 (17.7 %) | $P = 0.85$ |
| ER− PgR− | 121 (12.6 %) | 91 (13.4 %) | 30 (10.8 %) | $P = 0.27$ | 42 (13.6 %) | 79 (12.1 %) | $P = 0.51$ | 61 (13.0 %) | 59 (12.1 %) | $P = 0.70$ |
| ER− PgR+ | 6 (0.6 %) | 5 (0.7 %) | 1 (0.4 %) | $P = 0.68$* | 4 (1.3 %) | 2 (0.3 %) | $P = 0.088$* | 4 (0.8 %) | 2 (0.4 %) | $P = 0.44$* |
| ER+ | 833 (86.6 %) | 584 (85.9 %) | 248 (88.3 %) | $P = 0.33$ | 262 (85.1 %) | 571 (87.3 %) | $P = 0.34$ | 406 (86.2 %) | 425 (87.1 %) | $P = 0.69$ |
| PgR+ | 671 (70.0 %) | 468 (68.9 %) | 202 (72.4 %) | $P = 0.29$ | 214 (69.5 %) | 457 (70.2 %) | $P = 0.82$ | 329 (69.9 %) | 340 (70.1 %) | $P = 0.93$ |
| Missing | 35 | 22 | 13 | | 7 | 28 | | 12 | 23 | |
| *HER2 gene amplification*** | 80 (12.9 %) | 66 (14.4 %) | 14 (8.9 %) | $P = 0.075$ | 34 (15.2 %) | 46 (11.6 %) | $P = 0.20$ | 49 (15.1 %) | 30 (10.3 %) | $P = 0.08$ |
| Missing | 376 | 242 | 134 | | 92 | 284 | | 158 | 218 | |

* Fisher's exact test

** HER2 was routinely analyzed as of November 2005 in patients younger than 70 years of age with invasive tumors and is therefore missing for patients included prior to this date, for older patients, and for patients with carcinoma in situ

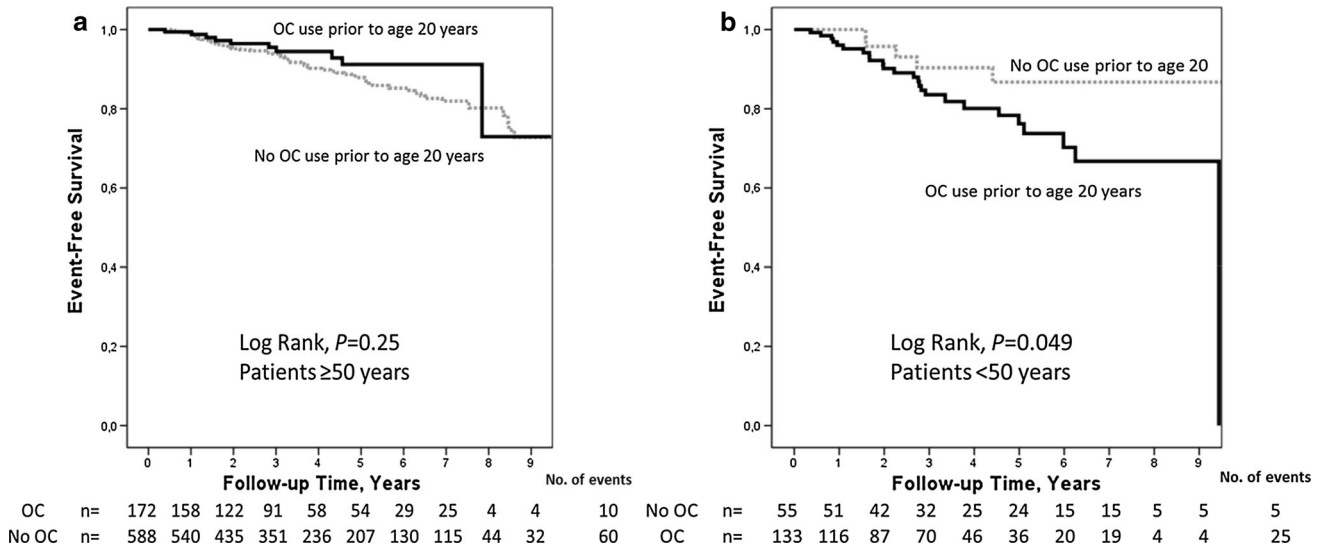


**Fig. 2** Kaplan–Meier survival curves showing that **a** OC use before age 20 was associated a non-significantly decreased risk of breast cancer events among patients ≥50 years (Log Rank, $P = 0.25$; adjusted HR 0.70 (95 % CI 0.33–1.46), adjusting for tumor and patient characteristics and **b** OC use before age 20 was associated with a significantly higher risk of breast cancer events among patients <50 years (Log Rank, $P = 0.049$; adjusted HR 3.26 (95 % CI 1.06–10.01), adjusting for tumor and patient characteristics

**Table 3** Multivariable analysis of risk for breast cancer events in relation to OC use before age 20 years in 760 patients aged 50 years or older and in 188 patients younger than 50 years

| | Patients ≥50 years | | | Patients <50 years | | |
|---|---|---|---|---|---|---|
| | HR | 95 % CI | | HR | 95 % CI | |
| | | Lower | Upper | | Lower | Upper |
| **OC use before age 20 years** | 0.70 | 0.33 | 1.46 | 3.26 | 1.06 | 10.01 |
| Invasive tumor size ≥21 or muscle or skin involvement | 1.99 | 1.21 | 3.29 | 1.41 | 0.59 | 3.40 |
| Axillary nodal involvement | 1.37 | 0.84 | 2.24 | 1.44 | 0.61 | 3.42 |
| Histological grade III | 1.51 | 0.82 | 2.77 | 2.79 | 1.20 | 6.49 |
| ER-status | 0.56 | 0.28 | 1.13 | 0.69 | 0.28 | 1.71 |
| Age, years | 0.99 | 0.96 | 1.03 | 0.95 | 0.89 | 1.01 |
| BMI ≥25 kg/m$^2$ | 1.36 | 0.83 | 2.23 | 0.98 | 0.45 | 2.17 |

## Discussion

In this study, early OC use was associated with a significantly increased risk of breast cancer events in patients <50 years, but not in older patients. Moreover, in patients ≥50 years with ER-positive tumors, previous OC use was associated with a significantly better response to AI-treatment. In contrast, the response to TAM-treatment was not associated with prior OC use.

The interaction between age at diagnosis, OC use before age 20, and risk of breast cancer events could be due to use of OCs with different doses. As previously stated, high-dose OCs disappeared from the Swedish market in 1974 [15]. The data suggest that low-dose OCs may confer worse prognosis than high-dose OCs in the present study, even though the model was adjusted for age at diagnosis, and patient and tumor characteristics. However, the use of a proxy variable for high- and low-dose OCs has its limitations and may lead to some misclassification. It is possible that patients with OC start prior to 1974 switched to low-dose OCs later on, and it is also possible that patients started to use low-dose OCs before 1974. The differential effects of OC use prior to 1974 and age at diagnosis were also hard to tease apart, since patients <50 years were significantly less likely to have started OCs prior to 1974 than patients ≥50 years. This cohort started in 2002, and therefore, most of the young patients had started any OC use after 1974. Most patients with OC start prior to 1974 and who were diagnosed <50 years were therefore not included in the cohort.

Never users and patients who started OC use at age 20 years or older were generally older at diagnosis. Most of the significant differences in patient characteristics could, to some extent, be explained by the significant age

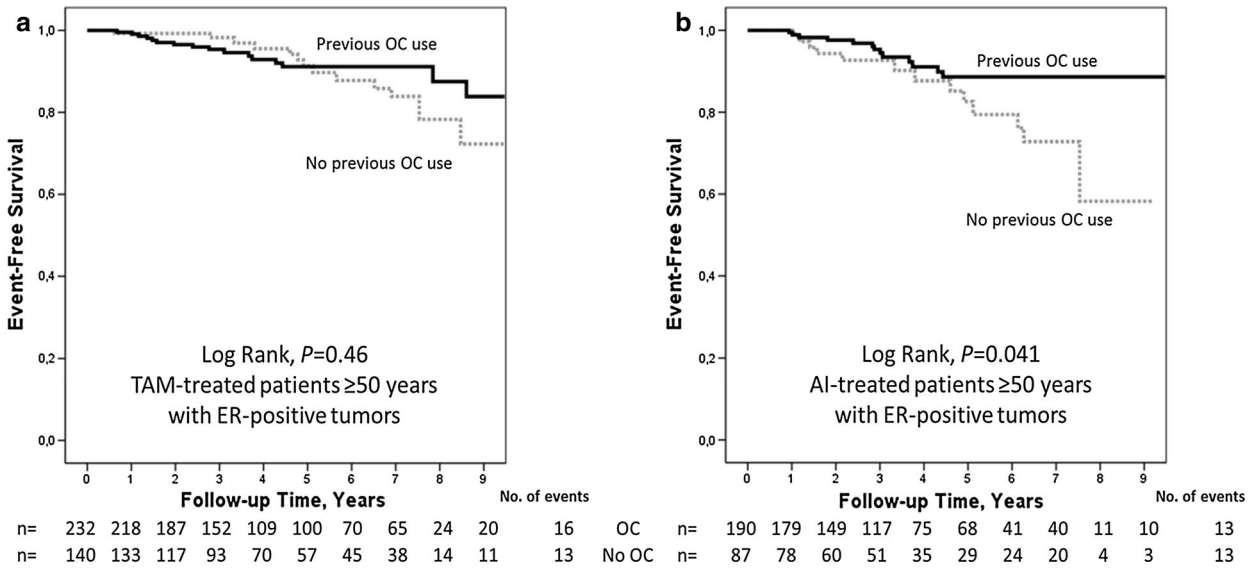


**Fig. 3** Kaplan–Meier survival curves showing that **a** OC use was not significantly associated with risk of breast cancer event among patients who received TAM-treatment (Log Rank $P = 0.46$; adjHR 0.82: 95 % CI 0.37–1.82), adjusted for tumor and patient characteristics, and AI-treatment and **b** OC use was associated with a significantly decreased risk of breast cancer events among patients who received AI-treatment (Log Rank $P = 0.041$; adjHR 0.37: 95 % CI 0.15–0.87) adjusted for tumor and patient characteristics, and TAM-treatment

difference [31–35]. The patients ≥50 years were more likely to have used treatment for menopausal symptoms. Studies have suggested that previous treatment for menopausal symptoms has a favorable influence on the prognosis of breast cancer [36, 37], which could have influenced the results in the patients ≥50 years. However, research has also implicated no difference in prognosis whether the patients received treatment for menopausal symptoms or not [38]. In the present study, there was no difference in risk of breast cancer events among patients ≥50 years, whether or not these patients had received prior treatment for menopausal symptoms (data not shown).

There was no association between OC duration before age 20 and increased risk of breast cancer events. This conclusion is in line with those of previous studies investigating the relationship between duration of ever use and mortality [6, 7]. Patients who used OCs before age 20 and those who used OCs before the first child constitute two groups that partly overlap, but the association between OC use and risk of breast cancer events could only be detected in the patients with OC use before age 20. This is in line with a study by Jernström et al. [17], where OC use had the greatest impact on breast cancer risk before age 20.

Early OC use may have different effects on the breast tissue depending on the genetic profile of the woman. Early OC use may alter hormonal levels such as those of insulin-like growth factor-1, estrogen, and androgens, or alter the expression of their respective receptors, thereby affecting tumor progression, age at diagnosis, and prognosis [19, 39–42]. Previous studies have come to various conclusions regarding whether there is an elevated risk for developing triple-negative breast cancer in patients with former OC use [1–3, 20, 21]. In the present study, there was no significant difference regarding ER and PgR negativity between the group with prior OC use and the group with no use. However, patients with ever OC use had smaller tumors, which is in line with a previous study [10]. The patients with OC use before age 20 or OC use before the first child had more often grade III tumors. These patients also had a longer duration of OC use compared to ever users. A similar pattern was seen in the study by Schönborn et al., where long-term OC use was significantly associated with poorly differentiated tumors, but a better prognosis [4].

Response to endocrine therapy was analyzed among patients 50 years and older with ER-positive tumors, since AI and TAM both are potential treatment options in this group of patients. Both TAM and AI may have several side effects, and unnecessary treatment should be avoided [43, 44]. In the present study, a significant effect modification of OC use on AI-treatment response was observed. The AI-treated patients with previous OC use had proportionally fewer events, compared to patients without previous OC use. No difference in TAM-response depending on OC status was observed. There was no significant difference in duration of AI-treatment between patients with and without previous OC use that could explain the difference in AI response (data not shown). Moreover, adjusting the multivariable models for preoperative alcohol use, smoking, or

WHR did not materially change the results (data not shown). To our knowledge, no other study has reported an interaction between OC use and response to endocrine treatment, and the mechanism behind the interaction is unknown. OCs may induce long-lasting changes in hormone or hormone receptor levels, which may contribute to the therapeutic efficacy of AI-treatment [19, 45–47].

This study has several strengths. Patients of all ages were included, in contrast to several other studies [6, 8, 9]. The study can be considered population-based, since breast cancer patients are not referred to other hospitals for surgery. The majority of patients with primary breast cancer receiving surgery in Lund were included in the study. The main reason for non-inclusion was lack of available research nurses. Included and non-included patients were comparable with respect to age and hormone receptor status [30]. Use of OCs was self-reported, and although accurate recall was not certain, the data are more complete than data collected from patient charts. Information on OC use was collected preoperatively and prior to any event that could have had an impact on the recall of OC use.

This study has some limitations. Since this is an exploratory study, no correction for multiple testing was performed, and the results need to be confirmed in an independent material. The questionnaire did not provide any information on the specific OC formulas used. The median follow-up time was relatively short. It has been shown that most breast cancer recurrences occur within the first 5 years following surgery [48]. However, tumors with ER-positivity are associated with late events [49]. A longer follow-up is needed to provide further knowledge of OCs' effects with respect to long-term prognosis. Some patients did not adhere to endocrine adjuvant treatment [50], but non-adherence did not account for the results (data not shown).

Use of OCs is more common in more developed countries, exceeding 80 % in some countries [12]. Therefore, the results may not be generalizable to breast cancer patients in all countries.

In conclusion, early OC use was associated with a threefold increased risk of breast cancer events in patients younger than 50 years. In older patients with ER-positive tumors, response to AI-treatment, but not TAM, was dependent on previous OC use. AI-treatment seemed to decrease the risk for breast cancer events in patients with previous OC use, but not in patients without previous OC use. If these results are confirmed in other patient populations, history of OC use may yield valuable prognostic information in addition to currently used criteria for treatment selection. New prognostic and treatment predictive markers could lead to better tailored endocrine therapy for breast cancer patients.

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## References

1. Dolle JM, Daling JR, White E, Brinton LA, Doody DR, Porter PL, Malone KE (2009) Risk factors for triple-negative breast cancer in women under the age of 45 years. Cancer Epidemiol Biomark Prev 18:1157–1166. doi:10.1158/1055-9965.EPI-08-1005
2. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Wactawski-Wende J, Kuller LH, Adams-Campbell LL, Lane D, Stefanick ML, Vitolins M, Kabat GC, Rohan TE, Li CI (2011) Reproductive history and oral contraceptive use in relation to risk of triple-negative breast cancer. J Natl Cancer Inst 103:470–477. doi:10.1093/jnci/djr030
3. Ma H, Wang Y, Sullivan-Halley J, Weiss L, Marchbanks PA, Spirtas R, Ursin G, Burkman RT, Simon MS, Malone KE, Strom BL, McDonald JA, Press MF, Bernstein L (2010) Use of four biomarkers to evaluate the risk of breast cancer subtypes in the women's contraceptive and reproductive experiences study. Cancer Res 70:575–587. doi:10.1158/0008-5472.CAN-09-3460
4. Schönborn I, Nischan P, Ebeling K (1994) Oral contraceptive use and the prognosis of breast cancer. Breast Cancer Res Treat 30:283–292
5. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME (2004) Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomark Prev 13:1558–1568
6. Trivers KF, Gammon MD, Abrahamson PE, Lund MJ, Flagg EW, Moorman PG, Kaufman JS, Cai J, Porter PL, Brinton LA, Eley JW, Coates RJ (2007) Oral contraceptives and survival in breast cancer patients aged 20 to 54 years. Cancer Epidemiol Biomark Prev 16:1822–1827. doi:10.1158/1055-9965.EPI-07-0053
7. Schouten LJ, Hupperets PS, Jager JJ, Volovics L, Wils JA, Verbeek AL, Blijham GH (1997) Prognostic significance of etiological risk factors in early breast cancer. Breast Cancer Res Treat 43:217–223
8. Lu Y, Ma H, Malone KE, Norman SA, Sullivan-Halley J, Strom BL, Simon MS, Marchbanks PA, McDonald JA, West DW, Henderson KD, Deapen D, Ursin G, Bernstein L (2011) Oral contraceptive use and survival in women with invasive breast cancer. Cancer Epidemiol Biomark Prev 20:1391–1397. doi:10.1158/1055-9965.EPI-11-0022
9. Wingo PA, Austin H, Marchbanks PA, Whiteman MK, Hsia J, Mandel MG, Peterson HB, Ory HW (2007) Oral contraceptives and the risk of death from breast cancer. Obstet Gynecol 110:793–800. doi:10.1097/01.AOG.0000284446.22251.6e
10. Sauerbrei W, Blettner M, Schmoor C, Bojar H, Schumacher M (1998) The effect of oral contraceptive use on the prognosis of node positive breast cancer patients. German Breast Cancer Study Group. Eur J Cancer 34:1348–1351

11. Larsson G, Blohm F, Sundell G, Andersch B, Milsom I (1997) A longitudinal study of birth control and pregnancy outcome among women in a Swedish population. Contraception 56:9–16
12. Cogliano V, Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F (2005) Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment. Lancet Oncol 6:552–553
13. Sjövall H (1972) Abortion and contraception in Sweden 1870-1970. Zeitschrift für Rechtsmedizin 70:197–209
14. Meirik O, Lund E, Adami HO, Bergström R, Christoffersen T, Bergsjö P (1986) Oral contraceptive use and breast cancer in young women. A joint national case-control study in Sweden and Norway. Lancet 2:650–654
15. Bottiger LE, Boman G, Eklund G, Westerholm B (1980) Oral contraceptives and thromboembolic disease: effects of lowering oestrogen content. Lancet 1:1097–1101
16. Russo J, Moral R, Balogh GA, Mailo D, Russo IH (2005) The protective role of pregnancy in breast cancer. Breast Cancer Res 7:131–142. doi:10.1186/bcr1029
17. Jernström H, Loman N, Johannsson OT, Borg Å, Olsson H (2005) Impact of teenage oral contraceptive use in a population-based series of early-onset breast cancer cases who have undergone BRCA mutation testing. Eur J Cancer 41:2312–2320. doi:10.1016/j.ejca.2005.03.035
18. Collaborative Group on Hormonal Factors in Breast Cancer (1996) Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet 347:1713–1727
19. Elebro K, Butt S, Dorkhan M, Jernström H, Borgquist S (2014) Age at first childbirth and oral contraceptive use are associated with risk of androgen receptor-negative breast cancer: the Malmo Diet and Cancer Cohort. Cancer Causes Control 25:945–957. doi:10.1007/s10552-014-0394-2
20. Turkoz FP, Solak M, Petekkaya I, Keskin O, Kertmen N, Sarici F, Arik Z, Babacan T, Ozisik Y, Altundag K (2013) Association between common risk factors and molecular subtypes in breast cancer patients. Breast 22:344–350. doi:10.1016/j.breast.2012.08.005
21. Beaber EF, Malone KE, Tang MT, Barlow WE, Porter PL, Daling JR, Li CI (2014) Oral contraceptives and breast cancer risk overall and by molecular subtype among young women. Cancer Epidemiol Biomark Prev 23:755–764. doi:10.1158/1055-9965.EPI-13-0944
22. Swedish Breast Cancer Group (2013) Nationella riktlinjer för behandling av bröstcancer (Swedish National Guidelines for Breast Cancer Treatment). http://www.swebcg.se. www.swebcg.se/Files/Docs/Nationella_riktlinjer130501.doc. Accessed 24 Sept 2014
23. Howell A, Buzdar A (2005) Are aromatase inhibitors superior to antiestrogens? J Steroid Biochem Mol Biol 93:237–247. doi:10.1016/j.jsbmb.2005.02.004
24. Regan MM, Pric KN, Giobbie-Hurder A, Thurlimann B, Gelber RD, International Breast Cancer Study G, Group BIGC (2011) Interpreting Breast International Group (BIG) 1–98: a randomized, double-blind, phase III trial comparing letrozole and tamoxifen as adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive, early breast cancer. Breast Cancer Res 13:209. doi:10.1186/bcr2837
25. Gibson L, Lawrence D, Dawson C, Bliss J (2009) Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Ddatabase Syst Rev 30:343–375
26. Ringberg A, Bågeman E, Rose C, Ingvar C, Jernström H (2006) Of cup and bra size: reply to a prospective study of breast size and premenopausal breast cancer incidence. Int J Cancer 119:2242–2243. doi:10.1002/ijc.22104 author reply 2244
27. Bågeman E, Ingvar C, Rose C, Jernström H (2008) Coffee consumption and CYP1A2*1F genotype modify age at breast cancer diagnosis and estrogen receptor status. Cancer Epidemiol Biomark Prev 17:895–901. doi:10.1158/1055-9965.EPI-07-0555
28. Simonsson M, Markkula A, Bendahl PO, Rose C, Ingvar C, Jernström H (2014) Pre-and postoperative alcohol consumption in breast cancer patients: impact on early events. SpringerPlus 3:261. doi:10.1186/2193-1801-3-261
29. Markkula A, Simonsson M, Rosendahl AH, Gaber A, Ingvar C, Rose C, Jernström H (2014) Impact of COX2 genotype, ER status and body constitution on risk of early events in different treatment groups of breast cancer patients. Int J Cancer J Int Du Cancer 135:1898–1910. doi:10.1002/ijc.28831
30. Lundin KB, Henningson M, Hietala M, Ingvar C, Rose C, Jernström H (2011) Androgen receptor genotypes predict response to endocrine treatment in breast cancer patients. Br J Cancer 105:1676–1683. doi:10.1038/bjc.2011.441
31. Sorkin JD, Muller DC, Andres R (1999) Longitudinal change in the heights of men and women: consequential effects on body mass index. Epidemiol Rev 21:247–260
32. Hoe AL, Mullee MA, Royle GT, Guyer PB, Taylor I (1993) Breast size and prognosis in early breast cancer. Ann R Coll Surg Engl 75:18–22
33. Aksglaede L, Sørensen K, Petersen JH, Skakkebaek NE, Juul A (2009) Recent decline in age at breast development: the Copenhagen Puberty Study. Pediatrics 123:e932–e939. doi:10.1542/peds.2008-2491
34. Statens folkhälsoinstitut Socialstyrelsen (2012) Folkhälsan i Sverige, årsrapport 2012 (Health in Sweden, The National Public Health Report 2012). http://www.socialstyrelsen.se/. http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18623/2012-3-6.pdf. Accessed 23 Sep 2014
35. Statistics Sweden Unit of Social Welfare (2007) Use of alcohol and tobacco-Living Conditions. Report No. 114. http://www.scb.se/. http://www.scb.se/statistik/_publikationer/LE0101_2004I05_BR_LE114SA0701.pdf. Accessed 21 May 2012
36. Baumgartner AK, Hausler A, Seifert-Klauss V, Schuster T, Schwarz-Boeger U, Kiechle M (2011) Breast cancer after hormone replacement therapy–does prognosis differ in perimenopausal and postmenopausal women? Breast 20:448–454. doi:10.1016/j.breast.2011.04.010
37. Jernström H, Frenander J, Fernö M, Olsson H (1999) Hormone replacement therapy before breast cancer diagnosis significantly reduces the overall death rate compared with never-use among 984 breast cancer patients. Br J Cancer 80:1453–1458. doi:10.1038/sj.bjc.6690543
38. Chlebowski RT, Manson JE, Anderson GL, Cauley JA, Aragaki AK, Stefanick ML, Lane DS, Johnson KC, Wactawski-Wende J, Chen C, Qi L, Yasmeen S, Newcomb PA, Prentice RL (2013) Estrogen plus progestin and breast cancer incidence and mortality in the women's health initiative observational study. J Natl Cancer Inst 105:526–535. doi:10.1093/jnci/djt043
39. Jernström H, Olsson H, Borg Å (1997) Reduced testosterone, 17 beta-oestradiol and sexual hormone binding globulin, and increased insulin-like growth factor-1 concentrations, in healthy nulligravid women aged 19–25 years who were first and/or second degree relatives to breast cancer patients. Eur J Cancer Prev 6:330–340
40. Jernström H, Olsson H (1994) Suppression of plasma insulin-like growth factor-1 levels in healthy, nulliparous, young women using low dose oral contraceptives. Gynecol Obstet Invest 38:261–265
41. Jernström H, Sandberg T, Bågeman E, Borg Å, Olsson H (2005) Insulin-like growth factor-1 (IGF1) genotype predicts breast volume after pregnancy and hormonal contraception and is associated with circulating IGF-1 levels: implications for risk of

early-onset breast cancer in young women from hereditary breast cancer families. Br J Cancer 92:857–866. doi:10.1038/sj.bjc.6602389
42. Hietala M, Sandberg T, Borg Å, Olsson H, Jernström H (2007) Testosterone levels in relation to oral contraceptive use and the androgen receptor CAG and GGC length polymorphisms in healthy young women. Hum Reprod 22:83–91. doi:10.1093/humrep/del318
43. Garreau JR, Delamelena T, Walts D, Karamlou K, Johnson N (2006) Side effects of aromatase inhibitors versus tamoxifen: the patients' perspective. Am J Surg 192:496–498. doi:10.1016/j.amjsurg.2006.06.018
44. Nystedt M, Berglund G, Bolund C, Fornander T, Rutqvist LE (2003) Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: a prospective randomized study. J Clin Oncol 21:1836–1844. doi:10.1200/JCO.2003.04.024
45. Kotsopoulos J, Narod SA (2012) Androgens and breast cancer. Steroids 77:1–9. doi:10.1016/j.steroids.2011.10.002
46. Campagnoli C, Pasanisi P, Castellano I, Abba C, Brucato T, Berrino F (2013) Postmenopausal breast cancer, androgens, and aromatase inhibitors. Breast Cancer Res Treat 139:1–11. doi:10.1007/s10549-013-2505-2
47. Hou X, Huang F, Macedo LF, Harrington SC, Reeves KA, Greer A, Finckenstein FG, Brodie A, Gottardis MM, Carboni JM, Haluska P (2011) Dual IGF-1R/InsR inhibitor BMS-754807 synergizes with hormonal agents in treatment of estrogen-dependent breast cancer. Cancer Res 71:7597–7607. doi:10.1158/0008-5472.CAN-11-1080
48. Saphner T, Tormey DC, Gray R (1996) Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 14:2738–2746
49. Grasic-Kuhar C, Bracko M, Zakotnik B (2008) Risk factors for late relapse and death in patients with early breast cancer. Neoplasma 55:416–420
50. Markkula A, Hietala M, Henningson M, Ingvar C, Rose C, Jernström H (2012) Clinical profiles predict early nonadherence to adjuvant endocrine treatment in a prospective breast cancer cohort. Cancer Prev Res 5:735–745. doi:10.1158/1940-6207.CAPR-11-0442