Correlation of age at oral contraceptive pill start and age at breast cancer diagnosis

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Abstract **200 words**

Text **2230 words**

Tables **2**

Figures **2**

Running Title: OCP use and age at breast cancer diagnosis

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ABSTRACT:

Background: Breast cancer is progressively diagnosed with increasing age. This study aimed to determine whether women who started using the oral contraceptive pill (OCP) at an early age developed breast cancer earlier than women who started using the OCP later in life.

Methods: A database review of 1010 breast cancer patients, who had used the OCP at some point in their life, was carried out. Associations of age at OCP start with age at breast cancer diagnosis were determined by multiple linear regression analysis, considering year of birth, year of diagnosis, age at first pregnancy, number of live births, age at menarche and length of OCP use.

Results: There was evidence of a linear trend between age at OCP start and age at breast cancer diagnosis. Women who started using the OCP aged 18 or younger were on average 4 years younger at breast cancer diagnosis than women who started using the OCP over the age of 30, and women who started using the OCP aged 22 to 25 were on average 3 years younger (p-value for trend < 0.001).

Conclusion: The age when the OCP was started was positively associated with the age when breast cancer was first diagnosed.

INTRODUCTION

The risk of developing breast cancer is strongly associated with age. 80% of breast cancer cases occur in women over 50 years old and only rarely it is diagnosed in young individuals under the age of 30.

A number of factors have been identified that potentially increase the risk of breast cancer development in younger patient groups. Early menarche (1,2), first child at a late age (3,4), use of the oral contraceptive pill (OCP) (5), a positive family history of breast cancer (6) and taller height (7,8) all seem to be associated with a higher disease risk. Breast-feeding (9), increased number of children (3,4) and a high body mass index (BMI) in pre-menopausal patients (10) have been shown to be protective.

Only a few studies have, however, looked at potential relationships between initial age at exposure to a risk factor and subsequent age at breast cancer diagnosis. Previous reports from this unit have suggested that an early menarche (11) and an early start to the OCP lead to earlier onset of breast cancer (12).

The present study focuses on women with a history of OCP use who had all developed breast cancer later in life. It aims to evaluate any correlation between the age when the OCP was started and the age when breast cancer was diagnosed. Other known risk factors for early onset breast cancer were considered.

METHODS

Data collection

All data analysed for this study were recorded at a single institution over a 27-year period between January 1980 and October 2007.

Data on OCP use, pregnancy, breast feeding details and age at menarche had been obtained from questionnaires that were completed by each patient before first clinic visits. The information was stored on a database at the time of collection.

Patient selection

Figure 1 shows a flowchart of patients included in the study. The whole dataset contained information on 3777 patients that were diagnosed with breast cancer. Patients with an initial diagnosis before 1980 were excluded because data collection in the earlier time periods was less complete. Other exclusion criteria were: i) diagnosis with ductal carcinoma in situ (DCIS) but no evidence of invasive disease ii) no date of birth recorded and iii) no residual tumour at definitive surgery (previous malignant biopsy). This resulted in 3257 eligible patients of whom 1010 had used the OCP at some point in their life.

Statistical analysis

Patient demographics and diagnostic facilities may have varied over time and therefore categories for diagnosis year were created: 1980-1996; 1997-2002; 2002-2007. Patient characteristics (age, details on OCP use, age at menarche, number of children, maternal age at first birth and breast feeding [= total time that a woman breast fed all her children]) were compared by diagnosis year group.

Factors associated with the age at which women started the OCP were analysed with linear regression analyses whereby the age at OCP start was the continuous dependent variable.

Further linear regression models were used to assess the correlation of possible risk factors for early onset breast cancer with age at breast cancer diagnosis. For these analyses age at breast cancer onset was the dependent continuous variable. Age at OCP start was categorised into age bands (≤ 18, 19-21, 22-25, 26-30, ≥ 31) and added to the model as explanatory variable. A p-value for trend was obtained by including age at OCP start in the same model as a continuous instead of a categorical variable. The following risk factors were subsequently adjusted for by adding them as explanatory variables: year of birth, year of diagnosis, duration of OCP use, age at menarche, number of pregnancies, age at first pregnancy and cumulative breast feeding time. Interaction factors of age at OCP start and year of birth were included to evaluate any changes of OCP effects on the age at breast cancer diagnosis in relation to the year that women were born. The severity of multicollinearity for each variable was assessed by calculation of the variance inflation factor (VIF).

RESULTS

Demographics

Figure 2 shows demographic data on women with breast cancer grouped by year of diagnosis. 342 women were diagnosed between 1980 and 1996, 345 women between 1997 and 2002 and 323 women between 2003 and 2007. The median age at breast cancer diagnosis increased over time (48 years in 1980-1996 versus 53 years in 2003-2007). In patients diagnosed more recently, the age of OCP start was decreased (21 versus 26 years in 1980-1996). There was evidence of a longer average duration of OCP use in those with a recent diagnosis (5 versus 8 years) and the age when a woman had her first child was higher (27 versus 23 years). Age at menarche, length of breast feeding and the average number of live births per women did not change by year of diagnosis.

Factors influencing age at OCP start

Table 1 shows the number of patients who used the OCP by age group in relation to year of birth. Whilst the majority of patients born between 1900 and 1940 started using the OCP over the age of 30, there was a gradual change and most patients born more recently had started the OCP before the age of 18.

There was a positive association between the number of live births and the age when the OCP was started. Women with 4 or more children started using the OCP about 3 years later than those with only one child (estimate of the mean difference between the two groups: 2.78, 95% confidence interval 0.95 to 4.61; $p = 0.003$). Furthermore, there was a trend of a negative relationship between age at OCP start and the woman's age when the first child was born. Women who had their first child at an early age (before 21 years) were on average one year older when they first used the OCP than women

who had their first child after the age of 30 (estimate of the mean difference: 1.08, 95% confidence interval 0.01 to 2.16; p = 0.048; model adjusted for year of birth).

Correlation of age at OCP start with age at breast cancer diagnosis

There was a strong positive relationship between age at starting the OCP and age at breast cancer onset (correlation coefficient r = 0.58, p < 0.001). This relationship remained for nulliparous women (n = 619, r = 0.67, p < 0.001) and also for women who started using the OCP after their first pregnancy (n = 380, r = 0.72, p < 0.001). Table 2 shows the estimated effect sizes by age band of OCP start relative to the age group ≥ 31**.** In the unadjusted model, women who started the OCP at age ≤ 18 were on average 17 years younger at breast cancer onset than women who started using the OCP over the age of 30. A large proportion of this difference in diagnosis age was accounted for by year of birth and the age difference reduced to an average of 3 years (estimate of the mean difference between the two groups: -2.74, 95% confidence interval -4.51 to -0.97). Further adjustment for diagnosis year, age at first pregnancy, number of live births, age at menarche and length of OCP use narrowed the confidence intervals and an early start to the OCP was associated with an approximately 4 year earlier breast cancer onset (estimate of the mean difference: -4.11, 95% confidence interval -5.35 to -3.10). There was no interaction evident between age at OCP start and the year women were born on age at breast cancer diagnosis (p = 0.12). Breast feeding time was initially included in this model but later removed for multicollinearity with variance inflation factors (VIF) above 10. The relative predictive power (r^2) of the regression models increased from 0.33 (model 1) to 0.56 (model 2) and to 0.84 (model 3). The mean VIF in model 3 was 1.82 (range 1.15 to 3.65).

Association of other known risk factors with age at breast cancer diagnosis

Other factors showing an independent positive association with age at breast cancer diagnosis were: year of diagnosis and age when the first child was born; there was a negative association with birth year (all p-values < 0.001). There was no evidence of a relationship between age at breast cancer onset and age at menarche, number of children or of the length of time that the OCP was taken for.

DISCUSSION

Breast cancer is an uncommon disease in young women. A number of risk factors have been suggested that may lead to the development of early onset disease (13).

The results of the present study suggest a linear relationship between age at OCP start and age at breast cancer onset. In the UK the OCP was first introduced in 1961 and subsequently there was significant variation in the age of OCP start over time which is demonstrated in the current analysis. But the observed correlation remained even after adjusting for birth year in the statistical model. This finding is consistent with other reports that found the use of the OCP to be the strongest predictor for breast cancer presentation at a young age (14,15).

OCP use as a possible causal factor in early breast cancer development

A potential causal relationship between breast cancer incidence and OCP use has been much debated over the last decades. Some studies have shown a small risk increase for developing breast cancer in women using the OCP whilst other studies were unable to demonstrate a correlation (16-19). Kahlenborn et al (20) in a recent meta-analysis of 34 case control studies that were published after 1980 estimates a small but significant risk increase with an Odds Ratio of 1.19 (95% confidence interval 1.09 to 1.29).

The study design of the present report does not allow an assessment of a potential breast cancer risk increase with OCP use. The observed linear trend would, however, be consistent with a causal relationship even if the effect was small.

The OCP is thought to potentially increase breast cancer risk by inducing high breast proliferation rates. Alternatively it has been suggested that oestrogen metabolites may directly act as carcinogenic agents (21). Anderson et al (22) found a highly significant increased proliferation activity in nulliparous women using the OCP. In the current

study there was a continuous linear association between OCP use and breast cancer age but no difference between nulliparous women and women starting to use the pill after their first pregnancy. This would suggest a degree of vulnerability in relation to OCP use at any age and corresponds with results of the Collaborative Group on Hormonal Factors in Breast Cancer (5). In a meta-analysis this reported a slight transient increase in breast cancer risk for up to 10 years after stopping the pill. The duration of use had little effect on breast cancer risk in their analysis. Similarly results in the present study did not show an association between duration of OCP use and age at breast cancer onset

OCP use and its association with early breast cancer development being possibly non-causal

~~as a possible confounding variable~~

It might be considered that the relationship between the start of OCP use and early breast cancer development may ~~act as a confounding factor for~~be confounded by other behavioural choices of women that can directly influence an early breast cancer diagnosis.

Women of higher socio-economic status are at higher risk for the development of breast cancer (23,24). An explanation for this is seen in reproductive factors that may increase oestrogen exposure throughout life. Women from less deprived backgrounds tend to have an earlier menarche and later menopause (25,26). A higher and longer education is associated with advanced maternal age at first childbirth (27,28) and on average fewer children (28). It has also been suggested that women of lower socio-economic status are less likely to use the OCP (28,29). In the current analysis early OCP use was related to women with fewer children and to increasing age at first pregnancy and this finding would be consistent with an earlier OCP use in women of higher socio-economic status.

Women with higher educational status may also be more likely to seek medical advice or to take part in breast cancer screening programmes (30), leading to earlier stage diagnoses. Therefore, early OCP use could be a reflection of the behaviour of women of higher socio-economic status. They may be diagnosed with breast cancer at earlier ages than women of lower socio-economic status because they accumulate more risk factors to develop the disease and they are more likely to be diagnosed at an early stage.

One limitation of this study is the reliance on self reported data for the analysis of OCP usage and the results may be affected by recall bias. It is also possible that the reported trend to an earlier start to the OCP over time may be biased by the increasing social acceptability of admitting to its use as a teenager. Some reports, however, have suggested a very accurate self-reported history of oral contraceptive use in interviews or in questionnaires (31,32), and it also seems likely that many women will be able to relate their past OCP use to the current ages of their children.

Conclusion

The results of this study indicate a positive correlation between the age of OCP start and the age at breast cancer diagnosis. This effect may suggest a causal relationship between the OCP and breast cancer development. It may also reflect other associated lifestyle factors of early OCP users that are known to increase the risk of breast cancer.

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Age at OCP start	**Year of birth**				
	1900 to 1940	1941 to 1950	1951 to 1960	1961 to 1980	Overall
≤ 18 years	0 (0.00)	31 (7.79)	109 (43.60)	78 (66.67)	218 (21.58)
19 to 21 years	4 (1.63)	115 (28.89)	78 (31.20)	21 (17.95)	218 (21.58)
22 to 25 years	24 (9.80)	125 (31.41)	43 (17.20)	16 (13.68)	208 (20.59)
26 to 30 years	76 (31.02)	97 (24.37)	11 (4.40)	2 (1.71)	186 (18.42)
≥ 31 years	141 (57.55)	30 (7.54)	9 (3.60)	0 (0.00)	180 (17.82)

Table 1. Age at starting the OCP in relation to year of birth. Percentages by columns in brackets.

Age at OCP start	***Estimated effect sizes relative to the age group ≥ 31***		
	Model 1	Model 2	Model 3
≤ 18 years	-16.58 (-18.56 to -15.00)	-2.74 (-4.51 to -0.97)	-4.11 (-5.35 to -3.10)
19 to 21 years	-11.50 (-13.08 to -9.92)	-2.32 (-3.94 to -0.70)	-3.72 (-4.74 to -2.70)
22 to 25 years	-9.55 (-11.15 to -7.96)	-2.32 (-3.86 to -0.78)	-2.94 (-3.90 to -1.99)
26 to 30 years	-4.82 (-6.46 to -3.18)	-1.70 (-3.11 to -0.29)	-2.61 (-3.48 to -1.74)
≥ 31 years	0 (Ref)	0 (Ref)	0 (Ref)
p-value for linear trend	< 0.001	< 0.001	< 0.001

Table 2. Linear regression model with age at breast cancer onset as dependent variable

Model 1: no adjustment

Model 2: adjusted for year of birth

Model 3: adjusted for year of birth, breast cancer diagnosis year, age at first pregnancy, number of live births, age at menarche and length of OCP use

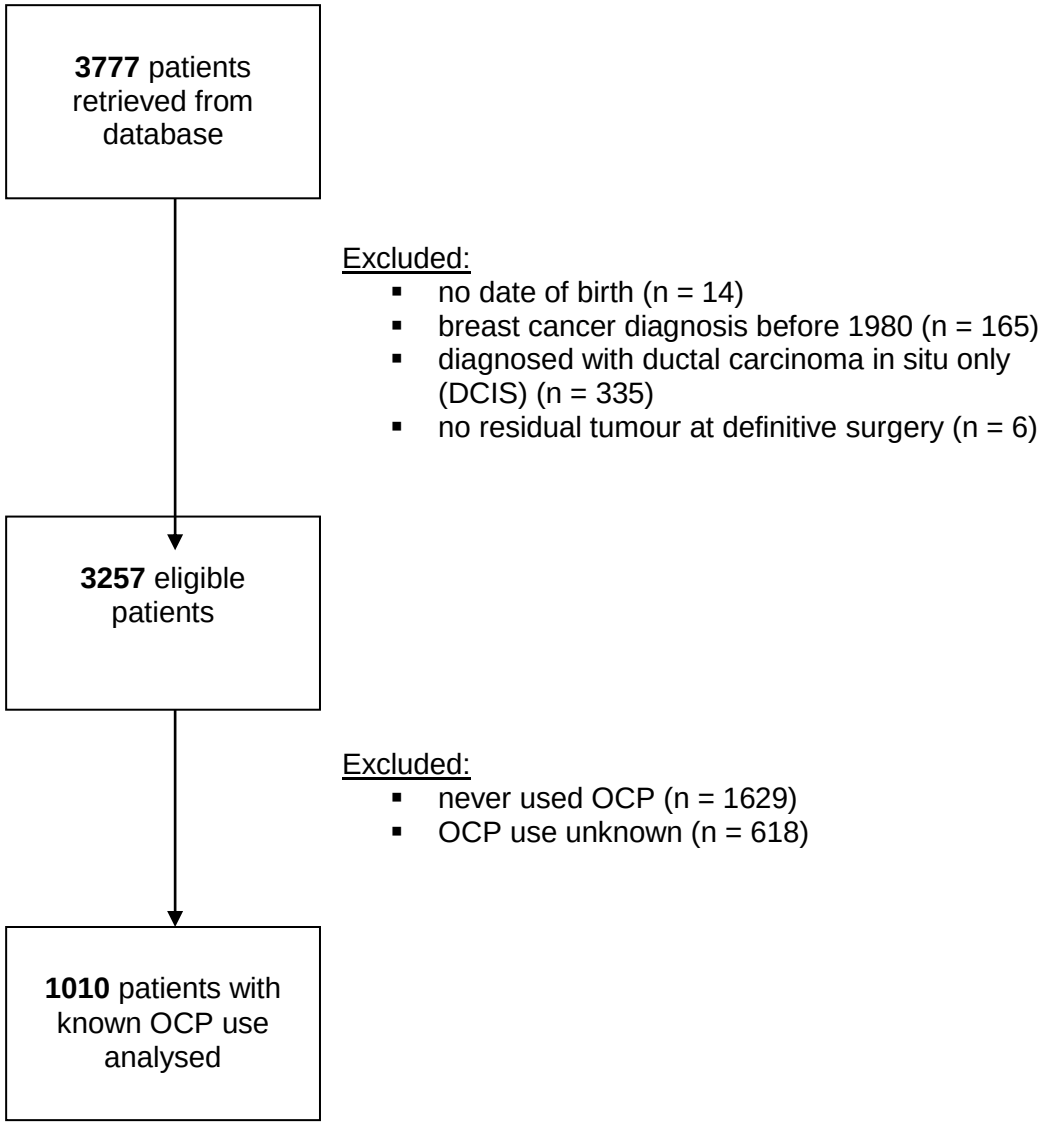

Figure 1. Flowchart with the number of breast cancer patients analysed and criteria for exclusion. OCP = oral contraceptive pill.

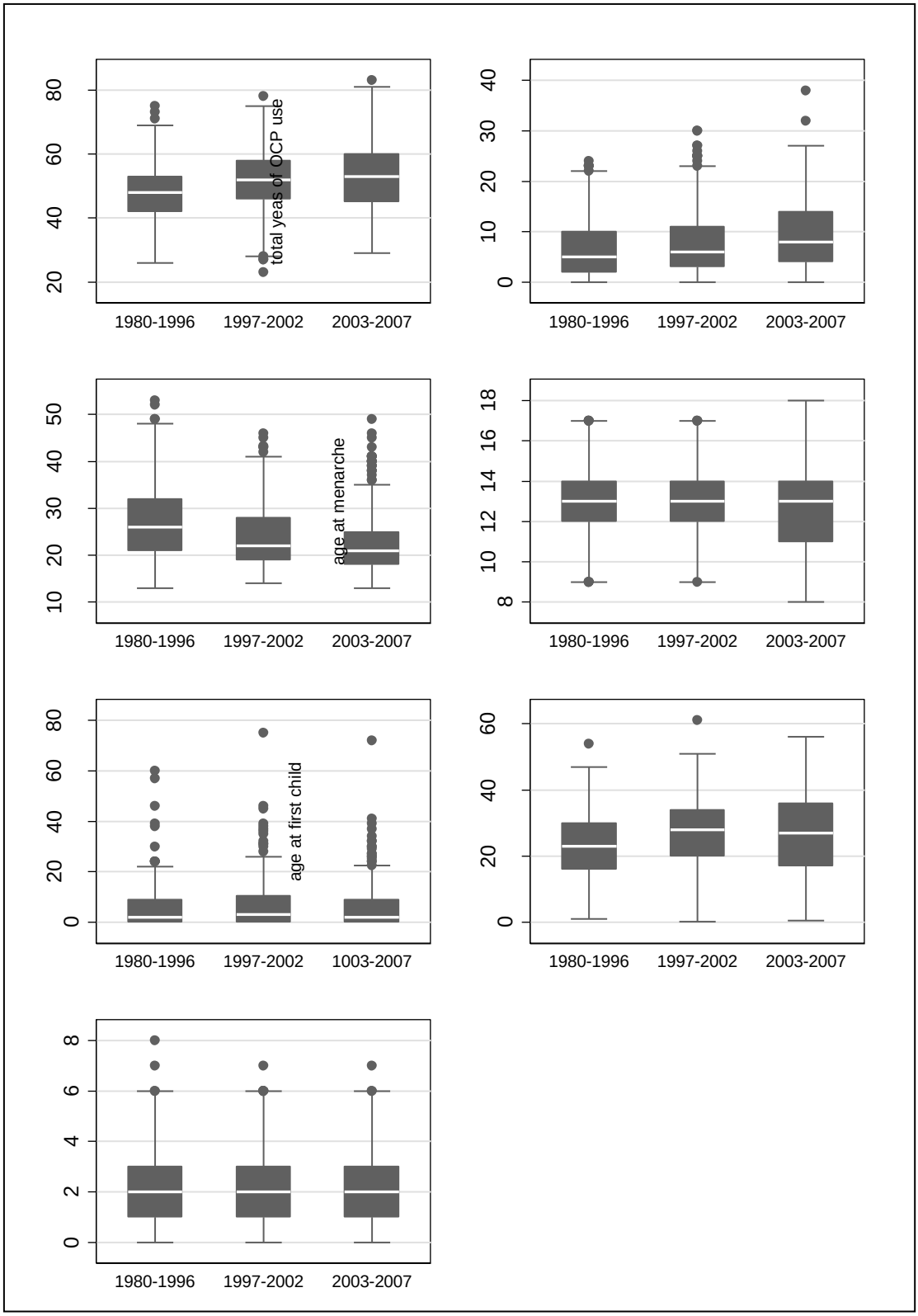

Figure 2. Patient characteristics compared by diagnosis year group. Box represents 50% of values with horizontal line marking the median. Whiskers demarcate upper and lower adjacent values. Dots show outlying values.