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Navarro Silvera, Stephanie A.; Miller, Anthony B.; and Rohan, Thomas E., "Oral contraceptive use and risk of breast cancer among women with a family history of breast cancer: a prospective cohort study" (2005). *Department of Public Health Scholarship and Creative Works*. 107.
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Cancer Causes and Control (2005) 16:1059–1063
DOI 10.1007/s10552-005-0343-1
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# Oral contraceptive use and risk of breast cancer among women with a family history of breast cancer: a prospective cohort study

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Received 7 February 2005; accepted in revised form 9 May 2005

*Key words:* breast neoplasm, oral contraceptives, family history, prospective cohort, National Breast Screening Study.

## Abstract

Family history of breast cancer is an established risk factor for breast cancer. In addition, there is evidence that oral contraceptive use may be associated with a moderate increase in breast cancer risk. The three cohort studies that have investigated the relationship between oral contraceptive use and breast cancer risk among women with a family history of breast cancer have yielded mixed results, possibly due to the relatively small sample sizes employed and/or differences in the selection of covariates for inclusion in multivariate models. Therefore, we examined the association between oral contraceptive use and breast cancer risk in a large cohort study in Canada. The cohort consisted of the 27,318 women in the Canadian National Breast Screening Study who reported a family history of breast cancer on enrolment into the study. Linkages to national mortality and cancer databases yielded data on deaths and cancer incidence, with follow-up ending between 1998 and 2000, depending upon the province. During a mean of 16.0 years of follow-up, we observed 1707 incident cases of breast cancer among women with any history of breast cancer of which 795 cases occurred among women with a mother, sister, and/or daughter with breast cancer. Among women with any family history of breast cancer, ever use of oral contraceptives was associated with a 12% reduction in risk of breast cancer (95% confidence interval [CI] = 0.73–1.07), and there was an inverse trend with increasing duration of use of borderline statistical significance ($p_{trend} = 0.03$). Although we also observed a 25% lower risk of breast cancer associated with oral contraceptive use of greater than 84 months *versus* never use among women with a first degree relative with breast cancer, this finding was not statistically significant (95% CI = 0.47–1.19, $p_{trend} = 0.48$). Our data raise the possibility that relatively long duration of oral contraceptive use may be inversely associated with risk among women with a family history of breast cancer.

## Introduction

Breast cancer is the most common cause of cancer death among women worldwide [1]. Having a family history of breast cancer is an established risk for increasing a woman's own risk [1]. Oral contraceptive use has also been found to be associated with a modest increased risk of breast cancer [2]. Because women with a family history of breast and/or ovarian cancer may be counseled to use oral contraceptives to reduce ovarian cancer risk [3, 4], the potential association with breast cancer risk in this population is also of interest, particularly given evidence that oral contraceptive use may increase breast cancer risk among women with BRCA1 [5, 6] and BRCA2 mutations [6].

To date, there appear to have been only three cohort studies of oral contraceptive use and breast cancer risk among women with a family history of breast cancer. Lipnick *et al.* [7], in analyses of data from the Nurses' Health Study (71 incident cases), observed no association between oral contraceptive use among women with a family history of breast cancer. Colditz *et al.* [8] reanalyzed these data in 1996 (310 incident cases) and

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found a statistically non-significant 2.5-fold increased risk among current oral contraceptive users with a family history of breast cancer. In addition, Grabrick *et al*. [9] analyzed data from an historical cohort of women and found that OC use was positively associated with breast cancer risk among sisters and daughters of breast cancer cases, but found no association with risk among granddaughters and nieces of cases. Given the conflicting results in the existing literature, we examined the association between oral contraceptive use and breast cancer risk in a large cohort study, which consisted of 27,323 Canadian women who had a family history of breast cancer.

## Methods

### *Study population*

The design of our study has been described in detail elsewhere [10]. Briefly, 89,835 women aged 40 to 59 years were recruited into the Canadian National Breast Screening Study (NBSS) between 1980 and 1985 from the general Canadian population [11].

### *Questionnaires*

At recruitment into the cohort, participants completed self-administered questionnaires that sought information on demographic characteristics, lifestyle factors, menstrual and reproductive history, and use of oral contraceptives and replacement estrogens. Specifically, participants were asked if they had ever used oral contraceptives either for birth control or menstrual irregularities. Women who responded 'yes' were then queried as to their duration of use, and if they were no longer using oral contraceptives, the year in which they stopped using them. Women were also asked if they had a family history of breast cancer; those who responded in the affirmative were then asked to indicate the nature of that relationship. Women who reported having a mother, sister, and/or daughter who had breast cancer were classified as having a first degree relative with breast cancer. Women who reported having a grandmother or aunt with breast cancer were classified as having a second degree relative.

### *Ascertainment of incident breast cancer cases and deaths*

Incident cases of breast cancer and deaths from all causes were ascertained respectively by means of computerized record linkages to the Canadian Cancer Database and to the National Mortality Database, both of which are maintained by Statistics Canada. The linkages to the databases yielded data on cancer incidence and mortality to 31 December 2000 for women in Ontario, 31 December 1998 for women in Quebec, and 31 December 1999 for women in other provinces.

### *Statistical analysis*

Of the 89,835 women recruited into the study, we excluded women with no family history of breast cancer (n = 62,828) leaving 27,975 women with any family history of breast cancer (1707 incident cases) amongst whom 10,914 reported having a first degree relative with breast cancer (795 incident cases) and 13,155 reported having a second degree relative with breast cancer (968 incident cases). The remaining 214 subjects were more distantly related to women with breast cancer.

Cox proportional hazards models (using age as the time scale) were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between oral contraceptive use and breast cancer incidence. For these analyses, cases were considered at risk from their date of enrollment until the date of diagnosis of their breast cancer, and non-cases were considered at risk from their date of enrollment until the termination of follow-up (the date to which cancer incidence data were available for women in the corresponding province) or death, whichever occurred earlier. Multivariate models included the variables listed in the footnote of Table 2. To test for trend we fitted the median value of each category of duration of oral contraceptive use as an ordinal variable in the risk models, and evaluated the statistical significance of the coefficient using the Wald test [12]. Use of the lifetest procedure in SAS™ showed that the proportional hazards assumption was met in this dataset. All analyses were performed using SAS version 9 (SAS Institute Cary, NC).

## Results

The average duration of follow-up for cohort members was 16.0 years, corresponding to a total of 448,629 person-years of follow-up for the cohort. The mean (S.D.) age at diagnosis for the cases was 58.3 ($\pm$7.7) years. Overall, 59% of women included in these analyses reported ever using oral contraceptives, which is similar to the prevalence of use among women who reported no family history of breast cancer (58%, not included in these analyses). Among women with a first degree relative with breast cancer, 56% reported ever using oral contraceptives, and 62% of women with a

*Table 1.* Baseline characteristics of the women with any family history of breast cancer by outcome

| | Non-cases | Cases |
|---|---|---|
| No. of Individuals | 26.268 | 1.707 |
| Age at baseline in years (SD) | 48.5 (5.7) | 49.5 (5.6) |
| Body mass index (SD)[a] | 25.1 (4.7) | 25.3 (4.6) |
| No vigorous physical activity (%) | 28.7 | 31.1 |
| Alcohol consumption (% ever drinker) | 26.6 | 25.0 |
| Smoking history (% ever smoker) | 49.3 | 50.6 |
| Oral contraceptive use (% ever) | 59.4 | 56.4 |
| Mean (SD) duration of oral contraceptive use (months)[b] | 54.2 (51.5) | 52.3 (51.0) |
| HRT (% ever)[c] | 52.8 | 55.6 |
| History of breast disease (% yes) | 17.7 | 20.9 |
| Age at menarche (% > 12 years) | 58.5 | 59.2 |
| Nulliparous (%) | 14.9 | 18.8 |
| Mean (SD) age at first live birth (years)[d] | 24.3 (4.7) | 24.8 (4.9) |
| Postmenopausal at baseline (%) | 42.9 | 45.0 |

[a] BMI = Body mass index ($kg/m^2$).
[b] Duration of oral contraceptive use among ever users.
[c] HRT = hormone replacement therapy; among postmenopausal women only.
[d] Among parous women.

second degree relative with breast cancer reported ever using oral contraceptives (data not shown).

Table 1 shows the demographic characteristics of the study population by case status at the end of follow-up. Briefly, cases and controls were broadly similar in all variables except history of breast disease and parity (Table 1). Cases were more likely to have a personal history of breast disease and more likely to be nulliparous than non-cases (Table 1).

Table 2 shows the associations between oral contraceptive use and breast cancer risk among women with a family history of breast cancer by degree of relatedness. Among women with any family history of breast cancer, ever use of oral contraceptives was associated with a slightly lower risk of breast cancer (HR = 0.88, 95% CI = 0.73–1.07) and we observed a statistically significant inverse trend with duration of oral contraceptive use of borderline statistical significance ($p_{trend} = 0.03$), after adjustment for potential confounding variables. We observed similar patterns of association among women who reported having an aunt and/or grandmother with breast cancer, although the findings were not statistically significant (Table 2). Table 2 also shows the associations between oral contraceptive use and breast cancer risk among women with a first degree relative (mother, sister, and/or daughter) with breast cancer. In multivariate-adjusted models, we observed no association between ever use of oral contraceptives and risk of breast cancer (HR = 1.03, 95% CI = 0.78–1.38). Although we observed a 25% lower risk for the highest level of duration of use compared to never users, this difference was not statistically significant (95% CI = 0.47–1.19, $p_{trend} = 0.48$).

## Discussion

In the prospective study reported here, there was some suggestion of an inverse association between duration of oral contraceptive use and breast cancer risk among women with any family history of breast cancer. The association between oral contraceptive use of relatively long duration and risk among women with a first degree relative with breast cancer was of similar magnitude to that observed overall and to that for women with a second degree relative with breast cancer, although in neither of these sub-groups were the associated trends with duration of use statistically significant.

Case-control studies by Ursin *et al.* [6] and Narod *et al.* [5] have examined the association between oral contraceptive use and breast cancer risk among women with BRCA1 and/or BRCA2 mutations. While Ursin *et al.* observed an increased risk associated with long term oral contraceptive use (>48 months, $p_{trend} = 0.004$) prior to a first full-term pregnancy, this finding was based on 14 cases only (9 with a BRCA1 mutation and five with a BRCA2 mutation). Narod *et al.* [5] observed a statistically significant 20% increased risk among BRCA1 mutation carriers (981 cases) who had ever used oral contraceptives, but noted that this association did not hold for oral contraceptive use after age 30. Narod

*Table 2.* Breast cancer risk and OC use among women with a family history of breast cancer

| | Cases/Person-years | Unadjusted | | Adjusted[a] | |
|---|---|---|---|---|---|
| | | HR | 95% CI | HR | 95% CI |
| Women with any family history of breast cancer[b,c] | | | | | |
| Never user | 745/182,112 | 1.00 | Referent | 1.00 | Referent |
| Ever user | 962/266,497 | 0.97 | 0.88–1.08 | 0.88 | 0.73–1.07 |
| Former | 917/255,315 | 0.97 | 0.87–1.08 | 0.88 | 0.72–1.07 |
| Current | 45/10,968 | 0.99 | 0.72–1.37 | 1.01 | 0.56–1.81 |
| Duration of use | | | | | |
| 1–12 months | 230/54,419 | 1.10 | 0.94–1.29 | 1.05 | 0.79–1.42 |
| 12–36 months | 226/60,731 | 0.99 | 0.85–1.16 | 0.94 | 0.70–1.26 |
| 36–84 months | 263/80,230 | 0.90 | 0.77–1.04 | 0.85 | 0.64–1.12 |
| ≥84 months | 243/71,101 | 0.93 | 0.78–1.08 | 0.74 | 0.55–0.99 |
| $p_{trend}$ | | | 0.12 | | 0.03 |
| Women with 1st degree relative with breast cancer[d] | | | | | |
| Never user | 362/75,561 | 1.00 | Referent | 1.00 | Referent |
| Ever user | 433/98,521 | 1.04 | 0.89–1.21 | 1.03 | 0.78–1.38 |
| Former | 413/94,481 | 1.04 | 0.89–1.21 | 1.04 | 0.78–1.39 |
| Current | 20/3,922 | 1.12 | 0.70–1.81 | 1.06 | 0.43–2.62 |
| Duration of use | | | | | |
| 1–12 months | 100/19,854 | 1.21 | 0.96–1.52 | 1.18 | 0.75–1.38 |
| 12–36 months | 107/22,552 | 1.08 | 0.86–1.37 | 1.24 | 0.82–1.88 |
| 36–84 months | 120/29,643 | 0.94 | 0.76–1.18 | 1.07 | 0.72–1.59 |
| ≥84 months | 106/26,471 | 0.97 | 0.78–1.22 | 0.75 | 0.47–1.19 |
| $p_{trend}$ | | | 0.62 | | 0.48 |
| Women with 2nd degree relative with breast cancer[e] | | | | | |
| Never user | 284/79,596 | 1.00 | Referent | 1.00 | Referent |
| Ever user | 414/132,202 | 0.93 | 0.79–1.10 | 0.74 | 0.54–1.00 |
| Former | 396/126,653 | 0.94 | 0.79–1.10 | 0.73 | 0.53–0.99 |
| Current | 18/5,487 | 0.90 | 0.54–1.50 | 0.88 | 0.35–2.18 |
| Duration of use | | | | | |
| 1–12 months | 101/26,738 | 1.04 | 0.82–1.33 | 0.92 | 0.58–1.44 |
| 12–36 months | 92/29,706 | 0.94 | 0.73–1.20 | 0.72 | 0.45–1.17 |
| 36–84 months | 110/40,237 | 0.84 | 0.70–1.06 | 0.52 | 0.32–0.84 |
| ≥84 months | 111/35,504 | 0.94 | 0.75–1.18 | 0.84 | 0.55–1.27 |
| $p_{trend}$ | | | 0.24 | | 0.06 |

[a] Multivariate models adjusted for age (as time to event variable), alcohol consumption, history of breast disease, age at menarche, parity, age at first birth, menopausal status, HRT use, BMI, and participation in vigorous physical activity, study center, and randomization group.
[b] Analysis includes women who reported any family history of breast cancer including, but not limited to, first and second degree relatives.
[c] Additional adjustment for number of relatives with breast cancer.
[d] Additional adjustment for number of first degree relatives with breast cancer.
[e] Additional adjustment for number of second degree relatives with breast cancer.

*et al.* [5] also observed no association between oral contraceptive use and breast cancer risk among BRCA2 mutation carriers (330 cases). In contrast, Milne *et al.* [13], in a multi-center population based case-control study (1156 incident cases), observed an inverse association between oral contraceptive use and risk of early-onset (before age 40) breast cancer for BRCA1 mutation carriers, but not for BRCA2 mutation carriers. In addition, three previous cohort studies (two prospective, one retrospective) have examined the relationship between oral contraceptive use and breast cancer risk among women with a family history of breast cancer. Our results support the findings of Lipnick *et al.* [7] who analyzed data from the Nurses' Health Study in 1986 (71 incident cases) and observed no association between ever use of oral contraceptives and age-adjusted breast cancer risk among women with either a mother or sister with breast cancer. In a reanalysis of data from the Nurses' Health Study in 1996 (310 incident cases), Colditz *et al.* [8] observed a 2.5-fold increased risk of breast cancer among current oral contraceptive users with any family history of breast cancer (95% CI = 0.88–6.94), after adjustment for age, age at menarche, parity, menopause and age at menopause, history of benign breast disease, and use of postmenopausal hormones. This analysis, however, was based on only four breast cancer cases among current oral contraceptive users and was not statistically significant [8]. Unlike these analy-

ses, which included fewer than 7000 women with a family history of breast cancer, our study included approximately 27,000 women with a family history of breast cancer. More recently, Grabrick *et al*. [9] analyzed data from an historical cohort which included relatives of breast cancer cases (394 first degree relatives/38 cases and 3002 second degree relatives/115 cases), and observed a three-fold increased risk of breast cancer associated with ever use of oral contraceptives among sisters and daughters of women with breast cancer (95% CI = 1.6–6.7) and no association among nieces and granddaughters of women with breast cancer (RR = 1.2, 95% CI = 0.8–2.0) after adjustment for age and birth cohort. However, this study differed from ours in that the mean age at breast cancer diagnosis was younger the mean duration of oral contraceptive use was longer.

The prospective design and the large sample size are strengths of our study. However, although we adjusted our estimates for a wide range of potentially confounding variables, uncontrolled confounding other factors cannot be excluded. In addition, family history of breast cancer was assessed only at baseline and therefore misclassification due to change in family history during the follow-up period cannot be ruled out. Detection bias may have influenced our results if women with a family history, particularly those with a first degree family history who used oral contraceptives, were more likely to have had mammograms. Although we did adjust for randomization group, thus limiting the possibility of detection bias, we were not able to account for differences in mammography frequency after the end of the active follow-up phase of the NBSS and therefore detection bias cannot be ruled out completely.

Finally, information on BRCA1/BRCA2 mutation carrier status for the women in this population was not available. Recent analyses of the association between oral contraceptive use and breast cancer risk among women with BRCA1 and BRCA2 mutations have been carried out by Narod *et al*. [5] and Milne *et al*. [13]. Both studies found no association among women with BRCA2 mutations [5, 13]. The results for women with BRCA1 mutations, however, have been mixed. Narod *et al*. [5] observed a positive association between breast cancer and oral contraceptive use among women with BRCA1 mutations while, in contrast, Milne *et al*. [13] observed an inverse association among women with BRCA1 mutations. Additional studies are needed to further examine any potential association between oral contraceptive use and breast cancer risk by mutation carrier status, particularly among with BRCA1 mutations.

In conclusion, our study raises the possibility that relatively long duration of oral contraceptive use may be inversely associated with breast cancer risk among women with a family history of breast cancer. However, these observations require confirmation in other studies, particularly those that assess BRCA1/BRCA2 mutation carrier status.

## Acknowledgements

Funded in part by the National Cancer Institute of Canada. We thank Statistics Canada, the provincial and territorial Registrars of Vital Statistics, and the Cancer Registry directors for their assistance in making the cancer incidence and mortality data available.

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