Int. J. Cancer: **87,** 591–594 (2000)

Publication of the International Union Against Cancer

LONG-TERM ORAL CONTRACEPTIVE USE INCREASES BREAST CANCER RISK IN WOMEN OVER 55 YEARS OF AGE: THE DOM COHORT

Carlijn VAN HOFTEN[1,2], Huibert BURGER[1,2]*, Petra H.M. PEETERS[2], Diederick E. GROBBEE[2], Paul A.H. VAN NOORD[2] and Hubert G.M. LEUFKENS[1]

[1]*Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Utrecht, The Netherlands*
[2]*Julius Center for Patient Oriented Research, University Medical Center Utrecht, Utrecht, The Netherlands*

The role of past oral contraceptive use in the development of breast cancer is unclear, particularly in postmenopausal women. The authors investigated this relationship among pre- and postmenopausal middle-aged women in a nested case-control study within the population-based DOM cohort, Utrecht, the Netherlands. Among a total population of 12,184 women followed up for an average of 7.5 years, 309 breast cancer cases aged 42 to 63 years, diagnosed from November 1982 through May 1996, and 610 controls were examined. Overall, duration of oral contraceptive use was not clearly related to breast cancer. In women older than 55 years, however, oral contraceptive use for more than 10 years was associated with a 2-fold increased risk of breast cancer (odds ratio (OR) 2.1, 95% confidence interval (CI) 1.1–4.0). We conclude that long duration of oral contraceptive use increases the risk of breast cancer in women over 55 years of age but not in younger women. *Int. J. Cancer* 87: 591–594, 2000.

Breast cancer is the most common cancer among women in the United States and other Westernized societies (Forbes *et al.*, 1997). Since hormonal factors are most likely involved in the etiology of breast cancer (Paul *et al.*, 1986; Magnusson *et al.*, 1999), numerous studies addressed the relation between oral contraceptive use and breast cancer (Lipworth *et al.*, 1995; Malone *et al.*, 1993; Romieu *et al.*, 1990; La Vecchia *et al.*, 1995; Wingo *et al.*, 1993). The majority of these studies, however, showed no evidence of an overall increased risk of breast cancer in women taking oral contraceptives (Malone *et al.*, 1993; Romieu *et al.*, 1990; Thomas and Noonan, 1991). Although some studies have addressed subgroups such as long-duration oral contraceptive users, current users, early starters, or users before the first full-term pregnancy (Collaborative Group on Hormonal Factors in Breast Cancer, 1996; Van Leeuwen and Rookus, 1989; Malone *et al.*, 1993; Romieu *et al.*, 1990), postmenopausal women were generally not analyzed as a separate group. Also the most recently published review article on this topic (Collaborative Group on Hormonal Factors in Breast Cancer, 1996), while presenting age-stratified results, omitted paying specific attention to breast cancer risk in women older than 55 years.

In this study, we have examined the relationship between previous oral contraceptive use and breast cancer in middle-aged women. Women over 55 years of age at diagnosis were studied separately to see whether this relationship is modified by age.

MATERIAL AND METHODS

This is a report of a population-based nested case-control study of past oral contraceptive use and breast cancer risk among Dutch middle-aged women.

Source population and data collection

From January 1982 to April 1984, all women born between 1932 and 1941 and living in the city of Utrecht and vicinity, the Netherlands, were invited for a breast cancer screening program. Out of these women, 12,184 participated (overall response rate 44 percent). This group of women is known as the DOM3 cohort (DOM is short for Doorlopend Onderzoek Morbiditeit/Mortaliteit) (De Waard *et al.*, 1984). All participants were mailed and filled out a self-administered questionnaire, which was brought along to the screening visit and checked for completeness by clinical assistants. The questionnaire was composed of questions on medical history, use of oral contraceptives, use of other medications, cigarette smoking, alcohol consumption, marital status, education, maternal history of breast cancer, previous breast surgery, and reproductive history. The women were asked to mark the years in which they had used oral contraceptives for at least 3 months on a calender that was designed especially for this study. Trained clinical assistants measured weight and height. Further baseline assessments comprised screening for breast cancer by clinical examination and mammography as described previously (De Waard *et al.*, 1984).

Study population

Follow-up lasted from November 1982 to May 1996. Cases were cohort members with histologically confirmed breast cancer diagnosed during follow-up. These women were identified through linkage with the regional cancer registry covering the total population of the province of Utrecht including all DOM-cohort members. A total of 399 breast cancer cases were detected, on average 7.5 years after baseline. Initially, 798 control subjects were selected at random from the non-cases in the cohort. Women were subsequently excluded from the study if they had a history of breast cancer (1 case and 0 controls) or if they used drugs for the treatment of menopausal complaints (15 cases and 37 controls). Women were also excluded if they had undergone oophorectomy, hysterectomy, medical or X-ray treatment of the ovaries, all leading to artificial menopause (64 cases and 140 controls). Ten cases and 11 controls were excluded from the analyses because of missing data. As a result of the above selection, 309 case and 610 control subjects remained for analyses.

Determinant assessment

Exposure to oral contraceptive use was characterized as ever use of oral contraceptives and duration of oral contraceptive use. Ever use was defined as a history of oral contraceptive use for at least 3 months. To calculate the total number of years that a woman had used oral contraceptives, we assumed that a woman who indicated for a particular year that she had used them for at least 3 months actually had used these pills during the whole year. So, duration of oral contraceptive use in years was defined as the sum of those years in which a woman had used oral contraceptives for 3 months or more. Potential confounders were also assessed at the time of the questionnaire. Education was defined as the highest education level attained. Current cigarette smoking was defined as having smoked cigarettes during the past year and past cigarette smoking as having smoked the last cigarette longer than one year ago. Alcohol consumption was assessed as the time since the last alcoholic beverage. Body mass index was calculated as weight/(height)^2.

*Correspondence to: Huibert Burger, Julius Center for Patient Oriented Research, University Medical Center Utrecht, PO Box 85500, NL-3508 GA Utrecht, The Netherlands. Fax: +31 30 250 5480.
E-mail: H.Burger@jc.azu.nl

Received 8 November 1999; Revised 10 February 2000

Data analysis

Logistic regression was used to examine the association between oral contraceptive use and breast cancer. In all analyses, the reference group consisted of women who had never used oral contraceptives. First, the association between the various measures of oral contraceptive use and breast cancer was estimated while controlling for age at the time of the questionnaire only. Second, these associations were studied simultaneously, adjusting for a full set of potential confounders. Besides age at the time of the questionnaire, these appeared to be age at menarche, menopausal status at baseline, marital status, age at first delivery, number of children, education, cigarette smoking, and a maternal history of breast cancer. Variables were not considered confounders when inclusion into the logistic model did not essentially change the magnitude of the association between oral contraceptive use and breast cancer. All variables were analyzed as categorical variables and duration of use was additionally analyzed as a discrete variable to test for trends of increasing risk of breast cancer with number of years of pill use. The associations are presented as odds ratios as measures of relative risk with 95%confidence intervals. Because specific information on menopausal status was not available at the time of diagnosis, we assumed at least 85% of women older than 55 years at diagnosis to be postmenopausal (Van Noord *et al.*, 1997), and we analyzed them separately to tentatively explore whether any association would depend on menopausal status.

RESULTS

Table I summarizes the characteristics of the study population. The age of the cases at the time of the breast cancer diagnosis varied between 42 and 63 years (mean 53 years). Women who were never married, smoked cigarettes, had fewer than 3 children, had an early menarche, were still premenopausal, or reported a history of maternal breast cancer at the time of the questionnaire had an increased risk of breast cancer. For year of birth, age at the time of the questionnaire, education, alcohol consumption, body mass index, and age at first delivery, no such relation was seen. A total of 192 cases (62.1%) and 352 controls (57.7%) had ever used oral contraceptives. Table II shows the relationship between the 2 measures of oral contraceptive use and breast cancer. Although women with a history of oral contraceptive consumption had a slightly increased risk of breast cancer, especially those over the age of 55 years, the associations between ever use of oral contraceptives and breast cancer were not statistically significant, neither for the total group of women or for the 2 subgroups of age. The mean duration of oral contraceptive use for the cases was 7.5 years and for the controls 7.2 years. A small and nonsignificantly increased risk of breast cancer for a duration of use between 1 and 10 years was seen, not essentially different between the age groups. In the total group of women, an increased risk of breast cancer associated with the highest category of duration of oral contraceptive use was observed, but this association was not statistically significant. When analyzed in strata of age at diagnosis, it appeared that this increase in risk of breast cancer was mainly attributable to a doubling of risk in women over 55 years. No continuous trend of increasing relative risk with duration of oral contraceptive use was seen for the total group of women ($p = 0.41$), nor for women aged 55 years or younger ($p = 0.79$) nor for women over 55 years of age ($p = 0.18$) at the time the breast cancer diagnosis.

TABLE I – BASELINE CHARACTERISTICS OF THE BREAST CANCER CASES AND CONTROLS

Characteristic	Cases: n = 309		Controls: n = 610	
	Number	%	Number	%
Year of birth				
1938–1941	127	41.1	241	39.5
1935–1937	97	31.4	205	33.6
1932–1934	85	27.5	164	26.9
Age (years)[1], mean	45.4		45.5	
40–44	98	31.7	179	29.3
44–47	126	40.8	261	42.8
47–52	85	27.5	170	27.9
Marital Status				
Ever married	279	90.3	580	95.1
Never married	30	9.7	30	4.9
Education[2]				
Elementary school	83	26.9	165	27.0
Lower vocational/general secondary education	138	44.7	266	43.6
Intermediate vocational education	42	13.6	59	9.7
Higher general secondary education	18	5.8	52	8.5
Higher vocational education/university	28	9.1	68	11.1
Alcohol consumption				
Never/≤1 month ago	87	28.2	165	27.0
1 month–1 week ago	27	8.7	66	10.8
Last week	195	63.1	379	62.1
Cigarette smoking				
Never	156	50.5	363	59.5
Past smoker	48	15.5	67	11.0
Current smoker ≤10 cigarettes/day	39	12.6	81	13.3
Current smoker >10 cigarettes/day	66	21.4	99	16.2
Body mass index (kg/m^2)[3], mean	24.7		24.6	
<21	37	12.0	79	13.0
21–27	205	66.3	410	67.2
>27	65	21.0	120	19.7
Number of children				
0	46	14.9	77	12.6
1–2	149	48.2	276	45.2
≥3	114	36.9	257	42.1
Age at first delivery (years)[4], mean	22.1		22.6	
16–22	39	14.8	93	17.4
23–26	119	45.2	229	43.0
27–30	76	28.9	153	28.7
>30	29	11.0	58	10.9
Age at menarche (months), mean	161.1		163.0	
120–150	94	30.4	139	22.8
151–170	142	46.0	298	48.9
171–219	73	23.6	173	28.4
Menopausal status				
Premenopausal	287	92.9	524	85.9
Postmenopausal	22	7.1	86	14.1
Maternal history of breast cancer				
No	276	89.3	587	96.2
Yes	33	10.7	23	3.8

[1]Age at the time of the questionnaire.–[2]Based on the Dutch school system.–[3]Missing data for 2 cases and 1 control.–[4]Excluding nulliparous women.

DISCUSSION

The present study shows that a duration of oral contraceptive use for more than 10 years is associated with a 2-fold increased risk of breast cancer risk in women over 55 years of age. The fact that the association was limited to women older than 55 years suggests that menopausal status plays a role. Besides being age-specific, the association was confined to the highest category of duration of use, which may point to the existence of a threshold value.

The prospective population-based design, combined with a regional cancer registry providing complete case ascertainment, radically limits the possibility of 2 common forms of bias. First, selection bias may occur if the probability of inclusion into the study is, differently for cases and controls, related to oral contraceptive use. This type of bias is, however, very unlikely, since

TABLE II – ODDS RATIOS AND 95% CONFIDENCE INTERVALS OF BREAST CANCER IN RELATION TO VARIOUS MEASURES OF ORAL CONTRACEPTIVE USE

OC[1] use	Number of cases/controls	All women OR[3] (95% CI)	OR[4] (95% CI)	Number of cases/controls	≤55[2] OR[3] (95% CI)	OR[4] (95% CI)	Number of cases/controls	>55[2] OR[3] (95% CI)	OR[4] (95% CI)
OC use at any time									
Never	117/258	1.00	1.00	80/258	1.00	1.00	37/258	1.00	1.00
Ever	192/352	1.19 (0.90–1.58)	1.31 (0.96–1.79)	128/352	1.10 (0.79–1.53)	1.24 (0.86–1.78)	64/352	1.35 (0.87–2.11)	1.45 (0.89–2.37)
Total duration of OC use (years)									
0	117/258	1.00	1.00	80/258	1.00	1.00	37/258	1.00	1.00
1–10	141/265	1.16 (0.86–1.57)	1.27 (0.92–1.77)	99/265	1.11 (0.78–1.57)	1.25 (0.85–1.82)	42/265	1.21 (0.74–1.96)	1.26 (0.74–2.14)
>10	51/87	1.29 (0.86–1.95)	1.43 (0.92–2.22)	29/87	1.08 (0.66–1.78)	1.22 (0.72–2.07)	22/87	1.77 (0.97–3.23)	2.05 (1.07–3.95)

[1]Oral contraceptive.–[2]Age in years at the time of the diagnosis of breast cancer.–[3]Odds ratio adjusted for age at the time of the questionnaire.–[4]Odds ratio adjusted for age, menopausal status, marital status, education, cigarette smoking, and number of children at the time of the questionnaire, age at first delivery, age at menarche, and maternal history of breast cancer.

complete case ascertainment was accomplished and controls were randomly chosen. Also at baseline, selection bias may have occurred if relatively healthy women were more willing to take part in the investigation. In a case-control study on oral contraceptive use and breast cancer in young women, Lund (1989) observed that responders were more likely to have used these pills and to have a lower risk of breast cancer due to higher parity than those who did not respond. Even if a similar selection occurred in our study, a bias in the association between oral contraceptive use and breast cancer would not result. Such bias would only be observed if those with a high risk of breast cancer from other causes were more (or less) likely to be responders in case they also had a history of oral contraceptive use. We consider this very unlikely. Second, by virtue of the prospective character of this study, information bias is virtually impossible since at the time of filling out the questionnaire there was, as far as we know, no possibility that women could foresee their case-control status. Although it is not possible in an observational study to completely rule out confounding, most common confounders were, if necessary, adjusted for. A relative advantage of this study is the long follow-up period of 14 years as compared with other studies. Since women in our cohort were 21 to 28 years of age at the time oral contraceptives were introduced in the Netherlands, we could study the long-term effects of oral contraceptives in pre- and postmenopausal women. Advantages relating to the statistical power of the study comprise the large size of the study, as well as the high prevalence of oral contraceptive use (Rookus and Van Leeuwen, 1994) and high incidence of breast cancer in the Netherlands (Van der Santen *et al.*, 1995).

The study also has limitations. At the time of the questionnaire, 42 (13.6%) cases and 55 (9.0%) controls were current oral contraceptive users. The resulting incomplete exposure information may have caused underestimation of the magnitude of association. In addition, we could not analyze actual differences by estrogenic potencies or progestational components of the oral contraceptives because it is unknown which specific preparations the women used. Therefore, it was not possible to attribute the increased risk to a specific substance. Further, age at menopause could not be considered a potential confounder because at the time DOM-cohort women approached menopause, oral contraceptives were also prescribed for reducing menopausal complaints, which, in turn, may have postponed the moment of manifestation of menopause.

We have no explanation for our finding that oral contraceptive use was most strongly related to breast cancer in the older, probably postmenopausal women. Although modification by menopausal status would point to a role for declining endogenous estrogen levels, its connection to the etiology of breast cancer is unclear. Unfortunately, we could not evaluate a possible confounding role of hormone replacement therapy, which appears to be a risk factor for breast cancer (Magnusson *et al.*, 1999) and may have been preferentially used by women with a history of long-term oral contraceptive use.

The majority of reports, including the most recently published review (Collaborative Group on Hormonal Factors in Breast Cancer, 1996), could not disclose an increased risk in women with a history of long-term oral contraceptive use (Paul *et al.*, 1986; Rossing *et al.*, 1996; Primic-Zakelj *et al.*, 1995; Malone *et al.*, 1993). Nonetheless, in these studies women older than 55 years at breast cancer diagnosis were not considered as a separate group. In women aged 40 to 59 years, for example, Ewertz (1992) detected no association between long-term oral contraceptive use, i.e., 12 years or more, and breast cancer risk. Rossing *et al.* (1996), who studied women aged 50 to 64 years at diagnosis, also reported no increase in risk for those using oral contraceptives for more than 10 years. In 2 studies, Rosenberg *et al.* observed no increased risks in the subgroups of women who were 45 to 59 (1996), 40 to 49, 50 to 59, and 60 to 69 years (1992) of age at diagnosis and had used oral contraceptives for 10 years or more. The statistical power of showing such association in women aged 60 to 69 years from the latter study, however, was relatively small since there were only 3 cases in this subgroup who had used oral contraceptives for more than 10 years. In the age group 46 to 54 years at diagnosis, Rookus and Van Leeuwen (1994) found a highly significant trend of higher risk with duration of oral contraceptive use (relative risk per year of use is 1.06 and $p = 0.004$). This relative risk was 2.3 (95% CI 1.1–4.7) for women who had used oral contraceptives 12 years or more. Shorter durations of oral contraceptive use were not associated with increased risks. As far as we know, the only study separately examining women aged 55 years and over was a cohort study conducted by Schuurman *et al.* (1995) in which it was suggested that women who had used oral contraceptives for at least 15 years have an almost 2-fold increased risk of breast cancer at age 55 to 69 years. Although our findings are logically not in line with the suggestion that the increased risk subsides 10 years after cessation of use (Collaborative Group on Hormonal Factors in Breast Cancer, 1996), it is nevertheless possible that in older women, a group that is not well researched as a separate group, the fall in endogenous hormones, possibly in combination with other physiologic changes, discloses an increased risk of breast cancer from long-term pill use in the past. In fact, our results and those of Schuurman *et al.* (1995) call for more studies in older, postmenopausal women.

In conclusion, our results show that a history of oral contraceptive use for more than ten years is associated with a twofold increased risk of breast cancer in women over 55 years of age.

ACKNOWLEDGEMENTS

The authors acknowledge B.J. Slotboom for data management and Dr. Ch. Gimbrère (Integraal Kanker Centrum Midden Nederland) as well as all collaborating general practitioners for their help in follow-up.

REFERENCES

COLLABORATIVE GROUP ON HORMONAL FACTORS IN BREAST CANCER, Breast cancer and hormonal contraceptives: collaborative study 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 (1996).

DE WAARD, F., COLLETTE, H.J.A., ROMBACH, J.J., BAANDERS-VAN HALEWIJN, E.A. and HONING, C., The DOM project for the early detection of breast cancer, Utrecht, the Netherlands. *J. Chron. Dis.,* **37,** 1–44 (1984).

EWERTZ, M., Oral contraceptives and breast cancer risk in Denmark. *Europ. J. Cancer,* **28A,** 1176–1181 (1992).

FORBES, J.F., The incidence of breast cancer: the global burden, public health considerations. *Semin. Oncol.,* **24** (suppl 1), S1-20–S1-35 (1997).

LA VECCHIA, C., NEGRI, E., FRANCESCHI, S., TALAMINI, R., AMADORI, D., FILIBERTI, R., CONTI, E, MONTELLA, M., VERONESI, A., PARAZZINI, F., FERRARONI, M. and DECARLI, A., Oral contraceptives and breast cancer: a cooperative Italian study. *Int. J. Cancer,* **60,** 163–167 (1995).

LIPWORTH, L., KATSOUYANNI, K., STUVER, S., SAMOLI, E., HANKINSON, S.E. and TRICHOPOULOS, D., Oral contraceptives, menopausal estrogens, and the risk of breast cancer: a case-control study in Greece. *Int. J. Cancer,* **62,** 548–551 (1995).

LUND, E., The validity of different control groups in a case-control study. Oral contraceptive use and breast cancer in young women. *J. Clin. Epidemiol., 42,* 987–993 (1989).

MAGNUSSON, C., BARON, J.A., CORREIA, N., BERGSTRÖM, R., ADAMI, H.-O. and PERSSON, I., Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. *Int. J. Cancer,* **81,** 339–344 (1999).

MALONE, K.E., DALING, J.R. and WEISS, N.S., Oral contraceptives in relation to breast cancer. *Epidemiol. Rev.,* **15,** 80–97 (1993).

PAUL, C., SKEGG, D.C.G., SPEARS, G.F.S. and KALDOR, J.M., Oral contraceptives and breast cancer: a national study. *Brit. Med. J.,* **293,** 723–726 (1986).

PRIMIC-ZAKELJ, M., EVSTIFEEVA, T., RAVNIHAR, B. and BOYLE, P., Breast-cancer risk and oral contraceptive use in slovenian women aged 25 to 54. *Int. J. Cancer,* **62,** 414–420 (1995).

ROMIEU, I., BERLIN, J.A. and COLDITZ, G., Oral contraceptives and breast cancer. Review and meta-analysis. *Cancer,* **66,** 2253–2263 (1990).

ROOKUS, M.A. and VAN LEEUWEN, F.E., Oral contraceptives and risk of breast cancer in women aged 20–54 years. Netherlands Oral Contraceptives and Breast Cancer Study Group. *Lancet,* **344,** 844–851 (1994).

ROSENBERG, L., PALMER, J.R., CLARKE, E.A. and SHAPIRO, S., A case-control study of risk of breast cancer in relation to oral contraceptive use. *Amer. J. Epidemiol.,* **136,** 1437–1444 (1992).

ROSENBERG, L., PALMER, J.L., RAO, R.S., ZAUBER, A.G., STROM, B.L., WARSHAUER, M.E., HARLAP, S. and SHAPIRO, S., Case-control study of oral contraceptive use and risk of breast cancer. *Amer. J. Epidemiol.,* **143,** 25–37 (1996).

ROSSING, M.A., STANFORD, J.L., WEISS, N.S. and HABEL, L.A., Oral contraceptive use and risk of breast cancer in middle-aged women. *Amer. J. Epidemiol.,* **144,** 161–164 (1996).

SCHUURMAN, A.G., VAN DEN BRANDT, P.A. and GOLDBOHM, R.A., Exogenous hormone use and the risk of postmenopausal breast cancer: results from the Netherlands Cohort Study. *Cancer Causes Control,* **6,** 416–424 (1995).

THOMAS, D.B. and NOONAN, E.A., Risk of breast cancer in relation to use of combined oral contraceptives near the age of menopause. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Cancer Causes Control,* **2,** 389–394 (1991).

VAN DER SANDEN, G.A., COEBERGH, J.W., SCHOUTEN, L.J., VISSER, O. and VAN LEEUWEN, F.E., Cancer incidence in The Netherlands in 1989 and 1990: first results of the nationwide Netherlands cancer registry. *Europ. J. Cancer,* **31,** 1822–1829 (1995).

VAN LEEUWEN, F.E. and ROOKUS, M.A., The role of exogenous hormones in the epidemiology of breast, ovarian and endometrial cancer. *Europ. J. Cancer Clin. Oncol.,* **25,** 1961–1972 (1989).

VAN NOORD, P.A.H., DUBAS, J.S., DORLAND, M., BOERSMA, H. and TE VELDE, E., Age at natural menopause in a population-based screening cohort: the role of menarche, fecundity, and lifestyle factors. *Fertil. Steril.,* **68,** 95–102 (1997).

WINGO, P.A., LEE, N.C., ORY, H.W., BERAL, V., PETERSON, H.B. and RHODES, P., Age-specific differences in the relationship between oral contraceptive use and breast cancer. *Cancer,* **71,** 1506–1517 (1993).