Use of Oral Contraceptives and Breast Cancer Risk: The Norwegian-Swedish Women's Lifestyle and Health Cohort Study[1]

Merethe Kumle,[2] Elisabete Weiderpass, Tonje Braaten, Ingemar Persson, Hans-Olov Adami, and Eiliv Lund

Institute of Community Medicine, University of Tromsoe, 9037 Tromsoe, Norway [M. K., T. B., E. L.]; Department of Medical Epidemiology, Karolinska Institutet, S-17177 Stockholm, Sweden [E. W., H-O. A.]; IARC, F-69372 Lyon, France [E. W.]; and Medical Products Agency, S-75103 Uppsala, Sweden [I. P.]

Abstract

Current use of oral contraceptives (OCs) has been reported to increase breast cancer risk slightly. In 1991/1992, a prospective cohort study specifically designed to examine the role of hormonal contraceptives in relation to breast cancer was conducted in Norway and Sweden. This study was entitled Women's Lifestyle and Health. Of 196,000 invited women aged 30–49 years, 106,844 women answered a 4-page questionnaire. Altogether, 103,027 women providing information on contraceptive use were included in the analysis presented here, and 1,008 primary invasive breast cancers were diagnosed throughout 1999 (end of follow-up). Proportional hazard regression was used to calculate relative risks (RRs) with adjustment for age and other possible confounders. An increased breast cancer risk was observed among women who were current/recent users of OCs of any type at the start of follow-up [RR, 1.6; 96% confidence interval (CI), 1.2–2.1]. Current/recent use (*i.e.*, use in the year preceding cohort enrolment) of combined OCs (RR, 1.5; 95% CI, 1.0–2.0) and progestin-only pills (RR, 1.6; 95% CI, 1.0–2.4) entailed similar levels of increased risk. An increased risk of borderline significance was found among short-term (*i.e.*, less than 13 months) users before age 20 years (RR, 1.3; 95% CI, 1.0–1.7) and before first full-term pregnancy (RR, 1.4; 95% CI, 1.0–1.8). Long-term users of OCs were at a higher risk of breast cancer than never users (test for trend, $P = 0.005$). Current/recent use of OCs is associated with an increased breast cancer risk. Use of combined OCs and progestin-only pills seem to increase the risk at the same level.

Received 2/22/02; revised 7/26/02; accepted 8/19/02.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] In Norway, the survey was supported by United States National Cancer Institute Grant CA 52449, Norwegian Cancer Society Grant DNK 90050, and the Aakre Foundation. In Sweden, the survey was supported by the Swedish Council for Planning and Coordination of Research, Swedish Cancer Society, Organon, Pharmacia, Medical Products Agency and Schering-Plough.

[2] To whom requests for reprints should be addressed, at Faculty of Medicine, Institute of Community Medicine, University of Tromsoe, 9037 Tromsoe, Norway. Phone: 47-77-64-48-84; Fax: 47-77-64-48-31; E-mail: merethe.kumle@ism.uit.no.

Introduction

Use of hormonal contraceptives has revolutionized the reproductive life of women since the 1960s (1). Such drugs can be divided into combined OCs[3] and progestin-only contraceptives, available as injections, implants, oral preparations (pills), and hormone-releasing intrauterine devices. OC is the common generic term for combined OCs and progestin-only pills when it is not specified which of the two is used. These contraceptives affect not only the reproductive system but also the incidence of various diseases, as reviewed recently (1). In particular, use of combined OCs has been reported to slightly increase breast cancer risk. The effect is highest among current users and vanishes within 10 years after cessation of use (2). With regard to use of progestin-only pills, the results are inconsistent, but there is some suggestion that the risk is slightly elevated in current and recent users (3).

Most data on the association between use of combined OCs and breast cancer risk come from case-control studies (1, 3), which are susceptible to recall bias (1, 4). The association between combined OCs and breast cancer has also been analyzed in several cohort studies, particularly in relation to drugs used until the early 1980s (1, 2, 5–14). For the association between breast cancer and progestin-only pills, there are a few case-control studies (15–17) and the pooled analysis of individual data made by the Collaborative Group on Hormonal Factors and Breast Cancer (3).

We report here the first results from the Women's Lifestyle and Health study, a large prospective cohort study that began in Norway and Sweden in the early 1990s. The study was specifically designed to examine the role of hormonal contraceptives in breast cancer risk.

Materials and Methods

Study Population. The cohort was enrolled during 1991 and 1992. In Norway, a sample of 100,000 women born between 1943 and 1957 (aged 34–49 years) was randomly selected from the Central Population Register. This register records the addresses of all persons alive and residing in the country, and the dates of death or migration to or from Norway since 1960. In this register, each person is identified by a unique 11-digit national registration number: the first six digits encode information on the date of birth, and the last five digits are based on an algorithm that ensures a unique number, which includes information on gender (18). In Sweden, a sample of 96,000 women born between 1943 and 1962 (aged 30–49 years), residing in the Uppsala Health Care Region (comprising about one-sixth of the Swedish population), was randomly selected from the Swedish Central Population Registry at Statistics Sweden. In this registry, each individual is identified by a

[3] The abbreviations used are: OC, oral contraceptive; RR, relative risk; CI, confidence interval; BMI, body mass index; HRT, hormone replacement therapy.

unique 10-digit national registration number, which encodes information on date of birth and gender (18).

A letter of invitation to participate in the study and a health survey questionnaire was sent to all women. In Norway, the questionnaire was mailed to 10 subgroups at regular intervals. In Sweden, two mailings were done (one in 1991 and one in 1992). The questions relevant to the analysis presented here were identical in the two countries. This common set of questions included a detailed assessment of contraceptive use, reproductive history, prevalent diseases, history of breast cancer in the mother and sister(s), and other lifestyle habits. To facilitate recall, a color brochure with pictures of almost all contraceptive pill packages ever sold in Norway and Sweden was sent to all women.

Follow-Up. The follow-up was performed through linkages between the cohort data set and various population-based registries. This was possible by use of the individually unique national registration numbers present in the cohort data set and in all national registries in Norway and Sweden. We obtained information on date of death for deceased persons from the death registers and on date of emigration from the registers of population migration. The national cancer registers, established in the 1950s in both countries, provided data on prevalent cancer cases at cohort enrollment and on incident cancers diagnosed in the cohort during follow-up. These registries are estimated to be almost complete (19, 20).

The start of follow-up was defined by the return of the questionnaire. The follow-up ended December 31, 1999 or at emigration, death, or primary breast cancer diagnosis, whichever occurred first. Of the 100,000 invited women in Norway, 57,585 (57.6%) returned a completed questionnaire, as did 49,259 of the 96,000 invited women (51.3%) in Sweden. Thus, the overall crude participation rate was 54.5% (106,844 of 196,000). We excluded 4 women from the cohort due to lack of vital status information (whether they were alive, dead, or had emigrated). Among the 106,840 women in the cohort, 789 emigrated, and 1,360 died during the follow-up period.

For the analysis presented here, we excluded 15 women who were dead or had emigrated before start of follow-up, 1,663 women who had been reported as having an invasive cancer at study enrollment, and 1,126 women without any information on use of hormonal contraceptives. Information about commercial names or brands in each period of use made it possible to classify the hormonal content of the preparations as combined OCs or progestin-only preparations (pills, injections, or implants). We restricted progestin-only preparations to pills (progestin-only pills) in this paper. Thus, women who ever used injectable depot medroxy-progesterone acetate or levonorgestrel implants were excluded from all analyses (n = 1,009). In summary, 103,027 women were included in the analysis presented here.

Exposure Classification. Information about exposure to OCs is based on the questionnaire administered at cohort enrollment. Questions about hormonal contraceptive use were summary measures, such as ever having used (Have you ever used hormonal contraceptives?), current use (Do you use hormonal contraceptives at the moment?), total duration of use (For how many years have you been using hormonal contraceptives?), age at first use (How old were you the first time you started with hormonal contraceptives?), and use before first full-term pregnancy (Did you use hormonal contraceptives before first pregnancy?). We also collected detailed information about each specific period of use. A period was defined as any continuous use of one specified hormonal contraceptive brand. Up to 10 different periods of use were reported. For each period, we asked the age at starting use, duration of use, and brand name. Based on a combination of the summary measures and the detailed information collected about each period of use, we calculated the total duration of use, time since last use, time since first use, and current/recent use. Total duration of use is the sum of each period of use, corrected for possible overlapping periods. Whenever information on periods was missing, the total duration of use given in the summary question was used. Time since last use was calculated as the interval between the end of use and start of the follow-up. Current/recent use was defined as use of OCs at the time of study enrollment or use within 1 year before the start of follow-up. Time since first use was defined as the interval between start of use of OCs and the start of follow-up.

The analyses of OCs and breast cancer were done with: (*a*) all women analyzed together regardless of information on brand (OCs); and (*b*) women classified according to OC regimens based on brand information as having used only combined OCs, only progestin-only pills, or both combined OCs and progestin-only pills or having used OCs with unknown brand in at least one period. In the analysis of current/recent use of combined OCs and progestin-only pills, the women were classified based on information of brand used in the most recent period (within the last 12 months before completing of the questionnaire), regardless of the completeness of earlier periods. Two separate groups were constructed based on this information, one with progestin-only pill users, and one with combined OC users. Women defined as current/recent users of combined OCs might have used progestin-only pills in earlier periods, and current/recent users of progestin-only pills may have used combined OCs in earlier periods.

Information on menopausal status was obtained from the questionnaire. We have no information about menopausal status after start of follow-up. Only women who reported a natural menopause or a bilateral oophorectomy at cohort enrolment were considered as postmenopausal during the follow-up. All other women were considered premenopausal, regardless of age, hysterectomy, or use of HRT.

Statistical Analysis. We calculated relative hazards using the Cox proportional hazard models (21), considering use of OCs as the independent variable and breast cancer as the dependent variable. We interpreted relative hazards as estimates of RRs. RRs are given with 95% CIs. Women who had never used OCs were considered as the comparison group, if not otherwise specified.

We kept the following covariables in the final multivariate models: age at enrollment into the cohort (as a continuous variable in years), parity (0, 1, 2, 3 or more children), age at first birth (<21, 22–24, 25 years or more), age at menarche (as a continuous variable), use of HRT (ever or never used), history of breast cancer in mother or sister(s), total duration of breastfeeding (as a continuous variable in months), BMI, calculated as weight in kilograms divided by the square of height in meters (as a continuous variable), and menopausal status (pre- or postmenopausal at start of follow-up). Known possible confounders such as age at menarche, age at first birth and number of full-term pregnancies, menopausal status, and use of HRT were kept in the models, even though they did not affect the association between OC use and breast cancer. Levels of recreational physical activity and education were not kept in the models as covariables because they did not improve the goodness of fit or change risk estimates meaningfully. Possible interaction (effect modification) between age at start of fol-

low-up and use of hormonal contraceptives and interaction between BMI and menopausal status were evaluated by including appropriate product terms in the models. A significant interaction (effect modification) between current use of OCs and age at start of follow-up was found ($P = 0.03$). Therefore, we stratified women in two age groups: women aged 30–39 years at enrollment and women aged 40–49 years at enrollment. This division into two age groups was made according to their possible menopausal status at end of follow-up. The interaction term between BMI and menopausal status was included in the final models, even though the fit of the model did not change significantly, because of the known differential effect of BMI on breast cancer risk according to menopausal status (22). Tests for trend were calculated by introduction of ordinal variables obtained by assigning consecutive integers to values of the categorized variables.

The responsible data inspection boards and ethical committees in both countries approved the study design, and all women gave informed consent prior to participating in the study.

Results

General Characteristics. Among the 103,027 women included in the study, 1,008 primary invasive breast cancers were diagnosed by the end of follow-up. The median age at diagnosis was 47 years (30–57 years at time of diagnosis), and the median year of diagnosis was 1996. On average, women who developed breast cancer tended to be older, have lower parity and higher age at first birth, and are of slightly lower BMI than the members of the whole cohort (Table 1). Women who developed breast cancer reported having a first-degree relative with a history of breast cancer more often than women in the study cohort as a whole.

At time of enrollment to the cohort, 63% of the women were former users, and 9% were current/recent users, whereas 28% had never used OCs. The proportion of ever-users of OCs among women aged 30–34 years was higher (87%) than that among women aged 45–49 years (64%). The number of current/recent OC users decreased strongly with age at cohort enrollment, from 22% to 3%. Nearly 70% of the women aged 45–49 years, compared with 8% of the women aged 30–34 years, ceased using OCs 15 years or more before cohort enrollment. The number of short-term users (less than 5 years) of OCs increased with increasing age at enrollment. Use of OCs for more than 10 years, use before age 20 years, and use before first full-term pregnancy were most common in the youngest age group.

Risk by Pattern of OC Use. Women having ever used OCs presented a 30% higher risk of developing breast cancer than never-users (Table 2). RR for breast cancer among ever-users of OCs remained significantly increased after exclusion of current/recent users from the analysis (RR = 1.2). Results were similar when we excluded breast cancer cases occurring in the first 2 years of follow-up. Compared with never-users of OCs, women who were current/recent users at the start of follow-up had a 60% increased breast cancer risk, and former users had a 20% increased breast cancer risk. We found a weak but statistically significant association between duration of OC use and increased risk of breast cancer (test for trend, $P = 0.005$; Table 2).

When we explored differences by age at start of follow-up, the risk estimates among ever-users of OCs in the younger age group (30–39 years) were only marginally higher than those in the older age group (40–49 years; Table 3). For current/recent users, the RRs were almost identical in the two age groups.

Table 1 Characteristics of the study population in the Women's Lifestyle and Health Study

Characteristics	Study population	Breast cancer cases
	No. (%)	No. (%)
Country of residence		
Norway	55,710 (54.1)	541 (53.7)
Sweden	47,317 (45.9)	467 (46.3)
Age at enrollment (yrs)		
30–34	12,332 (12.0)	49 (4.9)
35–39	31,862 (30.9)	218 (21.6)
40–44	29,902 (29.0)	310 (30.8)
45–49	28,931 (28.1)	431 (42.8)
Mean age (±SD)	40.7 (5.1)	42.7 (4.7)
Mean height (±SD)	166.3 (5.7)	166.9 (5.6)
Mean weight (±SD)	64.3 (10.6)	63.8 (10.7)
BMI (kg/m^2)		
Less than 18.5	2,159 (2.1)	16 (1.6)
18.5–24	72,542 (72.5)	753 (76.4)
25–29	20,264 (20.3)	178 (18.1)
30 or more	5,111 (5.1)	38 (3.9)
Mean BMI (±SD)	23.2 (3.6)	22.9 (3.5)
Age at menarche (yrs)		
12 or less	33,181 (32.7)	306 (30.9)
13	29,946 (29.5)	302 (30.5)
14 or more	38,329 (37.8)	382 (38.6)
Mean age at menarche (±SD)	13.1 (1.4)	13.1 (1.3)
Postmenopausal at entry	4,166 (4.0)	41 (4.1)
Ever used hormonal replacement therapy	3,389 (3.9)	58 (5.6)
History of breast cancer in mother/sister(s)	4,997 (4.9)	104 (10.3)
Parity		
Nulliparous	12,169 (11.8)	136 (13.5)
One child	14,536 (14.1)	155 (15.4)
Two children	44,907 (43.6)	449 (44.5)
Three or more children	31,415 (30.5)	268 (26.6)
Mean number of children (±SD)[b]	2.0 (1.1)	1.9 (1.1)
Age at first birth (yrs)		
Less than 21 y	20,928 (23.0)	162 (18.6)
21–24	32,756 (36.0)	308 (35.3)
25 or more	37,309 (41.0)	402 (46.1)
Mean age at first birth (±SD)	24.0 (4.4)	24.7 (4.6)
Mean duration of breast-feeding (±SD)	11.8 (10.8)	11.4 (10.3)

[a] BMI, weight (kg)/height (m^2).
[b] Among all women.

Neither time since last use (except for use less than 1 year ago, *e.g.*, current/recent use) nor time since first use was clearly associated with increased risk (Table 4). A 30% increased risk was found among short-term users (*i.e.*, <13 months) before age 20 years and before first full-term pregnancy (RR, 1.4; 95% CI, 1.0–1.8). However, no significant trend was revealed for duration of use before age 20 years or for duration of use before first full-term pregnancy. Age at first use of OCs was not associated with an increased breast cancer risk (P for trend = 0.6).

We found a significant interaction (effect modifications) between current/recent use of OCs and age at start of follow-up ($P = 0.03$), but no interaction between former use and age at enrollment ($P = 0.7$).

Combined OCs and Progestin-Only Pills. Women who had ever exclusively used progestin-only pills were not at an increased breast cancer risk, whereas those who had exclusively used combined OCs were at 30% increased risk (Table 5). In contrast, current/recent use of progestin-only pills and com-

Table 2 RRs and 95% CIs of developing breast cancer according to use of OCs, The Women's Lifestyle and Health Study

Use of OCs	Study population	Breast cancer cases	RR (95% CI)	
			Age-adjusted	Multivariate[a]
Never-users	28,171	261	1.0 (reference)	1.0 (reference)
Ever-users	74,856	747	1.2 (1.1–1.4)	1.3 (1.1–1.5)
Current/recent users at start of follow-up	9,299	91	1.6 (1.2–2.0)	1.6 (1.2–2.1)
Former users at start of follow-up	65,557	656	1.2 (1.1–1.4)	1.2 (1.1–1.4)
Duration of use (yrs)				
<5	38,742	384	1.2 (1.0–1.4)	1.2 (1.0–1.5)
5–9	18,876	178	1.3 (1.0–1.5)	1.2 (1.0–1.5)
10–14	10,803	113	1.4 (1.1–1.8)	1.4 (1.1–1.8)
15+	5,441	63	1.3 (1.0–1.8)	1.3 (1.0–1.8)
Test for trend			$P = 0.001$	$P = 0.005$

[a] Multivariate analysis, adjusted for: age (continuous variable), parity (0, 1, 2, 3+), age at first birth (−20, 21–24, 25+), age at menarche (continuous variable), use of HRT (ever/never), menopausal status (pre-/postmenopausal), history of breast cancer in first-degree relatives (yes/no), duration of breastfeeding (continuous variable), BMI (continuous variable), region (Sweden and five health regions in Norway), and a term for interaction between BMI and menopausal status.

Table 3 RRs and 95% CIs of developing breast cancer according to use of OCs, stratified on age at start of follow-up, The Women's Lifestyle and Health Study

Use of OCs	Study population	Breast cancer cases	RR (95% CI)	
			Age-adjusted	Multivariate[a]
Age group 30–39 yrs[b]				
Never-users	8,829	41	1.0 (reference)	1.0 (reference)
Ever-users	35,365	226	1.5 (1.1–2.1)	1.5 (1.1–2.1)
Current/recent users at start of follow-up	6,626	44	1.7 (1.0–2.0)	1.7 (1.1–2.7)
Former users at start of follow-up	28,739	182	1.4 (1.0–2.0)	1.5 (1.0–2.1)
Age group 40–49 yrs				
Never-users	19,342	220	1.0 (reference)	1.0 (reference)
Ever-users	39,491	521	1.2 (1.0–1.4)	1.2 (1.0–1.4)
Current/recent users at start of follow-up	2,673	47	1.7 (1.2–2.3)	1.6 (1.2–2.3)
Former users at start of follow-up	36,818	474	1.2 (1.0–1.4)	1.2 (1.0–1.4)

[a] Multivariate analysis adjusted for: age (continuous variable), parity (0, 1, 2, 3+), age at first birth (−20, 21–24, 25+), age at menarche (continuous variable), use of HRT (ever/never), menopausal status (pre-/postmenopausal), history of breast cancer in first-degree relatives (yes/no), duration of breastfeeding (continuous variable), BMI (continuous variable), region (Sweden and five health regions in Norway), and a term for interaction between BMI and menopausal status.
[b] Menopausal status and the interaction term between BMI and menopausal status were not included in the multivariate model.

bined OCs entailed a similar 50–60% increased risk of breast cancer as compared with never use. For women aged 30–39 years at cohort enrollment, current/recent use of combined OCs significantly increased breast cancer risk 2-fold, whereas corresponding risk estimates for progestin-only pills had a wide CI. Among the age group 40–49 years at cohort enrollment, neither current/recent use of combined OCs (RR, 1.2; 95% CI, 0.7–1.9) nor current/recent use of progestin-only pill (RR, 1.6; 95% CI, 0.9–2.6) was associated with a significantly increased risk for breast cancer.

Discussion

Our prospective study, probably the largest thus far among premenopausal women, confirmed that the use of OCs is associated with an increased breast cancer risk and that this association is most pronounced among current/recent users. The 30% increased risk of breast cancer among ever-users of OCs was only explained to a small extent by current/recent use.

Recently, the Collaborative Group on Hormonal Factors in Breast Cancer (3) has pooled together data from almost all studies published until the mid-1990s on use of contraceptives and breast cancer risk. Results of this pooled analysis indicate that current/recent use of combined OCs increases breast cancer risk by 24%. They also indicate that current/recent use of OCs is probably the main contributor to the increase in breast cancer risk related to ever use of hormonal contraceptives. When the analysis was restricted to cohort studies, ever use of combined OCs increased breast cancer risk by only 7% (2). More recently, a cohort study from the Netherlands (12) showed RRs similar to ours among women aged ≤55 years, although not significantly different from unity.

Our finding of an increased risk of breast cancer even 15 years or more after cessation of OC use is not in accordance with the Collaborative Group on Hormonal Factors in Breast Cancer study, where no excess risk could be found 10 or more years after stopping OC use. The reason why we could not confirm this finding is not obvious.

This is the first prospective study of breast cancer risk designed to specifically study the use of progestin-only pills and combined OCs separately. Combined OCs and progestin-only pills prevent pregnancy through different mechanisms: combined OCs (containing both a synthetic estrogen and a progestin) inhibit ovulation and down-regulate the production of hormones by the ovaries, whereas progestin-only pills (consisting of solely a synthetic progestin) act mainly by altering cervical mucus (1). Progestin-only pills are mainly used in Scandinavia, the United Kingdom, and New Zealand (1), and they had less than 10% of the market of all OCs in Norway and Sweden at the time of our cohort recruitment. They have been prescribed mostly for women aged 35 years or more because the risk for thromboembolic diseases is lower than that with estrogen-progestin preparations.

Table 4 RRs and 95% CIs of developing breast cancer among ever-users of OCs, according to different pattern of use, The Women's Lifestyle and Health Study

Use of OCs	Study population	Breast cancer cases	RR (95% CI)	
			Age-adjusted	Multivariate[a]
Never-users	28,171	261	1.0 (reference)	1.00 (reference)
Time since last use (from start of follow-up; yrs)[b]				
<2	9,299	91	1.6 (1.2–2.2)	1.6 (1.2–2.3)
2–4	5,711	40	1.2 (0.8–1.7)	1.2 (0.8–1.8)
5–9	11,447	101	1.4 (1.0–1.8)	1.4 (1.0–1.8)
10–14	14,475	127	1.2 (1.0–1.5)	1.2 (1.0–1.6)
15+	29,267	348	1.2 (1.0–1.4)	1.3 (1.0–1.5)
P for linear trend within users			0.1	0.1
Time since first use (before start of follow-up; yrs)[b]				
<5	819	9	1.9 (1.0–3.6)	1.9 (1.0–3.9)
5–9	2,388	19	1.3 (0.8–2.2)	1.3 (0.8–2.1)
10–14	8,727	68	1.3 (1.0–1.8)	1.3 (1.0–1.8)
15–19	26,264	204	1.2 (1.0–1.4)	1.2 (1.0–1.5)
20–24	24,554	266	1.1 (0.9–1.3)	1.1 (0.9–1.3)
25+	11,414	173	1.2 (0.9–1.4)	1.2 (0.9–1.5)
P for linear trend within users			0.1	0.2
Age at first use (yrs)[b]				
<20	30,959	229	1.0 (0.8–1.3)	1.1 (0.8–1.4)
20–24	28,881	332	1.2 (1.0–1.5)	1.2 (1.0–1.5)
25–29	10,477	128	1.1 (0.9–1.4)	1.2 (0.9–1.5)
30+	3,849	50	1.2 (0.9–1.7)	1.3 (0.9–1.7)
P for linear trend within users			0.4	0.6
Duration of use before age 20 (months)[b]				
≤12	8,801	83	1.3 (1.0–1.7)	1.3 (1.0–1.7)
13–36	9,886	59	0.9 (0.6–1.2)	0.9 (0.6–1.2)
37+	3,342	19	1.0 (0.6–1.6)	1.0 (0.6–1.7)
P for linear trend within users before age 20			0.9	0.9
Duration of use before first full-term pregnancy (months)[b]				
≤12	8,165	87	1.4 (1.1–1.8)	1.4 (1.0–1.8)
13–60	17,140	157	1.3 (1.0–1.6)	1.2 (0.9–1.5)
61+	7,210	67	1.5 (1.1–2.0)	1.3 (0.9–1.9)
P for linear trend within users before first full-term pregnancy			0.7	0.8

[a] Multivariate analysis adjusted for: age (continuous variable), parity (0, 1, 2, 3+), age at first birth (−20, 21–24, 25+), age at menarche (continuous variable), use of HRT (ever/never), menopausal status (pre-/postmenopausal), history of breast cancer in first-degree relatives (yes/no), duration of breastfeeding (continuous variable), BMI (continuous variable), region (Sweden and five health regions in Norway), and a term for interaction between BMI and menopausal status.
[b] Adjusted for total duration of use.

The observation of an increased risk of breast cancer among women who were current/recent users of progestin-only pills as well as combined OCs is compatible with the "estrogen augmented by progesterone" theory. This theory implies that the combination of hormones induces more cell divisions than estrogen alone (23). Use of combined OCs increases levels of estrogen as well as progestogen, whereas progestin-only pills only increase levels of progestogen without influencing estrogen level. However, our estimates for breast cancer risk among progestin-only pill users are based on few cases and thus have limited statistical power.

Strengths of our study include its prospective design, large size, and complete follow-up. Our study was designed and carried out simultaneously in Norway and Sweden using largely identical protocols. Because cancer registration is compulsory in both countries, the assessments of cases are virtually complete. Although data on use of OCs and on all potential confounders were ascertained in great detail at cohort entry, some women have likely changed their use during the follow-up period. This would entail nondifferential misclassification, which attenuates the strength of any true association (24). Most women aged 40 years and over who were current/recent users of OCs at cohort entry will probably have ceased their contraception use during the follow-up, and this might have caused underestimation of the excess in risk for breast cancer.

An increased breast cancer risk among current users of OCs has been hypothesized to be due to increased medical surveillance (4). A surveillance bias could potentially arise if mammographic screening is related to the main factor of interest in the study, namely, OC use. There is indeed some evidence that women who are users of OCs may be more likely to attend mammographic screening (25). However, the overall attendance rate is high (in Sweden, it is close to 80%), and the absolute difference in attendance rate between users and nonusers of OCs is therefore likely limited, and so is the potential for surveillance bias. In Norway, surveillance bias is even less likely because during the period of follow-up, only 4 of 19 Norwegian counties offered mammographic screening and then only to women aged 50–69 years.

Information on stage of disease could potentially shed some light on this issue, notably if one could demonstrate that the association between OC use and breast cancer is confined to early-stage cancer. However, we were skeptical of using this information for two reasons. First, it would be available only in the Norwegian cohort. Second, stage of disease is not only crudely classified in the cancer register but also substantially misclassified in a nation-wide setting. It is, for example, well known that T stage depends strongly on the way tumor diameter is measured. Moreover, N stage depends completely on the surgical technique used for clearance of the axilla and on the

Table 5 RRs and 95% CIs of developing breast cancer according to exclusive use of progestin-only oral pills (POPs) or combined OCs (COCs), The Women's Lifestyle and Health Study

Use of OCs	Study population	Breast cancer cases	RR (95% CI)	
			Age-adjusted	Multivariate[a]
Never-users	28,171	261	1.0 (reference)	1.00 (reference)
Ever-users of				
POPs	3,435	29	1.1 (0.8–1.6)	1.1 (0.8–1.7)
COCs	42,811	444	1.3 (1.1–1.5)	1.3 (1.1–1.6)
Both POPs and COCs or missing values on brand	28,610	274	1.2 (1.0–1.4)	1.2 (1.0–1.4)
Current/recent users at start of follow-up				
POPs	2,189	25	1.6 (1.1–2.5)	1.6 (1.0–2.4)
COCs	6,691	60	1.6 (1.2–2.2)	1.5 (1.0–2.0)
Age-stratified analysis				
Current/recent users at start of follow-up				
Age at start of follow-up 30–39 yrs[b]				
Never-users	8,829	41	1.0 (reference)	1.0 (reference)
POPs	1,251	8	1.6 (0.8–3.4)	1.7 (0.8–3.7)
COCs	5,130	36	1.9 (1.2–3.1)	2.0 (1.2–3.2)
Age at start of follow-up 40–49 yrs				
Never-users	19,342	220	1.0 (reference)	1.0 (reference)
POPs	938	17	1.7 (1.0–2.8)	1.6 (0.9–2.6)
COCs	1,561	24	1.5 (1.0–2.3)	1.2 (0.7–1.9)

[a] Multivariate analysis, adjusted for: age (continuous variable), parity (0, 1, 2, 3+), age at first birth (−20, 21–24, 25+), age at menarche (continuous variable), use of HRT (ever/never), menopausal status (pre-/postmenopausal), history of breast cancer in first-degree relatives (yes/no), duration of breastfeeding (continuous variable), BMI (continuous variable), region (Sweden and five health regions in Norway), and a term for interaction between BMI and menopausal status.
[b] Exclusive use of progestin-only pills and exclusive use of combined OCs.
[c] Menopausal status and the interaction term between BMI and menopausal status were not included in the multivariate model.

extensiveness of the histopathological examination of the tissue specimen. These considerations led us to believe that we would have minimal possibility to clarify whether surveillance bias is a problem or not.

The response rates in our study are relatively low (55%). It is well accepted that the internal validity (the relationship between the exposure and the outcome) is not affected by the response rate (26). Without influencing risk estimates, a low response rate may preclude inference about exposure prevalence in the entire source population. However, in Norway, a methodological study indicates that use of OCs, smoking, and height were unrelated to response rates (27). The proportion of nulliparous women was slightly lower among the responders than among the general population.

Our study confirms previously published results indicating that current/recent use of OCs does increase breast cancer risk. Duration of OC use might also be of importance in the development of breast cancer. Additional studies are needed to elucidate whether progestin-only pills and combined OCs have different effects on breast cancer.

Contributions. M. Kumle and E. Weiderpass were responsible for data management in Norway and Sweden, respectively, and coordination of manuscript writing. T. Braaten performed the combined Norwegian-Swedish data management and performed the statistical analysis of the data. I. Persson participated in the planning of the study and in manuscript writing. E. Lund and H-O. Adami, principal investigators and initiators of the project in Norway and Sweden, respectively, participated in all phases of the study.

Acknowledgments

We thank all of the women who contributed to this study. We are grateful to Mikael Ustad and Jarle Mathiassen, who participated in the early phases of this study.

References

1. IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans, Volume 72. Lyon, France: WHO, IARC, 1999.

2. Collaborative Group on Hormonal Factors in Breast Cancer. 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. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet, *347:* 1713–1727, 1996.

3. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: further results. Contraception, *54:* 1S−106S, 1996.

4. Shapiro, S. Bias in the evaluation of low-magnitude associations: an empirical perspective. Am. J. Epidemiol., *151:* 939–945, 2000.

5. Hankinson, S. E., Colditz, G. A., Manson, J. E., Willett, W. C., Hunter, D. J., Stampfer, M. J., and Speizer, F. E. A prospective study of oral contraceptive use and risk of breast cancer (Nurses' Health Study. United States). Cancer Causes Control., *8:* 65–72, 1997.

6. Kay, C. R., and Hannaford, P. C. Breast cancer and the pill: a further report from the Royal College of General Practitioners' oral contraception study. Br. J. Cancer, *58:* 675–680, 1988.

7. Beral, V., Hermon, C., Kay, C., Hannaford, P., Darby, S., and Reeves, G. Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46,000 women from Royal College of General Practitioners' oral contraception study. Br. Med. J., *318:* 96–100, 1999.

8. Mills, P. K., Beeson, W. L., Phillips, R. L., and Fraser, G. E. Prospective study of exogenous hormone use and breast cancer in Seventh-day Adventists. Cancer (Phila.), *64:* 591–597, 1989.

9. Vessey, M. P., McPherson, K., Villard, M. L., and Yeates, D. Oral contraceptives and breast cancer: latest findings in a large cohort study. Br. J. Cancer, *59:* 613–617, 1989.

10. 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.

11. Tryggvadottir, L., Tulinius, H., and Gudmundsdottir, G. B. Oral contraceptive use at a young age and the risk of breast cancer: an Icelandic, population-based cohort study of the effect of birth year. Br. J. Cancer, *75:* 139–143, 1997.

12. Van Hoften, C., Burger, H., Peeters, P. H., Grobbee, D. E., van Noord, P. A., and Leufkens, H. G. Long-term oral contraceptive use increases breast cancer risk in women over 55 years of age: the DOM cohort. Int. J. Cancer, *87:* 591–594, 2000.

13. Romieu, I., Willett, W. C., Colditz, G. A., Stampfer, M. J., Rosner, B., Hennekens, C. H., and Speizer, F. E. Prospective study of oral contraceptive use

and risk of breast cancer in women. J. Natl. Cancer Inst. (Bethesda), *81:* 1313–1321, 1989.

14. Lipnick, R. J., Buring, J. E., Hennekens, C. H., Rosner, B., Willett, W., Bain, C., Stampfer, M. J., Colditz, G. A., Peto, R., and Speizer, F. E. Oral contraceptives and breast cancer. A prospective cohort study. J. Am. Med. Assoc., *255:* 58–61, 1986.

15. Oral contraceptive use and breast cancer risk in young women. UK National Case-Control Study Group. Lancet, *1:* 973–982, 1989.

16. Clavel, F., Andrieu, N., Gairard, B., Bremond, A., Piana, L., Lansac, J., Breart, G., Rumeau, R. C., Flamant, R., and Renaud, R. Oral contraceptives and breast cancer: a French case-control study. Int. J. Epidemiol., *20:* 32–38, 1991.

17. Skegg, D. C., Paul, C., Spears, G. F., and Williams, S. M. Progestogen-only oral contraceptives and risk of breast cancer in New Zealand. Cancer Causes Control, *7:* 513–519, 1996.

18. Lunde, A. S., Lundeborg, S., Lettenstrom, G. S., Thygesen, L., and Huebner, J. The person-number systems of Sweden, Norway, Denmark, and Israel. Vital. Health Stat., *2:* 1–59, 1980.

19. Lund, E. Pilot Study for the Evaluation of Completeness of Reporting to the Cancer Registry. Incidence of cancer in Norway, 1978, pp. 11–14. Oslo, Norway: The Cancer Registry of Norway, 1981.

20. Mattsson, B., and Wallgren, A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol. Oncol., *23:* 305–313, 1984.

21. Cox, D. R. Regression models and life-tables. J. R. Stat. Soc. Series B (Methodological), *34:* 187–220, 1972.

22. van den Brandt, P. A., Spiegelman, D., Yaun, S. S., Adami, H. O., Beeson, L., Folsom, A. R., Fraser, G., Goldbohm, R. A., Graham, S., Kushi, L., Marshall, J. R., Miller, A. B., Rohan, T., Smith-Warner, S. A., Speizer, F. E., Willett, W. C., Wolk, A., and Hunter, D. J. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am. J. Epidemiol., *152:* 514–527, 2000.

23. Pike, M. C., Spicer, D. V., Dahmoush, L., and Press, M. F. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol. Rev., *15:* 17–35, 1993.

24. Gerstman, B. B. Inaccuracy in epidemiologic studies, part II (bias). *In:* Epidemiology Kept Simple: An Introduction to Classic and Modern Epidemiology, pp. 183–200. New York: Wiley-Liss, 1998.

25. Lagerlund, M., Sparen, P., Thurfjell, E., Ekbom, A., and Lambe, M. Predictors of non-attendance in a population-based mammography screening programme; socio-demographic factors and aspects of health behaviour. Eur. J. Cancer Prev., *9:* 25–33, 2000.

26. Rothman, K., and Greenland, S. Modern Epidemiology. Philadelphia, PA: Lippincott-Raven, 1998.

27. Lund, E., and Gram, I. T. Response rate according to title and length of questionnaire. Scand. J. Soc. Med., *26:* 154–160, 1998.

Use of Oral Contraceptives and Breast Cancer Risk: The Norwegian-Swedish Women's Lifestyle and Health Cohort Study

Merethe Kumle, Elisabete Weiderpass, Tonje Braaten, et al.

Cancer Epidemiol Biomarkers Prev 2002;11:1375-1381.