Pergamon

European Journal of Cancer Vol. 30A, No. 3, pp. 351–354, 1994

0959-8049/94 $6.00+0.00

0959-8049(93)E0055-U

Oral Contraceptives and Prognosis in Breast Cancer: Effects of Duration, Latency, Recency, Age at First Use and Relation to Parity and Body Mass Index in Young Women With Breast Cancer

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The aim of this study was to examine associations between oral contraceptive (OC) use, body mass index (BMI = weight/height^2) and prognosis in invasive breast cancer diagnosed before the age of 45. Survival analyses of a consecutive sample of breast cancer patients were undertaken. The cases were initially registered in a nationwide case–control study of OC use and risk of premenopausal breast cancer in Sweden and Norway. All 422 cases were under 45 years of age at diagnosis, and recruited from the reports to cancer registries (Sweden) or from surgical departments (Norway) during May 1984 through May 1985. Detailed information about OC exposure was obtained in the initial face-to-face interview. With Cox's proportional hazards analyses, a significantly lower hazard rate [relative hazard (RH) = 0.54; 0.31–0.94] was seen in short-term users (<4 years)—but not in long-term (≥4 years) users—than in never-users of OC. Non-significant estimates for RHs lower than 1.0, i.e. better prognosis, with long recency (>5 years) and latency (≥10 years) of OC use were noted. Prognosis was not influenced by age at first OC use or of its timing in relation to the first pregnancy. A higher BMI was associated with a poorer prognosis, RH 5.9 (2.0–17.8) for BMI ≥ 29 versus BMI < 19, but BMI was not a confounder or an effect modifier of the association between OC use and prognosis. This study does not indicate that OC use prior to the diagnosis of breast cancer has any adverse effect on the prognosis, at least not in women under 45 years of age at diagnosis.
Eur J Cancer, Vol. 30A, No. 3, pp. 351–354, 1994

INTRODUCTION

ASSOCIATIONS BETWEEN oral contraceptive (OC) use and prognosis in breast cancer may shed light on possible hormonal effects on the initiated cancer, on disseminated cancer cells and on tumour–host relations. Moreover, unfavorable effects of OCs on the prognosis of breast cancer would further increase the concern caused by the possible increase in the incidence of the disease that may follow long-term use.

Research hitherto has not resolved the question of whether the use of OCs prior to the diagnosis of breast cancer affects the prognosis. Several studies report a beneficial influence [1–3] or no effect on survival [4–6], whereas others [7,8] report a negative effect of OC in patients diagnosed before the age of 35 years [7] or in those first given OC before the age of 20 years [8]. The possible impacts of duration of use, recency and latency on prognosis have been analysed in only one study [5].

We report analyses of breast cancer survival in women under 45 years of age at the time of diagnosis in a nationwide series of patients diagnosed in Sweden and Norway. The effects of duration of use, latency, recency, type of compound and use at an early age or before the time of the birth of the first child are reported after adjustment for a number of possible confounding factors.

MATERIALS AND METHODS

This analysis is based on the 422 cases collected in a joint case–control study in Sweden and Norway, undertaken to analyse the risk of development of breast cancer before the age of 45 in relation to the use of OCs. The design and the data collection procedure have been described in earlier papers [9,10].

Identification of cases

Sweden. Women who had histologically confirmed invasive breast cancer, newly diagnosed between May 1984 and May 1985, inclusive, were resident in Sweden on 1 January 1960, were less than 45 years of age at the time of diagnosis, and had no history of malignant disease, were identified by means of the

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Revised 14 Oct. 1993; accepted 29 Nov. 1993.

six regional cancer registers, which cover the whole of Sweden. All newly diagnosed cases of cancer are reported separately by a clinician and a pathologist to these registers. All women under 40 years of age at diagnosis and every second woman between 40 and 45 years of age were eligible for the study. Of the 359 eligible women, 317 (88.3%) were interviewed and included in the study.

Norway. In Norway, new cases of invasive breast cancer were identified with the assistance of all 71 departments of surgery in the country. The calender period of recruitment was May 1984 to April 1985, inclusive. Three months after the end of the accrual period, the Norwegian Cancer Register was searched and an additional 8 cases were identified. In Norway, only women under 40 years of age at the time of diagnosis were included, and residence in Norway on 1 January 1960 was not required, otherwise the criteria were the same as in Sweden. A total of 114 women were identified and 105 (92.1%) were interviewed.

Interviews

Specially trained professional female interviewers interviewed the patients in Sweden 3–12 months after diagnosis. In Norway, 10 specially trained health professionals interviewed the patients. The same questionnaire was used in Sweden and Norway. It included questions on the reproductive and contraceptive histories, social background and lifestyle factors. A calender was employed to help record the ages at menarche, cohabitation, marriage, divorce, childbirth, lactation, abortions; the contraceptive history was then recorded in relation to these life events. The interviewers used a looseleaf notebook with photographs of the different packages of OCs used in Sweden and Norway during 1964–1984, and they also had information on the dates when they were approved for marketing and when they were removed from the market.

Follow-up

Complete follow-up with regard to survival was achieved through July 1989 by means of record linkages. In Sweden, for every death reported, the copy of the transcript of the death certificate filed in the population register was inspected for verification of the date and the cause of death. In Norway, information on the cause of death was obtained from the National Cancer Register. Death from all causes was the end-point. In all cases where death from breast cancer was mentioned, it was the primary cause in the certificates.

Statistical analysis

Survival curves were constructed by the Kaplan–Meier method. The log-rank test was used to test differences between survival curves. The effects of the various explanatory variables on survival were studied by means of the Cox proportional hazards model. This model was used in both univariate and multivariate analyses. Continuous variables were analysed in both basic continuous form and categorised form. The Wald test was used to test the significance of individual parameters. Results are reported in the form of relative hazards (RH).

RESULTS

During the observation period, 63 women died in Sweden and 31 in Norway. According to the death certificate, all but two women died of breast cancer. Other characteristics are given by country in Table 1. Women under the age of 40 at diagnosis had lower 5-year survival rates—75.0% in Sweden and 68.9% in Norway—than did those aged 40–44 years (83.1%; Fig. 1). When Swedish patients younger than 40 years were used as a reference, a Cox proportional hazards analysis revealed a non-significantly higher RH of 1.3 (95% confidence interval 0.8–2.0) for women under the age of 40 years in Norway and a significantly lower hazard [RH = 0.6, 95% confidence interval (CI) 0.30–0.95] for the 40–44 year age group in Sweden. All subsequent Cox analyses were corrected for age and country of residence at diagnosis.

Table 1. Characteristics of patients by country

	Sweden		Norway	
	n	(%)	*n*	(%)
Total number of cases	317	(100)	105	(100)
Age at diagnosis (years)				
<35	67	(21.1)	26	(24.8)
35–39	129	(40.7)	79	(75.2)
40–49	121	(38.2)		
Number of deaths	63	(19.9)	31	(29.5)
Duration of OC use				
Never	60	(18.9)	36	(34.3)
≤3 years	110	(34.7)	46	(43.8)
4–7 years	64	(20.2)	16	(15.2)
≥8 years	83	(26.2)	7	(6.7)
Use before first child	118	(37.2)	25	(23.8)
Age at first use (years)				
<20	84	(26.5)	14	(13.3)
20–24	108	(34.1)	39	(37.1)
≥25	65	(20.5)	16	(15.2)
Nulliparous	44	(13.9)	15	(14.3)

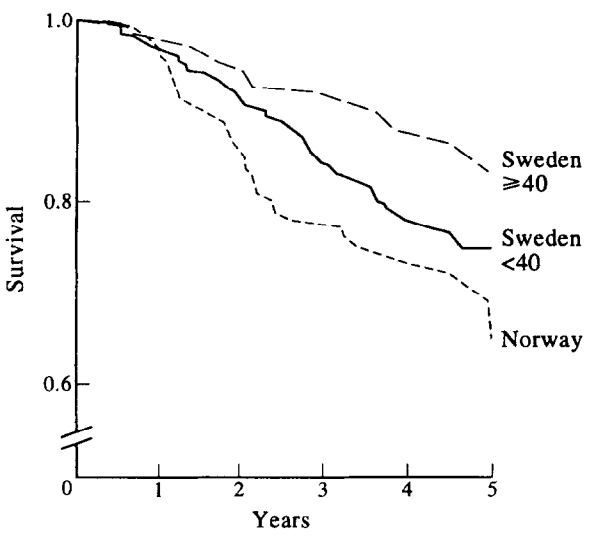

Fig. 1. Kaplan–Meier estimates of overall survival in Sweden and Norway and by age groups less than 40 and 40–45 years of age. In Norway, all women were less than 40 years of age.

Characteristics of OC exposure and prognosis

Figure 2 shows the Kaplan–Meier survival curves for the different categories of duration of OC use. Survival estimates (SE) at 5 years were 69.9% (6.0) for never-users, 83.7% (3.1) for users of OC for less than 4 years, 73.4% (6.3) for users of OC for 4–7 years, 68.6% (6.5) for those with 8–11 years' duration of use, and 74.4% (7.0) for users with a 12 or more years' duration. An overall log-rank test was statistically non-significant ($P = 0.13$).

Possible associations between characteristics of OC use and prognosis were further quantified with proportional hazard analyses (Table 2). The relative hazard was significantly lower among short-term users (less than 4 years) than among never-users of OC. Otherwise, the estimates were not statistically significant and close to unity. With increasing latency, recency and duration of use before the first full-term pregnancy, irregular patterns were seen without any apparent trends or significant differences, as compared to never-users. The point estimates for long periods of recency (>5 years) and latency (≥10 years) were generally below 1.0. No clear associations were seen between age at first use of OC and prognosis.

Other prognostic factors

Analyses with Cox models adjusted for age and country were performed for parity, age at first birth, level of education and body mass index [BMI = weight (kg)/height (m)^2, calculated on self-reported height and weight 18 months prior to diagnosis]. With the exception of BMI, no estimates were significantly different from unity (data not shown).

When BMI was analysed in categorised form (Table 3), the relative hazard increased with an increasing BMI, with a significantly higher hazard for women in the highest category, as compared to the lowest. For BMI analysed as a continuous variable, the increase in risk of death was 8% per unit increase in BMI (RH = 1.08, 1.03–1.14). When BMI was taken into account as a possible confounder in the main analyses of OC use and survival, the general pattern seen in Table 2 was not altered.

Table 2. Cox proportional hazards analysis model corrected for country and age

	n	RH	(95% CI)
Nulliparity	59	1.31	(0.83–2.09)
Duration (years)			
Never	96	1.0	(Ref)
1–3	156	0.54	(0.31–0.94)
4–7	80	1.20	(0.65–2.22)
8–11	51	1.31	(0.69–2.50)
≥12	39	1.14	(0.54–2.40)
Latency (years)			
Never	96	1.0	(Ref)
≤9	44	1.01	(0.52–1.98)
10–14	89	0.56	(0.30–1.06)
15–19	152	0.89	(0.53–1.50)
≥20	41	0.46	(0.15–1.35)
Recency (years)			
Never	96	1.0	(Ref)
Current	80	1.13	(0.63–2.03)
≤5	75	1.19	(0.64–2.21)
6–11	81	0.58	(0.30–1.11)
≥12	90	0.61	(0.32–1.15)
Use before first full term pregnancy (para only) (years)			
Never	81	1.0	(Ref)
After but not before	139	0.95	(0.55–1.67)
≤3	92	0.52	(0.26–1.05)
4–7	37	1.24	(0.58–2.63)
≥8	14	0.75	(0.22–2.58)
Age at first use			
Never	96	1.0	(Ref)
<20 years of age	98	0.67	(0.36–1.24)
20–24 years of age	147	0.84	(0.50–1.40)
≥25 years of age	81	0.73	(0.38–1.39)

DISCUSSION

Overall, the findings in this study are reassuring, since there is little evidence that breast cancer in women under 45 years of age diagnosed after OC use had a poorer prognosis than did breast cancers not associated with OC use. If anything, a lower relative hazard was seen in the patients with a short duration of OC use, and with long recency and latency periods. It is virtually impossible, however, to unravel these three time-dimensions reliably since they are so closely interrelated. We found no evidence of a worse prognosis if OCs were used before the birth of the first child or at a young age at first use.

The number of patients and deaths makes this study the

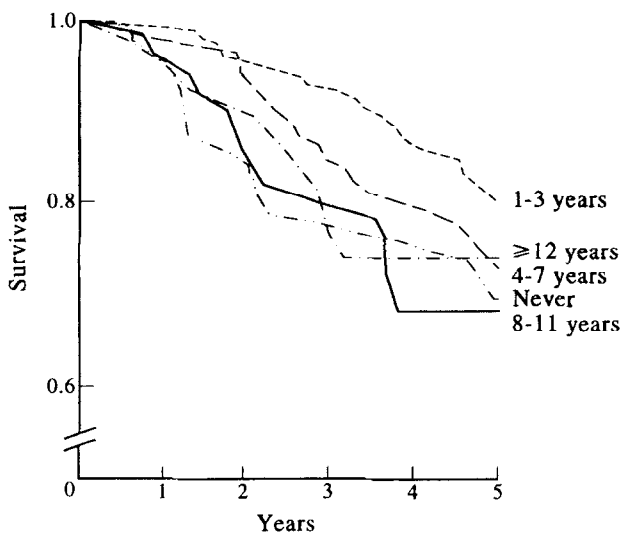

Fig. 2. Kaplan–Meier estimates of overall survival by total duration of use of oral contraceptives.

Table 3. Cox proportional hazard analysis for BMI as a determinant for survival

		Corrected for country and age	
BMI	*n*	RH	(95% CI)
<19	36	1.0	(Ref)
19–20	124	1.70	(0.65–4.43)
21–22	133	1.66	(0.64–4.30)
23–24	65	1.88	(0.67–5.24)
25–28	46	2.38	(0.84–6.77)
≥29	16	5.93	(1.98–17.8)

second largest that has addressed the possible association between the prognosis of breast cancer and OC use, and the largest which has analysed such hypotheses in more detail. The case series was population-based and follow-up was complete. However, the case series is restricted to patients under 45 years of age at diagnosis. The patients comprised 90.3% of all eligible incident cases in the two defined populations, which makes it less likely that the pattern of non-participation could have influenced the results. The relationship between age and prognosis found by us is in accordance with population-based studies in both countries [11, 12].

Theoretically, a bias could be introduced if women with OC use were more carefully followed and diagnosed at an earlier stage. However, a diagnostic bias is most likely to exist for current users and if anything recency was inversely related to prognosis in our analysis. We had no information on stage at diagnosis. Strong suspicion of a diagnostic bias would be the only reason to control for stage in the analysis. Since this is not at hand, stage should rather be viewed as an intervening variable of biological interest, and an adjustment would then not be justified.

Six other studies [1–6] have not confirmed that prior OC use adversely influences the prognosis after breast cancer is diagnosed. Indeed, three [1–3] suggested that the prognosis was even better in women given OCs. However, these trends should be interpreted cautiously, because of a possible diagnostic bias (more careful follow-up in the exposed group, resulting in earlier diagnosis) [2] and a small sample size [1, 3].

Two studies [7, 8] claiming an adverse effect on the prognosis of breast cancer after OC use give an ambiguous picture. Statistically significant effects were seen only in subgroups. In one report [7], the subgroup showing an unfavorable prognosis was characterised by young age at the time of diagnosis, but in the second report [8], the subgroup were those with first use before age 20. The present study was better able to detect any harmful effects of the kind reported in these studies, but did not do so.

The relationship between increasing BMI and lower survival confirms earlier findings in relation to weight [13–17] or BMI [17–20]. Two studies found a relationship between high weight and the risk of recurrence, but no clear relationship between BMI and survival [21, 22]. Our findings, however, are inconsistent with the negative results of three other studies [23–25]. The mechanisms responsible for a possible negative influence on the prognosis of overweight remain unclear, but the sum of evidence showing a negative effect on prognosis—even when the analyses were corrected for the stage of the disease [13–16, 18–21]—points to the importance of further investigations.

In summary, this study does not support the hypothesis that OC use prior to the diagnosis of breast cancer has any adverse effect on prognosis.

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