Pergamon

European Journal of Cancer, Vol. 34, No. 9, pp. 1348–1351, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(98)00139-7

Original Paper

The Effect of Oral Contraceptive Use on the Prognosis of Node Positive Breast Cancer Patients

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The effect of oral contraceptive (OC) use as a risk factor for breast cancer was recently assessed in a large meta-analysis, but currently available data on the prognostic effect are still insufficient. We investigated the relationship between OC use and standard prognostic factors and the effect of OC use on recurrence-free survival (RFS) and overall survival (OS) in 422 premenopausal pT1a-3aN + M0 patients from two trials of the German Breast Cancer Study Group (GBSG). 137 patients (32.5%) were OC users. They were younger on average (mean age 41.5 years versus 45 years for non-OC users) and the percentage of patients with smaller tumours was higher in the group of OC users. Based on 163 events for RFS and 103 events for OS, no significant effect of OC use on RFS and OS could be demonstrated in univariate and multivariate analyses. In our study of node positive breast cancer cases, OC users were younger and had smaller tumours. This may be an effect of earlier detection of breast cancer, but OC users did not have a better prognosis, both before and after adjustment for tumour size and other prognostic factors. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: node positive breast cancer, oral contraceptive use, prognosis, survival
Eur J Cancer, Vol. 34, No. 9, pp. 1348–1351, 1998

INTRODUCTION

RECENTLY THE Collaborative Group on Hormonal Factors in Breast Cancer published a meta-analysis on the relationship between breast cancer risk and the use of oral hormonal contraceptives (OC) [1, 2]. They re-analysed the individual data on more than 50 000 women with breast cancer and approximately 100 000 women without breast cancer from 54 studies. Apart from their main emphasis on risk assessment of OC, they also investigated tumour spread and provided some evidence that breast cancer diagnosed in OC users is less advanced clinically than in never users. However, this analysis was based on simple criteria for tumour spread (localised to breast, spread to lymph nodes only or distant metastases) in a subpopulation of their study. No data on the prognostic effect of OC use on recurrence-free survival (RFS) and overall survival (OS) time were available.

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Received 26 Aug. 1997; revised 3 Feb. 1998; accepted 24 Mar. 1998.

In the literature, there are several studies investigating the prognostic effect of OC use. Most are based on rather small and heterogeneous patient populations [3–7]. An assessment of the prognostic effect of OC use is only possible in an extremely homogeneous study or by means of a multivariate analysis, where the relevant factors influencing simultaneously the prognosis of the patients are adjusted for. This, however, requires a sufficiently large study population and that the relevant factors are known. Three studies have been published which are based on a larger patient population (between 300 and 500 patients) investigating the effect of OC use adjusted for the basic prognostic factors in breast cancer. They showed inconsistent results. The study by Rosner and Lane [8] reported neither an effect of OC use on the extent of the disease nor on prognosis. The study by Vessey and colleagues [9] reported a better prognosis for patients having taken OC within the last year before breast cancer diagnosis, which may be due to an early detection bias, since these patients had less advanced tumours. After adjusting the

analysis for clinical stage, the beneficial effect disappeared. The study by Schönborn and associates [10] showed a positive effect of OC use on survival, especially for long-term and current users, even after adjustment for important prognostic factors. Schönborn and associates [11] investigated, in the same patient population, the question of whether patients having taken OC present at diagnosis with less advanced tumours or with tumours of different histological type, grade of malignancy and immunohistochemical factors. They found no differences between OC users and non-users in this respect.

In 1984, the German Breast Cancer Study Group (GBSG) started two trials to investigate several adjuvant treatment regimens for patients with node positive breast cancer. In both trials, a comprehensive cohort study design, allowing the inclusion of randomised patients and patients with a preference for one of the treatments under investigation, was applied [12]. All patients had a mastectomy and chemotherapy (either three or six cycles cyclophosphamide, methotrexate and fluorouracil (CMF)); subgroups received additionally either radiotherapy or hormonal treatment with tamoxifen. The use of OCs with the corresponding time span was documented and detailed information on the standard prognostic factors and follow-up of patients was available in these clinical trials. We investigated the relationship of OC use and standard prognostic factors, as well as the potential prognostic effect of OC use in a multivariate survival model adjusting for the other prognostic variables.

As most of the postmenopausal patients in the GBSG studies were at least in their late thirties when the pill became popular, the percentage of OC users in this group was very low. Therefore, we restricted the analysis in this paper to premenopausal patients. Thus, possible effects caused by hormonal changes because of the menopause, as well as natural mortality in older patients, cannot influence the results.

PATIENTS AND METHODS

In both GBSG trials the principal inclusion criterion was a histologically proven primary breast cancer of stage T1a–3a N+ M0. None of the particular exclusion criteria are considered associated with OC use. Primary local treatment was a modified radical mastectomy (Patey) with en bloc axillary dissection with at least six identifiable lymph nodes. In one trial, a 2×2 factorial design was used to compare three versus six cycles of CMF and to investigate the additional effect of 2 years of hormonal therapy with tamoxifen. In December 1986, the protocol was modified with premenopausal patients receiving only chemotherapy. Further details about the study and the results of the randomised part based on approximately 5 years' median follow-up have been previously reported [13]. In the other trial with identical inclusion and exclusion criteria, all patients received six cycles of CMF and the additional effect of radiotherapy was investigated. Both trials used a comprehensive cohort study design where patients were preferably randomised, but were also included into the trial if they chose one of the treatments. Details and results of these two trials have been previously published [12].

In total, 1,048 patients, of whom 434 were premenopausal, entered the two trials, 269 (63.7%) women have been randomised. In this analysis, we included 422 premenopausal patients where information on OC use was available. 137 (32.5%) of them had taken the pill. Details of the duration, start and end of OC use are given in Table 1.

Table 1. Timing of oral contraceptive (OC) use of patients ever using OC (n = 137)

Characteristic of OC use	Number of patients
Age at first use (years)	
< 20	12
20–30	56
30–35	29
> 35	29
Unknown	11
Duration of use (years)	
< 1	17
1–4	19
4–10	40
> 10	50
Unknown	11
Time between first use and breast cancer (years)	
< 5	25
5–15	48
> 15	53
Unknown	11
Time between last use and breast cancer	
< 4 months (current users)	65
4 months–10 years	40
> 10 years	26
Unknown	6

Table 2. Relationship between oral contraceptive (OC) use and standard prognostic factors

	OC use ($n = 422$)	
Factor	Yes ($n = 137$)	No ($n = 285$)
Age at breast cancer diagnosis (years)		
≤ 40	60 (44)	51 (18)
41–45	29 (21)	82 (29)
> 45	48 (35)	152 (53)
Tumour size (mm)		
≤ 20	41 (31)	81 (29)
21–30	68 (51)	100 (35)
> 30	25 (18)	102 (36)
Unknown	3	2
No. positive lymph nodes		
≤ 3	83 (61)	166 (58)
4–9	36 (26)	80 (28)
≥ 10	17 (13)	38 (14)
Unknown	1	1
Tumour grade		
1	16 (12)	30 (11)
2	82 (60)	173 (61)
3	37 (27)	81 (28)
Unknown	2	1
Oestrogen receptor (ER) (fmol)		
< 20	66 (50)	124 (45)
≥ 20	67 (50)	151 (55)
Unknown	4	10
Progesterone receptor (PR) (fmol)		
< 20	56 (42)	101 (37)
≥ 20	77 (58)	173 (63)
Unknown	4	11
Tumour location		
Lateral	78 (57)	172 (60)
Medial	59 (43)	113 (40)

Categorisations were chosen based on the meta-analysis of risk factors [1, 2].

The patients received the following adjuvant treatments: 192 patients six cycles CMF, 30 patients six cycles CMF and tamoxifen, 55 patients six cycles CMF and radiotherapy, 117 patients three cycles CMF and 28 patients three cycles CMF and tamoxifen. For the description of prognostic factors we used categorisations which were defined in earlier analyses [12, 13] and which are often used in the literature. RFS was defined as the time from mastectomy to the first occurrence of either locoregional recurrence, distant metastases, contralateral tumour, secondary tumour, or death; OS was defined as the time from mastectomy to death. After a median follow-up time of approximately 5 years, 163 events for RFS and 103 events for OS were observed. RFS and OS rates were estimated by the Kaplan–Meier product limit method [14]. The differences between survival curves were tested by the log-rank test [14] using a significance level of 0.05. The effects of prognostic factors in univariate and multivariate analyses were estimated in terms of relative risks, i.e. hazard ratios, using Cox's proportional hazards regression model [14], which was stratified for treatment.

RESULTS

OC users were younger on average (range 21–53 mean 41.5 years) as compared with never users (range 27–60 mean 45.0 years). Table 2 shows that 44% of the women in the first group were younger than 40 years in comparison with only 18% in the latter group. Furthermore, the percentage of women with a tumour size larger than 30 mm was

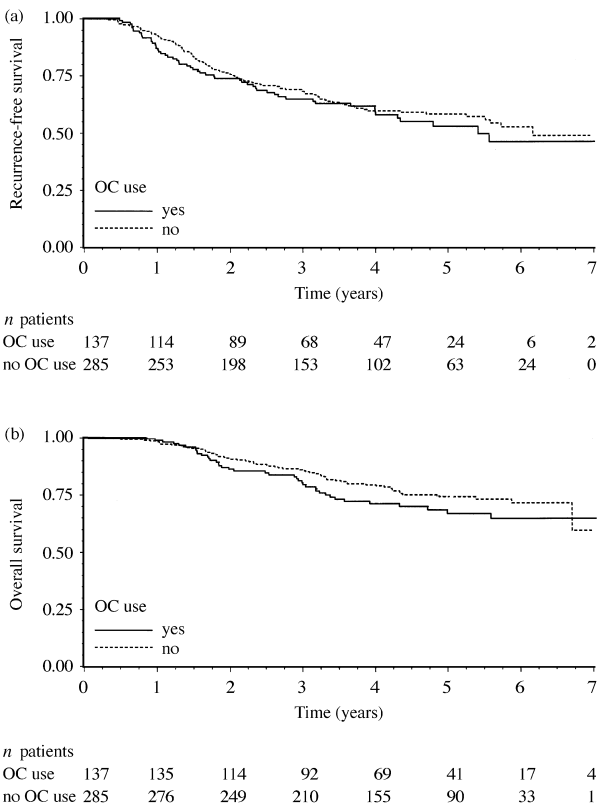

Figure 1. Kaplan–Meier estimates of recurrence-free (a) and overall (b) survival according to oral contraceptive use.

Table 3. *Prognostic models for recurrence-free and overall survival time including all standard factors listed and oral contraceptive (OC) use, stratified by treatment (*n = 402 *patients)*

	Recurrence-free survival			Overall survival		
Factor	RR	(95% CI)	*P* value	RR	(95% CI)	*P* value
OC use						
No	1	–	0.90	1	–	0.27
Yes	1.02	(0.71–1.47)		1.28	(0.82–1.98)	
Age (years)						
≤ 40	1	–	0.007	1	–	0.23
41–45	0.71	(0.46–1.09)		0.92	(0.55–1.55)	
> 45	0.54	(0.36–0.79)		0.67	(0.40–1.10)	
Tumour size (mm)						
≤ 20	1	–	0.55	1	–	0.78
21–30	1.14	(0.74–1.76)		0.93	(0.55–1.58)	
> 30	1.29	(0.82–2.03)		1.10	(0.63–1.92)	
Positive lymph nodes						
≤ 3	1	–	0.001	1	–	0.001
4–9	2.54	(1.73–3.71)		2.48	(1.51–4.05)	
≥ 10	3.39	(2.18–5.28)		4.03	(2.37–6.85)	
Tumour grade						
1	1	–	0.18	1	–	0.13
2	2.05	(0.93–4.53)		5.96	(0.81–43.92)	
3	1.83	(0.78–4.29)		7.34	(0.97–55.72)	
Oestrogen receptor (fmol)						
< 20	1	–	0.51	1	–	0.040
≥ 20	0.88	(0.60–1.29)		0.58	(0.35–0.98)	
Progesterone receptor (fmol)						
< 20	1	–	0.009	1	–	0.003
≥ 20	0.60	(0.41–0.88)		0.47	(0.28–0.77)	
Tumour location						
Lateral	1	–	0.82	1	–	0.65
Medial	0.96	(0.70–1.34)		1.10	(0.73–1.66)	

RR, relative risk; CI, confidence interval.

substantially lower for OC users (18% compared with 36%). The distributions of all other factors considered were comparable in the two groups (Table 2). This was confirmed by a multivariate logistic regression model (data not shown).

In univariate analysis, OC users had slightly lower RFS and OS rates (Figure 1). The RFS rates were 65% (95% confidence interval 57–73%) after 3 years and 53% (43–63%) after 5 years for OC users. For never users, the corresponding figures were 69% (63–74%) and 58% (52–64%), respectively. For OS, the rates for OC users were 80% (73–87%) after 3 years and 67% (58–76%) after 5 years. Never users had higher rates with 86% (82–90%) and 75% (69–81%). For both survival criteria the differences were not significant. The corresponding relative risks of OC use versus never use, as estimated by univariate Cox models, were 1.15 (95% confidence interval 0.83–1.60) for RFS and 1.35 (0.90–2.02) for OS, respectively. A comparison of the small subgroup of current users ($n = 65$) versus past users ($n = 66$) (together 52 (RFS), 36 (OS) events) exhibited a slightly but non-significant increased risk for the past users (1.26 (0.72–2.22) for RFS and 1.32 (0.67–2.60) for OS).

The results of multivariate analyses adjusted for the other prognostic factors given in Table 2 and furthermore stratified by treatment are displayed in Table 3. After adjustment, the relative risk estimates decreased to 1.02 for RFS and 1.28 for OS. The multivariate results were based on 402 premenopausal patients with complete data (157 events for RFS and 100 events for OS). The important prognostic factors for RFS were age, number of positive lymph nodes and progesterone receptor. The risk of patients older than 45 years was approximately halved in comparison with patients younger than 40 years. An even stronger effect was seen for the number of positive lymph nodes. For OS, the number of positive nodes, progesterone and oestrogen receptor status exhibited strong effects; age showed a similar trend as for RFS, but the effect was weaker and not significant. For both survival criteria, the subgroup of patients with a grade I tumour had a better prognosis than grade 2 and 3, for which the survival rates were similar. However, because the group of grade 1 tumours was small (11%), this effect was not significant.

DISCUSSION

In the data from two prospective trials of the GBSG for node positive breast cancer, we investigated the association between OC use and standard prognostic factors in premenopausal patients. In our study, OC users were several years younger on average; the percentage of patients with a large tumour was substantially reduced in comparison with women who have never used OC. Both findings may be seen as a possible effect of early detection because of more regular visits of OC users to a doctor. This may have resulted in an earlier diagnosis of breast cancer.

This obvious explanation, which should theoretically have resulted in longer RFS and OS times, was not supported by patients' survival data. In univariate analyses, estimates for both survival criteria demonstrated slightly, but not significantly, increased risk of OC users for recurrence or death. For RFS, this effect disappeared completely in multivariate analysis (relative risk 1.02), for OS, the relative risk of OC users remained still slightly (relative risk 1.28), but not significantly increased. As discussed in the literature, there is some evidence that young age is associated with a poor prognosis and generally the results from our multivariate analysis agree with the current discussion about the importance of standard prognostic factors.

Although data on duration of OC use, age at first use, time since first use to breast cancer and time since last use to breast cancer diagnosis were available, we decided to postpone a more detailed analysis, because we considered the number of events too small at the moment. With longer follow-up, more information will be available from our trials, but additional studies are necessary to provide definitive evidence on the role of OC use as a prognostic factor in breast cancer.

Two [8, 9] of the three larger studies [8–10] described in the Introduction showed, in accordance with our study, no effect of OC use, whereas the study by Schönborn and colleagues [10] found a positive effect of OC use on survival time. These three studies all include node negative and node positive patients. Because nodal status is known as the dominant prognostic factor in breast cancer, also determining choice of treatment, studies should be analysed separately by using this criterion. In this respect, our study provides the largest, homogeneous population to investigate the important and controversial issue of the prognostic effect of OC use in breast cancer patients.

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Acknowledgements—The study was sponsored by the Ministry of Research and Technology (BMFT) of the Federal Republic of Germany.