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ORAL CONTRACEPTIVES AND RISK OF BREAST CANCER IN WOMEN AGED 20-54 YEARS

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Section: Articles Summary
Although the use of oral contraceptives (OCs) is not generally associated with increased risk of breast cancer, higher risks have been reported for some subgroups of users. We have carried out a population-based case-control study in the Netherlands to assess the effect of timing and duration of OC use on the risk of breast cancer developing at various ages. 918 women with breast cancer (20-54years at diagnosis) were pair-matched by age with controls randomly selected from municipal registries. Information on OC use obtained from women and their prescribers was combined according to standard decision rules.

Overall, long-term use of OCs (>/-12 years) had an associated relative risk (RR) of 1.3 (95% CI 0.9-1.9; test for trend in risk with months of use p = 0.03). This positive trend was found in both the youngest (< 36 years; p = O. 08) and the oldest (46-54years, p = 0.004) age groups, but not in women aged 36-45 years. The RR of developing breast cancer before age 36 was 2.1 (1.0-4.5) for 4 or more years of OC use compared with shorter use. In women younger than 36, risk increased for longer OC use before age 20 (1-44per year, p = 0.04). Recent use (previous 3 years) was associated with increased risk in women of 46-54 (RR 1.9 [0.9-4.1], p=0.02).

We conclude that 4 or more years of OC use, especially if partly before age 20, is associated with an increased risk of breast cancer developing at an early age. There is limited evidence that the excess risk disappears as the cohort of young OC users ages, but this issue needs confirmation. ***Lancet*** 1994; 344:844-51

Introduction

Since the introduction of oral contraceptives (OCs) about 30 years ago, more than 50 studies have investigated the relation between OC use and the risk of breast cancer. The results have been inconsistent.[1.2] Although the use of OCs (ever vs never) appears generally not to be associated with breast cancer risk, increased risk has been reported for certain subgroups of women. Some studies suggest that long-duration OC use is related to increased breast cancer risk,[3] whereas others have suggested that the timing of OC use in a woman's life is critical to OC-related risk.[46] Results from the UK National Case-Control Study,[7] reanalyses of two older studies,[8, 9] and four meta-analyses [1, 10-12] led to the hypothesis that long-term OC use may specifically increase the risk of breast cancer developing at an early age. If the increased risk in young women is real, is it attributable to long-term

OC use per se or to long-term OC use at an early age? Even more importantly, is the excess risk in young women transient or likely to extend to older age groups in the future? These issues can only be resolved by continuing to monitor the first cohort of young OC users.

We carried out a case-control study of OC use and breast cancer risk in the Netherlands, where the proportion of women using OCs-has been among the highest world wide.[13] A unique feature of our study is that we were able to examine the effect of long durations of OC use on the risk of breast cancer developing at different ages up to age 55. Misclassification bias was kept to a minimum by combining OC information from women and prescribers according to standard decision rules.

Subjects and methods Case and control selection

All patients had invasive breast cancer diagnosed between Oct 1, 1986, and June 1, 1989, and lived in the areas covered by the population-based Regional Cancer Registries of the Comprehensive Cancer Centres Amsterdam, Eindhoven, East, and West. The population living in these areas constitutes 43% of the Dutch female population and is served by 60 hospitals. Patients were eligible if they were younger than 45 (younger than 55 in the areas covered by the Eindhoven and eastern centres), were Dutch speaking, did not have a previous breast cancer diagnosis, were not living in a home for psychiatric patients, and had been living in the Netherlands on Jan 1, 1963, when OCs were introduced in the country. The date of the first positive biopsy sample result was taken as the date of diagnosis. Patients were identified through the cancer registry. Registration clerks supplied the medical records of eligible patients with an explanatory letter, in which women were asked to join a study of life-style risk factors in relation to breast cancer risk. Patients received this letter, and a reply form, from their treating specialists. Those who chose not to take part were not asked to return the reply form, since the local ethics committees did not approve of collecting information from non-participants.

During the intake period, breast cancer was diagnosed in 1544 patients in the relevant age categories. Reply forms were received from 978 (63 %) women. However, 21 women subsequently refused to continue because they were too ill, 2 women died, and 4 women could not be traced. Overall, 951 women were interviewed. Of these, 33 women could not be matched with a suitable control. Thus, 918 (59%) patients were left for analysis. Response rates varied from 45% to 68% among the four study areas. After correction for eligibility criteria, the overall response rate of the cases was 60%. The mean time between diagnosis and interview was 10 months (SD 7.3), and 79% of the patients were interviewed within 1 year of diagnosis.

In the Netherlands, the population is fully covered by municipal population registries. Controls were randomly selected from these registries, with the same exclusion criteria as for the patient sample. Each breast cancer patient was matched with one control for age (within 1 year) and area. We wrote an explanatory letter to selected controls. If a control did not return the reply form she was reinvited by telephone. If she refused to take part in the home interview she was asked to agree to a short telephone interview (3 min).

1276 eligible controls had to be approached to identify 1 control for each of the 918 breast cancer patients. 9 women had moved to unknown addresses and 349 women did not return the reply form; of the latter, 165 agreed to the short interview by telephone, 55 refused, and the remaining 129 could not be contacted by phone. Thus, 918 (72%) control women were recruited to the study.

Data collection

Both the case and her matched control were interviewed at home by the same trained female interviewer. We did not attempt to keep interviewers unaware of case-control status, because most women referred to their illness early in the 1.5 h interview. The interviewer used a structured questionnaire and two memory aids--a calendar on which all major life events were indicated and a book with photographs of packages and strips of the 62 OC preparations that have been marketed in the Netherlands. For each preparation the period of marketing was indicated.

During the interview, information was collected on possible confounding factors. For each OC preparation mentioned, specific brand names and starting and stopping dates were sought. Women were asked for the names of all doctors who had prescribed OCs to them and all health-care facilities attended for OC prescriptions. Each woman was asked to give written permission for us to collect information on the use of OCs and other hormonal preparations from her (former) prescribers and to collect clinical information (tumour characteristics and primary therapy) on breast cancer from the cancer registry. 9 patients and 6 controls did not grant permission. Women who said they had

never used OCs were asked for permission to check this was true with their current general practitioner.

All prescribers were sent an explanatory letter about the purpose of the study. The woman's permission form was enclosed, and a standard form that requested the prescriber to give specific brand names and starting and stopping dates of all hormone preparations used by the woman. Prescribers who did not respond initially were followed up with one or two telephone contacts. 100% of prescribers responded, but we received information that was usable according to the decision rules for only 72% of women who had taken OCs. By combining information from women and prescribers, we could reduce the number of unknown brands from 9% to 0.1% of all OC preparations mentioned.

The cancer registries supplied data on tumour characteristics of all women eligible for our study according to age and date of diagnosis. Stage was classified according to postsurgical turnout node metastasis (TNM) score.[14] If postsurgical TNM was unknown or not applicable, clinical TNM was used.

Combination of two sources of OC information

OC information from the woman and her prescribers was combined according to strictly formulated and pre-tested decision rules. Important factors in determining the most likely actual life-time OC use for each woman were: the woman's certainty about dates of OC use, important life events near starting and stopping dates of specific brands, and the specific brand names mentioned by the prescriber.[15] If the duration of use of a specific brand was not given by woman or prescriber, a duration of 3 months was assumed. Decisions were made by four trained research assistants (PB, MH, CW, NO; see Study Group members), and difficult cases were discussed with us. If necessary, we verified whether the prescriber had given information on the right woman. For 100 women whose OC information did not agree with that given by their prescribers, the decision rules were applied by two research assistants. They arrived independently at exactly the same most probable OC history for 84 of the 100 women.

Statistical methods

Each control was assigned a date of pseudo-diagnosis--the date on which she was the same age as her matched case was at diagnosis. The analysis was restricted to events that had occurred in the period before (pseudo) diagnosis. Mutivariate logistic regression methods for individually matched case-control studies were used for the estimation of relative risks (RRs),[16] All our analyses were planned beforehand, except for explanatory analyses relating to brand-specific use in subgroups found to be at increased risk.

If a value was missing for either the case or the control of a pair, both women of the pair were arbitrarily assigned the value of the reference category. Thus, this pair did not contribute to the risk estimation of the variable concerned. Tests for trends were calculated by fitting actual months of use as a continuous variable in the logistic model. All statistical tests were two-sided.

In assessing the breast cancer/OC relation, we looked at the following possible confounders: marital status, education, nulliparity, number of children, age at first pregnancy lasting longer than 28 weeks (full-term), breastfeeding, age at menarche, menopausal status, age at menopause, biopsy for benign breast disease, family history of breast cancer, frequency of alcohol use during the year preceding (pseudo)diagnosis, body-mass index, smoking behaviour, and use of injectable contraceptives. In the Netherlands, injectable contraceptives have been used by a highly selected group of women (very young age at first full-term pregnancy, medical indication for psychosocial reasons). Since OC use may reduce the risk of certain types of benign breast disease, we included only biopsies for benign breast diseases taken before the earliest age of starting OC use within a case-control pair. [17] A woman was regarded as postmenopausal if her last menstruation was longer than 6 months ago. An artificial menopause was defined as a bilateral oophorectomy. Menopausal status was taken as unknown and treated as missing if the uterus had been removed (with or without one ovary) when the woman was premenopausal; if the woman was older than 40 and currently using OCs; or if the woman had stopped OC use less than 6 months before (pseudo)diagnosis and still did not menstruate. Stepwise confounder selection was based on a more than 5% change in the risk estimate of the exposure variable of interest (ie, duration of OC use) for the study population overall and for the age group under 36 years, since breast cancer at a very young age may be aetiologically different from that at older ages.

Analyses were done on OC use according to the women and according to the combined information from women and prescribers. The results were fairly similar, although generally the RR was somewhat lower when based on the combined information. We chose to present the results based on the combined information, because these data

were judged to be more plausible and less subject to misclassification bias.

Brands were classified according to their oestrogen content (>/=50 mug vs < 50 mug) and according to progestagen type. The classification of the progestagens into seven groups was based on their molecular structure and their metabolic pathway--norethisterone (acetate); norethynodrel, ethynodiol diacetate; norgestrel, levonorgestrel; lynoestrenol; desogestrel; megestrol acetate, medroxyprogesterone acetate, and chlormadinone acetate; and cyproterone acetate.

Results

The mean age of both cases and controls was 42 years; since the cases and controls were matched for age the distributions were identical (132 [14.4%] </= 35,219 [23.8%] 36-40, 320 [34.9%] 41-45, 247 [26.9%] 46-54). 31-8% of pairs were from the Amsterdam region, 27.2% from Eindhoven region, 28.8% from the east, and 12.2% from the west. Characteristics of the 918 cases and their matched controls are given in table 1. The adjusted RR was high for nulliparous women, though the test for a trend in the number of children was not significant (p=0.20 for unadjusted, 0-88 for adjusted RR). The RRs were significantly increased for women with a late age at first full-term pregnancy with a significant trend (p=0.01, 0'008, respectively). RRs were also significantly raised for women with a low education, a previous biopsy for benign breast disease, or a positive family history of breast cancer. Only women who were certain about their age at menarche were found to be protected by a late age at menarche (RR 1.0, 0.7, 0.8 for ages 12 years, 13 years, and >/=14 years, respectively, with </= 11 years as the reference category). Subsequently, analyses for the whole cohort and for the age groups 36-45 and 46-54 were adjusted for number of children, age at first full-term pregnancy, a family history of breast cancer, education, body-mass index, and ever use of injectable contraceptives. The factors used to adjust the RR in women of 35 or less were weeks of breastfeeding, age at first full-term pregnancy, age at menarche, family history of breast cancer, education, and body-mass index.

85 % of the study sample had ever used OCs. Overall, the use of OCs (ever vs never) was not associated with risk of breast cancer (RR=1.1 [95% CI 0.8-1.4]). The mean duration of OC use was 7.1 (SE 0.2) years for the cases and 6.6 (0.2) years for the controls. Based on information from the women only, the RRs were 1.0, 1.1, 1.1, and 1.3 for less than 4 years, 4-7 years, 8-11 years, and 12 years or more of OC use (never use=reference category; test for trend p = 0-03). Based on the combined information from women and prescribers, the RRs and trend with months of use were similar (table 2). In both data sets, the 95% CI for the RR estimates for the highest categories of OC use (>/= 12 years of use) still included 1-0. All other results are based on the combined information.

For women aged 36-45 or 46-54 years at diagnosis, there was no association between OC use (ever vs never) and risk of breast cancer. Since there were only 4 cases and 4 controls under age 36 who had never used OCs, the association with ever use could not be assessed in this age group; the effect of OC duration was calculated with 0-4 years' OC use as the reference category (table 2). In this age group, the use of OCs for 4 or more years, compared with shorter-term use, was associated with double the risk of breast cancer before age 36 (RR = 2.1 [95% CI 1-0-4.5]). The trend for duration of use almost achieved significance (p = 0.08). No trend was found for the age groups 36-40 and 41-45 years. For the oldest age group (46-54years at diagnosis), a highly significant trend for duration of OC use was found (p = 0.004). Women who had used OCs for 12 or more years had an RR of 2.3 (1.1-4.7). No RRs associated with shorter duration of use were increased.

The association between OC use and breast cancer risk did not differ between parous and nulliparous women (RR per year of use 1.01 vs 1.02). For parous women, use before age at first full-term pregnancy was not positively associated with breast cancer risk after adjustment for age at first birth. No differences in risk patterns were found according to age at diagnosis.

McPherson and colleagues[18] suggested that OCs might exert their effect only after a latent period. To study whether the timing of OC use is important to the risk of breast cancer, we did analyses with OC use subdivided into that before and after various cut-off times before diagnosis (3, 6, 9,and 12 years, table 3). Contrary to the latency hypothesis, the strongest associations with the risk of breast cancer were found for OC use within the 3 years before diagnosis (RR 1.12 per year of use, p = 0.04). The increase in risk with recent use was most pronounced in the oldest age group. The RR at ages 46-54 was 1.9 (0.9-4.1) for OC use within the past 3 years, whereas the same duration of use (>4 years) before the 3-year cut-off was not associated with an increased risk. In young women (under 36), however, the findings were more in accordance with the latency hypothesis. 4 or more years' OC use before a 9-year cut-off was associated with an RR of 3.3 (1.1-9.6), whereas no increased risks were found for the

same durations within the past 9 years.

As expected, women in the youngest age group had started using OCs at an earlier age than women in older age groups (table 4). In all age groups combined, the increasing trend in RR per year of OC use was slightly stronger for use before age 20 than for use after that age (RRs 1.18 and 1.02, respectively, test of difference between trends p = 0.09). However, age-specific analyses showed that the increased risk associated with OC use before age 20 could be fully attributed to an effect in the youngest age group (trend in risk per year of OC use before and after age 20 RRs 1.44 and 1.04; test of difference between trends p=0.08). The increased risk for use before age 20 could not be explained by having other than contraceptive reasons for starting OC use (data not shown).

Table 5 gives RRs for combined OCs classified according to their oestrogen content. Rather than for high-dose OCs, an increased risk was found for long-duration use of low-dose pills (RRs for >/=8 years use vs never use 1.1 [0.8-1.4] and 3.0 [1.5-6.1], respectively; difference between trends p = 0.03). No RRs for shorter durations of use of low-dose pills were increased. Detailed analyses showed that the risk increase associated with long-duration use of low-dose pills could not be attributed to one specific age group.

When OCs were classified according to their progestogen type, increased risks were found for pills containing norethisterone (acetate) (> 4 years of use vs never use RR 2.0 [1.0-4.1], trend p = 0.08, based on 310/208 woman-years in cases/controls) or desogestrel (ever vs never use RR 1.7 [1.1-2.5], trend p=0.04, 159/95 woman-years in cases/ controls). Norethisterone (acetate) has mainly been used in combination with high oestrogen doses, whereas desogestrel has been used with low-dose ethinyl oestradiol only. The other progestogen groups showed no association with breast cancer risk, and no age-specific differences emerged.

Each specific combination of progestogen and oestrogen type and dose was investigated in relation to breast cancer risk, with adjustment for the total duration of use of all other brands (table 6). Pills with 50 mug ethinyl oestradiol and various doses of lynoestrenol, levonorgestrel, and norgestrel showed no stronger trend for higher progestogen doses. The trend for duration of use of the progestogen-only pill (Exluton, 0.5 mg lynoestrenol, 87.9/40.9 woman-years in cases/controls) was positive, though not significant (RR 1.16 per year of use, p=0.12). Age-specific analyses were not possible because of small numbers.

A specific brand (class) may be associated with an increased risk simply because it was used mainly by subgroups of OC users found to be at increased risk. However, there was too little use of low-dose pills before age 20 in our data-set to explain the association between low-dose pills and breast cancer risk. In addition, the increased risk associated with recent use in older women (46-54years) was of equal magnitude for low-dose and high-dose pills (RR per year of use within past 6 years 1.60 and 1.67, respectively), whereas the stronger trend for use of low-dose pills compared with high-dose pills persisted in women under age 46 (RR per year of use 1-06 vs 0.99, test for difference between trends p =0.05). Thus, the association between low-oestrogen-dose pills and breast cancer risk could not be explained by early use in the youngest age group or by recent use in the oldest age group.

We also examined the effect of pills with low and high oestrogen doses, adjusting for use of OCs that contained the progestagens associated with increased risk (norethisterone [acetate] and desogestrel). The difference between trends for use of low-dose and high-dose pills remained essentially the same (RR per year of use 1.05 vs 1.00, test between trends p = 0.05).

When designing this study, we made every attempt to incorporate the quantitative assessment of biases that may occur in epidemiological case-control studies of this kind.[19] First, misclassification bias was assessed on the basis of OC information from prescribers. Based on OC information from the physicians only (433 matched pairs), adjusted RRs were 1.1 (0.7-1.6), 1.1 (0.7-1.6), 1.8 (1.1-3.2), and 1.7 (0.9-2.4) for less than 4 years, 4-7 years, 8.11 years, and 12 or more years of OC use, respectively, compared with never use of OCs (RR per year of use, 1.04, p = 0.01). Thus, RRs were slightly higher than when OC use was based on the combined information (table 2).

We assessed the extent of differential misclassification bias by examining whether the difference in duration of OC use as reported by the women and their prescribers was equal for cases and controls. For this analysis we took into account only the duration of OC use that occurred within the period for which prescriber information was available for that woman (69 % of life-time O C use; cut-off dates were first and last dates mentioned by prescribers). Compared with the information from prescribers, controls tended to under-report and cases to over-report their OC use. The

mean difference was - 3.9 (SE 1.1) months for the cases and -5.0 (1.0) months for the controls (negative sign resulting from definition of period of analysis). Thus, with the prescriber information taken as a reference, cases reported 1.1 months longer OC use than controls. Thus, the extent of differential misclassification was small, only 2% of mean life-time duration of OC use. For the combined OC information on which our analyses are based, the extent of the differential misclassification was even smaller (0.6 months or 0.7% of mean OC use).

Selection bias could be addressed quantitatively on the basis of two non-response studies and additional information on turnout characteristics from the cancer registries. The non-response study among controls (a short telephone interview with 165 women) showed no differences between responding and non-responding controls as regards known risk factors for breast cancer. However, the non-responding controls were less well educated and fewer had used OCs (70 vs 85% of responding controls). Thus, as compared with the general population, women with low education may have been under-represented (table 1) and OC use may have been over-represented among our participating controls. These features could have led to a downward bias of the RRs for OC use. In the non-response study we did not elicit information on the duration of OC use, since the information from a short telephone interview would not have been comparable with the extensive OC history obtained during the home interview.

Obviously, patients could only consider participation in the study if they had been made aware of it by their treating physicians. Privacy regulations precluded the distinction between non-response by the patients themselves and non-response by the physicians. We were able to interview a very small sample of non-responding patients (40) extensively because they received adjuvant radiation therapy in our institution. Only 2 said they had been told about the study in the hospital where they underwent surgery. This finding, plus circumstantial evidence available to us from specialists and the regional cancer registries, strongly suggests that non-response of patients was due to lack of cooperation from the doctors rather than from the women themselves. Among the small group of non-responding patients whom we interviewed, slightly more women than the participating group had ever used OCs (95 vs 91%) and the duration of OC use was longer (7.5 vs 7.1 years).

A higher proportion of non-participating than of participating cases had had high-stage disease at diagnosis (stage IIIb or IV 19 vs 11%, table 7). This finding suggests that severe illness may well have been the reason for non-response. Furthermore, among participating cases, more of those who had ever used OCs than of never users had small rumours at diagnosis (stage I 36 vs 27%), which indicates possible detection bias. However, a lower stage was not related to a longer duration of OC use or to recent OC use (table 7). The same was true for tumour size. These findings suggest that substantial effects of detection or other types of selection bias on the OC duration-response relations are unlikely.

The more favourable stage at diagnosis for OC users compared with never users suggests that OC users may survive longer. Since the time from diagnosis to interview was a mean of 10 months, we examined whether survival bias had affected our results. Based on all cases interviewed within 9 months of diagnosis (513), adjusted RRs were no different from the findings in the whole cohort (1.0, 0.9, 1.2, and 1.4 for < 4 years, 4-7 years, 8-11 years, and >/= 12 years of OC use; test for trend p = 0.11). Thus, survival bias is not a likely explanation for our positive findings.

Discussion

Our findings strongly suggest that long-term OC use is related to the risk of breast cancer and that the association varies by age at cancer diagnosis. Among young women (< 36 at diagnosis), the use of OCs for 4 or more years was associated with double the risk found with shorter use. No duration-response relation was found in women 36-45 years of age, but long-term OC use (>/= 12 years) was also associated with double the risk of breast cancer (related to never use) at age 46-54.

Differential misclassification bias was only 0.6 months in the combined OC data (0.7% of the mean duration of OC use). This value is similar to estimates in the UK National Case-Control Study[7] and the East German part of the WHO study[10] (1% and 0.6 month, respectively). This bias alone would create a spurious RR of 1.04 (0.73-1.48) for 12 or more years' OC use. Thus, we can conclude that the influence of differential misclassification was negligible in our study.

Only 60% of eligible cases and 72% of eligible controls took part in this population-based study. The non-response study among controls showed that, compared with responders, fewer non-responding controls had used OCs, as was found in two other studies.[3, 7] This control selection may have resulted in an underestimation of the

association between OC use and breast cancer risk.

Since the response of cases was especially low (45%) in the area covered by the western cancer registry, we recalculated adjusted RRs after exclusion of this area. These findings were very similar to those based on the total sample. Various sources showed that most non-participating cases had not been introduced to the study by their doctors. Selective case sampling is less likely if all patients of a (small) subgroup of doctors do not participate, because the doctor does not respond, than if the same number of patients, distributed equally over the practices of all doctors in the study area, themselves refuse to take part in a study, especially in the Netherlands, where the patient populations treated by various specialists have similar socioeconomic distributions. Our small non-response study among cases showed that, compared with responders from the same region, non-responders were more likely to have ever used OCs, and for slightly longer. Moreover, since the timing and duration of OC use were unrelated to stage within the group of participating cases, we conclude that selection bias is an unlikely explanation for our positive findings.

We took into account all known and several suspected risk factors of breast cancer as potential confounders of the relation between OCs and breast cancer. Adjustment for these confounders generally resulted in slight increases of the estimated RRs. Thus, the positive association we found cannot be explained by measurement errors of these confounders. Still, it is possible that we missed an unknown but important confounding or selective factor, which is related to both duration of OC use and breast cancer risk. The results should be interpreted with this restriction in mind.

Reviews and meta-analyses[1, 2, 10-12] suggest that long-term OC use may increase the risk of breast cancer in premenopausal or young women. Our findings for women under age 36 at diagnosis strongly support this hypothesis. Pike et al[21] suggested that OC use during breast development might affect the risk of breast cancer. However, duration of OC use before first full-term pregnancy, or before age 25, or young age at first exposure has not consistently been found to be related to breast cancer risk.[1, 2, 11] It is possible however, that the indicators of early exposure used were too crude to investigate the hypothesis. Only two studies[7, 22] examined the actual duration of OC use during teenage years in relation to the risk of breast cancer in very young women. Both studies reported a slightly greater risk for early age at use of OCs. Other studies have found that use of OCs for more than 6 years before age 25, which implies at least some teenage years of use, is related to increased breast cancer risk in young women.[3, 5] These results support our findings that very early OC use it, creases breast cancer risk in young women.

The question remains whether increased risk associated with early long-term OC use is confined to young women, or whether it will persist at older ages. Our findings are reassuring so far in that we found no effect of OC duration, latency, or use before age 20 in our 36-40-year age group. The transient nature of the risk increase is supported by the findings of other studies[8, 9] that included women older than 45. However, the percentage of women with substantial OC use before age 20 strongly declines with age, so the power to examine an effect of long-term OC use before age 20 for women older than 35 is low (>/=2 years OC use before age 20, 14%, 3%, < 1% for ages <36, 36-40, and 41-45, respectively). Continuous monitoring of the first cohort of young OC users will remain very important in future studies.

We found evidence of increased breast cancer risk after recent OC use in our total sample (table 3). This association could not be explained by detection or survival bias. The effect of recent OC use was most pronounced in our oldest age group (46-54years). Increased risk associated with recent OC use by women older than 45 years has not been found consistently, however.[6, 23, 24] OC use through the perimenopausal period may increase hormone concentrations above what they would have been during natural perimenopause, when anovular cycles are common.

Associations between breast cancer risk and specific brands of OCs should be interpreted cautiously because of the strong cohort effect in brands used. Unexpectedly, we found that breast cancer risk was higher with low-oestrogen-dose pills than with high-dose pills. The risk increase associated with the low-dose pills could be explained neither by patterns of use associated with increased risk nor by the progestogen in the combination. Other studies have found no effect of oestrogen dose[23, 25, 26] or, if anything, a slightly stronger effect of high-dose pills.[7, 27]Thus, before any conclusion can be drawn, this finding should be confirmed by others, and a plausible biological mechanism put forward. One possible mechanism is the incomplete suppression of ovarian activity in some women taking low-dose pills.[28]

The effects of different progestagens on human breast tissue are not clear and no proper classification is available. We classified progestagens according to their molecular structure and metabolic pathway. We found that longer use of pills containing norethisterone (acetate) or desogestrel was associated with higher risk. These findings should be interpreted cautiously, since seven progestogen groups were compared and we had no a-priori hypothesis. However, 50 mug ethinyl oestradiol formulations with the highest dose of norethisterone acetate were associated with the highest risk in both the WHO and the UK National Case-Control studies.[7, 27] A similar result was reported in one other study,[23] and in another the three brands with the highest RRs all contained norethisterone (acetate). [25] Norethisterone acetate, ethynodiol acetate, norethynodrel, and lynoestrenol are all ultimately converted to norethisterone. Thus, there is no ready explanation for a potentially differential effect of these progestagens, although the biological availability may be larger if fewer activation steps are necessary. It is clearly too early to draw conclusions about a possible increase in breast cancer risk due to the use of norethisterone-(acetate)-containing or desogestrel-containing preparations.

In conclusion, our findings accord with the mass of evidence that OC use by women in the middle of their fertile years (25-39years) has no adverse effect on breast cancer risk.[29] However, our results strongly suggest that OC use during both the early and late fertile years is associated with an increased risk of breast cancer. The risk associated with recent use in older women deserves more attention in future studies, since even a small increase in risk will be important in this age group with a high incidence of breast cancer. We attributed the increased risk in women under age 36 to OC use of several years duration before age 20, but data on this issue are too sparse for definitive conclusions to be drawn. There is, so far, limited evidence that the increased risk due to very early OC use diminishes as women age. However, the effects of OC use during adolescence should be monitored in future epidemiological studies to verify our findings, to investigate whether use of low-oestrogen-dose pills before age 20 is also associated with increased risk, and to provide further evidence that the increased risk in women aged under 36 at diagnosis is indeed transient. If the risk is confined to women under age 36, 4 or more years of OC use might explain, at most, 1 of the 2 breast cancers that will develop in a cohort of 1000 healthy Dutch women before age 36.

Advice to women about OC use should be based on both positive and negative health effects. Vessey's risk-benefit analysis[29] showed that, even if long-term OC use increases breast cancer risk up to age 35, mortality of OC users and non-users is still virtually the same. However, if the increased breast cancer risk that we found to be associated with recent use in older women, and the use of low-dose pills in general, is confirmed in future studies, a reassessment of this position will be necessary.

Netherlands Oral Contraceptives and Breast Cancer Study Group

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Table 1: **Characteristics of cases and controls**

Characteristic	No(%) Cases	Controls	RR Unadjusted	Adjusted[a]
Marital status				
Single	118 (12.8)	100 (109)	1	1
Married/ cohabiting	800 (87.1)	818 (89.1)	0.8	10
Education				
Low	458 (49.9)	419 (45.6)	1	1
Medium	334 (36.4)	378 (41.2)	0.8[b]	0.7[d]
High	126 (13.7)	121 (13.2)	1.0	0.7[b]
Parous[d]				
Yes	759 (82.7)	801 (87.3)	1	1
No	159 (17.3)	117 (12.7)	15[c]	16[c]
No of children[f]				
1	124 (13.5)	123 (13.4)	1	1
2	431 (46.9)	445 (48.5)	0.9	1.1
3	156 (17.0)	174 (19.0)	0.8	1.1
>/=4	48 (5.2)	59 (6.4)	0.8	1.2
Age of first full-term pregnancy (years)				
</=21	115 (12.5)	152 (16.6)	11	
22-24	224 (24.4)	250 (27.2)	1. 2	1.2
25-26	179 (19.5)	176 (19.2)	1.4[b]	1.4
27-29	151 (16.4)	142 (15.5)	1.4[b]	1.6[b]
>/-30	90 (98)	81 (8.8)	1.5[b]	1.7[b]
Breastfeeding (weeks)[f]				
0	221 (24.1)	145 (15.8)	1	1
1-6	218 (23.8)	186 (20.3)	1.2	1.3
7-24	184 (20.0)	216 (23.5)	0.9	0.9
>24	178 (19.4)	212 (23.1)	0.9	1.0
Age at menarche (years)[f]				
</=11	160 (17.4)	153 (16.7)	1	1
12	229 (249)	191 (20.8)	1.1	1.1
13	249 (27.1)	283 (30.8)	0.8	0.8
>/=14	280 (30.5)	291 (31.7)	0.9	0.9

Menopausal status						
Pre/ perimenopausal	676	(73.6)	677	(73.7)	1	1
Postmenopausal	87	(9.5)	82	(8.9)	1.0	1.0
Artificial	14	(1.5)	14	(1.5)	0.8	1.0
Unknown	141	(15.4)	145	(15.8)	--	--
Age at menopause (years)[g]						
</=45	47	(5.1)	50	(5.4)	1	1
>46	54	(5.9)	46	(5.0)	1.5	1.5
Biopsy for benign breast disease						
Never	797	(86.8)	853	(92.9)	1[d]	1[d]
Ever	121	(13.2)	65	(7.1)	2.1[d]	2.0[d]
Family history of breast cancer						
No	600	(65.4)	703	(766)	1	1
First degree	19	(13.0)	57	(6.2)	23[d]	2.4[d]
Second degree	199	(21.7)	158	(17.2)	1.5[c]	1.6[d]
Alcohol consumption (glasses/ week)[f]						
0	247	(26.9)	247	(26.9)	1	1
1-3	205	(22.3)	224	(24.4)	0.9	0.9
4-9	213	(23.3)	221	(24-1)	1.0	1.0
>10	253	(27.6)	226	(24.6)	1.1	1.2
Body-mass Index (kg/m^2)[f]						
</=20	115	(12.5]	112	(12.2)	1	1
21-25	533	(58.1)	539	(58.7)	10	1.0
26-30	211	(23.0)	217	(23.6)	1.0	1.0
>30	59	(6.4)	50	(5.4)	1.2	1.2
Smoking						
Ever	630	(68.6)	596	(64.9)	1	1
Never	288	(31.4)	322	(36.1)	1.2	1.1

a All variables listed fitted simultaneously, as well as use of oral and injectable contraceptives; effect of menopausal status was fitted by replacing age at menopause.

b p< 005, c p<0.01 d p<0001.

e Estimated without taking ether parity-specific variables into account.

f Trend test not significant.

g Excluding pre/perimenopausal and unknown status.

Table 2: **Adjusted RR for breast cancer development at specific ages by duration of OC use**

Information is presented in the following order: duration of OC use (years); all women, RR (95% CI); all women, no of cases/controls; </=35 years, RR; </=35 years no of cases/controls; 36-45 years, RR; 36-45, no of cases/controls; 46-54 years, RR; 46-54 years, no of cases/controls.

Never; 1; 134/136; }1; 1; 54/62; 1; 76/70

<4; 1.0 (0.7-1.4); 245/269; }1; 24/34; 1.4; 158/147; 0.7; 67/92

- 4-7; 1.1 (0.8-1.5); 241/243; 2.0; 47/51; 1.3; 154/150; 0.8; 40/42
- 8-11; 1.1 (0.8-1.6); 162/162; 1.7; 41/39; 1.2; 98/101; 1.1; 23/22

>/=12; 1.3 (0.9-1.9); 136/108; 2.9; 20/8; 1.1; 75/79; 2-3[b]; 41/21

RR per year of use (p for trend)[*]; 1.02 (p=0.03); ; 1.08 (p=0.08); 1.00 (p=0.72); ; 1.06 (p=0.004)

a Actual months of use in analysis for RR. b $p < 0.05$.

Table 3: **Adjusted RR[*] for breast cancer by duration of OC use according to use before or after various cut-off points before diagnosis**

Information is presented in the following order: no heading; all women, cut-off 3 years before diagnosis, before cut-off; all women, cut-off 3 years before diagnosis, after cut-off; cut-off 9 years before diagnosis, before cut-off; cut-off 9 years before diagnosis, after cut-off; women </=35 years, cut-off 3 years before diagnosis, before cut-off; women </=35 years, cut-off 3 years before diagnosis, after cut-off; women </=35 years, cut-off 9 years before diagnosis, before cut-off; women </=35 years, cut-off 9 years before diagnosis, after cut-off; women 46-54 years, cut-off 3 years before diagnosis, before cut-off; women 46-54 years, cut-off 3 years before diagnosis, after cut-off; women 46-54 years, cut-off 9-years before diagnosis, women 46-54 years, cut-off 9-years before diagnosis, after cut-off.

OC use (years)

Never; 1; 1; 1; 1; --; --; --; --; 1; 1; 1; 1

0-1; --; --; --; --; 1; 1; 1; 1; --; --; --; --

<4; 1.0; 1.3; 1.0; 1.0; 1.7; 1.3; 2.8[b]; 0.5; 0.7; 1.9; 0.8; 1.1

- 4-7; 1.1; --; 1.1; 1.3; 3.7; --; 3.3[b]; 1.2; 0.8; --; 0.9; 1.3
- 8-11; 1.0; --; 1.1; 1.4; 2.0; --; --; 1.0; 0.9; --; 1.2; 4.3[c]

>/=12; 1.2; --; 0.8; --; --; --; --; --; 1.7; --; 1.5; --

RR per year of use (p for trend)[a]; 1.01; 1.12; 1.01; 1.03; 1.09; 1.05; 1.19; 1.; 04; 1.03; 1.63; 1.03; 1.11

; (0.43); (0.04); (0.45); (0.06); (0.14); (0.71); (0.06); (0.46); (0.24); (0.02); (0.25); (0.02)

a Categorised variables in analysis for both periods simultaneously, b $p < 0.05$, c $p < 0.01$.

Table 4: **RR[a] for breast cancer development at specific ages according to timing of OC use before and after age 20**

Information is presented in the following order: all women, RR; all women, no of cases/controls; </=35 years, RR; </=35 years no of cases/controls; 36-40 years, RR; 36-40, no of cases/controls; 41-45 years, RR; 41-45 years, no of cases/controls.

Use before age 20

Never; 1; 773/793; 144/65; 1176/178; 1306/304

Ever; 1.3; 145/123; 3.5[c]; 88/67; 1.0; 43/40; 0-9; 14/16

RR per year of use (p for trend)[b]

Before age 20; 1.18 (p=0.06); ; 1.44 (p=0.04); ; 0.99 (p=0.95); ; 0.70 (p=0.24)

After age 20; 1.02 (p=0.10); ; 1.04 (p=044); ; 1.00 (p=0.98); ; 0.99 (p=0.71)

a RRs adjusted for actual months of use in the complementary period as well as adjustment factors used in all analyses (see text). b Actual months of use. [c] p < 0 01.

Table 5: **RR for breast cancer development by duration of use of combined OCs, according to oestrogen dose**

	RR[a]	No of cases/ controls	Woman-years of use controls)	RR per year of use (p for trend)[b]
Use of nestrogen >\=50 mu g (years)				
Never	1	243/246	3528/3521	
<4	1.0	296/298	3528/3521	
4-7	1.1	236/228	3528/3521	1.00 (p=0.64)
8-11	1.0	94/100	3528/3521	
>/=12	1.2	49/46	3528/3521	
Use of estrogen <50 mu g (years)				
Never	1	618/6471	38/865	
<4	1.1	182/180	38/865	
4-7	1.2	86/7911	38/865	1.06 (p=0.007)
8-11	2.9[c]	27/9	38/865	
>/= 12	2.9[c]	5/3	38/865	

a Adjusted for use of sequential preparations and progestagen-only pills as well as other factors used in all analyses. Categorised variables used in analysis simultaneously. b Actual months of OC use in analysis. c p < 0.01.

Table 6: **RR for breast cancer development by hormone content of OCs**

Information is presented in the following order: brand[a]; oestrogen (mu g); progestagen (mg); RR per year of use[b]; woman years of use (cases/controls); p.

Mestranol

Lyndiol; 5; 150; Lynoestrenol (5.0); 1.11; 101/77; 0.21

Lyndiol; 75; Norethynodrel (2.5); 1.00; 709/736; 0.99

Ethinylloestradiol

Lyndiol 2.5 EE; 50; Lynoestrenol (2.5); 103; 479/458; 0.36

Ovanon EE; 50[c]; Lynoestrenol (1.36)[c]; 105; 95/83; 0.47

Ovostat EE and Pregnon; 50; Lynoestrenol (1.0); 0.96; 149/196; 0.38

Gynovlar; 50; Norethisterone acetate (3.0); 1.1; 690/36; 0.07

Neogynon 21 and 28; 50; Levonorgestrel (0.25); 1.00; 420/453; 0.91

Microgynon 50 + Neo-Stediril; 50; Levonorgestrel (0.125); 1.05; 332/264; 0.25

Eugynon 21 and 28 + Stediril; 50; Norgestrel (0.5); 0.95; 284/366; 0.15

Stediril-d; 50; Norgestrel (0.25); 1.00; 634/635; 0.99

Ministat+Minipregnon; 37.5; Lynestrenol (0.75); 1.03; 187/157; 0.58

Trigynon + Trinordiol; 32[c]; Levonorgestrel (0.09)[c]; 0.99; 178/157; 0.83

Microgynon 30; 30; Levonorgestrel (0.15); 105; 421/320; 0.11

Stediril-d 150/30; 30; Norgestrel (0.15); 1.03; 292/248; 0.45

Marvelon; 30; Desogestrel (0.15); 1.15; 158/94; 0.05

a Only brands with at least 90 women-years of use in cases or controls are listed.

b factual months of use and adjusted for total duration of use of all other brands as well as other factors used in all analyses.

c Diphasic or triphasic; mean daily dose is given.

Table 7: **Post-surgical TNM stage distribution of non-participating and participating cases by duration of OC use**

Information is presented in the following order: PTNM stage[a]; no (%) of non-participating cases (n = 626); no (%) of participating cases (n = 918), total; no (%) of participating cases (n = 918), duration of OC use, never; no (%) of participating cases (n = 918), duration of OC use, <8 years; no (%) of participating cases (n = 918), duration of OC use, >/=8 years; no (%) of participating cases (n = 918), latest OC use, Past[b]; no (%) of participating cases (n = 918), current.

I; 166 (29.0); 296 (34.4); 34 (26.8); 162 (35.6); 100 (35.8); 123 (34.6); 139 (36.8)

II; 276 (48.3); 444 (51.6); 66 (52.0); 233 (51.2); 145 (52.0); 183 (51.4); 195 (51.6)

IIIa; 24 (4.2); 25 (2.9); 7 (5.5); 13 (2.9); 5 (1.8); 9 (2.5); 9 (2.4)

IIIb; 72 (12.6); 80 (9.3); 16 (12.6); 38 (8.4); 26 (9.3); 34 (9.6); 30 (7.9)

IV; 34 (5.9); 16 (1.9); 4 (3.1); 9 (2.0); 3 (1.1); 7 (1.9); 5 (1.3)

Missing; 54; 57; 7; 31; 19; 30; 20

a If post-surgical TNM was unknown, clinical TNM stage was used.

b Stopped more than 6 months before diagnosis.

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