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The Risk of Breast Tumours and Lifetime History of Oral Contraceptive Use

Das Risiko von Mammatumoren und die Lebensgeschichte der Nutzung oraler Kontrazeptiva

Zusammenfassung

Hintergrund: Bisherige epidemiologische Studien haben in inkonsistenter Weise leicht erhöhte oder erniedrigte Brustkrebsrisiken bei Nutzern – von meist hochdosierten – oralen Kontrazeptiva (OC) gezeigt. Für benigne Mammatumoren zeigten die meisten früheren Studien erniedrigte Risiken. Wenig ist bekannt über den Effekt einer ausschließlichen Nutzung von niedrigdosierten OCs.

Methodik: Die Deutsche Kohortenstudie zur Frauengesundheit ist eine laufende Studie einer Freiwilligenkohorte, die die zurückliegende Zeit betrachtend, das lebenslange Tumorrisiko analysiert. Es wurden selbstberichtete Informationen von Frauen erfasst, die sich auf Teilnahmeaufrufe in den deutschen Bundesländern gemeldet haben. Die erfassten Daten umfassen Informationen zu Exposition und Zeitangaben, zur Art und Dosis der Exposition als zum Zeitpunkt des Auftretens von Ereignissen. Die ersten Kohortendaten bis 2000 wurden mittels logistischer Regression analysiert, um den Zusammenhang zwischen der lebenslangen OC-Nutzung und dem Auftreten von Mammatumoren zu untersuchen.

Ergebnisse: Die Kohortenstudie umfasst zum Zeitpunkt der Analyse 610 328 Frauen-Beobachtungsjahre (seit Geburt) bei 15 374 Teilnehmerinnen. 308 Fälle von Brustkrebs und 1309 Fälle benignen Mammatumoren wurden beobachtet. Das adjustierte relative

Abstract

Background: Previous epidemiological studies have inconsistently shown an increased or decreased risk of breast cancer in users of – mainly high estrogen dose – oral contraceptives (OCs). A reduced risk of benign breast tumours was associated to OC use in most of earlier studies. Little is known about the effects of exclusive use of low estrogen dose OCs.

Methods: The German Cohort Study on Women's Health is an ongoing study analysing the lifetime risk of tumours going back in time in a cohort of volunteers. Self-reported data were collected from women who responded to a call for participation circulated in all German states. The data include information on exposure and time, type and dose of exposure as well as time of occurrence of any outcome. Initial cohort data until 2000 were analysed using logistic regression to determine the association between lifetime OC use and the occurrence of tumours of the breast.

Results: The cohort currently covers 610 328 women years of observation since birth on 15 374 participants. 308 cases of breast cancer and 1309 cases of benign breast tumours were observed. The adjusted relative risk [RR] for the occurrence of breast cancer comparing users and never-users of OCs was 0.6 (95% confidence interval [95% CI]: 0.5 to 0.8). The comparison only of ever-users of low estrogen OCs versus never-users shows an adjusted RR of

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ve Risiko [RR] des Auftretens von Brustkrebs beim Vergleich von Nutzerinnen mit Niemalsnutzerinnen von OCs war 0,6 (95%-Konfidenzintervall [95%-CI]: 0,5 zu 0,8). Der Vergleich von ausschließlicher Nutzung niedrigdosierter OCs mit Niemalsnutzung erbrachte ein adjustiertes RR von 0,8 [95%-CI 0,5 zu 1,2], das für Frauen < 50 Jahren noch niedriger lag (RR 0,2 [95%-CI 0,1–0,4]). Ähnliche Risikoreduktion wurde bei benignen Brusttumoren und OC-Nutzung gefunden, besonders ausgeprägt bei jüngeren Frauen. Die Dauer der OC-Nutzung scheint bei benignen Mammatumoren eine Rolle zu spielen, nicht jedoch bei Brustkrebs. Die Dauer seit letzter OC-Nutzung ist offenbar kein bedeutsamer Einflussfaktor bei Brustkrebs, spielt jedoch eine Rolle bei benignen Mammatumoren von Frauen über 50.

Schlussfolgerungen: Jemalsnutzung von OCs ist mit einer deutlichen Reduktion des Risikos der Entwicklung von Brustkrebs oder benignen Mammatumoren verbunden. Bei jungen Frauen scheint die Risikoreduktion bei lebenslang ausschließlicher Nutzung von niedrigdosierten OCs sogar noch ausgeprägter zu sein.

Fazit für die Praxis: Die Akten über einen Zusammenhang von OC-Nutzung und Brustkrebsrisiko sind noch nicht geschlossen. Die Analyse der Daten der Deutschen Kohortenstudie zur Frauengesundheit zeigt ein reduziertes Brustkrebsrisiko bei OC-Nutzung und dies auch bei so genannten niedrigdosierten Pillen.

Schlüsselwörter

Tumorrisiko · Mammatumoren · Orale Kontrazeptiva · Kohortenstudie

Introduction

Oral contraceptives are known to be associated with a variety of non-contraceptive benefits due to ovulatory inhibition and the anti-estrogenic effects of the progestagens [1]. The discussion started particularly after the Royal College of General Practitioners' Study was published in 1968 [2]. Benefits include a reduction in general complaints like menstrual disorders, dysmenorrhagia, and premenstrual tension, but also a reduction of more serious medical conditions like ovarian cysts, benign breast tumours, iron-deficiency anaemia, pelvic inflammatory disease, and rheumatoid arthritis, as well as endometrial and ovarian cancer [3]. A recent overview showed, however, that an increased risk of breast cancer was often but not always reported [4,5]. Due to the public emphasis on reported risks, women are usually not fully aware of these benefits [6,7].

The objective of this publication is to analyse the breast cancer risk in users of modern OCs based on the data of over 15 000 participants of the German Cohorts Study on Women's Health. Whereas previous studies mainly focused on OC formulations with high doses of estrogen, little information is available on whether lower estrogen dose oral contraceptives convey different risks. This is somewhat difficult to evaluate, as women might have taken several different OC formulations in their lifetime. Such an evaluation requires a lifetime history of OC use (calendar method) so that users of old formulations can be distinguished from those who have used only low-dose OCs for long enough to permit an analysis of tumour manifestation, i.e., it depends on how long low-dose formulations are on the market. In a previous publication on the risk of tumours of the uterus and ovary

0.8 [95% CI 0.5 to 1.2]. This was lower in women < 50 years of age (RR 0.2 [95% CI 0.1–0.4]). Similar risk reductions were found for benign breast tumours in OC users, especially pronounced in younger women. Duration of OC use seems to play a role in benign breast tumours but not for breast cancer. Time since last OC use was not an effect modifier in breast cancer, but plays a role for benign tumours in women over 50.

Conclusion: Ever-use of OCs is associated with a markedly decreased risk of developing malignant or benign breast tumours particular in women under 50. In these younger women, the reduced risk associated with lifelong exclusive use of low estrogen OCs may be more pronounced.

Key words

Tumour risk · Breast tumours · Oral contraceptives · Cohort study

we have shown that the length of availability of low-dose OCs now permits such an evaluation [8].

Methods

Design and objectives

The protocol of the German Cohort Study on Women's Health has been published elsewhere [9] and the objectives of the current analysis of tumours was discussed in an earlier issue of this journal [8]. Briefly, the study was designed as a historical cohort study starting with birth. The accrual of participants began in 1998. Women were asked to provide information on lifetime history of sex steroid hormone use and the occurrence of important diseases and other conditions. These data were recorded by month and year of exposure and/or occurrence of any event in order to examine the potential benefits of oral contraceptives (OCs) of any formulation with regard to the long-term occurrence of medical conditions, particularly tumours. We were particularly interested in the effect of use of OCs with so-called low-dose estrogen (< 50 µg EE₂) formulations.

The participants were volunteers up to 65 years of age at the time of inclusion in this cohort. There were no inclusion or exclusion criteria. The study is coordinated by the Centre for Epidemiology & Health Research Berlin, Germany. A network of university-based and other collaborators ensures the feasibility of the study, its evaluation and interpretation.

Data collection, variables and database preparation

Time-related information on lifetime history of hormone use, reproductive life, lifestyle pattern, conditions/diseases, symptoms, and many other factors was obtained in a self-administered postal baseline questionnaire. Each participant will also complete an annual follow-up questionnaire as well as occasional questionnaires from optional sub-studies. If the questionnaire information was not sufficiently clear telephone interviews were done to improve the data quality.

Due to the importance of the temporal relationship of lifetime exposures with ensuing events, the database was structured to accommodate both concurrent as well as time-dependent variables. Concurrent variables are variables which describe the

woman's status at the time of questionnaire response, whereas all historic variables are time-dependent. While concurrent variables were held in a fixed dataset, a periodic dataset containing information on lifetime exposures and the occurrence of medical conditions along a time axis was created for the time-dependent variables of each participant, using months as a unit of measurement. In this dataset, all exposures (e.g. OC use) and medical events (such as gynaecological surgical procedures, benign and malignant tumours, infections, etc.) are mapped in time, so that the beginning, end and duration of any exposure and event are accurately positioned within each woman's lifetime. A set of rules was devised to resolve problems related to inaccuracies in dating the events (applied to 11% of the participants).

Analysis

The focus of this analysis is the association of prior use of oral contraceptives with the occurrence of benign and malignant tumours of the breast. All outcomes analysed for this paper are self-reported and have not yet been validated against physicians records. Therefore, relatively broad diagnostic categories were chosen for the time being: all malignant and all benign breast tumours without further specification. We excluded women with prior malignant tumour from the analysis of benign tumours.

Logistic regression was performed separately for benign and malignant tumours, adjusting for parity, gynaecological conditions in the past (pelvic inflammatory disease or ovarian cysts), and use of sex hormones for other reasons than contraception. Crude and adjusted risk ratios (RR) are reported with 95% confidence intervals (95% CI). Additionally, we analysed the impact of duration of OC use compared with never-use (categories: never, < 5 years, 5–9 years, ≥ 10 years). The time elapsed since last OC use to the manifestation of the respective tumour was categorised as follows: current OC use, < 5 years ago, 5–9 years, ≥ 10 years, never (referent). The cases amongst the cohort members were censored at the time of occurrence of their first malignant tumour or the time of occurrence of their last benign tumour.

All analyses were performed for the whole group, and separately for those OC users who had never used high-estrogen-dose OC ($EE_2 \geq 50 \mu\text{g}$) in their life, i.e. those who had used low-estrogen dose OCs ($EE_2 < 50 \mu\text{g}$).

The statistical package STATA 6.0 was used for all analyses.

Results

At the conclusion of this phase of the ongoing study, 15 374 participants had been accrued (Table 1), and were available for an analysis (about 610 328 women-years of observation). The age of the cohort members ranged between 18 and 65 at the time of the baseline survey (mean 39.1 years).

Number of children, education, marital and employment status show a similar spectrum as that observed in the general population. Slightly over 19% of our cohort members were nulliparous women. Self-reported weight and height as well as smoking status were in the expected range. The comparability of our cohort of volunteers with the German female population of the same age range was published in detail elsewhere [9].

Table 1 Baseline parameters of participants of the German Cohort on Women's Health at the time of questionnaire completion

	N	Mean (SD)
Age	15374	39.1 (12.9)
Number of children	15374	1.3 (1.1)
Body Mass Index	15186	24.3 (4.8)
	N	Percent (%)
Education		
– Abitur ¹	15245	13.5
– University ²	15245	27.6
Employment: Yes (including part-time)	14830	62.6
Smoking: Yes, current smoker	15316	23.3
OC use: Yes, current use	15374	27.6

N = number of women for whom data on that variable were available; ¹ Examination that certifies maturity for university; ² University (classical), technical universities and education with an equivalent diploma or master degree.

Table 2 Risk of breast cancer and ever-use of OCs. Cohort analysis with logistic regression: relative risk estimates (RR) and 95% confidence interval (95% CI)

OC use (any)	Cases	Controls	Crude RR (95% CI)	Adj. RR (95% CI) ¹
<i>All women (all ages)</i>				
Never use	98	2306	1.0 (Referent)	1.0 (Referent)
Ever use	210	12519	0.4 (0.3–0.5)	0.6 (0.5–0.8)
	308	14825		
OC use (any)	Cases	Controls	Crude RR (95% CI)	Adj. RR (95% CI) ²
<i>< 50 years</i>				
Never use	28	1087	1.0 (Referent)	1.0 (Referent)
Ever use	137	10468	0.5 (0.3–0.8)	0.5 (0.3–0.7)
	165	11555		
OC use (any)	Cases	Controls	Crude RR (95% CI)	Adj. RR (95% CI) ²
<i>≥ 50 years</i>				
Never use	70	1219	1.0 (Referent)	1.0 (Referent)
Ever use	73	2051	0.6 (0.4–0.9)	0.7 (0.5–0.95)
	143	3270		

¹ Adjusted by age, use of other sex steroids, parity, gynaecological conditions,

² Adjusted by use of other sex steroids, parity, gynaecological conditions.

Breast cancer

Of the participants, 308 reported having or having had a breast cancer (Table 2). Compared with never-users, the adjusted relative risk (RR) for breast cancer was 0.6 (95% CI: 0.5 to 0.8). The risk reduction of OC user is similar for the overall age group, and stratified under/over the age of 50.

Breast cancer showed no significant trend associated with duration of use or with time since last use (Table 3). Similarly, no clear time trend of risk was observed with increasing time since last OC use, which is true for younger and older women.

Table 3 Risk of breast cancer and use of OCs: The effect of duration of use and time since last OC use. Cohort analysis with logistic regression: relative risk estimates (RR) and 95% confidence interval (95% CI)

	All ages		Adj. RR (95% CI) ¹	< 50 years	≥ 50 years
	Cases	Controls		Adj. RR (95% CI) ²	Adj. RR (95% CI) ²
Duration of use					
Never	98	2306	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
< 5 years	55	3700	0.7 (0.5–0.9)	0.4 (0.2–0.7)	0.8 (0.5–1.3)
5–10 years	55	3842	0.7 (0.5–0.98)	0.4 (0.2–0.6)	0.9 (0.6–1.6)
10+ years	100	4977	0.6 (0.4–0.8)	0.6 (0.4–0.95)	0.5 (0.3–0.8)
Time since last use					
Never	98	2306	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Current use	33	4220	0.5 (0.3–0.7)	0.3 (0.2–0.5)	n.d. ³
< 5 years	39	3060	0.7 (0.5–1.0)	0.4 (0.2–0.6)	0.96 (0.5–2.0)
5–10 years	31	1660	0.6 (0.4–0.9)	0.6 (0.3–1.0)	0.5 (0.2–1.1)
10+ years	107	3579	0.6 (0.5–0.8)	0.8 (0.5–1.3)	0.7 (0.5–0.99)

¹ Adjusted by age, use of other sex steroids, parity, gynaecological conditions; ² Adjusted by use of other sex steroids, parity, gynaecological conditions; ³ No data

Table 4 Risk of breast cancer and use of only low estrogen OCs. Cohort analysis with logistic regression: relative risk estimates (RR) and 95% confidence interval (95% CI)

Low-dose OCs only	Cases	Controls	Crude RR (95% CI)	Adj. RR (95% CI) ¹
All women (all ages)				
Never use	98	2306	1.0 (Referent)	1.0 (Referent)
Ever use	29	4674	0.2 (0.1–0.2)	0.8 (0.5–1.2)
	127	6980		
< 50 years				
Never use	28	1087	1.0 (Referent)	1.0 (Referent)
Ever use	23	4585	0.2 (0.1–0.3)	0.2 (0.1–0.4)
	51	5672		
≥ 50 years				
Never use	70	1219	1.0 (Referent)	1.0 (Referent)
Ever use	6	89	1.2 (0.5–2.8)	1.2 (0.5–2.9)
	76	1308		

¹ Adjusted by age, use of other sex steroids, parity, gynaecological conditions;

² Adjusted by use of other sex steroids, parity, gynaecological conditions

Table 5 Risk of benign tumours of the genital tract and use of OCs. Cohort analysis with logistic regression: relative risk estimates (RR) and 95% confidence interval (95% CI)

OC use (any)	Cases	Controls	Crude RR (95% CI)	Adj. RR (95% CI) ¹
All women (all ages)				
Never use	377	2107	1.0 (Referent)	1.0 (Referent)
Ever use	932	11697	0.5 (0.4–0.5)	0.3 (0.3–0.4)
	1309	13804		
< 50 years old				
Never use	313	1021	1.0 (Referent)	1.0 (Referent)
Ever use	845	9879	0.3 (0.2–0.3)	0.3 (0.25–0.3)
	1158	10900		
≥ 50 years				
Never use	64	1086	1.0 (Referent)	1.0 (Referent)
Ever use	87	1818	0.8 (0.6–1.1)	0.8 (0.6–1.2)
	151	2904		

¹ Adjusted by age, use of other sex steroids, parity, gynaecological conditions;

² Adjusted by use of other sex steroids, parity, gynaecological conditions

When the analysis was restricted to users of low estrogen OCs (< 50 mcg EE₂), the adjusted RR was 0.8 (95% CI: 0.5 to 1.2), i.e. statistically not significant (Table 4). There is a significantly lower risk in women under 50 years of age, but no significant association in women over 50 years.

Benign breast tumours

Considerably more benign than malignant breast tumours were observed within this cohort (n = 1309). These also showed a significantly lower risk associated with OC use of any type for all

groups together (Table 5). There was a higher risk reduction of benign breast tumours in women under the age of 50 years.

The adjusted relative risk estimates for benign breast tumours showed a significantly declining trend with increasing duration of use, i.e. both for women under and over their 50's. No time trend was observed between increasing time since last OC use and the risk of benign breast tumours (Table 6). This particularly applies for women below the age of 50, however for older women, there is a downward trend of risk with increasing time since last OC use.

Table 6 Risk of benign breast tumours and use of OCs: The effect of duration of use and time since last < OC use. Cohort analysis with logistic regression: relative risk estimates (RR) and 95% confidence interval (95% CI)

	All ages			< 50	≥ 50
	Cases	Controls	Adj. RR (95% CI) ¹	Adj. RR (95% CI) ²	Adj. RR (95% CI) ²
Duration of use					
Never	377	2107	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
< 5 years	414	3428	0.5 (0.4–0.6)	0.4 (0.4–0.5)	1.1 (0.7–1.7)
5–10 years	265	3607	0.3 (0.2–0.4)	0.3 (0.2–0.3)	0.8 (0.5–1.4)
10+ years	253	4662	0.2 (0.2–0.3)	0.2 (0.1–0.2)	0.7 (0.5–1.1)
Time since last use					
Never	377	2107	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
Current use	383	4042	0.3 (0.3–0.4)	0.3 (0.3–0.4)	2.1 (0.6–7.1)
< 5 years	189	2904	0.2 (0.2–0.3)	0.2 (0.2–0.3)	1.3 (0.7–2.5)
5–10 years	127	1547	0.3 (0.3–0.4)	0.3 (0.2–0.4)	1.0 (0.6–1.8)
10+ years	233	3204	0.4 (0.3–0.5)	0.3 (0.3–0.4)	0.7 (0.5–1.1)

¹ Adjusted by age, use of other sex steroids, parity, gynaecological conditions; ² Adjusted by use of other sex steroids, parity, gynaecological conditions

Table 7 Risk of benign breast tumours and use of only low estrogen OCs. Cohort analysis with logistic regression: relative risk estimates (RR) and 95% confidence interval (95% CI)

Low-dose OCs only	Cases	Controls	Crude RR (95% CI)	Adj. RR (95% CI) ¹
All women (all ages)				
Never use	377	2107	1.0 (Referent)	1.0 (Referent)
Ever use	203	4477	0.3 (0.2–0.3)	0.1 (0.1–0.2)
	580	6584		
< 50 years				
Never use	313	1021	1.0 (Referent)	1.0 (Referent)
Ever use	198	4401	0.2 (0.1–0.2)	0.1 (0.1–0.2)
	511	5422		
≥ 50 years				
Never use	64	1086	1.0 (Referent)	1.0 (Referent)
Ever use	5	76	1.1 (0.4–2.9)	1.1 (0.4–2.9)
	69	1162		

¹ Adjusted by age, use of other sex steroids, parity, gynaecological conditions;

² Adjusted by use of other sex steroids, parity, gynaecological conditions

The restriction to users of low-dose OCs (Table 7) again yielded a lower adjusted RR (0.1; 95% CI: 0.1 to 0.2). The reduced risk associated with the use of low-dose OCs was focused on women under 50 years of age, whereas no risk reductions were found in older women.

Discussion

Morbidity and mortality of gynaecological tumours is high in most parts of the world including Germany [10]. Cancer of the breast is the most common incident cancer in women, the third

most common cancer overall. The incidence of, and death from this cancer is still increasing in many parts of the world, especially in developed societies. Very little is known about incidence and trends of benign breast tumours.

Recently, an expert panel of the American Institute of Cancer Research published an extensive review on “Food, Nutrition and the Prevention of Cancer” [11]. All potential risk factors were reviewed. The expert panel came to the conclusion: “Some factors that affect the risk for breast cancer probably act early in life. In particular, evidence that rapid early growth and greater adult height increase risk is convincing. In addition, diets high in vegetables and fruit decrease the risk of breast cancer; and alcohol and weight gain in adult life probably increase risk, as does high body mass after menopause” [11]. The clearest non-dietary risk factors are those associated with hormonal and reproductive factors, such as nulliparity, late age at first pregnancy, late menopause, but also some inherited abnormalities, finding their expression in a positive family history, for instance. The mechanism in which hormonal factors may affect breast carcinogenesis is unclear. It is thought that they may possibly play a promotional role [11].

If one discusses the effect of external hormones on breast cancer, one should remember that the lag time of developing breast cancer is likely to be long, may vary depending on complex unknown causal mechanisms, and is therefore an issue of complex time dependent potential risk factors. Particularly in case-control studies it is difficult to sufficiently account for time-dependent variables. Age, time and duration of use are only indicator variables. Observational studies, particular case-control studies are prone to bias and confounding, even if performed according to the “state-of art”. This is a particular methodological problem, because observed risk estimates were usually small, particularly those associated with OC ever use. Given the great potential for residual confounding and various biases, even a statistically significant small association might be inconclusive, because such associations could be well below a reliable resolution of the “epidemiological microscope”.

In this interim analysis of our ongoing German Cohort Study on Women's Health, we provide the first results of the effect of modern OCs on malignant and benign breast tumours.

In earlier cohort studies, the risk estimates for breast cancer and OC use ranged between 0.6 and 1.4 [4, 5]. The summary breast cancer risk of OC ever users was very small in the recent collaborative re-analysis of individual data of 53 297 breast cancer cases and 100 239 control women from 54 epidemiological studies: 1.07 for cohort studies, 1.02 for case control studies with population controls, and 1.07 for case-control studies with hospital controls [4, 5].

Although the cohort is differently defined, the findings of the historic analysis of our cohort of volunteers showed a risk estimate at the lower end of the other, earlier cohort studies. Similar to the Oxford FPA study [12] (RR = 0.6), we found a breast cancer risk of 0.6 for OC ever use compared with never use. Most other studies found that the excess risk of breast cancer associated to OC ever use is low or non-existent [13]. Some studies suggested an increased risk for sub-groups such as long-term OC use before first term pregnancy, long-term OC use at "early age" before the age of 25, and cancer diagnosis at young age (< 35/< 45 years) after long-term OC use. However, these reports are inconsistent, and often based on small numbers. Moreover, as discussed above, there might be problems with residual confounding (e.g., early menarche, parity, duration of lactation, induced abortion) and biases, such as diagnostic and referral bias, selection bias/surveillance bias, and recall bias, in both case-control and cohort studies.

We also examined the differences in breast cancer risk associated with OC use by age, because of reports of lower or higher risk in younger women. We found no substantial difference in the overall risk between women over/below 50 years of age, although risk estimates were numerically slightly higher in women of higher age. Other authors found higher breast cancer risk in younger women especially with long duration of use [14]. Our results are consistent with the notion that younger women may benefit more from OC use.

In contrast to some reports in the literature, we found no obvious impact of duration of OC use on breast cancer risk. This compares well with the compiled data analysis of the Oxford Group [4, 5], where the pooled risk estimates of 54 epidemiological studies varied up and down with increasing duration of use. However, due to the enormous number of cases and control subjects, there was a marginally significant trend shown towards higher risk with increasing duration of use. Other authors found a positive trend for duration of use and breast cancer risk [15–18], especially for younger women, some found no association of the risk with duration of use above this age.

We did not observe a time trend of breast cancer risk associated with increasing time since last OC use. However, the collaborative reanalysis of individual data of earlier studies performed by the Oxford group found such a trend [4, 5]: There was a significant downward trend of the breast cancer risk with increasing time since last OC use, although the change of point estimates over time was not impressive. The breast cancer risk reported by this pooled study was 1.24 for current OC user and it declined marginally and discontinuously during 10 years after stopping use toward the level of never user. We found for current OC use

a significantly decreased risk of 0.5 and no interpretable trend with increasing time since last OC use, although the risk estimates were numerically lower in younger women. One major difference is that the pooled analysis of the Oxford group referred to studies from the past, i.e. the majority of women were exposed to OCs which are not on the market for a long period of time. The majority of women in our study used either low-estrogen OCs only or a mixture of low and higher dose OCs in their life time. Rosenberg et al [17] found also no overall effect of time since last use but the recency of use was correlated with duration of use, and it was not possible to distinguish effects.

The question of whether the benefits of OC use are maintained with the lower-dose estrogen (< 50 µg EE₂) formulations has been raised previously [18]. For endometrial and ovarian cancer, one study in the 1980's reported relative risk estimates for low-dose OCs of similar magnitude to those of high-dose OCs, but the results were inconclusive because of small numbers; the risk estimates were also derived from multiple comparisons [19]. In a Dutch case-control study [14], the authors reported a higher breast cancer risk in long-term users of low estrogen OCs. Other studies found no effect of the estrogen dose on breast cancer risk [20–22] or suggested a higher breast cancer risk of high estrogen OC use [22–24].

We evaluated only the estrogen dose, not specific progestogens, for the classification of the lifetime OC use into OC ever-users who had only used low-dose OCs (< 50 µg EE₂) and those who had at some time or regularly used higher dose formulations (≥ 50 µg EE₂). Our findings suggest a similar risk of breast cancer for low estrogen OC users as was observed for high estrogen OCs or lifetime varying use of high and low dose formulations. The risk estimate was not statistically significant. Reduced breast cancer risk in users of low dose OCs was found only in younger women in our study.

It should however be kept in mind that low estrogen OCs do not have in general a lower progestogen potency which is the main component suppressing endogenous gonatropin and therefore ovarian activity.

There is much less literature on benign breast tumours than for malignancies. Most of the results point in the same direction. The majority observed a lowered risk of OC use on the development of benign breast tumours [3]. One difficulty in comparing our results with those of the published case-control studies is that the former usually evaluated histological tumour subtypes (such as fibrocystic tumours and fibroadenoma or classified "benign breast tumours"), whereas our results provide the aggregate of benign breast tumours without further specification. We observed 1309 benign breast tumours in the lifetime of roughly 16 000 women included in our cohort. A significantly decreased risk associated with OC use (RR 0.3) was found, which was numerically lower in women under the age of 50 than in older women. We also found evidence for a trend toward lower risk with increasing duration of OC use (not observed for malignant tumours), but no trend for declining risk with increasing time since last use in younger women (as shown for malignant tumours). In women above 50, however, a trend of declining risk was observed with increasing time since last OC use. The nature of our study (self-reported events) does not permit histological

profiling at present, so that only rough comparisons with other international studies can be made.

In 1972, Vessey [25] reported a non-significant 30% risk reduction of benign breast disease amongst OC users, and a risk reduction in the same range was reported by Fasal et al [26]. In a case-control study, Sartwell [27] observed a non-significant 13% risk reduction for fibrocystic but a 20% non-significant increase in risk for fibroadenoma in OC ever users. In a cohort study, Ory et al [28] observed a 50% reduced risk for fibroadenoma and 60% reduced risk for fibrocystic breast disease in women using OCs for more than 2 years. This is similar to the report of Brinton et al [29] from another cohort study that found significantly reduced risks between 30 and 60% for fibroadenoma of the breast, fibrocystic disease or unspecified benign breast disease. Ravnihar et al [30] showed a non-significantly decreased risk in a case-control study, as did Hsieh et al [31] a few years later. Significant risk reductions of benign breast disease were also reported by Franceschi et al [32], and non-significant reductions by Rohan et al [33] and Yu et al [34] in case-control studies. Berkowitz et al [35], however, observed an increased risk of fibrocystic breast disease both in pre- and postmenopausal women, statistically significant only in the latter group. The results of Berkowitz et al are not consistent with most of the above mentioned case-control and cohort studies as well our own results.

Our cohort study comprised entirely of volunteers and looking back in time for exposure is different from a cohort defined by exposure at entry and followed into the future. That means, one must consider the implicit limitations of this design. There are three main potential problem areas: self-selection and the potential for bias and possible lack of population representativeness, differential attrition of tumour patients and a subsequent underestimation of tumour incidence, and diagnostic uncertainty for both benign and malignant tumours owing to the self-reported nature of the data.

Although it is unlikely to be differential for the type of OC exposure, the self-selection of women to participate might be prompted by specific factors which affect the representativeness of this cohort. The direction of this bias is unknown, because women might be motivated to participate either because they are particularly health-conscious, or because their health is poor, or for any number of other reasons. We have therefore compared the baseline data of our cohort with those of representative population samples of German women and found re-assuring similarity concerning most characteristics such as social indicators, reproductive history, markers for the health status, and satisfaction with various aspects of life [8, 36]. In other words, the overall agreement of baseline parameters of cohort members with those of participants of representative studies was surprisingly good.

The study poses the risk of either missing tumour patients, particularly for those tumours with high case fatality rates, or of over-estimating tumour incidence, perhaps because women with tumours would be particularly interested to participate. We therefore compared the number of cancer cases observed in our cohort with that expected on the basis of data provided by various registries (Germany, Denmark, Netherlands, Switzerland-Basle) in order to determine the potential magnitude of error [36]. The range of estimates provided by these registries itself

is rather large, and for all cancers the number of cases found in the cohort is within the range of this variability. In terms of tumour rates, the cohort incidence of breast cancer for our current 610 000 women-years of observation is in the range of expected incidence relative to the information provided by the registries (data not shown), so that one can assume a relatively accurate reflection of population rates from the cohort, particularly with regard to breast cancer. Further, case attrition due to high case fatality, as may be assumed for breast cancer, will be most likely to affect the group of high-dose estrogen users, and lead to an overestimate of benefit in that group. Case attrition may also be the reason of a lack of gradient for time from last exposure found in our study in women over 50 years of age. However, there are also arguments for underestimating the benefit.

The self-reported nature of the data leads to a lack of diagnostic accuracy both for malignant and for benign tumours. The validation of these diagnoses with the treating physician is time-consuming and is still under way, but it is unlikely that histological findings will become available for all cases as it was not feasible in other cohort studies. Because of this, the focus of this paper is on tumours as they were reported from women, and our interpretations are mainly based on tumour-aggregates (i.e. malignant tumours of breast cancer) rather than on specific diagnoses. The same holds true for benign tumours. We doubt that these aggregated analyses of self-reported tumours are materially biased, but have no data yet to assess the magnitude of a potential misclassification bias.

There are other limitations of the study: Certainly, recall bias could be of concern in the comparisons between users and non-users of OCs. Although differential recall often tends to lead to inflated risk estimates, exposure to OCs might be better recalled by women with tumours because they were asked this frequently in the course of their treatment. Women without tumours might never have been questioned about their contraceptive use. This would tend to increase the tumour risk associated with OC use and cannot explain very low risk estimates.

Another potential source of bias is selection bias: It cannot be assumed that tumour cases are equally identified among OC users and non-users. Exposed subjects may have a higher likelihood of being selected into the study. For instance, OC users may be routinely advised by prescribing physicians to participate in screenings. Therefore, our risk estimates are likely to be conservative.

Overall, there is good agreement with regard to the magnitude of the risk reduction of OC use and with regard to the effect of lower estrogen dose OCs on the risk of malignant and benign breast tumours between our study and others, i.e., less for malignant than benign tumours. The consistency of the response of hormone-sensitive secondary reproduction organs is overwhelming and reassuring. The observed reduced risk of OC use on breast tumours must also be discussed in the context of potential selection bias (see above). It cannot be ignored that several cancer cases had no chance to become members of this cohort. Apart from the theoretical considerations concerning the potential direction of bias in terms of under- or overestimating risk, it is important to compare tumours where this bias is likely to work (serious cancers) and where this is unlikely (benign tumours where the diagnosis is often spurious, and without medical or

other consequence). The consistency of findings between benign and malignant (hormone-sensitive) tumours suggests that the results are not overly affected by selection bias.

Conclusion

The relative risk of developing a malignant or a benign breast tumour is decreased in ever-users of OCs compared to never-users. Duration of OC use seems to play a role in our study for benign breast tumours but not for breast cancer. There is apparently no important overall trend for time since last OC use and risk of malignant or benign breast tumours. The risk reduction associated with lifetime exclusive use of low estrogen OCs may be more pronounced than that of use of high-dose OCs, especially in younger women. If confirmed in other studies, these results could lead to a general reassessment of the risk-benefit characteristics of OC use. In the interpretation of the study results, the retrospective nature of this cohort analysis requires a careful assessment of all confounders and inherent biases. These may become more obvious during further follow-up and validation of outcomes. Nonetheless, the hypothesis of a greater risk reduction of low-estrogen dose OCs deserves serious consideration.

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