Contemporary hormonal contraception and risk of endometrial cancer in women younger than age 50: a retrospective cohort study of Danish women.

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Abstract

Objective

To examine the association between contemporary hormonal contraceptives and endometrial cancer risk in women younger than age 50.

Study design

Cohort study of women living in Denmark aged 15-49 years through 1995-2014. National registries provided information about hormonal contraception use, incident endometrial cancer and confounders. Ever, current or recent, and former users of any hormonal contraception were compared with non-users, using Poisson regression to calculate incident rate ratios (RR) with 95% confidence intervals. Duration, time since last use, tumor-specific and product-specific analyses, and population prevented fraction, were calculated.

Results

During 21.1 million person-years, 549 incident endometrial cancers occurred, with ever users of any hormonal contraception having a reduced premenopausal endometrial cancer risk compared with non-users; RR 0.60 (95% Confidence Interval 0.49 to 0.73). A lower risk of endometrial cancer was seen in all current or recent users of any hormonal contraception; 0.65 (0.52-0.83) and combined contraceptives; 0.57 (0.43 to 0.75), but not progestin-only contraceptives; levonorgestrel intrauterine system, LNG-IUS; 0.97 (0.66 to 1.42); other progestin-only contraceptives; 0.61 (0.27 to 1.37)]. Increased RRs were found for current use of any hormonal, combined contraceptives or LNG-IUS of ≤ one year, probably because of protopathic bias. Longer durations of use were associated with significant reductions that became stronger with longer use. Former users of any hormonal contraception continued to benefit from a reduced risk of endometrial cancer > 10 years after stopping.

There was little evidence of differences in risk reduction by the type of progestin in combined oral contraceptives.

Current or recent use of any hormonal contraception was associated with an approximate halving of risk of the most common tumor type I carcinoma, and an increased risk of the rarer sarcoma.

Overall the estimated absolute reduced risk of endometrial cancer in ever users of hormonal contraceptives was 1.4 per 100,000 person-years, or approximately one less endometrial cancer for every 71,400 women of reproductive age who used hormonal contraception for one year. Use of hormonal contraception was estimated to prevent 25% of endometrial cancers in this population.

Conclusions

Currently available combined hormonal contraceptives are still associated with enduring protection against endometrial cancer, particularly for type I carcinomas.

Keywords

endometrial cancer; hormonal contraception; combined contraceptives; progestin-only contraceptives; cohort

Implications

We report substantive evidence of the association between different types of contemporary hormonal contraception and endometrial cancer risk in a national cohort of young Danish women. Currently available combined hormonal contraceptives are still associated with enduring protection against endometrial cancer, particularly for type I carcinomas.

1.1 Introduction

In 2018, cancer of the corpus uteri (mostly endometrial) was estimated to be the sixth most frequent cancer in women globally, accounting for more than 382,000 new cases and 89,929 deaths [1]. Many countries have seen an increased incidence of endometrial cancer during the last 25 years, possibly because of rises in the prevalence of obesity, nulliparity and diabetes [2]. However, the absence of increased incidence in other countries has been attributed to long-lasting protective effects from use of combined oral contraceptives [2,3]. The Collaborative Group on Epidemiological Studies of Endometrial Cancer examined the association between oral contraceptive use and risk of endometrial cancer in an individual participant meta-analysis of 27,276 women with endometrial cancer and 115,743 controls [3]. The median age at diagnosis was 63 years, and median year of diagnosis 2001, meaning that most of the oral contraceptive use occurred during the 1960s and 1970s. Hormonal contraception has changed substantially since then, including a lowering of estrogen dose and introduction of different progestins in combined oral contraceptives. It is uncertain whether products used today are still associated with important endometrial cancer benefits. We report here the first substantive evidence of this relationship for all types of contemporary hormonal contraception used by a national cohort of women living in Denmark. In order to examine endometrial cancer risk associated with the hormonal contraceptives currently used by women of reproductive age, we studied women younger than age 50.

1.2 Material and methods

The Danish Sex Hormone Register Study [4,5] follows all women aged 15-79 years living in Denmark, to examine the relationship between hormone use and cardiovascular disease and cancer. Since 1968, each resident in Denmark has had a unique personal identification number in the Civil Registration System which is used as a unique identifier in all National Registries, enabling the accurate linkage of their content. The study links data from: the National Register of Medicinal Product Statistics [for redeemed hormonal contraceptive prescriptions since January 1995]; the Danish Cancer Registry [for histologically verified cancers since 1943 and family history of premenopausal (younger than 50 years) breast or ovarian cancer in mothers or sisters]; Statistics Denmark [for information about educational attainment]; the National Birth Register [for all births since 1973, smoking status of parous women since 1991 and body mass index (BMI) of parous women since 2004]; and the National Health Register [for hospital discharge diagnoses and surgeries since 1977].

For this paper the eligible study population (n=1,904,094) was all women living in Denmark age 15-49 years during the period January 1995 to December 2014, except women who moved into Denmark after 1995. We excluded women if they had venous thrombosis, treatment with ovarian stimulating drugs (Anatomical Therapeutic Chemical Classification code MG03G in the National Prescription Registry), hysterectomy, bilateral oophorectomy, endometrial hyperplasia or any cancer (except non-melanoma skin cancer) before study entry. The final population of 1,852,505 women was followed until: first diagnosis of endometrial cancer (International Classification of Diseases (ICD), tenth revision [6] code C54); emigration; death; age 50; or end of follow-up (31 December 2014). Women were censored permanently at the date of: diagnosis of another cancer (except non-melanoma skin cancer); venous thrombosis; treatment with ovarian stimulating drugs; bilateral oophorectomy, hysterectomy or endometrial hyperplasia (which can be a precursor to endometrial cancer). Women were censored temporarily whilst pregnant and for six months afterwards.

Information about redeemed prescriptions was updated daily. From this information we designated the date when: women started (date prescription was redeemed); stopped (date when the contraception was estimated to finish- based on the number of packs issued for oral contraceptives, usual length of use for other hormonal contraceptives, four years for the levonorgestrel intrauterine system (LNG-IUS) - unless a prescription for a different hormonal contraceptive was redeemed or pregnancy occurred beforehand); or switched type (date of prescription redemption for a different product) of hormonal contraceptive). Gaps between prescriptions of less than 28 days were filled in prospectively [7].

1.2.1 Statistical analysis

Throughout the follow-up period the hormonal contraceptive status of the women changed according to when they started, stopped or changed the type of hormonal contraception used. We categorized and aggregated the endometrial cancers and periods of observation according to the hormonal contraceptive status of the women throughout the study as: non-user (i.e. no redeemed prescription for hormonal contraceptives at date of entry to the study and continued not to redeem a prescription; if a prescription for a hormonal contraceptive was redeemed during the study her contraceptive status changed to current user on the date of redemption); current or recent (within one year of stopping) users; or former (more than one year since stopping) users of different hormonal contraceptives. An ever user had redeemed at least one prescription for hormonal

contraceptive during the study. Once a woman became a user, she could not return to being a non-user. Women could switch between current or recent and former user categories depending on their redemption of prescriptions. Our time-varying analyses allowed for these changes. The age distribution of the entire cohort was used as the standard to calculate age-standardized incidence rates of endometrial cancer per 100,000 person-years among the different user groups. Endometrial cancer risk among users of different products was calculated using Poisson regression in SAS version 9.3 (SAS Institute, Inc, Cary, North Carolina) using PROC GENMOD with the distribution set to Poisson and a log link function. Five-year age bands were used as the time scale in the Poisson regression. In each model non-users were the reference group and adjusted incidence rate ratios (RR) with their 95% confidence interval (CI) calculated. Time varying covariate effects were modelled by adding interactions between the partitioned constant baseline hazard and each pre-specified covariate. By doing this, we did not assume constant baseline hazard rates over fixed time intervals. Each model was adjusted such that the risk time was partitioned every time one of these covariates changed value. The covariates were: hormonal contraceptive use, calendar year, age (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49 years), educational attainment (elementary school only, high school only, further education excluding college/university, college/university education, university education with research qualifications, unknown); parity (0, 1, 2, 3, 4, >4); family history of premenopausal breast or ovarian cancer (no, yes); tubal sterilization (no, yes) and endometriosis (no, yes). Among parous women, additional models adjusted for smoking status (current, non-smoker, unknown) and BMI (<18.5, 18.5-25, >25-30, >30, unknown) ascertained at pregnancy. Smoking status and BMI were not available for other women.

Our main analysis compared ever, current or recent, and former users of any hormonal contraception with non-users. Separate analyses examined duration of use (with short-term use being ≤ one year) and time since last current use, with tests for trend conducted by including the duration or time since variable as an ordinal variable with values set to the median within each category [8]. We also stratified our data by tumor histology using the same sets of ICD-O-3 codes[9] (all ending with behavior invasive digit 3) as the Collaborative Group[3] (Table 1S).

To minimize any lingering effects from previous use of hormonal contraception, we examined risk estimates for different products in women followed during the study until their first change of hormonal contraception. We also calculated risk estimates among women aged 15 years on or after 1st January 1995, for whom complete contraceptive histories were known.

Some women may start or restart hormonal contraception because of symptoms (e.g. heavy bleeding) from an undiagnosed cancer which is subsequently diagnosed soon afterwards. This could artificially elevate events in current users of a hormonal contraceptive with a short duration of use. To explore whether this may have occurred, we undertook two sensitivity analyses on our full cohort and tumor specific datasets in which we ignored periods of observation for one and two years before cancer diagnosis date, allocating the event to the hormonal contraceptive group pertaining one or two years before diagnosis (unless the woman had less than one or two years of observation before the event in which case she was excluded from the analysis).

For the full cohort, we calculated the absolute reduction in risk of endometrial cancer in ever users of hormonal contraceptives. We also calculated the population prevented fraction (=$\text{prevalence}_{\text{exposure}}$ (1-RR)) associated with ever use of any hormonal contraception using the incidence RR of ever versus non-user of any hormonal contraception.

1.2.2 Ethics approval

Even though ethical approval is not required for register-based studies in Denmark, approval for the research was obtained from the Danish Data Protection Agency and Health Data Board. The data were held, with personal identification number codes encrypted, and analyzed within the secure data repository at Statistics Denmark. In accordance with the regulations of Statistics Denmark around statistical disclosure, outcomes where <3 endometrial cancers occurred are presented as <3, the corresponding total person-years is rounded to the nearest 5 and the RR (95% CI) is not shown.

1.3 Results

There were 362 incident endometrial cancers among non-users of hormonal contraceptives and 187 in ever users, during 21.1 million person-years of observation. Combined oral contraceptives containing gestodene, desogestrel or levonorgestrel accounted for almost two-thirds of all hormonal contraception use among current or recent users (Table 1). The LNG-IUS was the most commonly used non-oral hormonal contraceptive and was more frequently used among parous than nulliparous women. In the full cohort, women who had ever used any hormonal contraception had a reduced incidence rate of endometrial cancer in comparison to non-users; RR 0.60 (0.49 to 0.73) (Table 2). A similarly reduced RR of endometrial cancer was also observed among current or recent users of any hormonal contraception; RR 0.65 (0.52 to 0.83) and combined contraceptives; RR 0.57

(0.43 to 0.75), but not progestin-only contraceptives; LNG-IUS RR 0.97 (0.66 to 1.42); all other progestin-only products RR 0.61 (0.24 to 1.37). An increased RR was observed with one year or less of current use of any hormonal contraception, combined oral contraceptives or LNG-IUS (Table 2). Users of these products for longer durations had a reduced RR of endometrial cancer, an effect that strengthened with increasing duration of use. In former users of any hormonal contraception, there remained a reduced RR of endometrial cancer more than 10 years after stopping; RR 0.57 (0.36 to 0.89). When the data for former users were stratified by duration of previous use and time since last use, the protective effect of hormonal contraception was stronger with longer durations of use irrespective of time since stopping (Table 3).

The subset of women who were followed until their first switch in hormonal contraception, together with non-users, accounted for 71% (15,057,542/21,161,314 person-years) of all periods of observation in the cohort (Table 4). In this subset, ever, former and current or recent users of any hormonal contraceptives all had a more than a 30% reduced RR of endometrial cancer compared with non-users. An increased RR of endometrial cancer was observed again among those with less than one year of any hormonal contraception or the LNG-IUS. Longer durations of use of any hormonal or of combined contraceptives were associated with a reduced RR. The reduced RR of endometrial cancer in former users persisted at least 10 years after ceasing hormonal contraception. Current or recent users of combined hormonal contraceptives had a reduced RR of endometrial cancer; RR 0.41 (0.27 to 0.62), with a reduction seen among current or recent users of the most frequently used combined oral contraceptive containing gestodene. Although based on limited data, current or recent use of other progestin-only products (i.e. excluding the LNG-IUS) was not associated with endometrial cancer; RR 0.73 (0.23 to 2.27). Most cancers in LNG-IUS users (12/21) occurred within the first year of use; the median time between prescription redemption and cancer diagnosis was 281 days (interquartile range 41-698). Thus, the increased RR in LNG-IUS users overall was due to a high rate of endometrial cancers among users during the first year of use.

The pattern of risk estimates for the different products when the full cohort was examined was broadly similar to that in women followed until first switch, except for current or recent use of the LNG-IUS which was no longer associated with an increased RR of endometrial cancer (Table 2S). Similar risk estimates were found in the full cohort among parous women after adjustment for smoking and BMI (Table 3S) and after similar adjustments among those parous women followed until their first switch of hormonal contraception (data not shown). Only six endometrial cancers

occurred during 5.4 million person-years among women with a complete contraceptive history, precluding calculation of incidence RRs in this subset of the cohort.

Type I carcinomas accounted for 68% (373/549) of all endometrial cancers in the full cohort (Table 5). Both current or recent use of any hormonal contraception, combined contraception and former use had an approximate halving of RRs for type I carcinoma. Current or recent use of any hormonal contraception was associated with an increased RR of sarcoma; RR 1.82 (1.11 to 3.02), a relationship not seen in former users. When examined by type of hormonal contraception, there was an increased RR of sarcoma among current or recent users of LNG-IUS; RR 3.24 (1.43 to 7.34) but not combined products; RR 1.60 (0.90 to 2.84).

The sensitivity analysis which excluded from the full cohort dataset periods of observation one year before diagnosis, resulted in similar patterns overall albeit with smaller RRs (Table 2 & Table 4S). In this analysis, current use of hormonal contraceptives of any type for short durations was no longer associated with an increased RR of endometrial cancer. A similar pattern was seen when two years of observation was excluded, although the risk estimates were more imprecise (data not shown). In a sensitivity analysis of the tumor specific dataset, exclusion of one year's period of observation resulted in overall smaller RRs and the loss of statistical significance for the risk estimates for sarcoma among current or recent users of any hormonal contraception or the LNG-IUS (Table 5S). Similar results were again seen when two years of observation prior to the diagnosis of endometrial cancer were excluded from the analysis (data not shown).

Overall the estimated absolute reduced risk of endometrial cancer in ever users of hormonal contraceptives was 1.4 per 100,000 person-years, or approximately one less endometrial cancer for every 71,400 women of reproductive age who used hormonal contraception for one year. The population prevented fraction was estimated to be 25% i.e. use of hormonal contraception prevented 25% of endometrial cancers in the study population.

1.4 Discussion

In this cohort study of women of reproductive age in Denmark, current or recent use of any hormonal contraception and of combined contraceptives was associated with a reduced risk of

endometrial cancer. For combined contraceptives, there was little evidence of differences in risk reduction according to their progestin content. Reductions became stronger with longer duration of use and persisted among former users. It is unclear whether progestin-only contraceptives have the same benefits.

Strengths of our study include more than 1.8 million women studied, 21.1 million person-years of observation and the examination of all types of hormonal contraception in use between 1995 and 2014. Recall bias about contraceptive use was avoided by the prospective collection of information about redeemed prescriptions. We were able to adjust for several possible confounders, although information about smoking habits and BMI was available only for parous women for part of the study period. These adjustments did not materially change the risk estimates. It is possible, however, that residual confounding influenced our findings. An unknown proportion of women deemed to be non-users will have been previous users of hormonal contraceptives who stopped before our study began in January 1995. The effect of this misclassification of hormonal contraceptive status will be to move the RRs towards the null, thus underestimating the 'real' effects of hormonal contraceptives.

Risk estimates attributed to a particular product might reflect persisting effects from previous use of another contraceptive(s). We tried to minimize such effects by examining associations for different products among women followed until their first switch of hormonal contraception in the study, even though this approach meant that fewer cases of endometrial cancer among less popular preparations. Nevertheless, there was no evidence of important differences between combined contraceptives containing different progestins. Although it is likely that that protopathic bias occurred in short-tern users overall, there is less reason to suspect that this operated differently within the preparations containing different progestins. We were unable to calculate risk estimates in women for whom their full contraceptive history was known i.e. the subset of women who were 15 years on or after 1st January 1995, because of the low incidence of endometrial cancer in young women.

The Collaborative Group's reanalysis of 36 studies of oral contraceptives and endometrial cancer found an overall relative risk between ever and never users of 0.69 (0.67 to 0.72). We found a slightly stronger overall reduced risk among ever users of any hormonal contraception; RR 0.60 (0.49 to 0.73), possibly because our ever user group included a larger proportion of current or recent users

than women included in the Collaborative Group re-analysis. The Collaborative Group found a reduced risk of type I (typically considered to be estrogen-dependent) and II (estrogen-independent) carcinoma but not sarcoma. We also found a reduced risk of type I tumors. The Collaborative Group estimated that in 21 countries during 1965-2014 combined oral contraceptive use had prevented 400,000 endometrial cancers in women aged 30-74. In our study of younger women, the estimated population prevented fraction was 25%, suggesting continuing substantial endometrial cancer benefits from contemporary hormonal contraceptives- particularly combined products.

Few studies have examined the LNG-IUS in relation to endometrial cancer risk [10-12]. The Endometrial Cancer Consortium combined data from four cohort and 14 case-control studies to examine the endometrial cancer risk associated with type of intrauterine device [10]. Hormone-releasing devices did not appear to alter the risk although few women in the analysis had used these products (adjusted odds ratio 0.97, 95% CI 0.44 to 2.14). Soini et al followed 93,843 women who had used the LNG-IUS for menorrhagia treatment [11]. During more than 850,000 person-years of observation, users had a reduced risk of any type of corpus uteri cancer; standardized incidence ratio, SIR 0.59 (95% CI 0.45 to 0.77) and endometrial adenocarcinoma; SIR 0.46 (0.33 to 0.64), with evidence of more protection with increased duration of use. This study, however, could not adjust for previous use of oral contraceptives, which are associated with long-lasting protective effects on the endometrium [3,13]. The study did not find a reduced risk of uterine sarcoma; SIR 1.44 (0.86 to 2.28) [11]. We were also unable to find in either our main or sensitivity analyses a protective effect for sarcoma from hormonal contraception generally, and the LNG-IUS specifically.

A cohort study of 104,318 women enrolled in the Norwegian Women and Cancer Study also reported a reduced risk of endometrial cancer among ever users of the LNG-IUS; RR 0.22 (0.13 to 0.40) [12]. The study adjusted for several possible confounders including ever use of oral contraceptives but (unlike our study) almost 50% of the ever users of LNG-IUS in the cohort were peri- or post-menopausal. Our results do not confirm a protective effect associated with the LNG-IUS among premenopausal women. Indeed, among the subset followed until first switch, we found an increased risk of endometrial cancer in current or recent users of the LNG-IUS, mostly because of an increased risk during the first year of use. We did not have the reason why women redeemed a prescription for a hormonal contraceptive in our study. As well as for contraception, hormonal contraceptives can be used to treat menstrual irregularities such as heavy bleeding, including bleeding symptoms arising from pre-cancerous conditions such as endometrial hyperplasia. We

censored women at the date of diagnosis of endometrial hyperplasia. It is possible, however, that some women experienced menstrual irregularities and began using hormonal contraception specifically for this problem, which subsequently did not resolve and which after further investigation was found to be due to an undiagnosed endometrial cancer. The effect of such a protopathic bias would be to produce a higher risk of cancer early in the period of contraceptive use. Our sensitivity analyses in which we excluded periods of observation prior to diagnosis, and which no longer found an increased risk of endometrial cancer among current users of hormonal contraceptives with short durations of use, suggest that protopathic bias has affected our results. The overall effect will be to underestimate in ever users the 'true' protective effect of hormonal contraception on endometrial cancer risk. In other words, the overall estimates of endometrial cancer in ever users of hormonal contraceptives seen in our study are likely to be conservative. This bias may also explain our finding of an increased risk of sarcoma in association with current or recent use of progestin-only products.

Although the sensitivity analyses have addressed concerns about possible protopathic bias, they do not remove any lingering effects from previous use of combined hormonal contraceptives. It is possible that the significantly reduced risk of any endometrial cancer among current or recent users of the LNG-IUS (Table 4S), and type I endometrial cancer (Table 5S) results from previous combined hormonal contraceptive use rather than the LNG-IUS itself. Unfortunately, very few women in our study (i.e. <1% of ever hormonal contraceptive users for which we have full contractive history documented, data not shown) were exclusive users of progestin-only products, preventing a direct examination of the cancer risks associated with these products. We advise caution, therefore, when interpreting the progestin-only risk estimates.

1.4.1 Conclusion

Users of more recently available combined hormonal contraceptives continue to benefit from a substantial, persisting reduced risk of endometrial cancer. This appears to be a class rather than product-specific effect.

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1.7 References

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Table 1. Characteristics of non, former and current or recent users of different types of hormonal contraception.

Type of hormonal contraception used at/after 01/01/95	Dates on market during study*	Person-years	Age mean (SD)	Education† Elementary (%)	Education† University (%)	Nulliparous (%)	Tubal sterilization (%)	Endometriosis (%)	Family history‡ (%)	BMI§ mean(SD)	Smoking‖ (%)
Non-use¶		7,935,787	35.1 (11.9)	21.8	5.2	86.1	6.6	0.3	2.3	24.4 (5.2)	21.4
Former use (>12 months ago)		4,405,210	36.6 (8.0)	18.2	7.6	46.2	9.5	0.9	2.8	24.0 (4.8)	24.3
Current or recent use		8,820,317	29.2 (8.5)	13.8	5.1	74.8	1.1	0.5	2.5	24.1 (4.9)	24.7
Current or recent use of combined hormonal contraception:											
Oral 50 µg EE**											
Norethisterone	1995-2002	57,339	32.2 (8.8)	32.6	2.0	89.4	2.7	0.4	2.6	24.7 (5.3)	46.6
Levonorgestrel	1995-2009	82,384	34.6 (9.5)	31.3	3.4	86.5	3.3	0.9	2.5	24.7 (5.4)	46.0
Oral 20-40 µg EE											
Norethisterone	1995-	164,966	28.1 (7.9)	21.8	3.9	86.6	1.0	0.2	2.8	25.0 (5.3)	32.0
Levonorgestrel	1995-	1,014,902	30.5 (8.9)	15.0	3.3	77.1	0.9	0.4	2.3	24.2 (4.9)	27.5
Norgestimate	1995-	720,084	27.9 (8.0)	14.5	4.9	78.3	0.9	0.5	2.4	24.3 (5.0)	27.8
Desogestrel	1995-	1,657,589	27.6 (8.1)	13.1	4.9	79.8	0.7	0.6	2.4	24.3 (4.9)	26.1
Gestodene	1995-	2,983,440	27.7 (8.0)	13.8	4.7	79.7	0.7	0.4	2.5	24.4 (5.0)	26.5
Drospirenone	2001-	591,917	26.6 (7.9)	8.9	5.1	78.4	0.7	0.8	2.3	23.9 (4.7)	24.1
Cyproterone	1995-	317,600	27.3 (7.4)	11.6	6.4	85.3	0.7	0.4	2.4	23.5 (4.7)	28.0
E2V††, dienogest	2009-	13,990	33.8 (10.2)	8.7	6.9	55.4	2.5	1.7	2.3	23.5 (4.3)	19.0
Non-oral											
Patch	2003-	15,347	27.0 (7.8)	14.1	2.1	63.6	0.9	0.9	1.7	23.5 (4.7)	28.3
Vaginal ring	2002-	124,212	28.2 (7.1)	8.6	5.6	68.7	0.5	0.7	2.2	23.7 (4.5)	24.0
Current or recent use of progestin-only products:											
Oral											
Norethisterone	1995-	157,796	34.8 (8.3)	17.5	7.2	57.7	1.0	0.5	2.8	23.6 (4.6)	20.0
Levonorgestrel	1995-2005	11,513	37.6 (8.1)	22.1	7.9	80.0	1.1	0.2	2.9	24.1 (4.4)	18.2
Desogestrel	2001-	123,209	32.4 (8.3)	10.6	7.1	45.1	1.1	1.6	3.0	23.7 (4.6)	18.4
Non-oral											
MPA depot	1995-	27,783	27.7 (9.0)	36.8	0.4	72.5	2.2	0.6	2.4	25.7 (6.3)	54.5
Implant	1999-	58,269	26.9 (8.5)	18.0	1.8	68.4	1.6	0.5	2.1	25.0 (5.7)	35.3
LNG-IUS	1995-	697,977	39.9 (6.5)	12.3	9.6	33.1	4.0	1.1	2.9	23.9 (4.5)	18.6

*From this year onwards to end of the study. †Percentage with elementary school only education and percentage with University with research qualification education. ‡Family history of premenopausal breast or ovarian cancer. §Available since 2004 only in parous women n=322,619, 73% unknown BMI. ‖Available since 1991 only in parous women n=512,075, 57% unknown smoking. ¶No record of redeemed prescriptions for hormonal contraceptives during study period. **Ethinylestradiol. ††Estradiol valerate. Descriptive statistics were calculated as the average person-time with a given characteristic divided by the total amount of person-time on a specific hormonal contraception. The descriptive percentages represent the percentage of person-time with a given characteristic.

Table 2. Incidence rate ratio of endometrial cancer in users of hormonal contraception (full cohort)

	Person-years	Endometrial cancer, N	Age-adjusted incidence/100,000	Adjusted* rate ratio (95% confidence interval)
Non-use	7,935,787	362	3.3	1.00
Ever use (any hormonal)	13,225,527	187	1.9	0.60 (0.49 to 0.73)
Former use (any hormonal)	4,405,210	87	1.7	0.54 (0.42 to 0.70)
Current or recent use:				
Any hormonal	8,820,317	100	2.1	0.65 (0.52 to 0.83)
Combined	*7,743,769*	*62*	*1.8*	*0.57 (0.43 to 0.75)*
LNG-IUS	*697,977*	*32*	*2.7*	*0.97 (0.66 to 1.42)*
Other progestin-only	*378,571*	*6*	*2.2*	*0.61 (0.27 to 1.37)*
Duration of current use (any hormonal contraception)[†]				
≤1 year	1,262,134	38	7.6	2.48 (1.76 to 3.50)
>1-≤5 years	4,054,649	38	2.4	0.70 (0.50 to 0.98)
>5-≤10 years	2,575,287	14	0.9	0.28 (0.16 to 0.48)
>10 years	928,248	10	0.9	0.22 (0.12 to 0.42)
Duration of current use (combined)[‡]				
≤1 year	*1,183,171*	*25*	*6.2*	*1.95 (1.29 to 2.96)*
>1-≤5 years	*3,640,510*	*20*	*1.8*	*0.56 (0.35 to 0.90)*
>5-≤10 years	*2,201,667*	*11*	*1.0*	*0.32 (0.17 to 0.58)*
>10 years	*718,422*	*6*	*0.7*	*0.18 (0.08 to 0.41)*
Duration of current (LNG-IUS)[§]				
≤1 year	*23,511*	*12*	*26.6*	*7.97 (4.47 to 14.20)*
>1-≤5 years	*259,471*	*15*	*2.9*	*0.95 (0.56 to 1.61)*
>5 years	*414,995*	*5*	*0.9*	*0.24 (0.10 to 0.60)*
Time since last current use of any hormonal contraception[¶]				
>1-≤5 years	2,412,035	36	1.7	0.56 (0.40 to 0.80)
>5-≤10 years	1,357,368	28	1.5	0.51 (0.34 to 0.76)
>10 years	635,807	23	1.6	0.57 (0.36 to 0.89)
Sensitivity analysis: incidence rate ratio of endometrial cancer in users of hormonal contraception with one year period of exposure prior to diagnosis removed (see Table 4S for full results of sensitivity analysis)				
Non-use	*7,935,261*	*356*		*1.00**
Current or recent use:				
Any hormonal	*8,820,055*	*67*		*0.41 (0.31 to 0.55)*
Combined	*7,743,561*	*42*		*0.35 (0.25 to 0.48)*
LNG-IUS	*697,937*	*18*		*0.58 (0.36 to 0.95)*
Other progestin-only	*378,558*	*7*		*0.71 (0.33 to 1.51)*

*Adjusted for: calendar year, education, age, parity, family history of breast or ovarian cancer, tubal sterilization and endometriosis.

[†] p-trend <0.001; [‡] p-trend <0.001; [§] p-trend <0.001; [¶] p-trend <0.001

Table 3. Incidence rate ratio of endometrial cancer in former users of hormonal contraception by duration of use and time since last use (full cohort).

	Time since last use								
	>1-≤5 years			>5-≤10 years			>10 years		
Duration of use	Person-years	Events	RR (95% CI)*	Person-years	Events	RR (95% CI)*	Person-years	Events	RR (95% CI)*
≤1 year	658,343	16	0.84 (0.51 to 1.40)	455,697	12	0.62 (0.34 to 1.11)	302,238	14	0.63 (0.36 to 1.10)
>1-≤5 years	1,028,001	14	0.59 (0.34 to 1.02)	619,453	12	0.51 (0.28 to 0.92)	295,454	9	0.43 (0.22 to 0.87)
>5 years	725,692	6	0.24 (0.10 to 0.54)	282,218	4	0.26 (0.09 to 0.70)	38,110	<3†	n/a

*Adjusted for: calendar year, education, age, parity, family history of breast or ovarian cancer, tubal sterilization and endometriosis.

†Data not available for presentation due to less than three events, estimates therefore not available (n/a) and total person-years rounded to nearest five.

Table 4. Incidence rate ratio of endometrial cancer in users of different types of hormonal contraception in women followed up until first switch in hormonal contraception i.e. "no change cohort".

	Person-years	Endometrial cancer, N	Adjusted* rate ratio (95% confidence interval)
Non-use	7,935,787	362	1.00
Ever use (any hormonal)	7,121,755	111	0.61 (0.49 to 0.76)
Former use (any hormonal)	2,536,713	62	0.59 (0.44 to 0.78)
Current or recent use:			
Any hormonal	4,585,042	49	0.63 (0.47 to 0.86)
Combined	4,312,942	25	0.41 (0.27 to 0.62)
LNG-IUS	168,442	21	1.65 (1.05 to 2.59)
Other progestin-only	103,658	3	0.73 (0.23 to 2.27)
Current or recent use of combined hormonal contraception:			
Oral			
Norethisterone 50 µg EE	36,400	<3†	n/a
Levonorgestrel 50 µg EE	47,140	<3	n/a
Norethisterone 30-35 µg EE	115,940	<3	n/a
Levonorgestrel 30-35 µg EE	518,530	<3	n/a
Desogestrel 20-30 µg EE	988,159	5	0.43 (0.18 to 1.04)
Gestodene 20-35 µg EE	1,885,631	6	0.27 (0.12 to 0.60)
Drospirenone 20-35 µg EE	188,800	<3	n/a
Norgestimate 35 µg EE	375,374	7	1.61 (0.76 to 3.43)
Cyproterone 30 µg EE	141,980	<3	n/a
Estradiol valerate, dienogest	1,010	<3	n/a
Non-oral			
Patch	2,250	<3	n/a
Vaginal ring	11,730	<3	n/a
Current or recent use of progestin-only contraception:			
Oral			
Norethisterone	66,760	<3	n/a
Levonorgestrel	6,950	<3	n/a
Desogestrel	12,100	<3	n/a
Non-oral			
MPA depot	7,300	<3	n/a
Implant	10,550	<3	n/a
Duration of current use (any hormonal contraception)			
≤1 year	1,059,203	28	2.18 (1.46 to 3.23)
>1-≤5 years	2,309,005	15	0.46 (0.28 to 0.78)
>5-≤10 years	960,090	<3	n/a
>10 years	256,742	5	0.35 (0.14 to 0.85)
Duration of current use (combined)			
≤1 year	*1,000,323*	*16*	*1.46 (0.87 to 2.45)*
>1-≤5 years	*2,143,641*	*4*	*0.18 (0.07 to 0.49)*
>5-≤10 years	*919,150*	*<3*	*n/a*
>10 years	*249,829*	*4*	*0.30 (0.11 to 0.82)*
Duration of current use (LNG-IUS)			
≤1 year	*19,340*	*12*	*9.39 (5.27 to 16.70)*
>1-≤5 years	*118,170*	*8*	*0.90 (0.45 to 1.83)*
>5 years	*30,935*	*<3*	*n/a*
Time since last current use of any hormonal contraception			
>1-≤5 years	1,266,623	23	0.65 (0.42 to 0.99)
>5-≤10 years	806,785	18	0.51 (0.32 to 0.83)
>10 years	463,305	21	0.60 (0.38 to 0.96)

*Adjusted for: calendar year, age, education, parity, family history of breast or ovarian cancer, tubal sterilization and endometriosis. †Data not available for presentation due to less than three events, estimates therefore not available (n/a) and total person-years rounded to nearest five.

Table 5. Incidence rate ratio of different histological types of endometrial cancer associated with hormonal contraception (full cohort).

	Person-years	Endometrial cancer, N	Adjusted* rate ratio (95% confidence interval)
Type I			
Non-use	7,935,787	264	1.00
Current or recent use:			
Any hormonal contraception	8,820,317	52	0.47 (0.35 to 0.65)
Combined	*7,743,770*	*32*	*0.42 (0.28 to 0.61)*
LNG-IUS	*697,980*	*17*	*0.68 (0.41 to 1.13)*
Other progestin-only	*378,570*	*3*	*0.41 (0.13 to 1.29)*
Former use	4,405,210	57	0.47 (0.34 to 0.64)
Type II			
Non-use	7,935,787	22	1.00
Current or recent use:			
Any hormonal contraception	8,820,317	7	0.73 (0.28 to 1.86)
Combined	*7,7,43,770*	*<3†*	*n/a*
LNG-IUS	*697,980*	*5*	*2.99 (0.97 to 9.23)*
Other progestin-only	*378,570*	*<3*	*n/a*
Former use	4,405,210	5	0.56 (0.19 to 1.65)
Sarcomas			
Non-use	7,935,787	47	1.00
Current or recent use:			
Any hormonal contraception	8,820,317	27	1.82 (1.11 to 3.02)
Combined	*7,743,770*	*18*	*1.60 (0.90 to 2.84)*
LNG-IUS	*697,980*	*8*	*3.24 (1.43 to 7.34)*
Other progestin-only	*378,570*	*<3*	*n/a*
Former use	4,405,210	13	1.05 (0.53 to 2.05)
Malignant tumor not otherwise specified			
Non-use	7,935,787	29	1.00
Current or recent use:			
Any hormonal contraception	8,820,317	14	0.65 (0.32 to 1.30)
Combined	*7,743,770*	*11*	*0.69 (0.32 to 1.48)*
LNG-IUS	*697,980*	*<3*	*n/a*
Other progestin-only	*378,570*	*<3*	*n/a*
Former use	4,405,210	12	0.56 (0.27 to 1.16)

*Adjusted for: calendar year, age, education, parity, family history of breast or ovarian cancer, tubal sterilization and endometriosis. †Data not available for presentation due to less than three events, estimates therefore not available (n/a) and total person-years rounded to nearest five.

14 Table 1S. ICD-O-3 codes used to classify histological types of endometrial cancer.

Histological type	ICD-O-3 (9) codes (all ending with behavior invasive digit 3)
Type I	M8380/8381/8382/8383/8210/8211/8260/8262/8263/8570/8480/8481/8140
Type II	M8441/8460/8461/8050/8070/8071/8072/8560/8041/8323/8310
Sarcomas	M8800-8806/8810-8833/8850-8858/8890-8896/8900-8902/8910-8912/8930-8931
Malignant tumor not otherwise specified	All other morphology codes supplied with the C54 cancer registration

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Table 2S. Incidence rate ratio of endometrial cancer in users of different hormonal contraceptive products during follow-up of the full cohort.

	Person-years	Endometrial cancer, N	Adjusted* rate ratio (95% confidence interval)
Non-use	7,935,787	362	1.00
Current or recent use of combined hormonal contraception:			
Oral			
Norethisterone 50 µg EE	57,340	<3†	n/a
Levonorgestrel 50 µg EE	82,234	3	0.94 (0.30 to 2.92)
Norethisterone 30-35 µg EE	164,966	4	1.71 (0.63 to 4.59)
Levonorgestrel 30-35 µg EE	1,014,902	8	0.36 (0.18 to 0.73)
Desogestrel 20-30 µg EE	1,657,589	10	0.47 (0.25 to 0.88)
Gestodene 20-35 µg EE	2,983,440	18	0.47 (0.29 to 0.77)
Drospirenone 20-35 µg EE	591,917	8	1.32 (0.64 to 2.70)
Norgestimate 35 µg EE	720,084	10	1.07 (0.56 to 2.02)
Cyproterone 30 µg EE	317,600	<3	n/a
Estradiol valerate, dienogest	13,990	<3	n/a
Non-oral			
Patch	15,350	<3	n/a
Vaginal ring	124,210	<3	n/a
Current or recent use of progestin-only contraception:			
Oral			
Norethisterone	157,796	3	0.59 (0.19 to 1.83)
Levonorgestrel	11,510	<3	n/a
Desogestrel	123,210	<3	n/a
Non-oral			
MPA depot	27,780	<3	n/a
Implant	58,270	<3	n/a
LNG-IUS	697,977	32	0.95 (0.65 to 1.40)

*Adjusted for: calendar year, age, education, parity, family history of breast or ovarian cancer, tubal sterilization and endometriosis. †Data not available for presentation due to less than three events, estimates therefore not available (n/a) and total person-years rounded to nearest five.

Table 3S. Incidence rate ratio of endometrial cancer in users of different hormonal contraceptive products in follow-up of the full cohort: all parous women.

	Person-years	Endometrial cancer, N	Adjusted* rate ratio (95% confidence interval)
Non-use	5,501,750	216	1.00
Ever use (any hormonal)	9,934,478	130	0.66 (0.52 to 0.85)
Former use (any hormonal)	3,716,323	57	0.54 (0.39 to 0.74)
Current or recent use:			
Any hormonal	6,218,155	73	0.78 (0.59 to 1.04)
Combined	*5,282,426*	*40*	*0.65 (0.46 to 0.92)*
LNG-IUS	*657,424*	*27*	*1.08 (0.70 to 1.66)*
Other progestin-only	*278,304*	*6*	*1.02 (0.45 to 2.32)*
Current or recent use of combined hormonal contraception:			
Oral			
Norethisterone 50 µg EE	48,760	<3†	n/a
Levonorgestrel 50 µg EE	67,310	<3	n/a
Norethisterone 30-35 µg EE	138,811	3	2.23 (0.71 to 7.01)
Levonorgestrel 30-35 µg EE	623,426	4	0.31 (0.11 to 0.84)
Desogestrel 20-30 µg EE	1,135,914	6	0.51 (0.22 to 1.15)
Gestodene 20-35 µg EE	2,106,407	12	0.56 (0.31 to 1.01)
Drospirenone 20-35 µg EE	337,856	6	1.87 (0.82 to 4.29)
Norgestimate 35 µg EE	536,313	7	1.31 (0.61 to 2.79)
Cyproterone 30 µg EE	196,890	<3	n/a
Estradiol valerate, dienogest	8,235	<3	n/a
Non-oral			
Patch	9,260	<3	n/a
Vaginal ring	73,240	<3	n/a
Current or recent use of progestin-only contraception:			
Oral			
Norethisterone	134,453	3	0.91 (0.29 to 2.86)
Levonorgestrel	9,950	<3	n/a
Desogestrel	88,960	<3	n/a
Non-oral			
MPA depot	13,920	<3	n/a
Implant	31,020	<3	n/a
Duration of current use of any hormonal contraception			
≤1 year	850,560	27	2.95 (1.96 to 4.45)
>1-≤5 years	2,753,004	28	0.84 (0.56 to 1.26)
>5-≤10 years	1,907,157	10	0.32 (0.17 to 0.60)
>10 years	707,433	8	0.30 (0.14 to 0.62)
Time since last current use of any hormonal contraception			
>1-≤5 years	1,990,299	29	0.71 (0.48 to 1.06)
>5-≤10 years	1,168,143	14	0.38 (0.22 to 0.66)
>10 years	557,881	14	0.49 (0.27 to 0.87)

*Adjusted for: calendar year, age, education, parity, family history of breast or ovarian cancer, tubal sterilization, endometriosis, antenatal smoking status and body mass index. †Data not available for presentation due to less than three events, estimates therefore not available (n/a) and total person-years rounded to nearest five.

Table 4S. Sensitivity analysis: incidence rate ratio of endometrial cancer in users of hormonal contraception with one year period of exposure prior to diagnosis removed (full cohort).

	Person-years	Endometrial cancer, N	Adjusted* rate ratio (95% confidence interval)
Non-use	7,935,261	356	1.00
Ever use (any hormonal)	13,225,087	159	0.50 (0.40 to 0.61)
Former use (any hormonal)	4,405,032	92	0.59 (0.46 to 0.76)
Current or recent use:			
Any hormonal	8,820,055	67	0.41 (0.31 to 0.55)
Combined	*7,743,561*	*42*	*0.35 (0.25 to 0.48)*
LNG-IUS	*697,937*	*18*	*0.58 (0.36 to 0.95)*
Other progestin-only	*378,558*	*7*	*0.71 (0.33 to 1.51)*
Duration of current use (any hormonal contraception)[†]			
≤1 year	1,262,087	13	0.75 (0.43 to 1.31)
>1-≤5 years	4,054,530	32	0.55 (0.38 to 0.80)
>5-≤10 years	2,575,220	14	0.27 (0.16 to 0.47)
>10 years	928,219	8	0.20 (0.10 to 0.42)
Duration of current use (combined)[‡]			
≤1 year	*1,183,131*	*9*	*0.61 (0.31 to 1.19)*
>1-≤5 years	*3,640,418*	*18*	*0.45 (0.27 to 0.73)*
>5-≤10 years	*2,201,611*	*10*	*0.26 (0.14 to 0.49)*
>10 years	*718,401*	*5*	*0.17 (0.07 to 0.41)*
Duration of current (LNG-IUS)[§]			
≤1 year	*23,505*	*<3*	*n/a*
>1-≤5 years	*259,451*	*10*	*0.69 (0.37 to 1.31)*
>5 years	*414,980*	*6*	*0.36 (0.16 to 0.82)*
Time since last current use of any hormonal contraception[¶]			
>1-≤5 years	2,411,948	41	0.63 (0.45 to 0.88)
>5-≤10 years	1,357,312	30	0.55 (0.37 to 0.80)
>10 years	635,772	21	0.59 (0.37 to 0.94)

*Adjusted for: calendar year, education, age, parity, family history of breast or ovarian cancer, tubal sterilization and endometriosis.

[†] p-trend <0.001; [‡] p-trend <0.001; [§] p-trend <0.001; [¶] p-trend <0.001

Table 5S. Sensitivity analysis: incidence rate ratio of different histological types of endometrial cancer associated with hormonal contraception with one year period of exposure prior to diagnosis removed (full cohort).

	Person-years	Endometrial cancer, N	Adjusted* rate ratio (95% confidence interval)
Type I			
Non-use	7,935,261	259	1.00
Current or recent use:			
Any hormonal contraception	8,820,055	31	0.26 (0.18 to 0.39)
Combined	*7,743,560*	*20*	*0.23 (0.14 to 0.37)*
LNG-IUS	*697,937*	*7*	*0.30 (0.14 to 0.64)*
Other progestin-only	*378,560*	*4*	*0.55 (0.20 to 1.47)*
Former use	4,405,032	60	0.50 (0.37 to 0.68)
Type II			
Non-use	7,935,261	23	1.00
Current or recent use:			
Any hormonal contraception	8,820,055	4	0.39 (0.13 to 1.24)
Combined	*7,7,43,560*	*<3†*	*n/a*
LNG-IUS	*697,937*	*3*	*1.98 (0.52 to 7.53)*
Other progestin-only	*378,560*	*<3*	*n/a*
Former use	4,405,032	6	0.73 (0.26 to 2.02)
Sarcomas			
Non-use	7,935,261	45	1.00
Current or recent use:			
Any hormonal contraception	8,820,055	19	1.25 (0.71 to 2.22)
Combined	*7,743,560*	*13*	*1.11 (0.58 to 2.12)*
LNG-IUS	*697,937*	*5*	*2.15 (0.80 to 5.78)*
Other progestin-only	*378,560*	*<3*	*n/a*
Former use	4,405,032	14	1.20 (0.61 to 2.34)
Malignant tumor not otherwise specified			
Non-use	7,935,261	29	1.00
Current or recent use:			
Any hormonal contraception	8,820,055	13	0.64 (0.31 to 1.30)
Combined	*7,743,560*	*9*	*0.57 (0.25 to 1.30)*
LNG-IUS	*697,937*	*3*	*0.80 (0.23 to 2.77)*
Other progestin-only	*378,560*	*<3*	*n/a*
Former use	4,405,032	12	0.62 (0.30 to 1.30)

*Adjusted for: calendar year, age, education, parity, family history of breast or ovarian cancer, tubal sterilization and endometriosis. †Data not available for presentation due to less than three events, estimates therefore not available (n/a) and total person-years rounded to nearest five.