Association between contemporary hormonal contraception and ovarian cancer in women of reproductive age in Denmark: prospective, nationwide cohort study

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ABSTRACT

OBJECTIVES
To investigate the association between contemporary combined hormonal contraceptives (including progestogen types in combined preparations and all progestogen-only products) and overall and specific types of ovarian cancer.

DESIGN
Prospective, nationwide cohort study.

SETTING
Denmark, 1995-2014.

PARTICIPANTS
All women aged 15-49 years during 1995-2014 were eligible. Women were excluded if they immigrated after 1995, had cancer (except non-melanoma skin cancer), had venous thrombosis, or were treated for infertility before entry (final study population included 1 879 227 women). Women were categorised as never users (no record of being dispensed hormonal contraception), current or recent users (≤1 year after stopping use), or former users (>1 year after stopping use) of different hormonal contraceptives.

MAIN OUTCOME MEASURES
Poisson regression was used to calculate relative risk of ovarian cancer among users of any contemporary combined hormonal contraceptives and by progestogen type in combined preparations and all progestogen-only products, including non-oral preparations. Separate analyses examined women followed up to their first contraception type switch and those with full contraceptive histories. Duration, time since last use, and tumour histology were examined and the population prevented fraction were calculated.

RESULTS
During 21.4 million person years, 1249 incident ovarian cancers occurred. Among ever users of hormonal contraception, 478 ovarian cancers were recorded over 13 344 531 person years. Never users had 771 ovarian cancers during 8 150 250 person years. Compared with never users, reduced risks of ovarian cancer occurred with current or recent use and former use of any hormonal contraception (relative risk 0.58 (95% confidence interval 0.49 to 0.68) and 0.77 (0.66 to 0.91), respectively). Relative risks among current or recent users decreased with increasing duration (from 0.82 (0.59 to 1.12) with ≤1 year use to 0.26 (0.16 to 0.43) with >10 years' use; P<0.001 for trend). Similar results were achieved among women followed up to their first switch in contraceptive type. Little evidence of major differences in risk estimates by tumour type or progestogen content of combined oral contraceptives was seen. Use of progestogen-only products were not associated with ovarian cancer risk. Among ever users of hormonal contraception, the reduction in the age standardised absolute rate of ovarian cancer was 3.2 per 100 000 person years. Based on the relative risk for the never use versus ever use categories of hormonal contraception (0.66), the population prevented fraction was estimated to be 21%—that is, use of hormonal contraception prevented 21% of ovarian cancers in the study population.

CONCLUSIONS
Use of contemporary combined hormonal contraceptives is associated with a reduction in ovarian cancer risk in women of reproductive age—an effect related to duration of use, which diminishes after stopping use. These data suggest no protective effect from progestogen-only products.

Introduction
Hormonal contraception is popular. At least 100 million women worldwide use hormonal contraception every day.[1] In 2012, an estimated 238 719 women around the world were diagnosed with a new ovarian cancer and 151 917 died from the condition.[2] Survival from ovarian cancer is poorer than from many other cancers; with an overall, age standardised survival rate at five years of 30-40% worldwide, varying according to stage at diagnosis.[3] Previous research has shown a reduced risk of ovarian cancer in users of combined oral contraceptives, an effect that persists for many years after stopping use.[4-9] However, most of the evidence relates to the use of older and higher

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

Previous research relating to the use of older and higher dose preparations of oestrogen containing older progestogens has shown a reduced risk of ovarian cancer in users of combined oral hormonal contraceptives

This reduced risk has been shown to persist for many years after stopping use of these combined oral contraceptives

WHAT THIS STUDY ADDS

In this large, prospective, population based study of women aged 15-49 years in Denmark, use of contemporary combined oral contraceptives containing newer progestogens was associated with a reduction in the risk of ovarian cancer

Few women in the study were exclusive users of progestogen-only contraceptives; therefore, evidence regarding progestogen-only contraceptives was limited, with no evidence of beneficial ovarian cancer effects among exclusive users of these products

dose preparations of oestrogen containing older progestogens. Therefore, this evidence might not reflect the impact of substantial changes in hormonal contraception that have occurred over time. Such changes have occurred in formulations of combined oral contraceptives (notably reductions in oestrogen dose and the introduction of newer progestogens such as desogestrel, gestodene, and drospirenone), patterns of administration (continuous *v* monthly cycles in which 21 days of combined hormonal contraception is followed by seven hormone-free days during which a withdrawal bleed occurs), new non-oral routes of administration, and an increased use of progestogen-only preparations.[10]

It is important for users of contemporary combined oral contraceptives to know whether they are likely to experience the same pattern of ovarian cancer benefit as users in the older studies, and whether a benefit is specific to any particular formulation. Users of other hormonal contraceptive methods (including progestogen-only oral contraceptives and the levonorgestrel releasing intrauterine system) also should know whether they are at a reduced risk of ovarian cancer. Such information is important for putting into context the risks of other known cancers linked to contemporary hormonal contraception, such as breast cancer.[11] Current evidence is insufficient for combined oral contraception[4-9] as well as for other types of hormonal contraception.[12-16] We report here a large investigation of contemporary hormonal contraceptive use and ovarian cancer in a national cohort of young Danish women.

Methods
Data linkage
The Danish Sex Hormone Register Study, which has been described previously,[17 18] follows a national cohort of women aged 15-79 years. It was established to investigate the relation between hormone use and the risk of cancer or cardiovascular disease. The study dataset uses an individual's personal identification number in the Civil Registration System to link data from several national registries:

- Statistics Denmark, for education information
- National Register of Medicinal Product Statistics, for hormonal contraceptive prescriptions dispensed since January 1994 and considered complete since 1 January 1995
- Danish Cancer Registry, for histologically verified cancers since 1943 and family history of premenopausal (age <50 years) breast or ovarian cancer in mothers or sisters
- National Birth Register, for all births since 1973 and information on smoking status (since 1991) and body mass index (since 2004)
- National Health Register, for hospital discharge diagnoses and surgeries since 1977.

The personal identification number system, in use since 1968, assigns a unique number to each resident in Denmark and is used as a key personal identifier in all national registries, thereby ensuring accurate linkage of different databases.

Study population
All women living in Denmark aged 15-49 years from 1 January 1995 to 31 December 2014 were eligible for the study unless they immigrated after 1995 (total number eligible=1 904 094). Women were excluded if they had cancer (except non-melanoma skin cancer), had venous thrombosis, or were treated for infertility before study entry (indicated by a redeemed prescription for ovarian stimulating drugs, Anatomical Therapeutic Chemical Classification (ATC) system code MG03G in the National Prescription Registry). The final study population comprised 1 879 227 women. The women were followed up to first diagnosis of ovarian cancer (ICD-10 (international classification of diseases, 10th revision)[19] code C56), death, emigration, age 50 years, or end of follow-up (31 December 2014), whichever came first. During follow-up, women were censored permanently at the date of diagnosis of non-ovarian cancer (except non-melanoma skin cancer), infertility treatment, venous thrombosis, bilateral oophorectomy, or second unilateral oophorectomy. Women were censored temporarily during pregnancy and for six months after delivery.

Hormonal contraception
Information about redeemed prescriptions included date of redemption, ATC code, dose, number of packages, defined daily doses, and route of administration. These data were updated daily to allow identification of when women started use (date when prescription was redeemed), stopped use (estimated date when prescription finished, based on number of packs issued), or switched use of hormonal contraception (redemption date of prescription for a different product). Using the methods of Nielsen and colleagues,[20] gaps between prescriptions of fewer than 28 days were filled in prospectively. We assumed that the levonorgestrel intrauterine system was used for four years unless another hormonal contraceptive product was redeemed or pregnancy occurred before the end of the four year period. Women were categorised as never users (no record of being dispensed hormonal contraception), current or recent users (up to one year after stopping use), or former users (more than one year after stopping use) of different hormonal contraceptives.

Statistical analysis
We calculated age standardised incidence rates of ovarian cancers per 100 000 person years, using the age distribution of the cohort as standard. Risk of ovarian cancer among users of the different product groups was analysed by a Poisson regression model in SAS version 9.3 (SAS Institute). Adjusted incidence rate ratios (referred to here as relative risks) and their surrounding 95% confidence intervals were calculated for each model, with never users as the reference

group. The adjusted models included the following time varying covariates:

- Calendar year
- Hormonal contraceptive use
- Parity (0, 1, 2, 3, 4, >4)
- Age group (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49 years)
- Education (elementary school only, high school only, further education excluding college/university, college/university education, university education with research qualifications, unknown)
- Tubal sterilisation (yes, no)
- Hysterectomy (yes, no)
- Endometriosis (yes, no)
- Polycystic ovary syndrome (yes, no)
- Family history of breast or ovarian cancer (yes, no).

Additional models adjusting for smoking status (current smoker, non-smoker, unknown at the time smoking status was ascertained antenatally) and body mass index when ascertained antenatally (<18.5, 18.5-25, >25-30, >30, unknown), were carried out in the subset of parous women with this information.

The main analysis compared ever users, former users, and current or recent users of any hormonal contraception with never users as reference. Separate analyses stratified the data by duration of use, by time since last current use, and by ovarian tumour histology. Ovarian tumour histology used the same groupings as the Collaborative Group on Epidemiological Studies of Ovarian Cancer,[4] and used the following ICD-O-3 codes[21]: epithelial clear cell (M8310/8313), epithelial endometrioid (M8380), epithelial mucinous (M8470/8480/8490), and epithelial serous (M8441/8460); non-epithelial (M8620/8631/8650/8 862/8890/8933/8951/8963/9080/9084/9110); and malignant tumour not otherwise specified (all other morphology codes supplied alongside the C56 cancer registration) and ending with the behaviour invasive digit 3. We tested for the trends for duration of use and time since last current use by including the duration/ time since variables as an ordinal variable, with values set to the median duration within each category.[22]

Comparisons between main contraceptive groupings were also conducted for women followed up to their first change in hormonal contraception, for those aged 15 years on or after 1 January 1995 (that is, those with a fully documented hormonal contraceptive history), and for epithelial ovarian cancers only. Previous studies have indicated a persisting protective effect from previous use of oral combined contraception.[4] [6] [9] To minimise the effects of previous use while ensuring that we had sufficient data for analysis, our risk estimates for different hormonal preparations were derived mainly among women followed up to their first change in hormonal contraception during the study. Up to 31 December 2003, tumour staging in the Danish Cancer Registry used the International Federation of Gynaecology and Obstetrics (FIGO) staging classification,[23] after which the Union for International Cancer Control Tumour, Node, Metastasis

(TNM) classification was used.[24] When necessary, we converted TNM classification information into the FIGO stage classification.[25] We then examined tumour FIGO stage by age at diagnosis and calculated the frequency of the different tumour types by stage at diagnosis. We calculated the population prevented fraction (population prevented fraction=prevalence$_{exposure}$(1− relative risk)) associated with ever use of any hormonal contraception by using the relative risk of never use versus ever use of any hormonal contraception. The population prevented fraction is the proportion (expressed as a percentage) of the ovarian cancers in the cohort that has been prevented by ever use of any hormonal contraception.

Patient and public involvement
Patients or members of the public were not invited to comment on the research question, study design, or to interpret the results. Since this was a population study using existing data, asking them to share patient relevant outcomes was not possible. They were not invited to contribute to the writing or editing of this document for readability or accuracy. The results will be shared with the media and disseminated to members of the public through appropriate media channels.

Results
During the 20 year study period, 1249 women aged 15-49 years had incident ovarian cancer during more than 21.4 million person years of observation (about 11.4 years per woman). At study entry, 756 943 women younger than 20 years then had a mean follow-up of 10.8 years (standard deviation 6.0), 379 808 aged 20-29 years had a mean follow-up of 16.8 (5.0) years, 373 167 aged 30-39 years had a mean follow-up of 13.8 (4.2) years, and 369 309 aged 40 years and older had a mean follow-up of 4.7 (2.9) years. During 13 344 531 person years of follow-up, 478 ovarian cancers were found among ever users of any hormonal contraception. In never users, 771 ovarian cancers occurred during 8 150 250 person years. Median age at ovarian cancer diagnosis was 44.4 years (interquartile range 38.9-47.7). Most hormonal contraceptive use was related to combined oral contraception (86%, 7 612 267/8 839 374 person years of current or recent use; table 1). Current or recent users of the levonorgestrel intrauterine system were older and more likely to be parous than women using other products. Generally, a higher percentage of parous women were using non-oral routes of hormonal contraception or oral progestogen-only products than nulliparous women. Few women (contributing about 2-3% of total person years) had a family history of early (before age 50 years) ovarian or breast cancer.

The age adjusted incidence of ovarian cancer was highest in women who were never users of hormonal contraception (7.5 per 100 000 person years; table 2). Among ever users of hormonal contraception, reduction in the age standardised absolute rate of ovarian cancer

Table 1 | Characteristics of never, former, and current or recent users of different types of hormonal contraception

Type of hormonal contraception (dates on market during study*)	No of person years	Age (years; mean (SD))	Education (%)†		Nulliparous (%)	PCOS (%)	Tubal sterilisation (%)	Hysterectomy (%)	Endometriosis (%)	Family history (%)‡	BMI (mean (SD))§	Smoking (%)¶
			E	U								
Main use groups												
Never use	8 150 250	35.4 (11.8)	22.5	5.4	86.3	0.1	6.9	2.6	0.4	2.3	24.6 (5.3)	21.5
Former use, >12 months ago	4 505 157	36.8 (8.0)	18.0	9.4	46.7	0.3	9.9	2.2	1.0	2.8	24.2 (5.0)	24.5
Current or recent use	8 839 374	29.2 (8.3)	14.3	7.1	74.8	0.2	1.1	0.2	0.4	2.5	24.4 (5.0)	24.7
Current or recent use of combined hormonal contraception												
Oral, 50 µg ethinylestradiol												
Norethisterone (1995-2002)	57 516	32.3 (8.7)	32.6	2.0	89.4	0.03	2.7	0.3	0.2	2.5	24.8 (5.5)	46.6
Levonorgestrel (1995-2009)	82 756	34.6 (9.5)	31.4	3.5	86.5	0.06	3.3	0.4	0.5	2.5	24.9 (5.4)	45.9
Oral, 20-40 µg ethinylestradiol												
Norethisterone (1995-)	165 211	28.2 (7.7)	21.9	4.0	86.6	0.04	1.0	0.1	0.1	2.8	25.1 (5.3)	31.9
Levonorgestrel (1995-)	1 016 015	30.5 (8.8)	15.7	6.0	77.1	0.2	0.9	0.1	0.3	2.3	24.5 (5.0)	27.6
Norgestimate (1995-)	721 004	27.9 (7.8)	14.8	6.5	78.3	0.2	0.9	0.1	0.3	2.4	24.6 (5.1)	27.8
Desogestrel (1995-)	1 659 258	27.6 (7.9)	13.6	6.8	79.8	0.1	0.7	0.1	0.4	2.4	24.5 (5.0)	26.2
Gestodene (1995-)	2 985 909	27.7 (7.8)	14.2	6.3	79.7	0.1	0.7	0.1	0.3	2.4	24.7 (5.1)	26.5
Drospirenone (2001-)	592 556	26.6 (7.8)	9.8	8.8	78.4	0.5	0.7	0.1	0.5	2.3	24.1 (4.8)	24.2
Cyproterone (1995-)	317 961	27.3 (7.2)	11.8	8.6	85.3	1.1	0.7	0.1	0.3	2.3	23.7 (4.8)	28.0
Estradiol valerate, dienogest (2009-)	14 081	33.9 (10.1)	8.8	11.6	55.3	1.0	2.5	0.6	1.4	2.2	23.7 (4.6)	19.2
Non-oral												
Patch (2003-)	15 358	27.0 (7.7)	18.6	4.4	63.6	0.5	1.0	0.1	0.6	1.7	23.8 (4.9)	28.3
Vaginal ring (2002-)	124 280	28.2 (7.0)	9.8	12.5	68.6	0.4	0.5	0.0	0.5	2.2	24.0 (4.7)	24.0
Current or recent use of progestogen-only products												
Oral												
Norethisterone (1995-)	158 073	34.8 (8.3)	17.4	9.2	57.7	0.1	1.1	0.2	0.4	2.8	23.9 (4.7)	20.0
Levonorgestrel (1995-2005)	11 544	37.6 (8.3)	22.1	7.9	80.1	0.0	1.1	0.3	0.1	2.9	24.2 (4.5)	18.3
Desogestrel (2001-)	123 539	32.4 (8.3)	10.8	12.7	45.1	0.1	1.2	0.1	0.4	2.9	24.0 (4.8)	18.5
Non-oral												
MPA depot (1995-)	27 832	27.7 (8.9)	43.7	0.5	72.5	0.3	2.3	0.2	0.5	2.4	26.0 (6.4)	54.5
Implant (1999-)	58 371	26.9 (8.4)	24.2	2.7	68.4	0.3	1.6	0.2	0.3	2.1	25.3 (5.8)	35.4
LNG-IUS (1995-)	708 111	40.0 (6.6)	11.6	11.2	33.5	0.2	4.2	1.4	1.1	2.9	24.1 (4.7)	18.7

Descriptive statistics calculated as the average person time with a given characteristic divided by the total amount of person time on a specific hormonal contraceptive; descriptive percentages represent the percentage of person time with a given characteristic.
BMI=body mass index; E=elementary school; LNG-IUS=levonorgestrel intrauterine system; MPA=medroxyprogesterone acetate; PCOS; polycystic ovary syndrome; SD=standard deviation; U=university.
*From this year onwards to end of the study.
†Percentage of participants with elementary school education only and percentage with university education.
‡Family history of premenopausal breast or ovarian cancer.
§Available since 2004 only in parous women (n=322 641, 73% unknown body mass index).
¶Available since 1991 only in parous women (n=512 143, 57% unknown smoking).

was 3.2 per 100 000 person years. Overall, ever users of any hormonal contraception had a reduced risk of ovarian cancer compared with never users (relative risk 0.66 (95% confidence interval 0.58 to 0.76)). Reduced risk estimates were also observed for current or recent use of any hormonal contraception (0.58 (0.49 to 0.68)) as well as for former use (0.77 (0.66 to 0.91)). Current or recent users of progestogen-only products seemed to have a smaller reduction in ovarian cancer risk than users of combined oral contraceptives. The reduced risk of ovarian cancer among current users was stronger with increasing duration of hormonal contraceptive use. The reduced ovarian cancer risk among previous hormonal contraceptive users diminished with time since stopping use, and was non-significant by 10 years after last use. When both time since last use and duration were examined, evidence among former users of any hormonal contraception indicated greater protection with longer durations of use and a suggestion that the protection waned more quickly in those with shorter durations of use (table 3).

Among women followed in the cohort up to their first switch in hormonal contraception (71% of the total period of observation, 15 333 680 person years), there was little evidence of important differences between combined oral contraceptives containing different progestogens, at least for those with sufficient usage to produce precise risk estimates (table 4). In this analysis, progestogen-only products, including the levonorgestrel containing intrauterine system, did not protect against ovarian cancer. For combined products, the pattern of relative risks seen in the full cohort (that is, women followed beyond their first switch in hormonal contraception) were similar (table 1S). Overall similar risk estimates were found in both the full cohort and among parous women followed up to their first switch in hormonal contraception when we adjusted for smoking and body mass index (data not shown).

Restricting the analysis to women with a complete contraception exposure history (those aged 15 years on or after 1 January 1995) reduced the cohort to 596 395 women (31.7% of total number) contributing 25% of the total period of observation (5 417 268 person years) and 6% of all ovarian cancers, reflecting the younger age of this subset of women. Most of the risk

Table 2 | Relative risk of ovarian cancer in users of hormonal contraception according to time since last current use and duration of current use

Use category	No of person years	No of ovarian cancer events	Age standardised incidence per 100 000 person years	Adjusted relative risk (95% CI)*
Never use	8 150 250	771	7.5	1.00
Ever use (any hormonal contraception)	13 344 531	478	4.3	0.66 (0.58 to 0.76)
Former use (any hormonal)	4 505 157	244	5.0	0.77 (0.66 to 0.91)
Current or recent use (any hormonal)	8 839 374	234	4.0	0.58 (0.49 to 0.68)
Current or recent use (combined oral)	7 751 904	175	3.8	0.53 (0.45 to 0.64)
Current or recent use (progestogen only)	1 087 470	59	4.2	0.72 (0.55 to 0.95)
Duration of current or recent use of any hormonal contraception†				
≤1 year	1 265 020	42	5.9	0.82 (0.59 to 1.12)
>1-≤5 years	4 063 111	103	4.6	0.62 (0.50 to 0.77)
>5-≤10 years	2 580 300	71	4.4	0.57 (0.44 to 0.74)
>10 years	930 943	18	1.7	0.26 (0.16 to 0.43)
Time since last current use of any hormonal contraception‡				
>1-≤5 years	2 442 620	110	5.0	0.76 (0.61 to 0.93)
>5-≤10 years	1 397 257	83	4.3	0.78 (0.61 to 0.99)
>10 years	665 281	51	3.8	0.80 (0.59 to 1.08)

*Adjusted for calendar year, parity, age, education, tubal sterilisation, hysterectomy, endometriosis, polycystic ovary syndrome, and family history of breast or ovarian cancer.
†P_{trend}<0.001.
‡P_{trend}=0.03.

estimates were imprecise although broadly compatible with the results of the main analyses (table 2S).

Current or recent use of any hormonal contraception was associated with a reduced risk of any epithelial ovarian cancer, in particular endometrioid, mucinous, and serous epithelial cancer (table 5). There was not a significant reduction in clear cell epithelial or non-epithelial ovarian cancer. When the subset of epithelial ovarian cancers (773/1064, 73% of the total ovarian cancers) was examined among women followed up to their first switch in hormonal contraception (table 3S), the pattern of relative risks for different hormonal contraceptives was similar to that seen for all ovarian cancers.

Age at diagnosis was associated with FIGO stage with a higher percentage of women in the oldest age group being diagnosed at stage III or IV in comparison with younger women (table 4S; P_{trend}<0.001). Over 60% (323/502) of serous tumours were diagnosed at stage III or IV compared with 15% (30/204) of mucinous tumours (table 5S). Based on the relative risk for the never use versus ever use categories of hormonal contraception (0.66), the population prevented fraction was estimated to be 21%—that is, use of hormonal contraception prevented 21% of ovarian cancers in the study population.

Discussion
Principal findings
In this study of women of reproductive age (that is, younger than 50 years) living in Denmark, we found that ever use of any contemporary hormonal contraception was associated with a reduced risk of ovarian cancer, an effect that strengthened with longer periods of current use and persisted for several years after stopping use. Most of the hormonal contraceptive use related to combined oral contraceptives. There was little evidence of important differences between combined oral contraceptives containing different

types of progestogens. The reduced risk associated with hormonal contraception was seen with nearly all types of ovarian cancer. Our data do not suggest a protective effect from progestogen-only products; however, few women were exclusive users of such products, and so we had limited statistical power to detect such an effect.

Strengths and limitations of study
Strengths of our study included its nationwide coverage of nearly 1.9 million women, more than 21 million person years of prospective follow-up, and the examination of the many different forms of hormonal contraception currently available. The linkage of prescribing and cancer registration information avoided recall bias regarding patterns of hormonal contraception use. Similar to most studies of hormonal contraceptives, we have assumed that women who were dispensed a prescription subsequently used it. If some women did not (that is, they remained being a non-user when we incorrectly deemed them to be a user), such misclassification would underestimate the protective effects found. However, because of the time varying variables used in our study, this misclassification of current use would only be present for the time period of the redeemed prescription. Thereafter, the women would be classified as a non-taker.

The data linkage study design also enabled us to adjust for several important confounding variables. The cohort was younger than 50 years, and so few women will have used hormone replacement therapy known to increase ovarian cancer risk.[26] While this age restriction meant that we could be confident that we were examining the effects of oral contraception, it also meant that the study could not provide information on how contemporary hormonal contraceptives affected ovarian cancer risk in older women, in whom most cases of ovarian cancer occur. We were not able to adjust for some factors, such as breastfeeding, and

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Table 3 | Relative risk of ovarian cancer in former users of hormonal contraception by time since last current use and duration of use

| Duration of use | Time since last current use of hormonal contraception | | | | | | | | |
| | 1-<5 years | | | 5-<10 years | | | ≥10 years | | |
	No of person years	No of ovarian cancer events	Relative risk (95% CI)*	No of person years	No of ovarian cancer events	Relative risk (95% CI)*	No of person years	No of ovarian cancer events	Relative risk (95% CI)*
≤1 year	667 835	37	0.81 (0.58 to 1.13)	470 243	45	1.14 (0.84 to 1.56)	316 850	27	0.81 (0.54 to 1.21)
>1-≤5 years	1 038 886	47	0.84 (0.62 to 1.15)	635 891	29	0.66 (0.45 to 0.98)	308 126	22	0.76 (0.48 to 1.20)
>5 years	735 899	26	0.60 (0.39 to 0.91)	291 123	9	0.41 (0.21 to 0.81)	40 304	2	0.57 (0.14 to 2.33)

*Adjusted for calendar year, parity, age, education, tubal sterilisation, hysterectomy, endometriosis, polycystic ovary syndrome, and family history of breast or ovarian cancer.

information about endometriosis and polycystic ovary syndrome only related to women admitted to hospital for these conditions. Our findings, therefore, could be subject to residual confounding. Information on smoking and body mass index was only available in parous women for part of the study period. However, adjustment for these variables in the subset of women for whom these data were available did not materially change the risk estimates.

The low incidence of ovarian cancer among women followed up to their first switch in type of hormonal contraception meant that it was not possible to examine the association between duration of use and time since last current use among users of specific preparations. However, given the little evidence overall of major differences between preparations, it seems unlikely that there are important differences in these temporal associations.

We did not have information about hormonal contraceptives prescribed before entry to the study. Some women who were classified as never users could have used hormonal contraception previously. Such misclassification would underestimate the protective risk estimates, a problem that should diminish the further a woman was from her last use. Because older women are further away from their last use, and because most instances of ovarian cancer occur in older women (71% of our events were in women older than 40 years), we do not believe that our results were seriously affected by this misclassification. Some of the effects attributed to the use of a particular product could reflect lingering effects from the use of a previous product or products. Our analysis of women followed to their first switch of hormonal contraception in the study was intended to minimise such effects, while still providing enough data for reliable risk estimates. Little

Table 4 | Relative risk of ovarian cancer in users by different types of hormonal contraception in women followed up to their first switch in hormonal contraception (that is, the no change cohort)

	No of person years	No of cancer events	Adjusted relative risk (95% CI)*
Never use	8 150 250	771	1.00
Ever use (any hormonal contraception)	7 183 430	293	0.73 (0.63 to 0.84)
Former use (any hormonal)	2 590 322	164	0.85 (0.71 to 1.02)
Current or recent use (any hormonal)	4 593 109	129	0.61 (0.50 to 0.74)
Current or recent use (combined OC)	4 316 888	103	0.56 (0.45 to 0.70)
Current or recent use (progestogen only)	276 221	26	0.87 (0.59 to 1.29)
Current or recent use of combined hormonal contraception—oral			
Norethisterone, 50 µg ethinylestradiol	36 494	4	1.35 (0.50 to 3.61)
Levonorgestrel, 50 µg ethinylestradiol	47 335	6	1.21 (0.54 to 2.71)
Norethisterone, 30-35 µg ethinylestradiol	116 090	7	1.30 (0.62 to 2.76)
Levonorgestrel, 30-35 µg ethinylestradiol	519 113	11	0.33 (0.18 to 0.61)
Desogestrel, 20-30 µg ethinylestradiol	988 952	17	0.45 (0.27 to 0.73)
Gestodene, 20-35 µg ethinylestradiol	1 887 047	42	0.57 (0.41 to 0.79)
Drospirenone, 20-35 µg ethinylestradiol	188 928	5	1.08 (0.44 to 2.64)
Norgestimate, 35 µg ethinylestradiol	375 778	11	0.75 (0.41 to 1.37)
Cyproterone, 30 µg ethinylestradiol	142 147	0	—
Estradiol valerate, dienogest	1 022	0	—
Current or recent use of combined hormonal contraception—non-oral			
Patch	2 253	0	—
Vaginal ring	11 729	0	—
Current or recent use of progestogen-only contraception—oral			
Norethisterone	66 934	4	0.62 (0.23 to 1.64)
Levonorgestrel	6 972	1	1.16 (0.16 to 8.23)
Desogestrel	12 155	0	—
Current or recent use of progestogen-only contraception—non-oral			
MPA depot	7 321	3	6.56 (2.11 to 20.40)
Implant	10 575	0	—
LNG-IUS	172 265	18	0.84 (0.53 to 1.35)

LNG-IUS=levonorgestrel intrauterine system; MPA=medroxyprogesterone acetate.
*Adjusted for calendar year, parity, age, education, tubal sterilisation, hysterectomy, endometriosis, polycystic ovary syndrome, and family history of breast or ovarian cancer.

Table 5 | Relative risk of different histological types of ovarian cancer associated with hormonal contraception (full cohort), by categories of hormonal contraception use

Histology and use category	No of person years	No of cancer events	Adjusted relative risk (95% CI)*
Epithelial ovarian cancer			
Any epithelial ovarian cancer	—	902	—
Never use	8 150 250	566	1.00
Current or recent use	8 839 374	155	0.58 (0.47 to 0.70)
Former use	4 505 157	181	0.75 (0.62 to 0.91)
Clear cell epithelial ovarian cancer	—	61	—
Never use	8 150 250	41	1.00
Current or recent use	8 839 374	9	0.59 (0.28 to 1.27)
Former use	4 505 157	11	0.68 (0.32 to 1.41)
Endometrioid epithelial ovarian cancer	—	135	—
Never use	8 150 250	93	1.00
Current or recent use	8 839 374	21	0.58 (0.35 to 0.96)
Former use	4 505 157	21	0.64 (0.38 to 1.06)
Mucinous epithelial ovarian cancer	—	204	—
Never use	8 150 250	107	1.00
Current or recent use	8 839 374	45	0.65 (0.44 to 0.97)
Former use	4 505 157	52	0.96 (0.65 to 1.41)
Serous epithelial ovarian cancer	—	502	—
Never use	8 150 250	325	1.00
Current or recent use	8 839 374	80	0.55 (0.42 to 0.72)
Former use	4 505 157	97	0.72 (0.56 to 0.93)
Non-epithelial ovarian cancer			
No of ovarian cancer events	—	73	—
Never use	8 150 250	33	1.00
Current or recent use	8 839 374	21	0.64 (0.34 to 1.20)
Former use	4 505 157	19	1.09 (0.57 to 2.08)
Malignant tumour not otherwise specified			
No of ovarian cancer events	—	274	—
Never use	8 150 250	172	1.00
Current or recent use	8 839 374	58	0.57 (0.41 to 0.80)
Former use	4 505 157	44	0.73 (0.50 to 1.05)

*Adjusted for calendar year, parity, age, education, tubal sterilisation, hysterectomy, endometriosis, polycystic ovary syndrome, and family history of breast or ovarian cancer.

evidence of important differences was seen between the combined oral contraceptives. Furthermore, when we restricted our analysis to women with complete contraceptive histories (in whom misclassification from unknown previous use could not occur), the pattern of results for individual combinations was similar, albeit with imprecise, non-significant risk estimates.

Comparison with other studies

By contrast with most previous research, our study included women aged 15-49 years, most of whom will have been premenopausal. Thus, the periods of observation for ever users of hormonal contraceptives in this age group had a higher proportion of information relating to current or recent use than those for ever users in a study recruiting older women, because many would have stopped using hormonal contraception many years previously. The Collaborative Group on Epidemiological Studies of Ovarian Cancer's reanalysis of oral contraception data from 45 studies included women who were generally older than our cohort (mean age of diagnosis of ovarian cancer was 56 years, with only 18% of tumours diagnosed in women younger than 45 years).[4] The overall relative risk between ever and never users was 0.73 (95% confidence interval 0.70 to 0.76). The Collaborative Group's analysis found that younger and premenopausal women seemed to have greater percentage reductions in risk

of ovarian cancer per five years of oral contraceptive use.[4] However, after accounting for time since last use, no significant heterogeneity by menopausal status or age was seen, demonstrating that how recent a woman last used hormonal contraceptives was more important than the other two factors. Our slightly stronger reduced risk for any ovarian cancer among ever users of any hormonal contraception (relative risk 0.66 (95% confidence interval 0.58 to 0.76)) was possibly due to 58% of the total period of observation in ever users arising from current or recent use of combined oral contraceptives.

Similar to the Collaborative Group[4] and other more recent investigations,[5-9] we found that the risk reductions among current users of any hormonal contraception got stronger with longer durations of use and persisted for a number of years after stopping use. The apparent loss of protection 10 years after stopping hormonal contraception could be due to the loss of biological effect (assuming a causal association exists), or reduced statistical power to continue to observe a significant reduction due to the relatively small periods of observation (7% of total person years for ever use).

Studies[4 5] have not found differences in ovarian cancer risk by oestrogen dose of combined oral contraceptives (when assessed by decade of use). The same studies were unable to investigate associations with combined pills containing different progestogens.

The Nurses' Health Study II reported that short term use of preparations containing the oestrogen mestranol (hazard ratio 1.83, 95% confidence interval 1.16 to 2.88) and first generation progestogens (1.72, 1.11 to 2.65) were associated with an increased ovarian cancer risk, but found no relation with those containing second generation progestogens (levonorgestrel and norgestrel).[22] The Nurses' study had insufficient data to provide risk estimates for products containing desogestrel, norgestimate, or drospirenone.

Although we lacked power to examine patterns of risk by duration of use and progestogen type, we had good statistical power for the most often used progestogens and found little evidence of important differences in overall ovarian cancer risk among current or recent users of combined preparations containing different progestogens. It has been suggested that combined oral contraceptives do not differ from progestogen-only pills in their risk of ovarian cancer.[27] In our study, current or recent use of progestogen-only products among all women implied a smaller effect on ovarian cancer risk estimates, compared with users of combined products (table 2). In the no change cohort followed up to the first switch in hormonal contraception, no protection against ovarian cancer was seen in users of progestogen-only products (table 4). This risk estimate was based on only 26 events, and so had limited statistical power to detect a significant protective effect. Alternatively, the lack of significance could be because of an absence of biological effect from progestogen-only products, with the reduced risk estimates seen in the full cohort analysis due to lingering effects from previous combined pill usage, suggesting that the protection found in the full cohort analysis could be due to a lingering effect from previous combined pill usage.

Few studies have examined use of depot medroxyprogesterone,[14-16] with findings from those studies able to investigate exclusive use[14 16] suggesting a protective effect. Our finding of an increased risk was based on only three exposed ovarian cancers and a very small total observation period, resulting in very imprecise risk estimates.

Soini and colleagues[12 13] reported a standardised incidence ratio of 0.60 (95% confidence interval 0.45 to 0.76) for ovarian cancer and use of the levonorgestrel intrauterine system among women in Finland,[12] with decreased risks for mucinous, endometrioid, and serous ovarian carcinomas.[13] Our findings do not concur with those studies, possibly because the Finnish studies did not adjust for parity or previous use of oral contraceptives (shown to have a persisting protective effect).

The Ovarian Cancer Cohort Consortium (OC3) recently examined risk factors for different histological types of ovarian cancer among more than 1.2 million women from 21 prospective studies in Europe, Asia, and North America. The consortium found that a five year increase in duration of oral contraceptive use and more than 10 years of use were both associated with a decreased risk of serous, endometrioid, and clear cell tumours but not mucinous tumours.[28] Similarly,

the Collaborative Group on Epidemiological Studies of Ovarian Cancer found that oral contraceptive use was not associated with the incidence of mucinous tumours.[4] It is important to note that our study investigated women of reproductive age and who were younger than those in both the OC3 (median age at diagnosis 61.3-68.9 years depending on histological tumour type) and Collaborative Group (mean age at diagnosis 56 years) studies.

Our findings suggest that the protective effects of current or recent use of hormonal contraception is similar among endometrioid, mucinous and serous types of epithelial ovarian cancer. In line with current understanding, most mucinous tumours in our study were diagnosed at FIGO stage I.[29] However, only 3% of all ovarian cancers are now thought to be mucinous types,[29] indicating a relatively high incidence of mucinous tumours in our cohort. This high incidence of mucinous tumours has been observed previously in Denmark[30] and elsewhere,[28] and it is widely recognised that improvements in pathology, imaging, and serum markers will alter the reporting of the morphological subtypes of ovarian cancer.[29] Therefore, some of the epithelial tumours could have been misclassified as mucinous.[30] Recent understanding suggests that although ovarian cancer is clinically considered to be one disease, it is in fact a heterogeneous group of neoplasms with different pathogenesis pathways.[29] Combined hormonal contraceptives suppress ovulation so protection against neoplastic development is feasible, but the exact mechanisms by which hormonal contraceptives reduce ovarian cancer risk are unclear. Whatever the biological mechanisms, the epidemiological evidence suggests a longlasting protection against most types of ovarian cancer from combined oral contraception.[4 28]

It has been suggested that recent downward trends in ovarian cancer mortality rates in North America and Europe can be partly attributed to the use of combined oral contraceptives.[31] We found a population prevented fraction of 21% with use of hormonal contraception, which supports the notion that these ovarian cancer mortality benefits are likely to continue.

Conclusions
Based on results from our prospective study, contemporary combined hormonal contraceptives are still associated with a reduced risk of ovarian cancer in women of reproductive age, with patterns similar to those seen with older combined oral products. The reduced risk seems to persist after stopping use, although it is not yet known how long for. Presently, there is insufficient evidence to suggest similar protection among exclusive users of progestogen-only products.

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Web appendix: Supplemental tables