

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

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4 Lisa Iversen^a, Shona Fielding^b, Øjvind Lidegaard^c, Philip C Hannaford^a.

5 ^aAcademic Primary Care, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen,

6 AB25 2ZD, UK; l.iversen@abdn.ac.uk, p.hannaford@abdn.ac.uk

7 ^bMedical Statistics Team, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen,

8 AB25 2ZD, UK; s.fielding@abdn.ac.uk

9 ^cRigshospitalet, The Juliane Marie Centre, Department of Gynecology, University of Copenhagen,

10 Denmark; Oejvind.Lidegaard@regionh.dk

11 Correspondence to: Dr Lisa Iversen

12 Academic Primary Care

13 Institute of Applied Health Sciences

14 University of Aberdeen

15 Polwarth Building

16 Foresterhill

17 Aberdeen

18 AB25 2ZD, UK

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23 Professor Hannaford have nothing to disclose.

24 **Abstract**

25 **Objective**

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

28 **Study design**

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

35 **Results**

36 During 21.1 million person-years, 549 incident endometrial cancers occurred, with ever users of any
37 hormonal contraception having a reduced premenopausal endometrial cancer risk compared with
38 non-users; RR 0.60 (95% Confidence Interval 0.49 to 0.73). A lower risk of endometrial cancer was
39 seen in all current or recent users of any hormonal contraception; 0.65 (0.52-0.83) and combined
40 contraceptives; 0.57 (0.43 to 0.75), but not progestin-only contraceptives; levonorgestrel
41 intrauterine system, LNG-IUS; 0.97 (0.66 to 1.42); other progestin-only contraceptives; 0.61 (0.27 to
42 1.37)]. Increased RRs were found for current use of any hormonal, combined contraceptives or LNG-
43 IUS of \leq one year, probably because of protopathic bias. Longer durations of use were associated
44 with significant reductions that became stronger with longer use. Former users of any hormonal
45 contraception continued to benefit from a reduced risk of endometrial cancer > 10 years after
46 stopping.

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

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

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

55 **Conclusions**

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

58 **Keywords**

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

61

62 **Implications**

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

67 **1.1 Introduction**

68 In 2018, cancer of the corpus uteri (mostly endometrial) was estimated to be the sixth most frequent
69 cancer in women globally, accounting for more than 382,000 new cases and 89,929 deaths [1]. Many
70 countries have seen an increased incidence of endometrial cancer during the last 25 years, possibly
71 because of rises in the prevalence of obesity, nulliparity and diabetes [2]. However, the absence of
72 increased incidence in other countries has been attributed to long-lasting protective effects from use
73 of combined oral contraceptives [2,3]. The Collaborative Group on Epidemiological Studies of
74 Endometrial Cancer examined the association between oral contraceptive use and risk of
75 endometrial cancer in an individual participant meta-analysis of 27,276 women with endometrial
76 cancer and 115,743 controls [3]. The median age at diagnosis was 63 years, and median year of
77 diagnosis 2001, meaning that most of the oral contraceptive use occurred during the 1960s and
78 1970s. Hormonal contraception has changed substantially since then, including a lowering of
79 estrogen dose and introduction of different progestins in combined oral contraceptives. It is
80 uncertain whether products used today are still associated with important endometrial cancer
81 benefits. We report here the first substantive evidence of this relationship for all types of
82 contemporary hormonal contraception used by a national cohort of women living in Denmark. In
83 order to examine endometrial cancer risk associated with the hormonal contraceptives currently
84 used by women of reproductive age, we studied women younger than age 50.

85

86 **1.2 Material and methods**

87 The Danish Sex Hormone Register Study [4,5] follows all women aged 15-79 years living in Denmark,
88 to examine the relationship between hormone use and cardiovascular disease and cancer. Since
89 1968, each resident in Denmark has had a unique personal identification number in the Civil
90 Registration System which is used as a unique identifier in all National Registries, enabling the
91 accurate linkage of their content. The study links data from: the National Register of Medicinal
92 Product Statistics [for redeemed hormonal contraceptive prescriptions since January 1995]; the
93 Danish Cancer Registry [for histologically verified cancers since 1943 and family history of
94 premenopausal (younger than 50 years) breast or ovarian cancer in mothers or sisters]; Statistics
95 Denmark [for information about educational attainment]; the National Birth Register [for all births
96 since 1973, smoking status of parous women since 1991 and body mass index (BMI) of parous
97 women since 2004]; and the National Health Register [for hospital discharge diagnoses and surgeries
98 since 1977].

99 For this paper the eligible study population (n=1,904,094) was all women living in Denmark age 15-
100 49 years during the period January 1995 to December 2014, except women who moved into
101 Denmark after 1995. We excluded women if they had venous thrombosis, treatment with ovarian
102 stimulating drugs (Anatomical Therapeutic Chemical Classification code MG03G in the National
103 Prescription Registry), hysterectomy, bilateral oophorectomy, endometrial hyperplasia or any cancer
104 (except non-melanoma skin cancer) before study entry. The final population of 1,852,505 women
105 was followed until: first diagnosis of endometrial cancer (International Classification of Diseases
106 (ICD), tenth revision [6] code C54); emigration; death; age 50; or end of follow-up (31 December
107 2014). Women were censored permanently at the date of: diagnosis of another cancer (except non-
108 melanoma skin cancer); venous thrombosis; treatment with ovarian stimulating drugs; bilateral
109 oophorectomy, hysterectomy or endometrial hyperplasia (which can be a precursor to endometrial
110 cancer). Women were censored temporarily whilst pregnant and for six months afterwards.

111

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

120

121 1.2.1 Statistical analysis

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

131 contraceptive during the study. Once a woman became a user, she could not return to being a non-
132 user. Women could switch between current or recent and former user categories depending on
133 their redemption of prescriptions. Our time-varying analyses allowed for these changes. The age
134 distribution of the entire cohort was used as the standard to calculate age-standardized incidence
135 rates of endometrial cancer per 100,000 person-years among the different user groups. Endometrial
136 cancer risk among users of different products was calculated using Poisson regression in SAS version
137 9.3 (SAS Institute, Inc, Cary, North Carolina) using PROC GENMOD with the distribution set to
138 Poisson and a log link function. Five-year age bands were used as the time scale in the Poisson
139 regression. In each model non-users were the reference group and adjusted incidence rate ratios
140 (RR) with their 95% confidence interval (CI) calculated. Time varying covariate effects were modelled
141 by adding interactions between the partitioned constant baseline hazard and each pre-specified
142 covariate. By doing this, we did not assume constant baseline hazard rates over fixed time intervals.
143 Each model was adjusted such that the risk time was partitioned every time one of these covariates
144 changed value. The covariates were: hormonal contraceptive use, calendar year, age (15-19, 20-24,
145 25-29, 30-34, 35-39, 40-44, 45-49 years), educational attainment (elementary school only, high
146 school only, further education excluding college/university, college/university education, university
147 education with research qualifications, unknown); parity (0, 1, 2, 3, 4, >4); family history of
148 premenopausal breast or ovarian cancer (no, yes); tubal sterilization (no, yes) and endometriosis
149 (no, yes). Among parous women, additional models adjusted for smoking status (current, non-
150 smoker, unknown) and BMI (<18.5, 18.5-25, >25-30, >30, unknown) ascertained at pregnancy.
151 Smoking status and BMI were not available for other women.

152

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

159

160 To minimize any lingering effects from previous use of hormonal contraception, we examined risk
161 estimates for different products in women followed during the study until their first change of
162 hormonal contraception. We also calculated risk estimates among women aged 15 years on or after
163 1st January 1995, for whom complete contraceptive histories were known.

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

172

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

177

178 1.2.2 Ethics approval

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

185

186 1.3 Results

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

196 (0.43 to 0.75), but not progestin-only contraceptives; LNG-IUS RR 0.97 (0.66 to 1.42); all other
197 progestin-only products RR 0.61 (0.24 to 1.37). An increased RR was observed with one year or less
198 of current use of any hormonal contraception, combined oral contraceptives or LNG-IUS (Table 2).
199 Users of these products for longer durations had a reduced RR of endometrial cancer, an effect that
200 strengthened with increasing duration of use. In former users of any hormonal contraception, there
201 remained a reduced RR of endometrial cancer more than 10 years after stopping; RR 0.57 (0.36 to
202 0.89). When the data for former users were stratified by duration of previous use and time since last
203 use, the protective effect of hormonal contraception was stronger with longer durations of use
204 irrespective of time since stopping (Table 3).

205

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

222

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

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

231

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

239

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

250

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

256

257 **1.4 Discussion**

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

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

264 Strengths of our study include more than 1.8 million women studied, 21.1 million person-years of
265 observation and the examination of all types of hormonal contraception in use between 1995 and
266 2014. Recall bias about contraceptive use was avoided by the prospective collection of information
267 about redeemed prescriptions. We were able to adjust for several possible confounders, although
268 information about smoking habits and BMI was available only for parous women for part of the
269 study period. These adjustments did not materially change the risk estimates. It is possible,
270 however, that residual confounding influenced our findings. An unknown proportion of women
271 deemed to be non-users will have been previous users of hormonal contraceptives who stopped
272 before our study began in January 1995. The effect of this misclassification of hormonal
273 contraceptive status will be to move the RRs towards the null, thus underestimating the 'real' effects
274 of hormonal contraceptives.

275

276 Risk estimates attributed to a particular product might reflect persisting effects from previous use of
277 another contraceptive(s). We tried to minimize such effects by examining associations for different
278 products among women followed until their first switch of hormonal contraception in the study,
279 even though this approach meant that fewer cases of endometrial cancer among less popular
280 preparations. Nevertheless, there was no evidence of important differences between combined
281 contraceptives containing different progestins. Although it is likely that that protopathic bias
282 occurred in short-term users overall, there is less reason to suspect that this operated differently
283 within the preparations containing different progestins. We were unable to calculate risk estimates
284 in women for whom their full contraceptive history was known i.e. the subset of women who were
285 15 years on or after 1st January 1995, because of the low incidence of endometrial cancer in young
286 women.

287

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

292 than women included in the Collaborative Group re-analysis. The Collaborative Group found a
293 reduced risk of type I (typically considered to be estrogen-dependent) and II (estrogen-independent)
294 carcinoma but not sarcoma. We also found a reduced risk of type I tumors. The Collaborative Group
295 estimated that in 21 countries during 1965-2014 combined oral contraceptive use had prevented
296 400,000 endometrial cancers in women aged 30-74. In our study of younger women, the estimated
297 population prevented fraction was 25%, suggesting continuing substantial endometrial cancer
298 benefits from contemporary hormonal contraceptives- particularly combined products.

299

300 Few studies have examined the LNG-IUS in relation to endometrial cancer risk [10-12]. The
301 Endometrial Cancer Consortium combined data from four cohort and 14 case-control studies to
302 examine the endometrial cancer risk associated with type of intrauterine device [10]. Hormone-
303 releasing devices did not appear to alter the risk although few women in the analysis had used these
304 products (adjusted odds ratio 0.97, 95% CI 0.44 to 2.14). Soini et al followed 93,843 women who had
305 used the LNG-IUS for menorrhagia treatment [11]. During more than 850,000 person-years of
306 observation, users had a reduced risk of any type of corpus uteri cancer; standardized incidence
307 ratio, SIR 0.59 (95% CI 0.45 to 0.77) and endometrial adenocarcinoma; SIR 0.46 (0.33 to 0.64), with
308 evidence of more protection with increased duration of use. This study, however, could not adjust
309 for previous use of oral contraceptives, which are associated with long-lasting protective effects on
310 the endometrium [3,13]. The study did not find a reduced risk of uterine sarcoma; SIR 1.44 (0.86 to
311 2.28) [11]. We were also unable to find in either our main or sensitivity analyses a protective effect
312 for sarcoma from hormonal contraception generally, and the LNG-IUS specifically.

313

314 A cohort study of 104,318 women enrolled in the Norwegian Women and Cancer Study also
315 reported a reduced risk of endometrial cancer among ever users of the LNG-IUS; RR 0.22 (0.13 to
316 0.40) [12]. The study adjusted for several possible confounders including ever use of oral
317 contraceptives but (unlike our study) almost 50% of the ever users of LNG-IUS in the cohort were
318 peri- or post-menopausal. Our results do not confirm a protective effect associated with the LNG-IUS
319 among premenopausal women. Indeed, among the subset followed until first switch, we found an
320 increased risk of endometrial cancer in current or recent users of the LNG-IUS, mostly because of an
321 increased risk during the first year of use. We did not have the reason why women redeemed a
322 prescription for a hormonal contraceptive in our study. As well as for contraception, hormonal
323 contraceptives can be used to treat menstrual irregularities such as heavy bleeding, including
324 bleeding symptoms arising from pre-cancerous conditions such as endometrial hyperplasia. We

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

338

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

348

349 **1.4.1 Conclusion**

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

353

354

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357 study design; in the collection, analysis and interpretation of data, in the writing of the paper or in
358 the decision to submit the paper for publication.

359

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362 collaboration and in the initial discussions about the overall study design whilst they were employed
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364

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401

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 [†]		Nulliparous (%)	Tubal sterilization (%)	Endometriosis (%)	Family history [‡] (%)	BMI [§] mean(SD)	Smoking (%)
				Elementary (%)	University (%)						
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)
<i>Combined</i>	7,743,769	62	1.8	0.57 (0.43 to 0.75)
<i>LNG-IUS</i>	697,977	32	2.7	0.97 (0.66 to 1.42)
<i>Other progestin-only</i>	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)
<i>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)</i>				
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)
<i>Combined</i>	7,743,561	42		0.35 (0.25 to 0.48)
<i>LNG-IUS</i>	697,937	18		0.58 (0.36 to 0.95)
<i>Other progestin-only</i>	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).

Duration of use	Time since last use								
	Person-years	>1-≤5 years		Person-years	>5-≤10 years		Person-years	>10 years	
		Events	RR (95% CI)*		Events	RR (95% CI)*		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.

1 Table 4. Incidence rate ratio of endometrial cancer in users of different types of hormonal
 2 contraception in women followed up until first switch in hormonal contraception i.e. “no change
 3 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)
<i>Combined</i>	4,312,942	25	0.41 (0.27 to 0.62)
<i>LNG-IUS</i>	168,442	21	1.65 (1.05 to 2.59)
<i>Other progestin-only</i>	103,658	3	0.73 (0.23 to 2.27)
<u>Current or recent use of combined hormonal contraception:</u>			
<i>Oral</i>			
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
<i>Non-oral</i>			
Patch	2,250	<3	n/a
Vaginal ring	11,730	<3	n/a
<u>Current or recent use of progestin-only contraception:</u>			
<i>Oral</i>			
Norethisterone	66,760	<3	n/a
Levonorgestrel	6,950	<3	n/a
Desogestrel	12,100	<3	n/a
<i>Non-oral</i>			
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)
<i>Duration of current use (combined)</i>			
≤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)
<i>Duration of current use (LNG-IUS)</i>			
≤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)

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

7

8 Table 5. Incidence rate ratio of different histological types of endometrial cancer associated with
 9 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)
<i>Combined</i>	7,743,770	32	0.42 (0.28 to 0.61)
<i>LNG-IUS</i>	697,980	17	0.68 (0.41 to 1.13)
<i>Other progestin-only</i>	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)
<i>Combined</i>	7,743,770	<3 [†]	n/a
<i>LNG-IUS</i>	697,980	5	2.99 (0.97 to 9.23)
<i>Other progestin-only</i>	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)
<i>Combined</i>	7,743,770	18	1.60 (0.90 to 2.84)
<i>LNG-IUS</i>	697,980	8	3.24 (1.43 to 7.34)
<i>Other progestin-only</i>	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)
<i>Combined</i>	7,743,770	11	0.69 (0.32 to 1.48)
<i>LNG-IUS</i>	697,980	<3	n/a
<i>Other progestin-only</i>	378,570	<3	n/a
Former use	4,405,210	12	0.56 (0.27 to 1.16)

10 *Adjusted for: calendar year, age, education, parity, family history of breast or ovarian cancer, tubal
 11 sterilization and endometriosis. †Data not available for presentation due to less than three events,
 12 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

15

16 Table 2S. Incidence rate ratio of endometrial cancer in users of different hormonal contraceptive
 17 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
<u>Current or recent use of combined hormonal contraception:</u>			
<i>Oral</i>			
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
<i>Non-oral</i>			
Patch	15,350	<3	n/a
Vaginal ring	124,210	<3	n/a
<u>Current or recent use of progestin-only contraception:</u>			
<i>Oral</i>			
Norethisterone	157,796	3	0.59 (0.19 to 1.83)
Levonorgestrel	11,510	<3	n/a
Desogestrel	123,210	<3	n/a
<i>Non-oral</i>			
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)

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

21

22

23 Table 3S. Incidence rate ratio of endometrial cancer in users of different hormonal contraceptive
 24 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)
<i>Combined</i>	5,282,426	40	0.65 (0.46 to 0.92)
<i>LNG-IUS</i>	657,424	27	1.08 (0.70 to 1.66)
<i>Other progestin-only</i>	278,304	6	1.02 (0.45 to 2.32)
<u>Current or recent use of combined hormonal contraception:</u>			
<i>Oral</i>			
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
<i>Non-oral</i>			
Patch	9,260	<3	n/a
Vaginal ring	73,240	<3	n/a
<u>Current or recent use of progestin-only contraception:</u>			
<i>Oral</i>			
Norethisterone	134,453	3	0.91 (0.29 to 2.86)
Levonorgestrel	9,950	<3	n/a
Desogestrel	88,960	<3	n/a
<i>Non-oral</i>			
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)

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

28 Table 4S. Sensitivity analysis: incidence rate ratio of endometrial cancer in users of hormonal
 29 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)
<i>Combined</i>	7,743,561	42	0.35 (0.25 to 0.48)
<i>LNG-IUS</i>	697,937	18	0.58 (0.36 to 0.95)
<i>Other progestin-only</i>	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	<i>n/a</i>
>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)

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

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

33

34 Table 5S. Sensitivity analysis: incidence rate ratio of different histological types of endometrial
 35 cancer associated with hormonal contraception with one year period of exposure prior to diagnosis
 36 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)
<i>Combined</i>	7,743,560	20	0.23 (0.14 to 0.37)
<i>LNG-IUS</i>	697,937	7	0.30 (0.14 to 0.64)
<i>Other progestin-only</i>	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)
<i>Combined</i>	7,743,560	<3 [†]	n/a
<i>LNG-IUS</i>	697,937	3	1.98 (0.52 to 7.53)
<i>Other progestin-only</i>	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)
<i>Combined</i>	7,743,560	13	1.11 (0.58 to 2.12)
<i>LNG-IUS</i>	697,937	5	2.15 (0.80 to 5.78)
<i>Other progestin-only</i>	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)
<i>Combined</i>	7,743,560	9	0.57 (0.25 to 1.30)
<i>LNG-IUS</i>	697,937	3	0.80 (0.23 to 2.77)
<i>Other progestin-only</i>	378,560	<3	n/a
Former use	4,405,032	12	0.62 (0.30 to 1.30)

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

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