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Contraception Methods, beyond Oral Contraceptives and Tubal Ligation, and Risk of Ovarian Cancer

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Abstract

Purpose—Few studies have examined methods of contraception, beyond oral contraceptives (OCs) and tubal ligation, in relation to ovarian cancer risk.

Methods—Nine hundred two cases with incident ovarian/peritoneal/tubal cancer were compared to 1800 population-based controls. Women self-reported all methods of contraception using life calendars.

Results—Each of the contraceptive methods examined reduced the risk of ovarian cancer as compared to use of no artificial contraception. Comparing ever versus never use, after adjustment for potentially confounding factors and all other methods of contraception, the methods of contraception that emerged as protective were OCs (adj OR 0.75, 95% CI 0.61–0.93); tubal ligation (adj OR 0.63, 95% CI 0.51–0.77); intrauterine devices (IUDs) (adj OR 0.75, 95% CI 0.59–0.95); and vasectomy (adj OR 0.77, 95% CI 0.61–0.99). While for oral contraceptives and tubal ligation, the longer the duration of use, the greater the effect, for IUDs the pattern was reversed: significant protection occurred with short duration and progressively greater risk (albeit non-significant) was seen with longer duration of use.

Conclusions—In the largest case-control study to date, a range of effective methods of contraception reduced the risk for ovarian cancer. OCs and tubal ligation reduced ovarian cancer risk with lower odds ratios with longer duration of use, whereas IUDs reduced risk overall, having the greatest impact with short duration of use.

Keywords

contraception; contraceptive methods; oral contraceptives; tubal ligation; IUDs; ovarian cancer

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Several forms of contraception have been shown to reduce the risk of developing ovarian cancer. Oral contraceptives reduce risk in a duration-dependent fashion and the effects of oral contraceptives last for at least 20 years after cessation of use (1–4). Tubal ligation has also been shown to consistently reduce risk (5–8). Increasingly, oral contraceptives (OCs) are considered for chemoprophylaxis against ovarian cancer, particularly in high risk women (9–11).

Few studies have examined use of other methods of contraception in relation to ovarian cancer risk. Small case-control studies demonstrated some risk reduction with non-hormonal contraceptive methods but small numbers of women used each method, the findings were not entirely consistent by method, and risk reductions were not significant (1,12–14). Two larger studies reached somewhat conflicting conclusions. In a large, case-control study by our group, all methods of contraception (intrauterine devices or IUDs, barrier methods, and vasectomy, as well as OCs and tubal ligation) reduced ovarian cancer risk as compared to no contraception use; ever use versus never use also reduced risk in multiparous but not nulliparous women (15). An analysis from the prospective Nurses' Health Study cohort reported an increased risk associated with IUD use and no association for other contraceptive methods (16).

The finding that multiple contraceptive methods reduce ovary cancer risk must be scrutinized as possibly representing a bias by fertility status. Ovarian cancer rates are higher among infertile women (17,18). In turn, many infertile women spend long periods of time practicing unprotected intercourse. Contraceptive users may thus appear to be protected from ovarian cancer only because they are less likely to be infertile. Alternatively, the finding that methods of contraception beyond OCs and IUDs are protective, may provide insights into ovarian carcinogenesis.

Here we attempt to re-examine the results from our earlier case-control study in a newly conducted population-based case-control design. Our earlier study was conducted in the Delaware Valley in and around Philadelphia and our current study was conducted in Western Pennsylvania and surrounding regions (15). As we did previously, we attempt to separate parity from contraceptive use and to examine the specificity of contraceptive effects on risk reduction for ovarian cancer. Here we examine OCs, IUDs, any barrier methods, tubal ligation, and vasectomy (in a partner) in relation to ovarian cancer risk.

Subjects and Methods

Subjects were enrolled in a population-based case-control study conducted in a contiguous region comprising Western Pennsylvania, Eastern Ohio, and Western New York State. Cases were residents of this geographic region with histologically confirmed primary epithelial ovarian, fallopian tube, or peritoneal cancer diagnosed between February 2003 and November 2008. Both invasive and borderline tumors were included. Women were referred from hospital tumor registries, clinical practices, or pathology databases and contacted with the permission of their gynecologists. Eligible women were at least 25 years of age and within 9 months of initial diagnosis. Controls consisted of women at least age 25 who lived in telephone exchanges wherein cases resided. Random digit dialing was used to identify age-eligible women, and these were further screened by the study team to ensure that they had not had a previous oophorectomy or diagnosis of ovarian cancer. Eligible women were then invited to participate. Potential controls were frequency matched by 5-year age group and telephone exchange to cases in a ratio of approximately 2:1. Women were interviewed in their homes by trained interviewers. The questionnaire included a reproductive and gynecological history, a contraceptive history, a medical history, a family history, and

information on lifestyle practices. All study subjects gave informed consent for participation.

From Pennsylvania and Ohio, we identified 2458 potential cases with histologically confirmed borderline or invasive epithelial ovarian cancer or tubal/peritoneal cancer. After excluding women who were ineligible on the basis of age and time since diagnosis; deceased; residence outside of the counties in which referral hospitals were located; prior diagnosis of ovarian cancer; or inability to speak English, there were 997 who had incident cancer and were eligible for the study. Two hundred thirty one women were untraceable and 115 women refused to participate or their physicians refused on their behalf. Thus, 651 women completed case interviews. From New York, we identified 420 potential cases. After excluding women who were ineligible based on the criteria cited above, there were 273 who had incident cancer and were eligible for the study. Fourteen women were untraceable and eight women refused to participate or their physicians refused on their behalf, resulting in a sample of 251 women who completed interviews.

Overall, 902 women with ovarian, tubal/peritoneal cancer completed an interview and are included in these analyses. For brevity, we subsequently use the term ovarian cancer to describe all cases.

Controls were identified from 90,540 random digit dialing calls. Of these, 46,752 reached non-working numbers; 26,237 were unresolved (never reached a person); 14,899 reached an ineligible or indeterminate household (no woman within the age range or no information given); and 808 refused to participate. Of the 1844 eligible women willing to be interviewed in the initial screening, 1802 controls completed an interview. Two controls had an oophorectomy prior to the interview and were further excluded from our study, and 1800 controls completed an interview.

Cases included 677 women with invasive epithelial ovarian tumors, 97 with borderline epithelial ovarian tumors, 75 with peritoneal tumors, 32 with fallopian tumors, and 21 women with “other” or a missing type. The diagnosis of ovarian cancer was confirmed by local pathology in all cases.

CONTRACEPTIVE USE

Standardized 2-hour-long interviews were conducted by trained interviewers in the homes of participating women. A “life” calendar marked with important events that each participant recalled during her life was used to enhance memory of distant information. Using the calendar, the interviewer led each woman through a recall of her sexual activity, use of various contraceptive methods, pregnancy attempts, and reproductive events, for every month from sexual debut until a reference date. The reference date was calculated as 9 months before the interview (for both cases and controls) to ensure that exposures occurred before ovarian cancer diagnoses in cases and within a similar time frame for cases and controls. All contraceptive use was recorded, including the type of contraception, frequency of use, duration of use, and reason for use. Finally, we asked women about any medical consultation for fertility problems.

COVARIATES

Detailed information on demographic factors, physical characteristics, medical history, life-style, and family history was obtained by interview. These included factors that have been previously associated with ovarian cancer: race, education, family history of ovarian cancer, number of live births and pregnancies, and breast-feeding.

STATISTICAL ANALYSIS

All analyses were restricted to women who had ever had sexual intercourse with a man. Thirty three cases and 23 controls that had never had intercourse were excluded on the basis that they would not have had the opportunity for exposure to contraceptive methods for contraception. Because we did not engage in individual matching of cases and controls, we used unconditional logistic regression analyses. We adjusted the ORs for any residual effect of age and for gravidity (each as continuous variables), race (white/black/other), self-reported infertility (yes/no for diagnosis or use of infertility medications) and history of ovarian cancer in any first-degree relative (yes/no). We included these covariates because they were the strongest covariates related to ovarian cancer in our data. The inclusion of education and breast-feeding did not affect our results. We subsequently adjusted for all other forms of contraception other than the one of interest (eg. for OCs, this analysis included the covariates listed above plus ever use of IUD, tubal ligation and vasectomy). Oral contraceptive use was categorized as use for contraception, for non-contraceptive uses such as to control abnormal bleeding or menstrual pain, or for both contraception and other uses. Barrier methods included condoms, diaphragms, foam, sponges, or cervical caps. The reference group of no contraception included women who reported never using OCs, birth control implants, IUDs, any barrier methods, tubal ligation, or vasectomy (in a partner). These women may have used natural family planning (that is, having intercourse during times when the woman believed she was not ovulating), withdrawal, or nothing. We do not report as a separate category of contraception birth control implants, because the number of women using these methods in our study was small (16 cases and 46 controls).

Results

Study subjects were predominantly white, post-high school graduates, 60 or older, and post-menopausal (Table 1). The commonly-found protections with increasing education, numbers of pregnancies/live births and breast-feeding were observed. Cases were more likely to be African-American than controls, suggesting a selection bias among this small segment of subjects.

We found a reduction in the risk of ovarian cancer for ever versus never use of each of the methods for contraception analyzed (Table 2). However, after adjustment for age, race, family history of ovarian cancer, infertility, and gravidity, significant protection was seen only with IUDs as well as OCs for contraception and tubal ligation. After further adjustment for all other forms of effective contraception, IUDs, OCs for contraception, and tubal ligation remained significantly protective; now vasectomy also reached a level of significant protection.

As ever use of contraceptive methods is complicated by admixing users of other methods, mixed methods, and none of these methods over a lifetime, we also compared users of each method with women who used no artificial contraception, defined as use of only natural family planning, withdrawal, rhythm, or no contraception (Table 3). Each of the methods significantly reduced the risk of ovarian cancer as compared to no artificial contraception.

Next, we examined the association between contraception and ovarian cancer among women with zero, one, two or three or more pregnancies (Table 4). Both OCs for contraception and tubal ligation significantly reduced risk in some but not all gravidity categories, without a clear pattern of greater or lesser effects as gravidity increased. IUD use, despite generating protective odds ratios similar to those for OCs, did not produce significant results in any gravidity category, possibly due to small cell sizes. Vasectomy also did not produce significant reductions in risk in any gravidity category.

By duration, OCs had a progressively greater impact with 4 or fewer years, 5–9 years and 10 or more years of use (Table 5). Similarly, longer duration of tubal ligation was associated with lower risk. For IUD use, the pattern was reversed: significant protection occurred with short duration (≤ 4 years) use and progressively greater risk was seen with longer duration of use (adj ORs 0.53 for ≤ 4 years; 1.11 for 5–9 years; 1.40 for ≥ 10 years). We further explored whether time since last IUD use might drive these observations. Although there was a trend toward reduced risk with increasing time since last use, this was eliminated with adjustment for (i.e. not independent of) IUD duration. We did not have data on duration of vasectomy.

Additional analyses showed our observations to be robust. Contraception use before the first pregnancy or episode of trying was protective (OCs for contraception, OR = 0.87 (0.69–1.11); IUD, OR = 0.81 (0.41–1.60)). Adjustment for breast-feeding in the multivariate analyses had no substantial effect on our results for ever-never use. Analyses including only epithelial ovarian cancer (excluding fallopian and peritoneal cancers) essentially replicated those shown here with the result for vasectomy slightly enhanced in these analyses when adjusted for confounders plus all other contraceptive methods (OR 0.73, 95% CI 0.56–0.94).

Finally, we examined use of concomitant methods of birth control over a lifetime (Table 6). The majority of women used more than one contraceptive method over a lifetime and of these, the most common combination was OC use plus another method. For instance, of the 424 women whose contraceptive use included vasectomy, only 89 (21%) did not also use OCs.

Discussion

We report here the largest case-control study to examine whether effective methods of contraception, beyond OCs and tubal ligation, reduce the risk of ovarian cancer. Consistent with the results of our previous case-control analysis (15), we found that use of a variety of different contraceptive methods generally reduced risk of ovarian cancer as compared to use of no artificial contraception. Such an analysis is almost certainly confounded by fertility in that women who are infertile or sub-fertile would be less likely to use effective methods of contraception and more likely to develop ovarian cancer. In our current, more discriminating analyses of ever versus never use, comparisons to OCs, and use within parity categories, the methods of contraception that emerged as protective were OCs, tubal ligation, IUDs, and vasectomy. Vasectomy is intriguing but we were less informed about this relationship with ovarian cancer since we had no data on duration of use. IUDs were particularly interesting because 1) they are not traditionally thought to reduce the risk of ovarian cancer; 2) duration-response analyses showed a counter-intuitive pattern wherein shorter use reduced risk and longer use (albeit non-significantly) increased risk.

Our results replicated a plethora of earlier studies linking OCs and tubal ligation to reduced ovarian cancer risk (5–7,19–20). In particular, our results mirror adjusted ORs for ever-use of OCs reported from a meta-analysis (0.7) and a pooled analysis (0.66) (2,21). We partially, but did not fully, replicate a much more limited literature that has addressed the relation between other forms of contraception (barrier, IUD, or vasectomy) and the risk of ovarian cancer. In these studies, the reported ORs were generally less than 1.0; however, none of those studies had enough women in any contraception category, other than OCs, to show strong effects or to explore more fully comparisons between categories (1,12–15,22). In the only prospective study to examine contraception methods beyond OCs and tubal ligation, Tworoger et al. found a significant relative risk of 1.76 associated with IUD use (16). Unfortunately, only 18 IUD users informed the analysis and thus duration and time since last use of IUDs was not reported. Here, we did not show significant risk reductions for barrier

methods and vasectomy but we did find that shorter-duration IUD use reduced risk while longer duration IUD use increased risk.

In previous analyses stratifying by parity or gravidity groups, results have been mixed. In our previous study, we found risk reductions to be limited to multigravid women (15). In our current study, we found a patchy set of associations that did not clearly demonstrate a limitation by gravidity category but was not fully consistent between gravidity categories, perhaps on the basis of the sizes of individual stratification cells. All methods were protective before the first pregnancy, a time during which women might not yet know their fertility potential and thus not yet adjust their contraceptive strategy. All of this suggests that confounding by fertility status is an unlikely explanation for our observations.

A variety of biological explanations have been offered to explain the protective effect of OCs on ovarian cancer risk. These include: (1) excessive ovulation promotes risk; (2) elevated steroid hormone levels increase risk; (3) unopposed estrogen increases risk; and (4) pelvic inflammation increases risk (23–27). Tubal ligation has been posited to have an effect via a reduction in utero-ovarian blood flow resulting in altered local hormonal and growth factor levels, or via its protection against the ascension of inflammants (26–28). Some IUDs contain progestin, which has been proposed to reduce the risk of ovarian cancer (25). However, only a tiny fraction of IUD-users in the current analysis (N=14) reported using progestin-containing IUDs. IUDs, particularly older formulations, such as the Dalkon Shield, increased the risk for pelvic inflammatory disease. The hazard likely occurred because of the particular construction of the multifilament string attached to the Dalkon shield. But it also may have related to insertion through a cervix infected with the bacterial sexually transmitted infections that cause pelvic inflammatory disease, as suggested by the close temporal relationship between insertion and pelvic inflammatory disease, and the relative safety of modern-day use which is confined to women monogamous without cervical infections (29). These facts may explain our counterintuitive finding of a reversed duration-response relationship (longer use associated with increasing risk). IUDs must be replaced every 5–10 years depending on the product – longer use would imply more insertions and thus greater risk of infection and inflammation. Shorter use might actually reduce upper genital tract inflammation by virtue of killing sperm. Indeed, the marginal reduction in risk from vasectomy might suggest some protection from reduced exposure to sperm.

Strengths of this study include the population-based ascertainment of cases and controls, the large number of women interviewed, the use of life calendars and emphasis on recall of contraceptive use and reproductive experiences, and the structured interviews to enhance recall. All of these methodological features reduce the potential for selection and information bias. The greatest study limitation was the challenge of separating out the effects of various contraceptive methods since use of more than one method over a lifetime was the norm. We attempted to separately delineate methods by adjusting for all methods in logistic regression analyses and by comparing each method to no effective method. Nonetheless, residual confounding remains a real concern. Other study limitations included: (1) selection against women with short life expectancies post-diagnosis who may have become debilitated or died prior to interview and (2) inaccurate recall of past contraceptive experiences. Women may have incorrectly recalled past events, such as the duration of use of contraceptive methods. It is less likely that women would misremember ever versus never-use of contraceptive methods (30,31). Previous studies have found that among ever-users of OCs identified by medical records, 80% or more reported OC use; an even larger proportion of IUD users identified by medical records reported IUD use (30–35).

In summary, from this large study of contraceptive methods and ovarian cancer, we confirmed that OCs and tubal ligation reduced risk for ovarian cancer. Short-term IUD use reduced risk but long term IUD use tended toward elevating risk. Since contraceptive methods are modifiable and since ovarian cancer is highly lethal, these findings should be added to other considerations when selecting contraceptive methods.

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Abbreviations

IUD	intrauterine device
OC	oral contraceptive

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Table 1
Demographic and Reproductive Characteristics of Ovarian Cancer Cases and Controls in the HOPE Study

	Cases (n=869)	Controls (n=1779)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Race				
White	823 (95)	1734 (96)	1.00	-
Black	35 (4)	29 (3)	2.55 (1.55-4.19)	-
Other	11 (1)	16 (1)	1.45 (0.67-3.14)	-
Education				
Not high school graduate	80 (9)	82 (5)	1.00	1.00
High school graduate	294 (34)	527 (30)	0.58 (0.41-0.82)	0.53 (0.37-0.76)
Post- high school	495 (57)	1170 (66)	0.45 (0.33-0.63)	0.40 (0.28-0.56)
Age (years)				
≤ 30	13 (1)	24 (1)	1.00	-
30-< 40	43 (5)	107 (6)	0.74 (0.35-1.59)	-
40-< 50	155 (18)	391 (22)	0.73 (0.36-1.47)	-
50-< 60	270 (31)	563 (32)	0.88 (0.44-1.76)	-
≥ 60	388 (45)	694 (39)	1.03 (0.52-2.05)	-
Number of Pregnancies				
0	135 (16)	144 (8)	1.00	-
1	114 (13)	188 (11)	0.65 (0.46-0.90)	-
2	216 (25)	458 (26)	0.50 (0.38-0.67)	-
3	167 (19)	426 (24)	0.42 (0.31-0.56)	-
4	113 (13)	284 (16)	0.42 (0.30-0.59)	-
≥5	124 (14)	279 (16)	0.47 (0.34-0.65)	-
Number of Live Births				
0	181 (21)	207 (12)	1.00	1.00
1	117 (13)	228 (13)	0.59 (0.43-0.79)	0.63 (0.45-0.86)
2	263 (31)	593 (34)	0.50 (0.39-0.65)	0.59 (0.43-0.80)
3	170 (19)	418 (23)	0.47 (0.35-0.61)	0.56 (0.39-0.82)
4	73 (8)	190 (11)	0.44 (0.31-0.62)	0.54 (0.33-0.88)
≥5	65 (7)	143 (8)	0.52 (0.36-0.74)	0.72 (0.38-1.37)

	Cases (n=869)	Controls (n=1779)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Body Mass Index (kg/m ²)				
≤18.5	8 (1)	21 (1)	1.00	1.00
18.5–<25.0	289 (32)	645 (37)	1.18 (0.52–2.69)	1.03 (0.44–2.41)
25–<30	255 (30)	522 (29)	1.28 (0.56–2.93)	1.11 (0.48–2.60)
≥30	317 (37)	591 (33)	1.41 (0.62–3.22)	1.20 (0.52–2.81)
Age at menarche (%)				
≤11	174 (20)	439 (25)	1.00	1.00
12	247 (29)	458 (26)	1.36 (1.07–1.71)	1.33 (1.04–1.67)
13	235 (27)	478 (27)	1.24 (0.98–1.56)	1.26 (0.98–1.59)
≥14	213 (24)	404 (23)	1.33 (1.04–1.69)	1.28 (1.00–1.64)
Menopausal at interview				
No	259 (30)	562 (32)	1.00	1.00
Yes	590 (68)	1160 (65)	1.10 (0.93–1.32)	0.81 (0.63–1.05)
Unknown	20 (2)	56 (3)	0.78 (0.46–1.32)	0.74 (0.43–1.26)
Hysterectomy				
No	689 (80)	1472 (83)	1.00	1.00
Yes	180 (20)	306 (17)	1.26 (1.02–1.53)	1.24 (0.99–1.53)
Tubal ligation				
No	666 (77)	1162 (65)	1.00	1.00
Yes	201 (23)	616 (35)	0.57 (0.47–0.69)	0.62 (0.51–0.75)
Fibroid Tumors				
No	673 (77)	1451 (82)	1.00	1.00
Yes	196 (23)	327 (18)	1.29 (1.06–1.58)	1.34 (1.02–1.53)
Ever breastfed				
No	565(65)	893 (50)	1.00	1.00
Yes	304 (35)	886 (50)	0.54 (0.46–0.64)	0.62 (0.52–0.74)
Oral Contraceptive Use				
No	340 (37)	512 (28)	1.00	1.00
Yes	529 (63)	1267 (72)	0.64 (0.54–0.75)	0.67 (0.55–0.81)
Family history of ovarian cancer				
No	833 (96)	1723 (97)	1.00	-

	Cases (n=869)	Controls (n=1779)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Yes	36 (4)	56 (3)	1.33 (0.87–2.03)	-
Family history of breast cancer				
No	718 (83)	1522 (86)	1.00	1.00
Yes	151 (17)	257 (14)	1.25 (1.00–1.55)	1.23 (1.00–1.53)
Family history of endometrial cancer				
No	843 (97)	1726 (97)	1.00	1.00
Yes	26 (3)	53 (3)	1.00 (0.62–1.62)	0.99 (0.61–1.60)
Smoking Status				
Never	432 (50)	893 (51)	1.00	1.00
Former	282 (32)	543 (30)	1.07 (0.89–1.29)	1.09 (0.90–1.31)
Current	155 (18)	343 (19)	0.93 (0.75–1.16)	0.96 (0.77–1.21)

* Adjusted for age, number of pregnancies, race, and family history of ovarian cancer. Adjusted odds ratios were not calculated for age, number of pregnancies, family history of ovarian cancer, and race because these variables were used in the adjustment.

OR, odds ratio; CI, confidence interval

Table 2
Odds Ratios for Ovarian Cancer Comparison of Ever-Use of Contraceptive Methods with Never-Use

Variable	Cases	Controls	Crude OR	95% CI	Adjusted OR [*]	95% CI	Adjusted OR ^{***}	95% CI
OC use								
Neither	340 (39)	512 (29)	1.00		1.00		1.00	
OCs for contraception	370 (43)	880 (49)	0.63	0.53–0.76	0.66	0.54–0.81	0.75	0.61–0.93
OCs for non-contraception	53 (6)	108 (6)	0.74	0.52–1.06	0.73	0.51–1.06	0.76	0.53–1.11
OCs for both [#]	106 (12)	279 (16)	0.57	0.44–0.74	0.58	0.44–0.78	0.63	0.47–0.85
IUDs								
Never	763 (88)	1479 (83)	1.00		1.00		1.00	
Ever	104 (12)	299 (17)	0.67	0.53–0.86	0.69	0.54–0.89	0.75	0.59–0.95
Barrier								
Never	305 (35)	570 (32)	1.00		1.00		1.00	
Ever	564 (65)	1209 (68)	0.87	0.74–1.03	0.94	0.79–1.13	0.95	0.79–1.13
Tubal ligation								
Never	666 (77)	1162 (65)	1.00		1.00		1.00	
Ever	201 (23)	616 (35)	0.56	0.47–0.69	0.62	0.51–0.75	0.63	0.51–0.77
Vasectomy								
Never	746 (86)	1468 (83)	1.00		1.00		1.00	
Ever	121 (14)	309 (17)	0.77	0.61–0.97	0.84	0.67–1.06	0.77	0.61–0.99

^{*} Adjusted for age, number of pregnancies, race, infertility and family history of ovarian cancer

^{***} Adjusted for age, number of pregnancies, race, infertility, family history of ovarian cancer, ever use of oral contraceptives, ever use of IUDs, ever use of barriers, tubal ligation, and vasectomy.

[#] Both refers to the use of oral contraceptives for both contraception and non-contraception

[¥] Ever barrier use is defined as ever use of condoms, diaphragms, foam, sponges, or cervical caps.

OC, Oral Contraceptive

Table 3

Odds Ratios for Ovarian Cancer: Comparison of Ever Use of Contraceptive Methods with No Artificial Contraception

Variable	Cases	Controls	Crude OR	95% CI	Adjusted OR [*]	95% CI
OCs						
No contraception [‡]	111	119	1.00		1.00	
OCs for contraception	370	880	0.45	0.34–0.60	0.52	0.36–0.72
OCs for non-contraception	106	279	0.41	0.29–0.57	0.35	0.22–0.56
Intrauterine device						
No contraception [‡]	111	119	1.00		1.00	
IUD	104	299	0.37	0.27–0.53	0.41	0.27–0.62
Barrier						
No contraception [‡]	111	119	1.00		1.00	
Barrier	564	1209	0.50	0.38–0.66	0.58	0.43–0.79
Tubal ligation						
No contraception [‡]	111	119	1.00		1.00	
Tubal ligation	201	616	0.35	0.26–0.47	0.35	0.25–0.51
Vasectomy						
No contraception [‡]	111	119	1.00		1.00	
Vasectomy	121	309	0.42	0.30–0.59	0.48	0.31–0.79

[‡] Reference category^{*} Adjusted for age, pregnancies, race, infertility and family history of ovarian cancer[‡] No contraception refers to women who reported never using any contraceptive method (OC, IUD, barrier, tubal ligation, vasectomy, patch, shot, or cream); such women might have used family planning, withdrawal, or nothing.

Table 4

Adjusted Odds Ratios for Ovarian Cancer: Comparison of Ever-Use of Contraceptive Methods with Never-Use by Gravidity Group

Variable	Gravidity=0					Gravidity = 1					Gravidity = 2					Gravidity ≥ 3				
	Case	Control	Adj. OR [*]	95% CI		Case	Control	Adj. OR [*]	95% CI		Case	Control	Adj. OR [*]	95% CI		Case	Control	Adj. OR [*]	95% CI	
OCs																				
Neither	58	43	1.00	-		38	60	1.00	-		79	100	1.00	-		165	308	1.00	-	
For contraception	43	53	0.46	0.25-0.86		50	77	0.99	0.58-2.02		98	264	0.51	0.34-0.77		179	486	0.85	0.64-1.14	
For non-contraception	12	13	0.61	0.25-1.52		6	16	0.60	0.44-2.23		12	18	0.89	0.40-1.99		22	61	0.77	0.45-1.32	
For both [#]	21	34	0.31	0.15-0.67		20	35	0.99	0.22-1.69		27	76	0.50	0.28-0.88		38	134	0.70	0.45-1.09	
IUDs																				
Never	129	136	1.00	-		103	161	1.00	-		194	386	1.00	-		336	796	1.00	-	
Ever	3	7	0.32	0.07-1.56		11	27	0.67	0.32-1.40		22	72	0.59	0.36-0.99		68	193	0.84	0.62-1.16	
Tubal ligation																				
Never	126	128	1.00	-		102	151	1.00	-		165	300	1.00	-		273	583	1.00	-	
Ever	6	15	0.36	0.13-1.05		12	37	0.49	0.24-1.00		51	158	0.60	0.41-0.87		131	406	0.75	0.58-0.97	
Barrier																				
Never	52	60	1.00	-		40	73	1.00	-		78	135	1.00	-		134	301	1.00	-	
Ever	82	83	1.09	0.65-1.82		74	115	1.23	0.74-2.03		138	323	0.77	0.55-1.10		270	688	0.96	0.74-1.23	
Vasectomy																				
Never	120	133	1.00	-		100	165	1.00	-		179	359	1.00	-		346	811	1.00	-	
Ever	12	10	1.38	0.56-3.37		14	22	1.14	0.55-2.35		37	99	0.81	0.53-1.23		58	178	0.89	0.64-1.24	

^{*} Adjusted for age, race, family history of ovarian cancer, and infertility[#] Both refers to the use of oral contraceptives for both contraception and non-contraception

Table 5

	Duration											
	≤ 4 years				5–9 years				≥ 10 years			
	Cases	Controls	OR*	95% CI	Cases	Controls	OR*	95% CI	Cases	Controls	OR*	95% CI
OCs for contraception	255 (29)	555 (31)	0.91	0.75–1.10	78 (9)	194 (11)	0.78	0.59–1.05	37 (4)	131 (7)	0.52	0.35–0.76
OCs for non-contraception	44 (5)	93 (5)	0.93	0.64–1.36	7 (1)	8 (0)	1.60	0.58–4.47	2 (0)	7 (0)	0.53	0.11–2.62
OCs for both	57 (7)	99 (6)	1.22	0.87–1.73	29 (3)	84 (5)	0.72	0.46–1.12	20 (2)	96 (5)	0.40	0.25–0.67
IUDs #	58 (7)	228 (12)	0.53	0.39–0.72	20 (2)	34 (2)	1.11	0.63–1.96	25 (3)	33 (2)	1.40	0.82–2.39

* Adjusted for age, pregnancies, race, family history of ovarian cancer, and infertility.

[#]Data on duration of use of IUDs was unavailable for 4 women.

IUD, intrauterine device

OCs, Oral Contraceptives

Table 6**Contraception Methods Used by Cases and Controls**

Contraceptive Method	Total	Cases	Controls	P
Never Users	231			
Oral contraceptive only	153	56 (6)	97 (5)	0.30
IUD only	26	8 (1)	18 (1)	0.82
Tubal ligation only	75	24 (3)	51 (3)	0.88
Vasectomy only	20	11 (1)	9 (1)	0.03
Barrier only	373	153 (18)	220 (12)	0.0003
OC and IUD	24	4 (0)	20 (1)	0.09
OC and tubal ligation	156	38 (4)	118 (7)	0.02
OC and vasectomy	54	17 (2)	37 (2)	0.83
OC and barrier	471	166 (19)	305 (17)	0.21
IUD and tubal ligation	24	4 (1)	20 (1)	0.09
IUD and vasectomy	3	1 (0)	2 (0)	0.98
IUD and barrier	28	12 (1)	16 (1)	0.25
Tubal ligation and vasectomy	0	-	-	-
Tubal ligation and barrier	92	24 (3)	68 (4)	0.16
Vasectomy and barrier	56	18 (2)	38 (2)	0.92
OC, IUD and tubal ligation	41	7 (1)	34 (2)	0.03
OC, IUD and vasectomy	12	3 (0)	9 (1)	0.56
OC, IUD and barrier	80	28 (3)	52 (3)	0.67
OC, tubal ligation and vasectomy	5	1 (0)	4 (0)	0.54
OC, tubal ligation and barrier	288	71 (8)	217 (12)	0.002
OC, vasectomy and barrier	198	48 (6)	150 (8)	0.008
IUD, tubal ligation and vasectomy	0	-	--	-
IUD, tubal ligation and barrier	20	4 (0)	16 (1)	0.22
IUD, vasectomy and barrier	10	2 (0)	8 (0)	0.39
Tubal ligation, vasectomy and barrier	5	1 (0)	4 (0)	0.54
OC, IUD, tubal ligation and vasectomy	1	-	1 (0)	0.48
OC, IUD, tubal ligation and barrier	86	18 (2)	68 (4)	0.02
OC, IUD, vasectomy and barrier	42	10 (1)	32 (2)	0.21
OC, tubal ligation, vasectomy and barrier	18	6 (1)	12 (1)	0.96
IUD, tubal ligation, vasectomy and barrier	0	-	-	-
OC, IUD, tubal ligation, vasectomy and barrier	6	3 (0)	3 (0)	0.37