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Comparison of Effect Estimates from a Meta-Analysis of Summary Data from Published Studies and from a Meta-Analysis Using Individual Patient Data for Ovarian Cancer Studies

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To determine the relative merits of two quantitative methods used to estimate the summary effects of observational studies, the authors compared two methods of meta-analysis. Each quantified the relation between oral contraceptive use and the risk for ovarian cancer. One analysis consisted of a meta-analysis using summary data from 11 published studies from the literature (MAL) in which the study was the unit of analysis, and the second consisted of a meta-analysis using individual patient data (MAP) in which the patient was the unit of analysis. The authors found excellent quantitative agreement between the summary effect estimates from the MAL and the MAP. The MAP permits analysis 1) among outcomes, exposures, and confounders not investigated in the original studies, 2) when the original effect measures differ among studies and cannot be converted to a common measure (e.g., slopes vs. correlation coefficients), and 3) when there is a paucity of studies. The MAL permits analysis 1) when resources are limited, 2) when time is limited, and 3) when original study data are not available or are available only from a biased sample of studies. In public health epidemiology, data from original studies are often accessible only to limited numbers of research groups and for only a few types of studies that have high public health priority. Consequently, few opportunities for pooled analysis exist. However, from a policy view, MAL will provide answers to many questions and will help in identifying questions for future investigation. *Am J Epidemiol* 1997;145:917–25.

cost and cost analysis; meta-analysis; regression analysis

To increase their ability to detect small effects, researchers are increasingly using quantitative methods that combine results of observational studies. Quantitative methods for combining existing research results include overviews that combine original individual patient data and overviews that combine published and unpublished summary results. Although quantitatively combining results of randomized controlled trials is generally accepted as a way to summarize study results, combining data from observational studies may have more pitfalls because of inherent biases of observational studies and differences in the design of such studies. Nonetheless, large studies may take years to complete and are costly, and there are a large number of interventions and treatments that need to be evaluated. For these reasons, methods for quantitatively combining data from observational studies will have to be used. In addition, performing new, larger studies does not ensure that bias will be eliminated.

In the following discussion, we use meta-analysis of individual patient data (MAP) to denote methods of combining individual patient data in which the study is taken into account as a factor and meta-analysis to denote methods of combining published summary results from the literature (MAL) (1).

To determine the differences in results from a MAP and a MAL on the summary estimate of risk from observational studies, we compared the results of a published MAP (2) that included an analysis of the relation between oral contraceptive use and risk for epithelial ovarian cancer with the results of our original MAL of the studies used in the published pooled analysis. Because the protection against epithelial

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Abbreviations: CI, confidence interval; MAL, meta-analysis of summary data from published results from the literature; MAP, meta-analysis of individual patient data; OR, odds ratio.

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ovarian cancer offered by birth control pills is well-established, our major objective was to estimate the relative advantages and disadvantages of each quantitative method.

MATERIALS AND METHODS

For our MAL, we analyzed 11 published reports of the summary data on the effect of oral contraceptive use on epithelial ovarian cancer risk that were cited in the MAP of Whittemore et al. (2) (table 1). One of the studies included in the MAP, that of Wu et al. (12), reported data from two studies, one with hospital control subjects conducted from 1974 to 1977 (12, study 1) and one with community control subjects conducted from 1983 to 1985 (12, study 2). Data from both studies are found in one report (12). We excluded from the MAL studies that were included in the MAP but did not provide enough published information to calculate a confidence interval for the estimate of the mean dose-response slope or an odds ratio for ovarian cancer risk among women who had ever used oral contraceptives.

To determine the effect of ever having used oral contraceptives on ovarian cancer risk, we calculated a mean odds ratio, weighting each estimate by the inverse of the variance of the estimate for studies that presented results for women who had ever used oral contraceptives (13). Because duration (a measure of dose) is a risk factor in many exposures, for each study that provided sufficient data, we then calculated a dose-response slope from a least-squares linear model depicting the effects of duration of oral contraceptive use on the log odds ratio of ovarian cancer, again weighting each risk estimate for a given duration by the inverse of the variance of that risk (14). In one model, we assumed that all women were at similar risk before one group of women began oral contraceptive use, which is characterized by a dose-response relation with no (zero) intercept term in the model (equation 1). However, in order not to be reliant on this assumption, we also created a second model that omitted this assumption (equation 2). The two models are as follows:

$$\log(\mathrm{OR}_{ij}) = \beta_i(\mathrm{duration})_{ij} + E_{ij}, \quad (1)$$

$$\log(\mathrm{OR}_{ij}) = \alpha_i + \beta_i(\mathrm{duration}) + E_{ij}, \quad (2)$$

where α_i is the estimated log odds ratio (OR) for study i at duration zero, β_i denotes the slope for the ith study, the duration is measured in months, E_{ij} denotes the error term (the difference between the computed risk and the actual risk) for the ith study and jth duration, and OR_{ij} is the odds ratio for ovarian cancer at the jth duration from the ith study.

When the analysts reported only two durations of use, the variable-intercept model is inappropriate because two values uniquely determine a line; that is, the slope has no variance.

When investigators reported durations as "greater than" a given number of years, we used 120 percent of that duration for our analysis. (For example, a duration reported as ">10 years" was analyzed as 12 years or 144 months) (see reference 15 for rationale for this approach). When investigators reported durations as a range, we used the midpoint of the range. We converted all durations to months for consistency. In order to identify which studies were the source of the heterogeneity, we assessed homogeneity (16) at the 10 percent probability level. We investigated sources of heterogeneity among studies by performing two subgroup analyses. In one, we calculated separate mean estimated dose-response slopes for studies with hospital control subjects and for studies with community control subjects. In the other, we calculated the mean effect with and without studies whose results were statistical outliers (12). If heterogeneity was significant, we reported estimates from a random-effects model and reported results of subgroup analysis when possible. We tested for statistical outliers at a 1 percent probability level (17).

We estimated the summary effect of oral contraceptive use as a risk factor for ovarian cancer by calculating a mean weighted dose-response slope, assuming that the study populations were similar (i.e., by using a fixed-effects model):

$$\beta = \frac{\sum w_i \beta_i}{\sum w_i}, \quad (3)$$

where the study weight, w_i, is calculated as the inverse of the variance of the slope estimate (18) and where the weights are normalized to sum to one. In addition, we calculated the slope, assuming that the study populations differed (i.e., by using a random-effects model). With the random-effects model, the weights were as follows:

$$w^{\star}_i = (w_i^{-1} + \Delta_w^2)^{-1}, \quad (4)$$

where Δ_w is a term that accounts for interstudy variation (16), and the weights, $w^{\star}_i$, are normalized to sum to one.

We report effect size as the estimated odds ratio for ovarian cancer after 5 years of oral contraceptive use, which we calculated from the mean of the dose-response slopes for the fixed-effects and random-effects models. To obtain this estimated odds ratio, we multiplied the mean estimated dose-response slope estimate by 12 (months) and then by 5 (years) and

calculated the antilog (to base e so that we have $\exp\{\text{slope} \times 12 \times 5\}$). We present the results of the fixed-effects model as the best estimate of the odds ratio when studies are homogeneous and the results of the random-effects model when studies are heterogeneous. In some cases, for comparison, we present results of both models.

RESULTS

Of the 10 study reports that presented data on the effect of oral contraceptives on ovarian cancer (2), eight contained sufficient information to allow us to determine whether or not a significant relation existed between the duration of oral contraceptive use and the risk for ovarian cancer (4–7, 9–12), and eight reported the risk associated with any use of oral contraceptives (3, 5, 7–12) (table 2). All studies included women who took oral contraceptives for 6 years or longer with the exception of the study by Wu et al. (12), which included women who had used oral contraceptives for at least 3 years. The study by Nasca et al. (9) reported 20 years as the longest duration of use. All studies controlled for age at diagnosis, and six controlled for parity (3, 5, 8, 10–12). Five studies used hospitalized women as control subjects (3, 7, 8, 10, 12 (study 1)), and six used community women as control subjects (4–6, 9, 11, 12 (study 2)). Of the studies that included enough information to calculate dose-response slopes, three used hospitalized women as control subjects (7, 10, 12 (study 1)), and six used community women as control subjects (4–6, 9, 11, 12 (study 2)).

In table 3, we present dose-response slopes and their 95 percent confidence intervals calculated by using both regression models (equations 1 and 2) for the individual studies.

When we analyzed the effect of ever having used oral contraceptives, the results of the eight studies were significantly heterogeneous (table 4). The group of studies that used community control subjects were heterogeneous until we removed a statistical outlier (12, study 2); this study contained no long-term "ever users" of oral contraceptives. Studies that used hospital control subjects were homogeneous. The reduction in risk for ovarian cancer among women who used oral contraceptives appeared to be slightly greater in studies that used community control subjects. However, we found a significant reduction in risk when we included studies that used either hospital control subjects or community control subjects as the control group.

With neither model did we find a significant difference in summary odds ratios for ovarian cancer after 5 years of oral contraceptive use between studies with community control subjects and studies with hospital control subjects using any model (table 5). However, after excluding an outlier study (9), we found that, in most cases, the odds ratio was slightly lower (i.e., the measured protective effect was greater) in studies that used community control subjects than in studies that used hospital control subjects. Results of studies that used hospital control subjects were homogeneous. Results of studies that used community control subjects were homogeneous after we removed one statistical outlier (9). Results of our meta-analysis indicated that oral contraceptive use had a protective effect against ovarian cancer for both studies with hospital control subjects (OR = 0.64, 95 percent confidence interval (CI) 0.44–0.93) and studies with community control subjects (OR = 0.53, 95 percent CI 0.45–0.61). These results give consistent conclusions, but note that hospital control studies are less diverse and thereby yield a shorter confidence interval.

In comparison of the pooled analysis with meta-analysis, we found that results of our MAL were strikingly similar to those of the MAP (2) (table 6). In both analyses, the measured reduction in risk after 5 years of oral contraceptive use was greater in the studies that used community control subjects.

At least three studies (18–20) reported data on the effect of oral contraceptive use but did not meet inclusion criteria for the published pooled analysis (personal communication). When we included the one study (19) with sufficient information to calculate a dose-response slope of the effect of 5 years of oral contraceptive use on ovarian cancer risk, the summary odds ratio for studies with community control subjects was substantially the same when we included a study (9) identified as a statistical outlier (OR = 0.57, 95 percent CI 0.38–0.86, $\chi^2 = 142$, $p < 0.0001$) (4–6, 9, 11, 12 (study 2), 19) as it was when we excluded the outlier study (OR = 0.50, 95 percent CI 0.43–0.59, $\chi^2 = 3.5$, $p = 0.75$) (4–6, 11, 12 (study 2), 19).

MAP is by its nature more costly than MAL. Indeed, the combined cost of the planning grant ($23,000) and 2-year analytical grant ($235,000) for the pooled analysis was $259,300, approximately five times that of the meta-analysis (table 7). However, the pooled analysis published estimates of the association between ovarian cancer and 10 other reproductive variables, and the meta-analysis did not address these other variables.

DISCUSSION

The goal of this analysis was to compare the results of two methods for combining data from observational studies. For the MAP, we used conditional logistic regression to estimate odds ratios, adjusting for study, year of birth, and age at diagnosis (or interview for

TABLE 1. Studies of effect of oral contraceptive use on ovarian cancer risk

First author, date, reference number	Study		No. of cases/no. of controls	Ascertainment years	Age (years)	Adjustment variables	Risk estimate			
	Design	Type of controls								
McGowan, 1979 (3)	Case-control	Hospital	175/197	1974–1977	52.1 (cases), 52.2 (controls)	Parity	33% of cases and 28% of controls never used; exposed cases = 97*; exposed controls = 97; unexposed cases = 47; unexposed controls = 38			
							Duration (months)	Odds ratio	95% confidence interval	No. of cases/ no. of controls*
Casagrande, 1979 (4)	Case-control	Community	150/150	1973–1976	25–49	Age, race	≤6	1.0		109/100
							7–83	0.73		31/36
							≥84	0.62		10/14
Cash, 1987 (5)	Case-control	Community	439/3,867	1980–1982	20–54	Age, parity	Never†	1.0		242/1,532
							Ever	0.6	0.5–0.7	197/2,135
							3–6	0.6	0.4–0.9	26/280
							7–11	0.7	0.4–1.3	14/134
							12–24	0.7	0.5–0.9	65/602
							36–48	0.6	0.4–0.9	40/397
							60–108	0.4	0.3–0.6	39/594
							≥120	0.2	0.1–0.4	13/328
Cramer, 1982 (6)	Case-control	Community	238/238	1978–1981	18–80	Age, age at first use, race, residence	≤12			11/13
							13–36			13/11
							37–60			3/11
							>60			7/11 (trend $p = 0.41$)
Hartage, 1989 (7)	Case-control	Hospital	169/209	1978–1981	20–79	Age, race	Ever	1.0	0.7–1.7	
							1–11	1.6	0.7–3.4	
							12–35	1.0	0.4–2.3	
							36–59	0.8	0.3–2.3	
							≥60	0.8	0.4–1.5	(trend $p = 0.76$)
Hildreth, 1981 (8)	Case-control	Hospital	62/1,068	1976–1979	45–74	Race, age, parity	Ever	0.5	0.2–1.5	
Nasca, 1984 (9)		Community	403/806	1977–1980	20–79	Age, religion, education	Never	1.0		
							Ever	0.63	0.45–0.89	
							1–120	0.74	0.49–1.11	
							121–240	0.51	0.34–0.77	
							≥241	0.68	0.45–1.04	
Rosenberg, 1982 (10)	Case-control	Hospital	136/539	1976–1980	18–59	Race (89% white), age matched by decade. When possible geographic region. *Multivariate*: age at menarche, age at first full-term pregnancy, parity, menopausal status, age at menopause, regularity of menses, geographic area, year of interview, previous hospital admissions, education, use of noncontraceptive estrogen, and obesity index	Never	1.0‡		103/352
							Ever	0.6§	0.4–0.9	
							<12	0.7,‡ 0.9§		11/49
							12–48	0.5,‡ 0.6§		2/76
							≥60	0.3,‡ 0.3§		6/51

Weiss, 1981 (11)	Case-control	Community	112/552	1975–1979	35–54	State, age, parity (all white)	Never	1.0		91/345
							Ever	0.57		21/207 ($p = 0.4$)
							12–36	0.98	0.5–1.92	14/79
							48–96	0.17	0.05–0.56	3/83
							≥108	0.43	0.15–1.28	4/45
Wu, 1988 (12)	Case-control	Community, hospital	291/993	1974–1985	18–85	Age, race, hospital, admission date, telephone exchange, number of pregnancies > 20 weeks' gestation	Never	1.0		188/619
							Ever	0.74	0.52–1.0	111/392
							1–12	0.97	0.64–1.49	51/136
							13–36	0.81	0.45–1.44	24/69
							≥37	0.40	0.24–0.68	28/169
							Unspecified			8/18
Wu, 1970s participants (12, study 1)		Hospital	111/466	1974–1977	20–85	Age, race, hospital, admission date, number of pregnancies > 20 weeks' gestation	Never	1.0		86/370
							Ever	0.71	0.37–1.37	25/102
							1–12	0.72	0.3–1.72	9/39
							13–36	1.26	0.46–3.42	8/19
							≥37	0.53	0.2–1.43	8/38
							Unspecified			0/6
Wu, 1980s participants (12, study 2)		Community	180/527	1983–1985	18–74	Age, race, admission date, telephone exchange, number of pregnancies > 20 weeks' gestation	Never	1.0		102/294
							Ever	0.74	0.48–1.14	86/290
							1–12	1.03	0.63–1.70	42/97
							13–36	0.66	0.32–1.35	16/50
							≥37	0.37	0.2–0.68	20/131
							Unspecified			8/12

* Cell values.
† Durations were originally reported in years. We converted to months by multiplying 12 × the shortest and longest durations.
‡ Mantel-Haenszel odds ratio.
§ Multivariate odds ratio.

controls). Because we calculated study-specific as well as combined regression analyses, we were thus able to assess homogeneity among studies using a log-likelihood model. Furthermore, a related approach (analysis of variance) gives the identical results for a model with study as a factor and a meta-analysis of summary data (21). Thus, in an ideal experimental situation, we would not expect disparate results. The question that we answer, in part, is that, for applied public health studies in which there is heterogeneity, similar summary results are obtained.

Our principal finding was that the MAP and MAL of the relation between epithelial ovarian cancer and oral contraceptive use gave remarkably similar results in the magnitude of risk after 5 years of oral contraceptive use, in the magnitude of risk after any use, and in the effect of community versus hospital control subjects. The smaller measured effect that we obtained by combining studies that used hospital control subjects was similar to the results of an early meta-analysis in which the measured effect of estrogen replacement therapy on risk for breast cancer was smaller when hospital control subjects were used (15).

We identified the results of two studies (9, 12 (study 2)) as statistical outliers, which turned out to be important sources of heterogeneity. When the study by Nasca et al. (9) on the effect of 5 years of oral contraceptive use on risk was removed from the analysis of community controlled studies, the results were homogeneous. Nasca et al. (9), who included in their case group women who used other nonpermanent forms of contraceptives as well as those who used oral contraceptives, found that use of contraceptives had very little effect on ovarian cancer risk. Because methods of birth control other than oral contraceptives have not been postulated to decrease ovarian cancer risk, including women who used those methods probably diluted the effect of oral contraceptive use on risk. The difference between the results for women who took oral contraceptives for only 3 years or less (12, study 2) and the results of other studies may have been due to the absence of long-term, "ever-users" of oral contraceptives.

MAP has the advantage of allowing analysts to explore additional relations through subgroup analyses that may not have been included in the original analysis. For example, the MAP used in this comparison suggested for the first time that use of fertility drugs increased users' risk for epithelial ovarian cancer. This kind of information may be lost when only published reports are used. Thus, information that was collected but not thoroughly analyzed by the original authors may provide the basis of identifying additional risk factors.

TABLE 2. Studies included and excluded from the MAL* and MAP* by duration of use

		MAL†		MAL‡	
		Included	Excluded	Included	Excluded
MAP	Included	3, 5, 7–12	4,§ 6§	4–7, 9–12	3,¶ 8¶
	Excluded	None	None	19	None

* MAL, meta-analysis of summary data from published results from the literature; MAP, meta-analysis of individual patient data.
† Studies that report "ever use" of oral contraceptives.
‡ Studies that report "duration" of use of oral contraceptives.
§ Insufficient information to calculate a confidence interval for ever use.
¶ Insufficient information to calculate a dose-response slope.

Unlike MAL, MAP is possible even when published summary estimates of effects differ and cannot be combined. MAP may be preferable to MAL when a new issue is being investigated and only a few studies are available. MAP is preferable to MAL if covariates that were available but not reported in the original publication are to be included in an overview analysis.

On the other hand, MAP is more time consuming and costly than MAL with time and cost increasing with the number of studies included (22). MAP is also more subject to bias that may result because data from more recent studies are available while data from older studies are not. MAP is also frequently complicated by the existence of multiple copies of the data, each of which may be somewhat different. Further, if some authors do not wish (or are not able) to share data, a pooled analysis may have to be performed on only a portion of the studies. Even when the data are available, acquiring and coding data for a pooled analysis may still be difficult when data are not in an easily accessible, electronic form. Furthermore, after a uniform data set for all studies is constructed, sharing of these data sets without approval of the original investigators or data providers raises ethical concerns. Such a situation may arise if studies are published subsequent to MAP.

When we compared the cost of the two methods, we found that the MAP cost five times more than the MAL, and we believe that we have underestimated the cost of the pooled analysis. However, the meta-analysis would have cost more in time and money if we had searched the literature for appropriate reports and then reviewed the results of our search to see if the studies met inclusion criteria. More important, the

TABLE 3. Dose-response slopes of individual studies of the relation between oral contraceptive use and ovarian cancer risk

Reference	Slope, zero intercept model*	*p* value for H_0: $\beta = 0$	Slope, variable intercept model†	*p* value for H_0: $\beta = 0$
4	−0.0044 (−0.0113 to 0.0025)‡	0.10	NA§	
5	−0.0116 (−0.0145 to −0.0087)	0.0001	−0.0080 (−0.0520 to 0.0107)	0.0046
6	−0.0060 (−0.0199 to −0.0079)	0.20	−0.0134 (−0.3040 to 0.3041)	0.6519
7	−0.0029 (−0.0111 to 0.0054)	0.25	−0.0095 (−0.1040 to 0.1039)	0.1056
9	−0.0021 (−0.0033 to −0.0093)	0.0003	−0.0004 (−0.0805 to 0.7960)	0.8341
10	−0.0138 (−0.0240 to −0.0035)	0.004	−0.0092 (−0.1085 to 0.0902)	0.1747
11	−0.0094 (−0.0166 to −0.0023)	0.005	−0.0098 (−0.2050 to 0.2240)	0.5662
12	−0.0179 (−0.0283 to −0.0075)	0.0004	−0.0229 (−0.1788 to 0.1331)	0.1719
12¶	−0.0097 (−0.0290 to −0.0096)	0.16	−0.0071 (−0.0945 to 0.0413)	0.7857
12#	−0.0208 (−0.0332 to −0.0085)	0.0005	−0.0266 (−0.0945 to 0.0413)	0.0288
20	−0.0935 (−0.3383 to 0.1513)	0.23	NA	

* The zero intercept model assumes that all women were at similar risk before one group of women began oral contraceptive use.
† The variable intercept model assumes that women may have been at unequal risk before one group began oral contraceptive use.
‡ Numbers in parentheses, 95% confidence interval.
§ NA, not applicable (only two durations reported).
¶ Study 1.
# Study 2.

TABLE 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for ovarian cancer among women who have ever used oral contraceptives

	OR	95% CI	χ^2	*p*
All studies*	0.78	0.66–0.93	56.0	0.0001
Community control studies†	0.64	0.45–0.92	53.0	<0.0001
Community control studies‡	0.58	0.50–0.68	3.0	0.39
Hospital control studies§	0.85	0.78–0.92	4.9	0.43

* References 3, 5, 7–11, and 12 (studies 1 and 2).
† References 5, 9, 11, and 12 (study 2).
‡ References 5, 9, and 11 (outlier removed).
§ References 3, 7, 8, 10, and 12 (study 1).

TABLE 5. Ovarian cancer risk after 5 years of oral contraceptive use: combined dose-response slopes of all studies, studies using community control women, and studies using hospital control women

	Zero Intercept*			Variable intercept†		
	Fixed effects		Random effects (odds ratio)	Fixed effects model		Random effects model (odds ratio)
	Odds ratio	*p* for χ^2 for heterogeneity		Odds ratio	*p* for χ^2 for heterogeneity	
All studies‡	0.79 (0.74–0.84)§	<0.0001	0.60 (0.44–0.81)	0.44 (0.40–0.48)	≤0.0001	0.52 (0.29–0.91)
All studies¶	0.54 (0.47–0.62)	0.22	0.57 (0.46–0.70)	0.36 (0.33–0.40)	≤0.0001	0.47 (0.25–0.86)
All studies#	0.79 (0.74–0.85)	<0.0001	0.59 (0.43–0.83)	0.69 (0.61–0.77)	0.0001	0.61 (0.46–0.81)
Hospital controls**	0.64 (0.44–0.93)	0.438	0.62 (0.39–0.99)	0.57 (0.45–0.73)	0.99	Same as fixed effects
Community controls††	0.80 (0.75–0.85)	<0.0001	0.61 (0.43–0.86)	0.72 (0.64–0.81)	0.003	0.70 (0.51–0.96)
Community controls‡‡	0.53 (0.45–0.61)	0.23	0.55 (0.42–0.70)	0.61 (0.53–0.70)	0.95	Same as fixed effects

* The zero intercept model assumes that all women were at similar risk before one group of women began oral contraceptive use.
† The variable intercept model assumes that women may have been at unequal risk before one group began oral contraceptive use.
‡ References 4–7, 9–11, and 12 (studies 1 and 2).
§ Numbers in parentheses, 95% confidence interval.
¶ References 4–7, 10, 11, and 12 (studies 1 and 2) (outlier removed).
# References 4–7 and 10–12 (data combined from studies 1 and 2).
** References 7, 10, and 12 (study 1).
†† References 4–6, 9, 11, and 12 (study 2).
‡‡ References 4–6, 11, and 12 (study 2) (outlier removed).

TABLE 6. Odds ratios from selected pooled analysis and meta-analyses for ovarian cancer following oral contraceptive use

Type of analysis	Hospital control studies			Community control studies		
	Odds ratio	χ^2	*p*	Odds ratio	χ^2	*p*
MAP* (4–5 years of oral contraceptive use)	0.69 (0.42–1.10)†	3.2	0.52	0.58 (0.41–0.82)	10.0	<0.08
MAL* (5 years of oral contraceptive use)	0.64 (0.44–0.93)‡	2.7	0.438	0.61 (0.43–0.86)§	139.0	<0.0001
MAL (5 years of oral contraceptive use, outlier removed)	No outlier			0.50 (0.43–0.59)¶	3.1	0.54
MAP (any use)	0.70 (0.52–0.94)	5.4	0.25	0.66 (0.55–0.78)	17.1	<0.01
MAL (any use)	0.58 (0.50–0.68)#	3.0	0.39	0.64 (0.45–0.92)**	53	<0.01

* MAP, meta-analysis of individual patient data; MAL, meta-analysis of summary data from published results from the literature.
† Numbers in parentheses, 95% confidence interval.
‡ References 7, 10, and 12 (study 1).
§ References 4–6, 9, 11, and 12 (study 2).
¶ References 4–6, 11, and 12 (study 2).
# References 3, 7, 8, 10, and 12 (study 1).
**References 5, 9, and 11.

pooled analysis allowed analysts to investigate the effect of at least 10 other reproductive variables or variables related to exogenous estrogen use or pelvic surgery. If we had investigated all of the variables used in the pooled analysis, our costs would have increased substantially.

Others have found larger effect sizes and statistically significant results from MAL in contrast to re-

TABLE 7. Resources required for meta-analysis

Task	Time estimate		Type of personnel	Cost estimate ($)
	No. of hours	Hourly rate ($/hour)		
1. Prepare for analysis (do background reading; develop research questions and inclusion/exclusion criteria)	160	40	One subject matter expert One statistician	6,400
2. Conduct literature search (done by information specialist by using automated database and journals available on site)	24	27	One information specialist One librarian	648
3. Conduct first screening of papers (on the basis of 30 papers)	40	40	One subject matter expert	1,600
4. Conduct second screening of papers (read 25 papers for inclusion/exclusion)	40	40	Three subject matter experts	4,800
5. Extract data from 15 papers and tabulate for analysis	120	40	One subject matter expert	4,800
6. Proof data	4	40, 26		264
7. Review data extraction (five papers per reviewer, three reviewers)	40	40 x 3	Three subject matter experts	4,800
8. Analyze data (includes development of computer programs)	320	33	One subject matter expert One statistician	10,560
9. Review results (tabulate results and write commentary)	40	40	One subject matter expert	1,600
10. Meet to review results (discuss conclusions and additional analysis)	2	40 (two meetings)	Three subject matter experts	480 1,200
11. Conduct additional analysis (includes data extraction and analysis)	8 24	40 33	One subject matter expert One statistician	320 792
12. Add additional results to tables and write commentary	24	40	One subject matter expert	960
13. Write manuscript	160	40	One subject matter expert	6,400
14. Review and edit manuscript	4	40 x 6	Subject matter experts	960
15. Make changes and submit for clearance	4	40	One subject matter expert	160
16. Respond to reviewers (revisions)	32	40 x 4	Subject matter experts and statistician	5,120
Total for meta-analysis	1,046	(26 weeks)		48,665

sults from MAP when randomized controlled trials were combined (23, 24). In both cases, publication bias, patient exclusion, and length of follow-up may have contributed to differences in the magnitude and significance of results between MAP and MAL. In contrast, we found excellent agreement between a MAP and MAL of results from the same observational studies. Our results could not have been affected by publication bias, because we included the same studies that were included in the pooled analysis. The numbers of case women included differed in our comparison of MAL (n = 1,772) with MAP (n = 2,487). However, MAP is often impractical because of cost, the required time investment, and the unavailability of data and the large numbers of treatments being studied. The cost of MAP increases considerably with the addition of each study, whereas the cost of MAL is hardly changed.

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