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Tubal ligation and the risk of ovarian cancer: review and meta-analysis

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BACKGROUND: The reduction of ovarian cancer (OC) risk in women with a history of tubal ligation (TL) has been reported repeatedly, mostly on small populations. We have aimed to provide a critical overview of the studies available to date and to conduct a meta-analysis.

METHODS: There were 40 relevant studies identified. The studies were divided into two groups for strict and extended meta-analysis, respectively. Subgroup analysis was performed for age, time dependency since TL, histological types of OC and BReast CAncer (BRCA) mutation.

RESULTS: Meta-analysis of 13 strictly selected studies showed a reduced risk of epithelial OC by 34%. The protective effect of TL was confirmed even in a subgroup of women 10–14 years after the procedure. The risk reduction was confirmed for the endometrioid (RR = 0.40) and serous (RR = 0.73) cancers but not for mucinous.

CONCLUSIONS: The review of relevant articles, as well as the meta-analysis of selected studies, yields consistent data on a significant reduction of OC risk in women who had undergone TL. The results of this meta-analysis should provide an impulse for further research on the etiology of ovarian epithelial cancers, focusing particularly on the importance of retrograde transport of endometrial cells.

Key words: tubal ligation / BRCA mutation / ovarian cancer / meta-analysis

Introduction

In the 1970s, the theory of growing incidence of ovarian cancer (OC) as a result of increased exposure of ovaries to carcinogens that are transported to the peritoneal cavity through the fallopian tubes was first suggested (Woodruff, 1979). The protective effect of tubal ligation (TL) was later demonstrated in several case–control studies in 1980s (Mori *et al.*,1984, 1988; Hartge *et al.*, 1988; Whittemore *et al.*, 1988; Shu *et al.*, 1989). There have been several case-control studies published to date, as well as five prospective cohort studies, which mostly had consistent outcomes showing a reduced risk of OC in women after TL, although the odds ratios varied substantially. The

risk reduction was significant, comparable or even superior to that achieved by oral contraceptives (Risch et al., 1996; Tworoger et al., 2007). Unlike oral contraceptives, the protective influence of TL has received little attention particularly due to the elusive underlying mechanism. There were a number of theories debated, in particular, the prevention of carcinogenic talc transportation from the vagina and external genitalia into the peritoneal cavity, yet it was highly unlikely that any of those theories would explain the significant risk reduction. Over the past few years, however, there have been a growing number of arguments supporting the potential origin of ovarian epithelial tumors from tissues that are embryologically derived from the Müllerian ducts, including endometrial cells, which are transported from the endometrial cavity by retrograde menstruation (Dubeau, 2008).

The aim of this review was to summarize available studies, collating data on the OC risk in women who underwent TL and perform meta-analysis on the OC risk in such population and in subgroups according to age, time interval since the TL, histological types of OC and BRCA mutation.

Methods

Identification of studies

Papers were identified from review and original articles, using Medline and PubMed, up to September 2009. References from relevant articles were searched for additional relevant studies. A total of 32 case-control (Mori et al., 1984, 1988; Harlow et al., 1988; Hartge et al., 1988; Whittemore et al., 1988, 1992a, b; Booth et al., 1989; Shu et al., 1989; Irwin et al., 1991; Chen et al., 1992; Risch et al., 1994; Rosenberg et al., 1994; Cramer and Xu, 1995; Purdie et al., 1995; Risch et al., 1996; Rosenblatt and Thomas, 1996; Cornelison et al., 1997; Green et al., 1997; Modugno et al., 2001, 2004; Narod et al., 2001; Ness et al., 2001; Tung et al., 2003; McGuire et al., 2004; Mills et al., 2004; Pike et al., 2004; McLaughlin et al., 2007; Jordan et al., 2008; Moorman et al., 2008; Nagle et al., 2008), 5 prospective cohort (Hankinson et al., 1993; Miracle-McMahill et al., 1997; Tworoger et al., 2007; Antoniou et al., 2009; Dorjgochoo et al., 2009) and 3 historical cohort (Koch et al., 1984; Kreiger et al., 1997; Kjaer et al., 2004) studies were identified and included in the overview (Tables I–3).

The studies available were categorized into three groups for the main meta-analysis (Tables I–3). 'Excluded' were those studies not reporting any estimate of OC after TL, those with a substantially overlapping study population, those performed in high-risk population and finally those having only specific histological types of OC as an outcome. For a strict selection analysis, well-designed case-control studies having epithelial OC as an outcome were included. All other studies not excluded from the main analysis, including historical cohort ones, formed a group for an 'extended selection analysis'. Several studies not selected for the main meta-analysis were included in the subgroups, which evaluated secondary end-points, as they provided further stratification of results (Tables I–3). Overview of used end-points is summarized in Table 4.

Data analysis

Precision of effect size estimates in individual studies was assessed on the basis of confidence intervals or *P*-values. Standard error of the log relative risk estimate is given by:

$$\mathrm{SE} = \frac{\log \overline{\mathrm{RR}} - \log \underline{\mathrm{RR}}}{3.92},$$

where $\overline{\mathrm{RR}}$ and $\underline{\mathrm{RR}}$ are upper and lower limit of given 95% confidence interval, or

$$\mathrm{SE} = \frac{\log \mathrm{RR}}{Z_P},$$

where Z_P is the value of standardized normal test statistic corresponding to the given *P*-value.

Rare-disease assumption was verified for OC in normal-risk population and, therefore, we treated both odds ratios and rate ratios as estimates of relative risk (Greenland, 1987). Fixed-effect inverse-variance method was used for pooling results of primary studies.

Heterogeneity within given trial set was assessed using χ^2 distributed Cochran's Q statistic (null hypothesis is zero heterogeneity) computed as the sum of weighted square differences of individual study estimates and pooled estimate of the effect size. Measured I^2 is used for quantifying the percentage of total variation across the studies attributable to heterogeneity rather than a chance (Higgins et al., 2003).

Subgroup analysis was performed separately for groups by years from TL, cell type of OC and its behavior, age at TL and the presence of BRCA mutation. These results were presented by standard summary statistics according to data availability (Table 4). In these stratified analyses, both between-group and within-group heterogeneity were tested. Between-group heterogeneity was tested using χ^2 statistics. Observed heterogeneity within subgroups was always reported along with the results of statistical tests, as the resulting *P*-value for test of homogeneity between subgroups might be understated in such cases (Harris et al., 2008). All calculations were performed using metan command (Harris et al., 2008) in Stata 10.1 software (StataCorp, 2007).

Results

Risk in population

Following the exclusion of 16 case–cohort and 3 prospective cohort studies due to reasons listed previously and summarized in Tables I–3, the risk of OC in relation to TL was analyzed in 16 case–control, 3 retrospective cohort and 2 prospective cohort studies.

Of the 13 strictly selected studies, 7 of them found that TL significantly reduced the risk of OC. The other six studies did not find significant evidence of a difference; however, in five of these six studies, the direction of the effect was in favor of TL. Meta-analysis of the above 13 studies confirmed that TL reduces the risk of epithelial OC by 34% (RR = 0.66, 95% CI 0.60–0.73) (Fig. 1). Variability between primary studies appears to be of random origin (I^2 = 12.7%), and increased heterogeneity was not found by a χ^2 test ($P = 0.317$). The above results remained almost unchanged when adding eight additional studies in the extended selection (RR = 0.69, 95% CI 0.64–0.75) (Fig. 1). However, in the complete set

Table I Overview of investigated primary studies. Case–control studies of TL effect on OC risk.

Study ID	Main meta-analysis	Reason for exclusion from main meta-analysis	Geographical setting	Time period	Case/ outcome	Available subgroups	Cases	Controls	Total sample size	Measure	Result	CI
Mori *et al.* (1988)	Strict selection	-	Hokkaido, Japan	1980–1981 1985–1986	Epithelial OC	None	98	196	294	OR	0.47*	0.21–1.01*
Booth *et al.* (1989)	Strict selection	-	London and Oxford, England	1978–1983	Epithelial OC	None	213	420	633	OR	0.2	0.1–0.6
Shu *et al.* (1989)	Strict selection	-	Shanghai, China	1984–1986	Epithelial OC	Years since TL	172	172	344	OR	0.8	0.4–1.6
Irwin *et al.* (1991)	Strict selection	-	Multistate, USA	1980–1982	Epithelial OC	Years since TL, age at TL (with years since TL)	427	3447	3874	OR	0.69	0.50–0.95
Chen *et al.* (1992)	Strict selection	-	Beijing, China	1984–1986	Epithelial OC	None	112	224	336	OR	1	0.5–2.3
Whittemore *et al.* (1992a) (hospital)	Strict selection	-	Multistate, USA	1956–1986	Epithelial OC	None	517	1970	2487	OR	0.59	0.38–0.93
Whittemore *et al.* (1992b) (population)	Strict selection	-	Multistate, USA	1956–1986	Epithelial OC	None	766	4098	4864	OR	0.87	0.62–1.2
Rosenberg *et al.* (1994)	Extended selection	(Excluded from strict selection due to overlap with Whittemore 1992a)	Multistate, USA	1977–1991	Epithelial OC	None	441	2065	2506	OR	0.6	0.4–0.9
Risch *et al.* (1996)	Strict selection	-	Ontario, Canada	1989–1992	Epithelial OC	Invasive/ borderline, cell type	450	564	1014	OR	0.67	0.47–0.94
Rosenblatt and Thomas (1996)	Strict selection	-	International	1979–1988	Epithelial OC	Years since TL, age at TL, parity, cell type	385	2486	2871	OR	0.71	0.47–1.08
Cornelison' *et al.* (1997)	Extended selection	(Excluded from strict selection due to different case definition)	Roswell Park Cancer Institute, USA	1982–1988	OC	Age, age at TL, years since TL	300	606	906	OR	0.52	0.31–0.85
Green *et al.* (1997)	Strict selection	-	Multistate, Australia	1990–1993	Epithelial OC	Years since TL	824	855	1679	OR	0.61	0.46–0.85
McGuire *et al.* (2004)	Strict selection	-	San Francisco, USA	1997–2001	Epithelial OC	BRCA1 carrier	381	568	949	OR	0.65[1]	0.45–0.95
Modugno *et al.* (2004)	Strict selection	-	Multistate, USA	1993–2001	Epithelial OC	Endometriosis	2097	2945	5042	OR	0.63	0.54–0.73
Pike *et al.* (2004)	Strict selection	-	Los Angeles, USA	1992–1998	Epithelial OC	None	477	660	1137	OR	0.82	0.53–1.26
Jordan *et al.* (2008)	Extended selection	(Excluded from strict selection due to different case definition)	Australia	2002–2005	Serous OC	None	624	1487	2111	OR	0.87	0.69–1.09
Mori *et al.* (1984)	Excluded	Later publication available (Mori *et al.*, 1988)	Hokkaido, Japan	1980–1981	Epithelial OC	None	63	126	189	OR	0.4	
Harlow *et al.* (1988)	Excluded	Estimate of effect not published	Western Washington, USA	1980–1985	Borderline OC		116	158	274			

Continued

Table I *Continued*

Study ID	Main meta-analysis	Reason for exclusion from main meta-analysis	Geographical setting	Time period	Case/ outcome	Available subgroups	Cases	Controls	Total sample size	Measure	Result	CI
Hartge *et al.* (1988)	Excluded	Overlapping study population (Whittemore *et al.*, 1992a)	Washington DC, USA	1978–1981	Epithelial OC	None	151	144	295	OR	0.8	0.4–1.7
Whittemore *et al.* (1988)	Excluded	Overlapping study population (Whittemore *et al.*,1992b)	San Francisco, USA	1983–1985	Epithelial OC	Years since TL	188	539	727	OR	0.56	0.30–1.04
Risch *et al.* (1994)	Excluded	Later publication available (Risch *et al.*, 1996)	Ontario, Canada	1989–1992	Epithelial OC	Parity	450	564	1014	OR	0.75	0.53–1.04
Cramer and Xu (1995)	Excluded	Overlapping study population (Whittemore *et al.*,1992b)	Boston, USA	1978–1981	Epithelial OC	None	414	410	824	OR	0.9	0.4–1.7
Purdie *et al.* (1995)	Excluded	Later publication available (Green *et al.*,1997)	Australia	1990–1993	Epithelial OC	None	824	860	1684	OR	0.6	0.45–0.80
Modugno *et al.* (2001)	Excluded	Overlapping study population (Modugno *et al.*, 2004)	Delaware Valley, USA	1994–1998	Epithelial OC	Invasive/ borderline, cell type	767	1367	2134	OR	0.55	0.44–0.70
Narod *et al.* (2001)	Excluded	High-risk population	International	Time of diagnosis not clear	OC	Age at OC, age at TL	173	173	346	OR	0.39	0.22–0.70
Ness *et al.* (2001)	Excluded	Overlapping study population (Modugno *et al.*, 2004)	Delaware Valley, USA	1994–1998	Epithelial OC	None	727	1359	2086	OR	0.5	0.4–0.7
Tung *et al.* (2003)	Excluded	Overlapping study population (Modugno *et al.*, 2004)	Hawaii, California, USA	1993–1999	Epithelial OC	Invasive/ borderline, cell type	558	607	1165	OR	0.7	0.5–1.0
Mills *et al.* (2004)	Excluded	Different exposure	Central Valley, California, USA	2000–2001	Epithelial OC							
McLaughlin *et al.* (2007)	Excluded	High-risk population	International	Time of diagnosis not clear	OC	BRCA1/2	581	1782	2363	OR	0.8[2]	0.59–1.08
Moorman *et al.* (2008)	Excluded	Estimate of effect not published	North Carolina, USA	1999–2006	Epithelial OC	Menopausal status	896	967	1863			
Nagle *et al.* (2008)	Excluded	Cell type - endometroid	Australia	2002–2005	Endometrioid OC	None	142	1508	1650	OR	0.4	0.3–0.7
Nagle *et al.* (2008)	Excluded	Cell type - clear Cell	Australia	2002–2005	Clear cell OC	None	90	1508	1598	OR	0.7	0.4–1.2

[1]Result for BRCA1 non-carrier.
[2]Result for BRCA1 carrier.
*Reanalyzed results.

Table II Prospective cohort studies of TL effect on OC risk.

Study ID	Main meta-analysis	Reason for exclusion from main meta-analysis	Geographical setting	Time period	Outcome	Available subgroups	Total *N*	Measure	Result	CI
Tworoger *et al*. (2007)	Extended selection	-	Multistate, USA	1976	Epithelial OC	None	107 900	HR	0.66	0.50–0.87
Dorjgochoo *et al*. (2009)	Extended selection	-	Shanghai, China	1997–2000	OC	Years since TL, age at TL	66 661	HR	1.17	0.62–2.26
Hankinson *et al*. (1993)	Excluded	Later publication available (Tworoger *et al*., 2007)	Multistate, USA	1976	Epithelial OC	Talc using	77 544	HR	0.33	0.16–0.64
Miracle-McMahill *et al*. (1997)	Excluded	OC death as outcome	Multistate, USA	1982	OC death	Years since TL, age at TL, calendar year of TL	39 6114	HR	0.68	0.45–1.03
Antoniou *et al*. (2009)	Excluded	High-risk population	International	1997–2005	OC	BRCA1/2	3319	HR	0.43	0.24–0.75

Table III Historical cohort studies of TL effect on OC risk.

Study ID	Main meta-analysis	Geographical setting	Time period	Outcome	Available subgroups	Total *N*	Measure	Result	CI
Koch *et al*. (1984)	Extended selection	Alberta, Canada	1930–1969	Epithelial OC	Age (few cases)	666	RR	2.76	0.6–7.95*
Kreiger *et al*. (1997)	Extended selection	Ontario, Canada	1979–1993	OC	Years since TL, age, year of procedure	251 907	RR	0.57	0.41–0.80*
Kjaer *et al*. (2004)	Extended selection	Denmark	1977–1993	OC	Invasive/borderline, years since TL, cell type	65 232	RR	0.82	0.6–1.0

* Reanalyzed results.

Table IV Overview of end-points analyzed in the study.

End-points	Measure of end-point[1]	Methodical comment
Main analysis		
RR of OC after TL	Case–control studies: OR and its CI Prospective cohort studies: HR and its CI Historical cohort studies: rR and its CI	Two types of meta-analysis were performed, based on: (1) *strict selection* of studies (only epithelial OC examined in case–control design) (2) *extended selection* of studies including other types of OC and some of the cohort studies
Subgroups		
Years since TL	RR of OC in relation to time periods after TL	Meta-analysis of selected eligible studies was performed
Cell type of OC	RR of OC in relation to histology of OC	Meta-analysis in relation to invasive or borderline tumors was performed
Age at TL	RR of OC in relation to age at TL	Statistical summary of primary studies; meta-analysis not performed
BRCA1/2 carriers	RR of OC in BRCA mutation carriers in relation to TL	Summary of primary studies; meta-analysis not performed

[1]CI: confidence interval.
OC,ovarian cancer; TL,tubal ligation; OR,odds ratio; RR,relative risk; HR,hazard ratio.

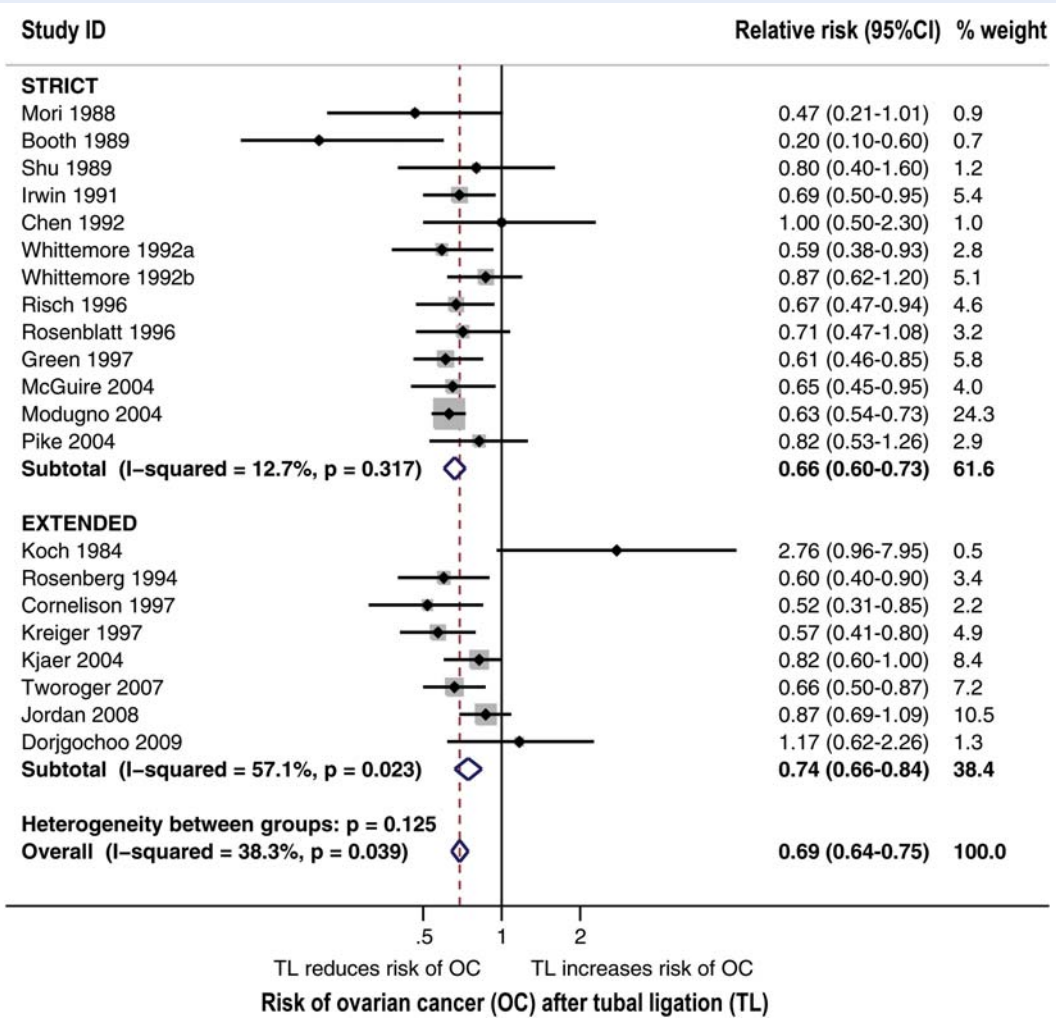

Figure 1 Relative risk for ovarian cancer after tubal ligation, analysis of two sets of studies (strict/extended selection) and result of overall meta-analysis. Subtotal and overall pooled estimates are supported by I^2statistics and statistical test for heterogeneity. Gray boxes represent weight of individual studies in overall meta-analysis and dashed line represents overall pooled relative risk estimate.

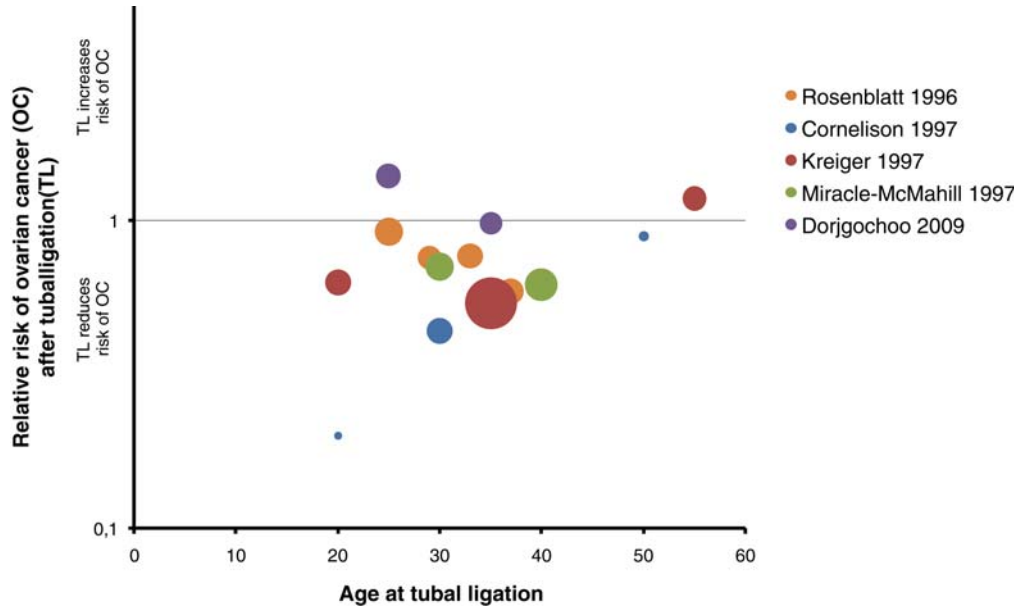

Figure 2 Relative risk of ovarian cancer after tubal ligation: relationship between age at tubal ligation (exact numerical values assigned from presented intervals) and size of effect. Size of circles represents relative precision of effect estimates (inverse-variance estimate).

(21 studies), noticeable increase in heterogeneity was observed ($I^2 = 38.3\%$, $P = 0.039$).

Age and time dependency of risk modulation

The analysis of the age when TL was performed and relative risk dependency on interval since the procedure are of great importance when discussing the potential bias affecting the assessment of OC risk. The presence of reduced risk only shortly after TL would suggest screening bias, i.e. the removal of impaired ovaries in the course of the procedure. A positive effect on the risk of OC in older women only would indirectly support the presence of selection bias, i.e. performing TL in women with higher parity and longer history of using oral contraceptives.

The results of the subanalysis on age at TL appear to be intrinsically heterogeneous and inconclusive. Some studies proved an increasing protective effect of TL with increasing age at TL (Rosenblatt and Thomas, 1996; Dorjgochoo *et al*., 2009), whereas others contradicted this observation (Cornelison *et al*., 1997; Kreiger *et al*., 1997). However, graphical display of data available on the relationship between age at TL and relative risk of OC did not show any apparent or significant trend (Fig. 2).

Estimates of relative risk in 5-year categories since TL were not mutually different with confidence intervals overlapping with each other (Fig. 3). The statistical significance of reduced RR was proved for the subgroup with the interval of 10–14 years since TL. Moreover, χ^2 test did not confirm increased heterogeneity between time-related subgroups ($P = 0.590$). Considering those results, we can conclude that the significant protective effect of TL against OC does not diminish in time, at least up to 14 years since the procedure.

Histological types of ovarian cancer

Evidence of a significant difference in risk-reducing effect of TL on different cell types of OC could greatly contribute to researching the mechanisms that play a role in ovarian carcinogenesis, in particular, when comparing the mucinous and non-mucinous epithelial cancers. A large-scale meta-analysis of 45 studies in 2008 showed a much more significant protective effect of oral contraceptive use on non-mucinous epithelial OCs, and there were several epidemiological studies demonstrating different risk parameters for mucinous epithelial histological types in comparison to serous or endometrioid types (Risch *et al*., 1996; Tung *et al*., 2003; Soegaard *et al*., 2007).

Only a limited number of studies listed above provided a subanalysis of individual histological types, and the results are further limited by the small size of patient populations. These results have, despite limitations, made it possible to conduct a meta-analysis. A significant decrease in risk for OC after TL was observed for invasive OCs (RR = 0.68, 95% CI 0.61–0.75), whereas the effect in borderline tumors was less apparent (RR = 0.86, 95% CI 0.67–1.10), with much wider confidence interval due to smaller group of cases (Fig. 4). Significantly higher risk reduction was found for endometrioid invasive cancers (RR = 0.40, 95% CI 0.30–0.53) in comparison with the other types. Less apparent but still significant reduction was shown for serous-invasive cancers (RR = 0.73, 95% CI 0.63–0.85), whereas it did not reach statistical significance for mucinous-invasive cancers ($P = 0.653$) (Fig. 5). There is statistically significant heterogeneity within the group of mucinous cancers ($I^2 = 72.8\%$, $P = 0.012$). Similar but statistically not significant reductions of risk were observed for serous (RR = 0.87, 95% CI 0.57–1.31) and mucinous (RR = 0.82, 95% CI 0.54–1.27) borderline tumors.

BRCA mutation carriers

The potential risk-reducing effect of TL is of great importance especially for those groups in the population that carry an elevated hereditary risk of OC. Although the lifetime risk of developing OC

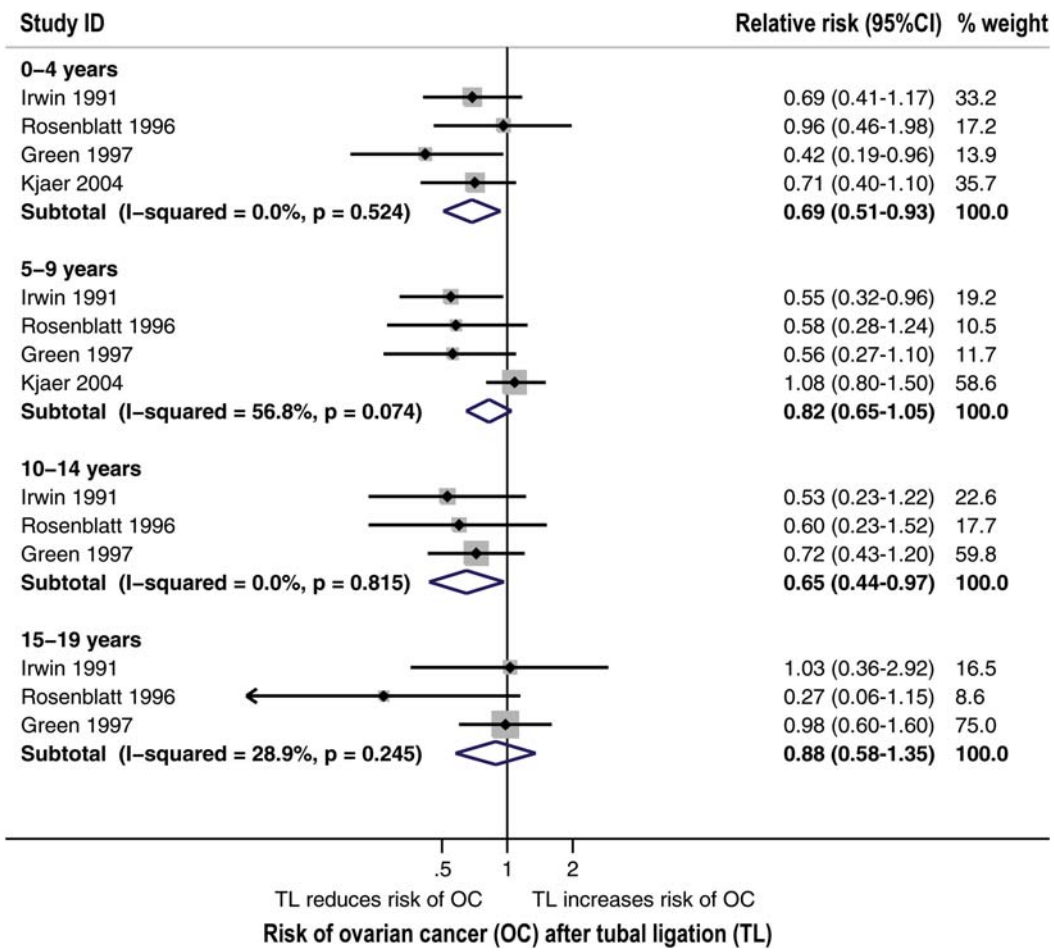

Figure 3 Relative risk of ovarian cancer after tubal ligation, analysis of subgroups by years since tubal ligation (categories 0–4 years, 5–9 years, 10–14 years, 15–19 years). Subtotal and overall pooled estimates are supported by I^2 statistics and statistical test for heterogeneity. Gray boxes represent weight of individual studies in overall meta-analysis.

is 1.8% in general population, it increases to 50–60% in BRCA1 and 25% in BRCA2 mutation carriers. Prophylactic adnexectomy proved to be the only method currently available, providing substantial risk reduction of both OC and breast cancers in BRCA mutation carriers (Kauff *et al*., 2002; Rebbeck *et al*., 2002). The possibilities for young women still planning conception or those refusing the prophylactic procedure are rather limited. The data available document a significant reduction of OC risk in long-term users of oral contraceptives for BRCA1 mutation carriers (Narod *et al*., 2002; McLaughlin *et al*., 2007).

Until now, there have been only three case–control and one prospective cohort study assessing the risk of OC in BRCA mutation carriers in relation to TL (McGuire *et al*., 2004; McLaughlin *et al*., 2007; Antoniou *et al*., 2009, Table 5). Although there was a positive trend in all these studies, the differences were largely insignificant mostly due to small sample sizes; those were reflected by wide confidence intervals. The largest recent study so far analyzed groups of 2281 BRCA1 carriers and 1038 BRCA2 carriers from the International BRCA1/2 Carrier Cohort Study, carried out in Europe and Canada (Antoniou *et al*., 2009). A weighted cohort approach was used to correct for biases caused by the selection of carriers from families with multiple diseases history and higher probability for genetic testing in younger age groups. Together, 400 unaffected women and 23 OC cases underwent TL, and the relative risk was significantly decreased for the whole group (RR = 0.43, 95% CI 0.24–0.75), and for BRCA1 carriers (RR = 0.42, 95% Modugno *et al*., CI 0.22–0.8), but this was not proved for BRCA2 carriers due to the limited number of cases. The ensuing risk reduction was comparable to the effect of oral contraceptive use.

Similar insignificant reductions of risk were observed for both BRCA1 and BRCA2 carriers in meta-analysis (Fig. 6). The precision of effect size estimation was higher in BRCA1 carriers and reached statistical significance. Effect sizes are reported as odds ratios, because rare-disease assumption is questionable within high-risk population. Prospective study reporting HR (Antoniou *et al*., 2009) was, therefore, excluded from this analysis.

Even though the results available to date are not sufficient for drawing an unequivocal conclusion for BRCA mutation carriers, the results of the largest Antoniou study as well as the positive trend in other publications support the presence of protective effect of TL even in this group with hereditary increased risk of OC.

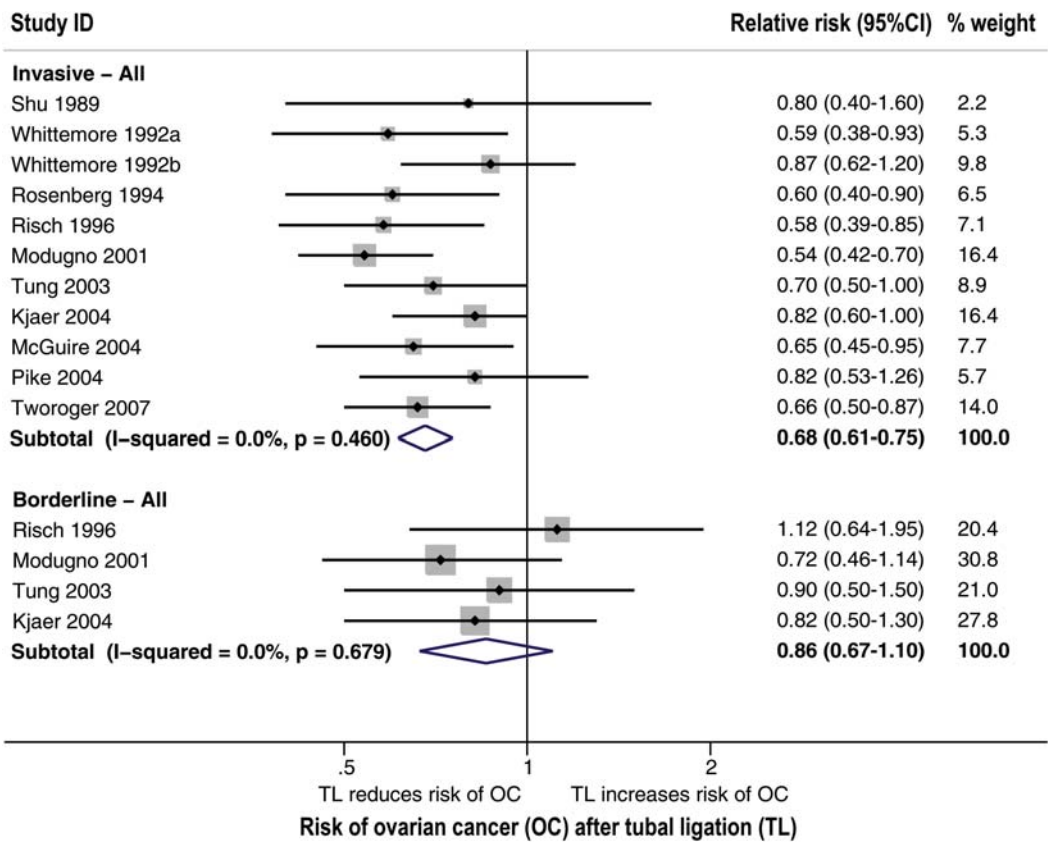

Figure 4 Relative risk of ovarian cancer after tubal ligation and analysis of subgroups by tumor behavior (categories invasive, borderline). Subtotal and overall pooled estimates are supported by I^2statistics and statistical test for heterogeneity. Gray boxes represent weight of individual studies in overall meta-analysis.

Discussion

This systematic review and meta-analysis of studies available documented a significant reduction of OC risk in women who had undergone TL (Table 6). The significant protective effect was shown even in a subgroup of women after 10–14 years since TL. The risk reduction was most profound in endometrioid cancers, smaller yet still present in serous cancers but unconfirmed for the mucinous tumors. A positive trend was observed also for borderline tumors and in the high-risk group of BRCA mutations carriers, but small size of the groups and less consistent outcomes did not make it possible to draw unequivocal conclusions.

The consistency of data available on risk reduction following TL was supported by the negligible heterogeneity in our meta-analysis of strictly selected studies. There were only two studies that found an insignificantly increased relative risk of OC in women after TL. The first of those was a retrospective historical cohort study, strongly limited by the small number of only four cases of OC with TL. Moreover, the results were only compared with the expected number of cancers obtained from another retrospective study (Koch *et al.*, 1984). The second being a large prospective cohort study from China, which followed more than 60 000 women for a medium follow-up of 7.5 years and did not find any preventive effect in relation to TL (Dorjgochoo *et al.*, 2009). Only 94 cases of OC were identified with the median follow-up of 7.5 years and only 19 of them had TL.

It should be emphasized that it will never be possible to carry out a prospective randomized trial evaluating the effect of TL on OC risk, and the evidence will always come from retrospective or observational studies. This paper has reviewed all the studies available, which were designed to address or at least contain data on the risk of OC in patients after TL. The main limitation of most studies proved to be the small patient populations, especially small number of cases of OC having undergone TL.

Two potential biases should be discussed, which may influence the assessment of TL effect on OC risk. Screening bias may result from the selective removal of suspicious ovaries during the TL (Harlow *et al.*, 1988; Whittemore *et al.*, 1988; Irwin *et al.*, 1991). Should this effect be significant, this would imply that the protective effect diminishes with time since the procedure. A majority of publications failed to confirm such vanishing trend (Shu *et al.*, 1989; Rosenblatt and Thomas, 1996; Cornelison *et al.*, 1997; Green *et al.*, 1997; Kreiger *et al.*, 1997; Miracle-McMahill *et al.*, 1997; Kjaer *et al.*, 2004). Moreover, some studies aimed at eliminating the screening bias and excluded cancers diagnosed during or soon after the procedure (Irwin *et al.*, 1991; Kreiger *et al.*, 1997; Miracle-McMahill *et al.*, 1997) and still confirmed a significantly reduced relative risk of

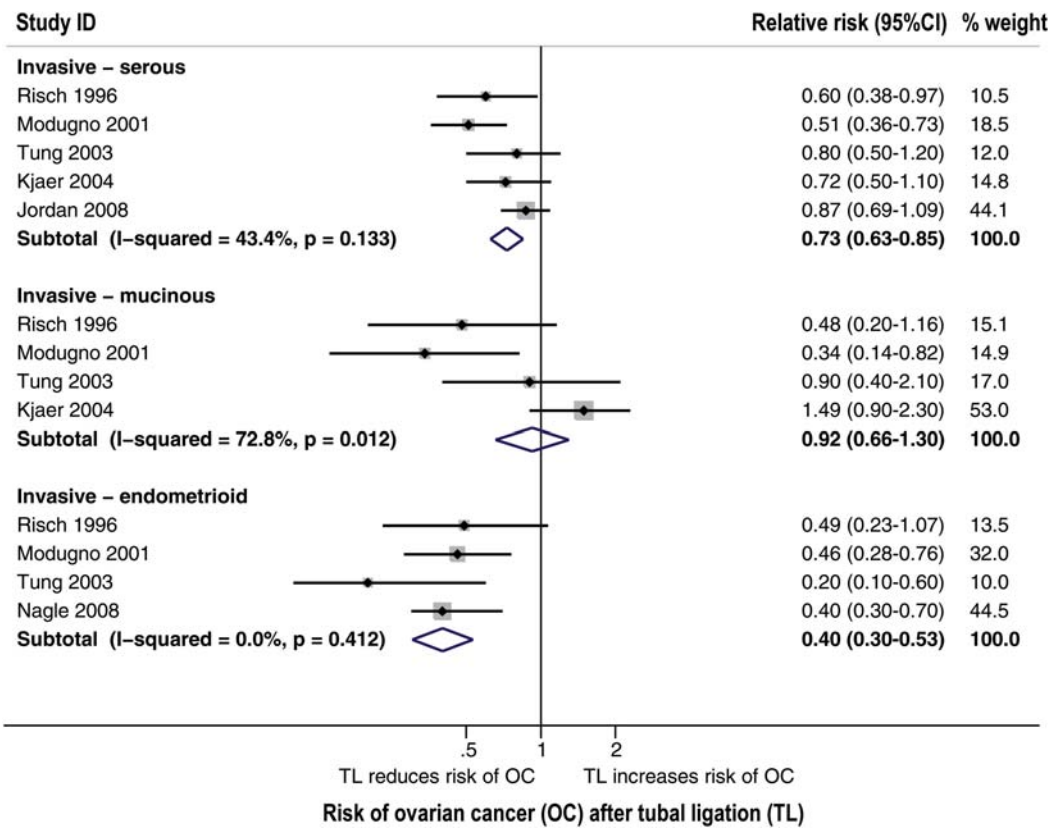

Figure 5 Relative risk of ovarian cancer after tubal ligation, invasive, analysis of subgroups by histology (serous, mucinous, endometrioid). Subtotal and overall pooled estimates are supported by I^2 statistics and statistical test for heterogeneity. Gray boxes represent weight of individual studies in overall meta-analysis.

Table V Literature search for association of tubal ligation in BRCA1/2 mutation carriers and relative risk of OC.

Study	Mutation	Odds ratio for OC	95% confidence interval
Narod *et al.* (2001)	BRCA1 carrier	0.39	0.22–0.70
	BRCA2 carrier	1.19	0.38–3.68
McGuire *et al.* (2004)	BRCA1 carrier	0.68	0.25–1.90
McLaughlin *et al.* (2007)	BRCA1 carrier	0.80	0.59–1.08
	BRCA2 carrier	0.63	0.34–1.15
Antoniou *et al.* (2009)*	BRCA1 carrier	0.42	0.22–0.80
	BRCA2 carrier	0.47	0.18–1.21

*Prospective study reporting HR instead of OR.

OC. Similarly, in our meta-analysis, a significantly reduced relative risk of OC was confirmed even in the subgroup 10–14 years after the procedure. From the above arguments, it would appear that the screening bias cannot explain the significant risk reduction observed after the TL.

Besides screening effect, the outcomes may be influenced also by selection bias, i.e. greater frequency of TL in women with more protective mechanisms in their history, i.e. higher parity or long-term use of oral contraceptives. Most studies have taken these aspects into consideration and adjusted the relative risk for parity and oral contraceptive use. Moreover, there was little heterogeneity observed in our meta-analysis, particularly with respect to the selected patient group, and thus a significant influence of interferences such as selection bias is very unlikely.

The protective effect of TL has, thus far, received little attention due to the inability to provide plausible explanation for the underlying mechanism. One plausible explanation of the TL effect is a mechanical barrier preventing retrograde transport of cancerogenic substances from the vagina and perineum. A potential effect of talc, as well as infectious agent, on ovarian cancerogenesis has been discussed (Longo and Young, 1979; Chen *et al.*, 1992; Harlow *et al.*, 1992; Wahlberg, 1994). Available data are not fully consistent, and many studies failed to confirm any significant effect of talcum powder (Whittemore *et al.*, 1988; Hankinson *et al.*, 1993; Nagle *et al.*, 2008). It is unlikely that the sole effect of talc use could fully explain OC risk reduction after TL.

A new and attractive mechanism seems to be the prevention of the ascent of endometrial epithelial cells, which could be the source of significant proportion of epithelial ovarian and peritoneal cancers. The evidence is accumulating that OC could arise from tissues that are embryologically derived from the Mullerian ducts, i.e. the fallopian

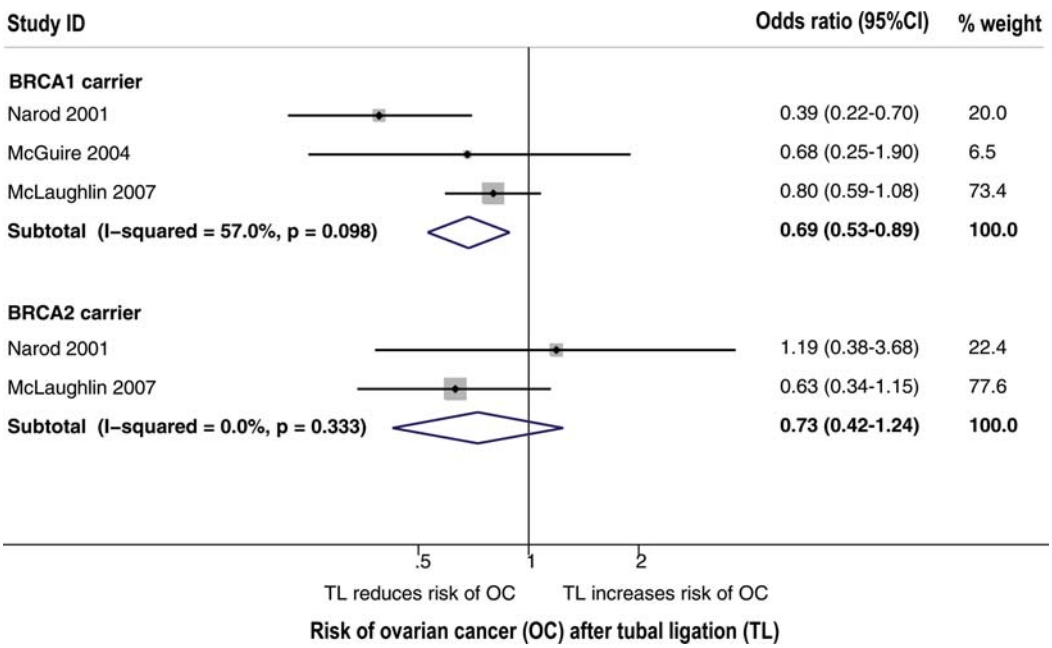

Figure 6 Odds ratio of ovarian cancer after tubal ligation and analysis of subgroups by carried mutation (BRCA1, BRCA2). Subtotals presented with I^2 statistics and statistical test for heterogeneity. Gray boxes represent weight of the study in subgroup meta-analysis.

Table VI Risk of OC after TL: final outcomes of performed meta-analyzes.

Analysis/outcome	Outcome of meta-analysis RR: relative risk			Comparison of subgroups (*P*-value)
	RR (95% CI)	*P*-value	Heterogeneity test: *P*-value	
Main analysis				
OC after TL/all studies/	0.69 (0.64–0.75)	<0.001	0.039	-
OC after TL/strict selection/	0.66 (0.60–0.73)	<0.001	0.317	0.125[2]
OC after TL/extended selection/	0.74 (0.66–0.84)	<0.001	0.023	
Subgroups				
Years since TL				
0–4	0.69 (0.51–0.93)	0.015	0.524	0.590
5–9	0.82 (0.65–1.05)	0.113	0.074	
10–14	0.65 (0.44–0.97)	0.034	0.815	
15–19	0.88 (0.58–1.35)	0.573	0.245	
Tumor type				
Invasive	0.68 (0.61–0.75)	<0.001	0.460	0.096
Borderline	0.86 (0.67–1.10)	0.227	0.679	
Histology of invasive OC				
Serous	0.73 (0.63–0.85)	<0.001	0.133	<0.001[2]
Mucinous	0.92 (0.66–1.30)	0.653	0.012	
Endometrioid	0.40 (0.30–0.53)	<0.001	0.412*	
BRCA1/2 mutation				
BRCA1	0.69 (0.53–0.89)	0.004	0.098	0.849[2]
BRCA2	0.73 (0.42–1.24)	0.243	0.333	

[1]CI: confidence interval.
[2]Statistically significant heterogeneity was observed within one of subgroups.
*RR for endometrioid tumors is significantly lower ($P < 0.001$) than RR for serous and mucinous tumors.

tube, the secondary Müllerian system and endometrial cells (Dubeau, 2008). Such mechanism would also provide a plausible explanation for the most profound risk reduction observed in our meta-analysis for endometrioid and serous types of cancer, which may originate from the endometrial epithelium.

In conclusion, this review summarized conclusive data on OC risk reduction after TL. Decreased risk, by 34%, was confirmed in meta-analysis. Protective effect is long-lasting, being significant in a subgroup with the interval of 10–14 years since the procedure. Our results should give an impulse for further research of the etiology of epithelial OCs as well as the importance of ascending transport of cells, possibly also other substances, originating from the uterine cavity. Furthermore, confirming the significant protection of BRCA carriers would make it possible to use TL in women who cannot undergo or do not accept prophylactic bilateral salpingo-oophorectomy.

Authors' roles

C.D.: main author; W.M.: co-author of discussion part; M.O. and D.L.: statisticians; meta-analysis, interpretation of results.

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