

# Tubal ligation and risk of ovarian cancer in carriers of *BRCA1* or *BRCA2* mutations: a case-control study

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## Summary

**Background** In several case-control and prospective studies, tubal ligation has been associated with a decreased risk of invasive epithelial ovarian cancer. We aimed to assess the potential of tubal ligation in reducing the risk of ovarian cancer in women who carry predisposing mutations in the *BRCA1* or *BRCA2* genes.

**Methods** We did a matched case-control study among women from Canada, the USA, and the UK who had undergone genetic testing and who carried a pathogenic mutation in *BRCA1* or *BRCA2*. Cases were 232 women with a history of invasive ovarian cancer, and controls were 232 women without ovarian cancer, and who had both ovaries intact. Cases and controls were matched for year of birth, country of residence, and mutation (*BRCA1* or *BRCA2*). The odds ratio for developing ovarian cancer was estimated for tubal ligation, adjusting for oral contraceptive use, parity, history of breast cancer, and ethnic group.

**Findings** In an unadjusted analysis among *BRCA1* carriers, significantly fewer cases than controls had ever had tubal ligation (30 of 173 [18%] vs 60 of 173 [35%], odds ratio 0.37 [95% CI 0.21–0.63];  $p=0.0003$ ). After adjustment for oral contraceptive use, parity, history of breast cancer and ethnic group, the odds ratio was 0.39 ( $p=0.002$ ). Combination of tubal ligation and past use of an oral contraceptive was associated with an odds ratio of 0.28 (0.15–0.52). No protective effect of tubal ligation was seen among carriers of the *BRCA2* mutation.

**Interpretation** Tubal ligation is a feasible option to reduce the risk of ovarian cancer in women with *BRCA1* mutations who have completed childbearing.

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## Introduction

Women with a pathogenic mutation in the *BRCA1* or *BRCA2* genes face a high lifetime risk of ovarian cancer. For carriers of *BRCA1* mutations, the risk is about 40%.<sup>1</sup> For *BRCA2* carriers, the risk is about 25%,<sup>2</sup> but can be higher if the mutation is situated within the ovarian cancer cluster region (OCCR).<sup>3</sup> About 10% of incident cases of invasive ovarian cancer in North America are caused by mutations in these two genes.<sup>4</sup>

Proposed strategies for reducing the risk of ovarian cancer include prophylactic oophorectomy, chemoprevention with oral contraceptives, and regular screening with ultrasound and serum CA-125.<sup>5</sup> Oral contraceptive use has been associated with a risk reduction of 50–60% in carriers of *BRCA* mutations,<sup>6</sup> but some patients and physicians are concerned that oral contraceptives could increase the risk of breast cancer. Ovarian cancer screening has not yet been shown to be effective as a means of reducing ovarian cancer mortality,<sup>7</sup> and the extent to which prophylactic oophorectomy reduces the ovarian cancer risk is not yet known.

Tubal ligation has been associated with a reduction in the risk of ovarian cancer in prospective<sup>8</sup> and case-control studies.<sup>9,10</sup> After 12 years of follow-up in the Nurses' Health Study,<sup>8</sup> a strong inverse relation between tubal ligation and ovarian cancer was seen (odds ratio 0.33 [95% CI 0.16–0.64]). In a meta-analysis of case-control studies of tubal ligation and ovarian cancer, the relative risk was estimated to be 0.59 or 0.87, dependent on whether hospital-based or community-based controls were used.<sup>9</sup> To date, no studies have assessed whether or not tubal ligation is associated with a reduced risk of ovarian cancer in carriers of *BRCA1* or *BRCA2* mutations. We therefore did a matched case-control study among women with pathogenic mutations in the *BRCA* genes to assess the possibility that tubal ligation protects against hereditary ovarian cancer.

## Methods

Information about patients with deleterious *BRCA* mutations was submitted to the study centre by investigators from 30 contributing centres in three countries (Canada, the USA, and the UK). The patients were identified through genetic counselling and risk-assessment programmes offered to women from high-risk families, and in the course of other research projects on families at high-risk of breast cancer. Patients were requested to complete a questionnaire about family history, reproductive and medical histories, and selected lifestyle factors. Specifically, the questionnaire asked whether the woman had ever had a tubal ligation, and if so, at what age. Information was obtained on all pregnancies, including stillbirths and miscarriages, and on use of oral contraceptives (ever or never use, dates of first and last use, and total duration of use). No specific information on contraceptive formulation was obtained.

Cases were defined as women who had been diagnosed with invasive ovarian cancer (excluding borderline ovarian carcinoma), and who had provided information on tubal ligation.

For each case, we attempted to identify a single matched control, selected from the women in the database with no diagnosis of ovarian cancer and who had not undergone a bilateral oophorectomy. The control was matched to the case for year of birth (within 2 years), mutation (*BRCA1* or *BRCA2*), and country of residence (Canada, USA, or UK). Within Canada, participants were also matched for ethnic origin (French-Canadian or other).

To estimate the odds ratio associated with tubal ligation, we did a matched analysis. The unadjusted odds ratio was estimated from the ratio of discordant pairs, and significance was assessed with McNemar's test. To adjust for the potential confounding effects of ethnic group, residence, parity, oral contraceptive use, and past history of breast cancer, we used conditional logistic regression. In these adjusted analyses, an indicator variable was created for each ethnic group (other white, Jewish, French-Canadian, other); oral contraceptive use was coded as ever or never use; and parity was coded as zero, one, two, three, and four or more births. Patients were also categorised according to past history of breast cancer (yes or no). Multivariate odds ratios were estimated with conditional logistic regression (SAS, version 8.0). To estimate the association by age of tubal ligation, we had to break the matching, and unconditional logistic regression was used for this analysis.

## Results

The study centre received 2139 questionnaires on carriers of *BRCA* mutations from the participating centres. Information on tubal ligation was missing for 316 women. Of the remaining 1823 women, 349 had been diagnosed with invasive ovarian cancer and were eligible to be cases. No cases of ovarian cancer were diagnosed at the time of a tubal ligation. We identified a matched control for 232 of the 349 potential cases.

The median age at which ovarian cancer was diagnosed in the cases was 51 years (range 24–81). Among cases, the

	Cases (n=232)	Controls (n=232)	p
Mean (SD) age (years)	58.7 (11.0)	58.7 (11.0)	..
<b>Mutation</b>			
<i>BRCA1</i>	173 (75%)	173 (75%)	..
<i>BRCA2</i>	59 (25%)	59 (25%)	..
<b>Country of residence</b>			
Canada	94 (40%)	94 (40%)	..
USA	130 (56%)	130 (56%)	..
UK	8 (4%)	8 (4%)	..
<b>Past history of breast cancer</b>			
Yes	81 (35%)	162 (70%)	..
No	151 (65%)	70 (30%)	p<0.0001
<b>Ethnic group</b>			
French-Canadian	22 (9%)	22 (9%)	..
Jewish	115 (50%)	92 (40%)	..
Other white	89 (38%)	113 (49%)	..
African-American	5 (2%)	3 (1%)	..
Asian	1 (1%)	0	..
Other/missing	0	2 (1%)	..
<b>Parity</b>			
Nulliparous	36 (15%)	32 (14%)	0.67
Mean (SD) parity	2.2 (1.4)	2.5 (1.5)	0.04
<b>Oral contraceptives</b>			
Ever use	123 (53%)	162 (70%)	0.0002
Mean (SD) duration (years)	2.0 (3.4)	3.4 (4.8)	0.0003

Table 1: Comparison of cases and controls

questionnaires were completed a median of 5 years after the date of diagnosis. 173 of the cases had a *BRCA1* mutation, and 59 had a *BRCA2* mutation. The cases and controls are described in table 1.

A tubal ligation was reported by 39 cases and 69 controls. Of the participants with *BRCA1* mutations, significantly fewer patients than controls had ever had tubal ligation. This association remained significant after adjustment for oral contraceptives, parity, personal history of breast cancer, and ethnic group (table 2). Among *BRCA2* carriers, no protective effect was seen (unadjusted odds ratio 1.00 [95% CI 0.38–2.66]; adjusted odds ratio 1.19 [0.38–3.68]). We therefore restricted the remaining analyses to the *BRCA1* subgroup.

Some variation was seen in the size of the protective effect of tubal ligation by age at cancer diagnosis (table 2); the greatest reduction in risk was seen for ovarian cancers diagnosed between the ages of 40 and 59 years, but only 55 cases were diagnosed outside this age range. Some variation in degree of protection was also seen by age at which the tubal ligation was done; the greatest protection was offered when it was done before age 30 years (table 2), but the differences in the size of risk by age were small and not significant (p=0.11).

We also saw a strong protective effect of oral contraceptives against ovarian cancer risk. The odds ratio for ovarian cancer associated with ever use of oral contraceptives was 0.44 (0.28–0.68). This finding was significant for carriers of *BRCA1* mutations (0.48 [0.29–0.80]) and *BRCA2* mutations (0.35 [CI 0.15–0.83]). The combination of oral contraceptives and tubal ligation offered greater protection than either method alone. Among *BRCA1* mutation carriers, tubal ligation and history of oral contraceptive use, compared with neither exposure, was associated with an odds ratio of 0.28 (0.15–0.52; p<0.0001).

## Discussion

We found tubal ligation to be associated with a decreased risk of ovarian cancer among women with predisposing mutations in the *BRCA1* gene. We did not see a similar protective effect among *BRCA2* mutation carriers, but this subgroup was small, and the confidence interval was large (0.38–3.68). We estimate that we had a statistical power of 62% to detect a significant odds ratio of 0.50 or less at the p=0.05 level in the *BRCA2* subgroup. Ovarian cancer in carriers of *BRCA2* mutations typically occurs 5–10 years later than it does in *BRCA1* mutation carriers.<sup>4,11</sup> In our study, the average age at diagnosis of ovarian cancer was 55.5 years among carriers of *BRCA2* mutations and 49.8 years among carriers of *BRCA1* mutations. The observed protective effect of tubal ligation was slightly lower for older women, and to some extent this finding might account for the difference between carriers of *BRCA1* and *BRCA2* mutations. The biological mechanisms of carcinogenesis could also differ for the two genes.

Our study results confirm those of several previous studies, including the Nurses' Health Study, in which a substantial reduction in ovarian cancer risk after tubal ligation was reported.<sup>8</sup> The mechanism by which tubal ligation protects against ovarian cancer is not known. In some studies, tubal ligation has been found to be associated with changes in local or circulating hormones,<sup>12</sup> possibly through reducing the ovarian blood supply. After tubal ligation, there is a slight increase in the frequency of menstrual irregularities.<sup>13</sup> Others suggest that tubal ligation reduces the potential for ovarian inflammation from infectious, or other, agents present in the genital tract.<sup>14</sup> Tubal ligation might reduce ovarian exposure to vaginal

	Cases (n=173)	Controls (n=173)	Univariate analysis		Multivariate analysis	
			Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
<b>Tubal ligation</b>						
Never	143 (83%)	113 (65%)	1.00		1.00	
Ever	30 (18%)	60 (35%)	0.37 (0.21–0.63)	0.0003	0.39 (0.22–0.70)	0.002
<b>Age at diagnosis of ovarian cancer (years)</b>						
<40	25	25	0.67 (0.19–2.4)	0.5	0.67 (0.13–3.6)	0.61
40–49	71	71	0.27 (0.11–0.67)	0.005	0.28 (0.10–0.75)	0.02
50–59	47	47	0.29 (0.09–0.87)	0.03	0.27 (0.07–0.98)	0.05
≥60	30	30	0.60 (0.14–2.5)	0.48	0.48 (0.10–2.4)	0.38
<b>Age at tubal ligation (years)</b>						
Never	143	113	1.00			
<30	7	15	0.36 (0.15–0.94)			
30–39	16	33	0.38 (0.20–0.73)			
40–51	7	12	0.46 (0.18–1.21)			

Table 2: Effect of tubal ligation on ovarian cancer risk in *BRCA1* carriers.

talc, but this mechanism is unlikely to account for an effect of this size. The increase in ovarian cancer risk associated with talc use is low,<sup>15</sup> and only 3.8% of the women in the registry reported having applied talc to the vaginal area. Others have reported that pelvic inflammatory disease<sup>16</sup> and endometriosis<sup>17</sup> are risk factors for ovarian cancer. However, most ovarian tumours associated with endometriosis are of endometrioid or clear-cell histology,<sup>12</sup> and these subtypes account for only about 5% of cancers found in *BRCA1* mutation carriers.<sup>4,10</sup> In keeping with the hypothesis that inflammation of the ovaries is carcinogenic, Cramer and colleagues reported that regular paracetamol use reduces the risk of serous ovarian cancer,<sup>18</sup> and suggest that this effect might be due to a lowering of serum gonadotropin concentrations.<sup>19</sup>

Past use of an oral contraceptive was associated with an odds ratio of 0.44 for ovarian cancer ( $p=0.002$ ). This confirms and extends the findings of our earlier report;<sup>6</sup> however, the current sample size was larger, all controls are now verified to be mutation carriers, and controls who had undergone an oophorectomy have been excluded. The combination of tubal ligation and oral contraceptive use was seen to be highly protective against ovarian cancer. We estimate the risk reduction for women with both oral contraceptive use and a tubal ligation to be 72% compared with women with neither exposure.

In the study population, contraceptives were used for fertility control and not for ovarian cancer prevention, and therefore women did not continue oral contraceptive use beyond the date of tubal ligation. We could not, therefore, address the question of whether or not oral contraceptive use should continue after tubal ligation. However, for women with fewer than 5 years of lifetime exposure to oral contraceptives, we suggest that it might be prudent to do so.

We believe that our study participants are representative of women who have had *BRCA* mutations identified during the course of genetic counselling. We studied prevalent cases; therefore, if ovarian cancers that develop in women with a history of tubal ligation are more likely to be fatal than those that develop in women without a tubal ligation, this design will result in an overestimation of the size of the risk reduction. However, this situation seems unlikely. Women's reporting of having had tubal ligation has been shown to be accurate,<sup>20</sup> and therefore recall bias is also unlikely.

A greater proportion of controls had a past history of breast cancer than did cases (70% *vs* 35%). We do not think that this observation implies that breast cancer is protective against subsequent ovarian cancer, but is a consequence of our sampling protocol. Relatively few individuals in the database older than 50 years had not been

diagnosed with either form of cancer; this finding reflects the high cancer penetrance associated with these genes, and the fact that testing is offered preferentially to affected women. Because of sample size considerations, we chose not to exclude women with a past history of breast cancer. Tubal ligation was about equally frequent in controls with and without a past history of breast cancer (50 of 163 [31%] and 19 of 69 [28%], respectively). Among cases, 24 of 150 (16%) women without breast cancer reported a tubal ligation compared with 15 of 82 (18%) women with a past history of breast cancer. Furthermore, we adjusted for past history of breast cancer in our multivariate analysis, and this adjustment had little impact on the size of the risk estimate for tubal ligation (table 2). Therefore inclusion of women with a past history of breast cancer is unlikely to have introduced confounding bias into the study. Tubal ligation has also been associated with ethnic group and parity,<sup>21</sup> therefore our risk estimates have been adjusted for these covariates as well.

We believe that our data, along with the data on use of tubal ligation in the general population, support the recommendation that tubal ligation be offered to women with *BRCA1* mutations as a means of reducing ovarian cancer risk. The side-effects of tubal ligation are few, although minor menstrual irregularities have been reported.<sup>13</sup> Many women choose to undergo oophorectomy to prevent ovarian cancer. The age at which oophorectomy is done should take into account the woman's desire to preserve fertility, the level of protection offered against breast and ovarian cancer, and the consequences of surgical menopause. Few women choose to have oophorectomy before age 35 years, but offering tubal ligation as soon as childbearing is complete is reasonable, and can be followed by an oophorectomy at a later date. In summary, we believe that tubal ligation is associated with a reduction in risk of ovarian cancer in women who carry *BRCA1* mutations. For maximum protection, tubal ligation should be considered in combination with oral contraceptives, oophorectomy, or both. We cannot yet make specific recommendations for carriers of *BRCA2*, and further studies are needed for this subgroup.

#### Contributors

Steven Narod was the principal investigator and study co-ordinator, and prepared the paper. Ping Sun did the statistical analysis. Study activities were supervised by Parviz Ghadirian at the University of Montreal hospitals, Henry Lynch at Creighton University, Claudine Isaacs at the Lombardi Cancer Center, Judy Garber at the Dana Farber Cancer Center, Barbara Weber at the University of Pennsylvania, Beth Karlan at the Cedars-Sinai Medical Center, David Fishman at Northwestern University, Barry Rosen at the University Health Network (Toronto), Nadine Tung at the Beth Israel Deaconess Hospital, and Susan Neuhausen at the University of Utah.

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