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## Tubal Ligation and Ovarian Cancer Risk in a Large Cohort: Substantial Variation by Histological Type

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Histopathological and molecular studies suggest that the different histological types of ovarian cancer have distinct origins. Tubal ligation (sterilization) has been associated with a reduced risk of ovarian cancer, but few epidemiological studies have been large enough to reliably explore possible variation by tumour histotype.

We investigated whether a woman's risk of ovarian cancer is associated with prior tubal ligation, and whether this differs for the four main histotypes (serous, mucinous, endometrioid and clear cell), in a prospective study of UK women. Participants were recruited in 1996-2001, and completed a detailed questionnaire. Follow-up was via routine data from central cancer registries. Using a Cox proportional hazards model, we estimated adjusted relative risks (RR) of ovarian cancer associated with tubal ligation.

The study population included 1.1 million women, aged 56 years on average at recruitment; 8,035 ovarian cancers accrued during mean follow-up of 13.8 years. Overall, women with tubal ligation had a 20% reduction in risk of ovarian cancer (RR: 0.80, 95% CI: 0.76-0.85), but there was substantial heterogeneity in risk by histotype (heterogeneity:  $p=0.0001$ ). For serous tumours, the most common histotype ( $n=3,515$ ), risks differed significantly between high-grade (RR: 0.77, 95% CI: 0.67-0.89) and low-grade tumours (RR: 1.13, 95% CI: 0.89-1.42); heterogeneity:  $p=0.007$ . Relative risks were almost halved for endometrioid ( $n=690$ , RR: 0.54, 95% CI: 0.43-0.69) and clear cell tumours ( $n=401$ , RR: 0.55, 95% CI: 0.39-0.77), but there was no association between tubal ligation and mucinous tumours ( $n=836$ , RR: 0.99, 95% CI: 0.84-1.18).

The significant differences by tumour histotype are unlikely to be due to confounding and are consistent with hypotheses that high-grade and low-grade serous tumours have different origins, and that some endometrioid and clear cell tumours might arise from cells and/or carcinogens travelling through the Fallopian tubes.