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Tubal ligation and incidence of 26 site-specific cancers in the Million Women Study

Kezia Gaitskell^{*,1}, Kate Coffey¹, Jane Green¹, Kirstin Pirie¹, Gillian K Reeves¹, Ahmed A Ahmed², Isobel Barnes¹ and Valerie Beral¹ on behalf of the Million Women Study collaborators³

¹Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Roosevelt Drive, Oxford OX3 7LF, UK and ²Nuffield Department of Obstetrics and Gynaecology and The Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford OX3 9DS, UK

Background: Tubal ligation is known to be associated with a reduction in ovarian cancer risk. Associations with breast, endometrial and cervical cancers have been suggested. We investigated associations for 26 site-specific cancers in a large UK cohort.

Methods: Study participants completed a questionnaire on reproductive and lifestyle factors in 1996–2001, and were followed for cancer and death via national registries. Using Cox regression models, we estimated adjusted relative risks (RRs) for 26 site-specific cancers among women with vs without tubal ligation.

Results: In 1 278 783 women without previous cancer, 167 430 incident cancers accrued during 13.8 years' follow-up. Significantly reduced risks were found in women with tubal ligation for cancers of the ovary (RR = 0.80, 95% CI: 0.76–0.85; $P < 0.001$; $n = 8035$), peritoneum (RR = 0.81, 0.66–0.98; $P = 0.03$; $n = 730$), and fallopian tube (RR = 0.60, 0.37–0.96; $P = 0.04$; $n = 168$). No significant associations were found for endometrial, breast, or cervical cancers.

Conclusions: The reduced risks of ovarian, peritoneal and fallopian tube cancers are consistent with hypotheses of a common origin for many tumours at these sites, and with the suggestion that tubal ligation blocks cells, carcinogens or other agents from reaching the ovary, fallopian tubes and peritoneal cavity.

Tubal ligation (female sterilisation) is known to be associated with a reduced risk of ovarian cancer (Sieh *et al*, 2013). Reports of associations with other cancers have varied. In particular, several investigators have described associations with breast (Irwin *et al*, 1988; Kreiger *et al*, 1999), endometrial (Kjaer *et al*, 2004), cervical (Mathews *et al*, 2012) and anal cancers (Coffey *et al*, 2015). We report here the associations between tubal ligation and risk of 26 site-specific cancers in a large cohort of UK women.

MATERIALS AND METHODS

Study design, data collection and follow-up. The Million Women Study is a prospective study of 1.3 million UK women, recruited in 1996–2001. Participants completed a questionnaire at recruitment, on socio-demographic, reproductive and lifestyle

factors. Information on tubal ligation came from responses to the question 'Have you been sterilised (had your tubes tied)?' on the recruitment questionnaire. The study design and methods have been described previously (The Million Women Study Collaborative Group, 1999; Million Women Study Collaborators, 2003) and questionnaires can be viewed online at <http://www.millionwomenstudy.org>.

Follow-up for outcomes was based on routine registers: participants have been flagged on the NHS Central Register for cancer registrations and deaths. Information on cancer provided to investigators includes the date of registration and cancer site (coded using the 10th revision of the International Classification of Diseases, ICD-10) (World Health Organization, 1992). All participants gave written consent to follow-up at recruitment. Ethical approval was granted by the Oxford and Anglia Multi-Centre Research Ethics Committee (MREC 97/01).

*Correspondence: Dr K Gaitskell; E-mail: kezia.gaitskell@ceu.ox.ac.uk

³Members of the Million Women Study collaborators are listed before the references.

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Statistical analysis. Women were excluded from the analyses if they had invasive cancer other than non-melanoma skin cancer (ICD-10 code C44) before recruitment ($n = 66\,221$ (5%)), or missing data on tubal ligation ($n = 40\,612$ (3%)). The remaining women ($n = 1\,278\,783$) contributed person-years from the date of recruitment until the earliest of the date of registration of any cancer (other than non-melanoma skin cancer), the date of death, or last date of follow-up (31st December 2013). About 1% of participants were lost to follow-up and contributed person-years until the date they were lost.

Cox (proportional hazards) regression models were used to estimate hazard ratios (referred to as relative risks (RRs)) of developing a given cancer by tubal ligation status. Attained age was the underlying time variable. Analyses were run separately for each of 26 cancer types or sites, defined by ICD-10 code, and for all cancer (any invasive cancer other than non-melanoma skin cancer, ICD-10 C44). Analyses were limited to cancer types for which 500 or more cases with an identified primary site had accrued. In addition, we conducted an analysis for fallopian tube cancers (ICD-10 C57.0), despite having fewer than 500 cases, as there is a reasonable prior hypothesis that surgery to the fallopian tube might affect the incidence of cancer at this site.

All analyses were stratified by geographical region (10 regions corresponding to the areas covered by the cancer registries) and quintiles of socioeconomic status (based on the Townsend deprivation index) (Townsend *et al*, 1988), and additionally adjusted for parity (0, 1, 2, 3+), age at first birth (<20, 20–24, 25–29, 30+), smoking (never, past, current <10 cigarettes/day, current 10–19 cigarettes/day, current 20+ cigarettes/day), average alcohol intake per week (none, ≤ 7 units, > 7 & ≤ 14 units, > 14 units), frequency of strenuous exercise (<once/week, \geq once/week), use of menopausal hormones (never, ever), use of the oral contraceptive pill (never, ever), hysterectomy (no, yes), and body mass index (<25 kg m⁻², 25–29 kg m⁻², 30+ kg m⁻²).

All adjustment variables were as reported at recruitment. For adjustment and stratification variables, missing values were assigned to a separate category. Exposure information was either missing or reported as unknown for $\leq 6\%$ of women for all potential confounders. Analyses of ovarian cancer risk were restricted to women without bilateral oophorectomy; those of endometrial and cervical cancer were restricted to women without hysterectomy; those of fallopian tube cancer were restricted to women without either bilateral oophorectomy or hysterectomy (as the fallopian tubes might potentially be removed as part of either surgery). Analyses were performed in Stata-14 (StataCorp, 2015). Figures were drawn in R (R Development Core Team, 2015) using Matthew Arnold's 'Jasper' package (Arnold, 2015).

RESULTS

The study population included 1 278 783 women without prior cancer, average age 56.1 (s.d. 4.9) at recruitment, 23% of whom reported a tubal ligation, at an average age of 34.5 (s.d. 5.3). Table 1 shows baseline characteristics of the cohort. A total of 167 430 cancers accrued, after a mean follow-up of 13.8 years (s.d. 3.4). The average age at cancer diagnosis was 65.6 years (s.d. 6.5). There was no association between tubal ligation and risk of all cancers combined (RR = 1.00, 95% confidence interval (CI): 0.98–1.01).

Figure 1 displays adjusted RRs and 95% CIs of 26 site- or type-specific cancers among women with vs without tubal ligation. There was a 20% reduction for ovarian cancer risk (RR = 0.80, 95% CI: 0.76–0.85; $P < 0.001$) and a reduction of similar magnitude for peritoneal cancers (RR = 0.81, 95% CI: 0.66–0.98; $P = 0.03$) (ICD-10 code C48, which includes both peritoneal and retroperitoneal cancers). We found a large reduction in risk of cancers of the fallopian tube, but confidence intervals were wide (RR: 0.60, 95% CI: 0.37–0.96, $P = 0.04$).

Table 1. Characteristics of the study population at recruitment, and details of follow-up, by tubal ligation status

Characteristics	Tubal ligation	
	No	Yes
Number of women	984 059	294 724
Mean (s.d.) age at recruitment (years)	56.3 (5.0)	55.4 (4.3)
Socioeconomic status, lowest quintile, % (n)	18.1 (176 985)	25.1 (73 503)
Nulliparous, % (n)	13.3 (130 818)	2.6 (7558)
Ever use of oral contraceptive pill, % (n)	56.5 (551 799)	69.5 (202 511)
Ever use of menopausal hormones, % (n)	47.5 (463 250)	58.2 (169 199)
Hysterectomy, % (n)	21.9 (215 280)	29.1 (84 514)
Mean (s.d.) body mass index (kg m ⁻²)	26.1 (4.6)	26.7 (4.9)
Current smoker, % (n)	18.5 (171 593)	26.9 (74 647)
Strenuous exercise \geq once/week, % (n)	39.5 (375 006)	37.1 (105 032)
Alcohol intake, ≥ 7 units/week, % (n)	23.3 (227 830)	24.8 (72 471)
Follow-up for cancer incidence		
Woman-years of follow-up (100 000s)	136.0	40.5
Mean (s.d.) follow-up time per woman	13.8 (3.4)	13.8 (3.3)
Number of incident cancers	129 531	37 899
Abbreviations: n=Number of women; s.d.=standard deviation. Notes: Means and percentages are calculated excluding missing values for the variable of interest.		

We also found increased risk of anal cancer (RR = 1.34, 95% CI: 1.11–1.63; $P = 0.002$), as previously reported (Coffey *et al*, 2015).

The small increase in risk of lung cancer (RR = 1.09, 95% CI: 1.05–1.13) may well be due to residual confounding from smoking — as women with tubal ligation were much more likely to be current smokers, and to smoke more cigarettes per day, than women without tubal ligation. There was no association between tubal ligation and lung cancer risk among never-smokers (RR = 1.04; 95% CI: 0.91–1.19).

There were no significant associations between tubal ligation and risk of cancers at the other sites, including cancers of the endometrium, cervix, breast and colorectum.

DISCUSSION

To our knowledge, this is the largest and most comprehensive analysis so far of the association between tubal ligation and subsequent risk of cancer. We found that tubal ligation was significantly associated with reduced risks of ovarian, peritoneal, and fallopian tube cancers, and an increased risk of anal cancer, but was not associated with breast, endometrial or cervical cancer, as had been suggested by others.

The reduction in ovarian cancer risk has been reported by others (Cibula *et al*, 2011; Rice *et al*, 2012; Sieh *et al*, 2013). We previously reported significant heterogeneity by histological type of ovarian cancer, finding that tubal ligation was associated with a modest reduction of serous tumours overall (RR = 0.84, 95% CI: 0.77–0.92), and about a 20% reduction in risk of high-grade serous carcinoma, and almost a halving of risk of endometrioid and clear cell ovarian tumours (Gaitskell *et al*, 2016). These findings are consistent with hypotheses regarding possible different origins of the ovarian cancer histotypes, and that many cases of high-grade serous ovarian cancer may arise from precursor lesions within the fallopian tubes, while some endometrioid and clear cell tumours may develop from endometriosis (Kurman and Shih, 2011; Prat, 2012). Although the precise mechanism by which tubal ligation reduces the risk of ovarian cancer is unclear, part of the explanation could be that it acts as a physical barrier to pro-carcinogenic substances passing through the fallopian tubes to the ovaries (whether endometriosis, fallopian tube epithelial cells, infectious agents, or exogenous carcinogens).

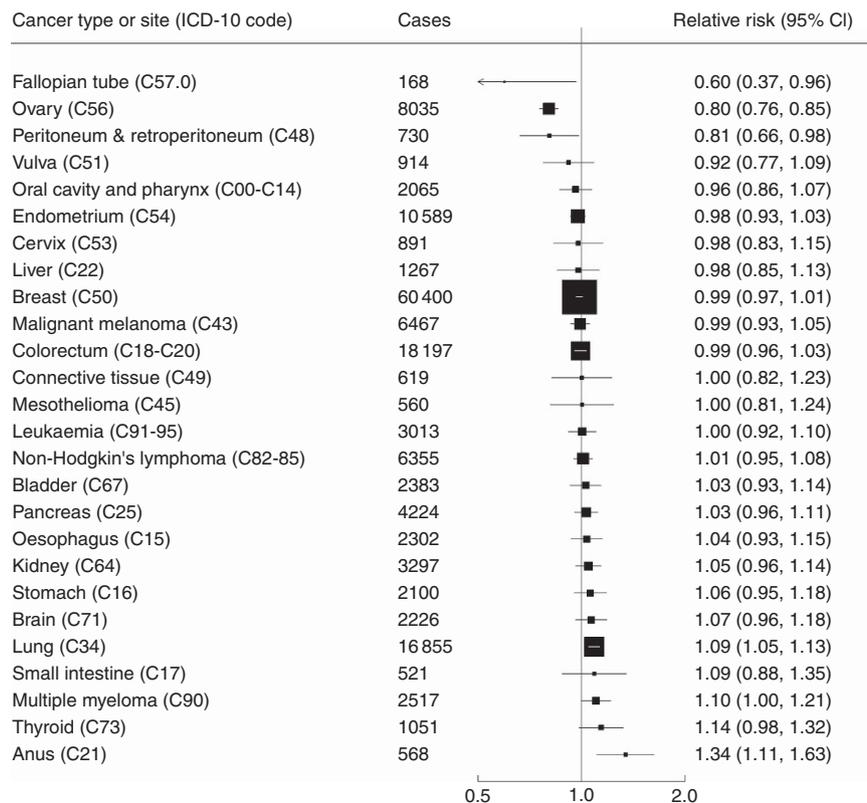


Figure 1. Relative risk of cancer incidence by site or type among women with vs without tubal ligation. Results are adjusted for age, region, socioeconomic status, parity, age at first birth, hysterectomy, smoking, alcohol intake, physical activity, body mass index, and use of the oral contraceptive pill or menopausal hormones. The analysis of fallopian tube cancer is restricted to women without bilateral oophorectomy or hysterectomy. The analysis of ovarian cancer is restricted to women without bilateral oophorectomy. Analyses of endometrial and cervical cancer are restricted to women without hysterectomy.

Few other studies have reported on the association between tubal ligation and risk of peritoneal cancer, and they have tended to be limited by small numbers of cases. Our study included 730 cases of peritoneal cancer; two retrospective studies have reported their findings—one study including 62 cases found no association (Grant *et al*, 2010); and another including 22 cases reported a reduced risk (Purdie *et al*, 1995; Green *et al*, 1997).

We believe that this is the first study to report that tubal ligation is associated with a significant reduction in risk of fallopian tube cancer (Riska *et al*, 2007; Vicus *et al*, 2010).

Our finding that tubal ligation is associated with a reduction in risk of ovarian, peritoneal and fallopian tube cancers perhaps reflects their histological and clinical similarity, and possible similar site of origin (Kurman *et al*, 2014). The majority of the peritoneal and fallopian tube cancers with specified histology were serous carcinomas, which is also the most common histotype of ovarian cancer (Gaitskell *et al*, 2016). There is increasing evidence from histological, molecular and genetics studies that many high-grade serous carcinomas found in the ovary or peritoneum may have originated from precursor lesions in the fallopian tube (reviewed in (Nik *et al*, 2014; Perets and Drapkin, 2016)).

As the majority of the putative precursor lesions for high-grade serous cancers are found within the fimbrial end of the fallopian tube (Przybycin *et al*, 2010; Gilks *et al*, 2015), adjacent to the ovary, it is perhaps surprising that tubal ligation (which normally involves surgery to the mid-portion of the tube) should reduce the risk of such tumours. It may be that, historically, some surgical sterilisation procedures involved cutting and removing a portion of the fallopian tube, rather than simply clipping the tube (as is now more common). Alternatively, it may be that surgery causes local vascular changes with consequent effects on the tubal

epithelium. One of the limitations of our study is that we do not have information on the type of surgical procedure performed, and thus are unable to explore possible differences in association between different surgical techniques.

For endometrial cancer, a reduced risk associated with tubal ligation was reported in a Danish cohort (Kjaer *et al*, 2004), but we and others have not replicated this association (Castellsague *et al*, 1996; Lacey *et al*, 2000). One group of investigators reported that tubal ligation was associated with an increased risk of cervical cancer (Mathews *et al*, 2012), but again, neither other findings (Li and Thomas, 2000) nor ours replicated this.

Reports of the relationship between tubal ligation and breast cancer risk have been varied, including suggestions of either a reduced (Kreiger *et al*, 1999; Calle *et al*, 2001) or increased risk (Irwin *et al*, 1988), although the majority of studies reported no significant association (Brinton *et al*, 2000; Eliassen *et al*, 2006; Iversen *et al*, 2007; Dorjgochoo *et al*, 2009; Press *et al*, 2011; Gaudet *et al*, 2013; Nichols *et al*, 2013), consistent with our findings.

We have previously reported in detail on the risk factors for anal cancer in the Million Women Study (Coffey *et al*, 2015); factors associated with an increased risk of anal cancer included tubal ligation, nulliparity, smoking, past use of the oral contraceptive pill, and not living with a partner. The strongest association was with a history of cervical intraepithelial neoplasia grade 3 (RR = 4.03, 95% CI: 2.59–6.28), reflecting the importance of high-risk strains of human papilloma virus as causative agents of both cervical (Walboomers *et al*, 1999) and anal (International Agency for Research on Cancer, 2009) cancers. It is unclear why tubal ligation should be associated with an increased risk of anal cancer, and it may be that this apparent association reflects confounding by sexual behaviour and exposure to human papilloma virus. For

example, as tubal ligation is usually performed for permanent contraception, it is likely to be more common among women who are sexually active, and who thus may be more likely to be exposed to sexually-transmitted infections, such as human papilloma virus, and the consequent increased risk of anal cancer.

There have been reports on possible relationships between tubal ligation and other cancers, including possible reductions in risk of colorectal (Cape and Kreiger, 1999; Rosenblatt *et al*, 2004) and stomach cancer (Dorjgochoo *et al*, 2009), and increased risks of thyroid cancer (Braganza *et al*, 2014) and lymphatic and haematopoietic malignancies (Kjaer *et al*, 2004). We did not replicate any of these findings.

The large size of the cohort, the individual information on possible confounding factors, and the complete and long follow-up, provided reliable estimates of risks associated with tubal ligation for 26 specific cancer sites, even relatively uncommon ones. We found no association between tubal ligation and the risk of cancers of the endometrium, breast, or cervix. By contrast, tubal ligation is associated with a clear reduction in risk of ovarian cancer, a reduction of similar magnitude of peritoneal cancer, and a reduction of fallopian tube cancer. That tubal ligation is associated with a reduced risk of cancers of the ovary, peritoneum and fallopian tube, but not of other hormonally-related cancers, is consistent with the hypothesis that many of the cancers at these sites have a shared origin in the fallopian tube, and that tubal ligation reduces cancer risk by acting as a barrier to cells, carcinogens or other agents reaching the ovary and peritoneal cavity, rather than by affecting hormone levels.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

MILLION WOMEN STUDY COLLABORATORS

Million Women Study Co-ordinating Centre Staff

Hayley Abbiss, Simon Abbott, Rupert Alison, Naomi Allen, Miranda Armstrong, Krys Baker, Angela Balkwill, Emily Banks, Isobel Barnes, Valerie Beral, Judith Black, Roger Blanks, Kathryn Bradbury, Anna Brown, Benjamin Cairns, Karen Canfell, Dexter Canoy, Andrew Chadwick, Barbara Crossley, Francesca Crowe, Dave Ewart, Sarah Ewart, Lee Fletcher, Sarah Floud, Toral Gathani, Laura Gerrard, Adrian Goodill, Jane Green, Lynden Guiver, Michal Hozak, Isobel Lingard, Sau Wan Kan, Oksana Kirichek, Nicky Langston, Bette Liu, Kath Moser, Kirstin Pirie, Gillian Reeves, Keith Shaw, Emma

Sherman, Helena Strange, Sian Sweetland, Sarah Tipper, Ruth Travis, Lyndsey Trickett, Lucy Wright, Owen Yang, Heather Young.

Million Women Study Advisory Committee

Emily Banks, Valerie Beral, Lucy Carpenter, Carol Dezateux, Jane Green, Julietta Patnick, Richard Peto, Cathie Sudlow.

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