SHORT COMMUNICATION

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Tubal ligation in relation to menopausal symptoms and breast cancer risk

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Background: Local inflammation after tubal ligation may affect ovarian function and breast cancer risk.

Methods: We analysed tubal ligation, menopausal characteristics, and breast cancer risk in the Sister Study cohort ($N = 50\,884$ women).

Results: Tubal ligation was associated with hot flashes (hazard ratio (HR) 1.09; 95% confidence interval (CI): 1.06–1.12) but not menopausal age (HR 0.99; 95% CI: 0.96–1.02). Tubal ligation did not have an impact on breast cancer overall (HR 0.95; 95% CI: 0.85–1.06), but had a suggested inverse relation with oestrogen receptor+/progesterone receptor+ invasive tumours (HR 0.84; 95% CI: 0.70–1.01), possibly because of subsequent hysterectomy/bilateral oophorectomy.

Conclusion: Tubal ligation does not influence overall breast cancer risk.

The US Collaborative Review of Sterilization reported reduced menstrual bleeding and pain and increased cycle irregularity after tubal ligation (Peterson *et al*, 2000). These findings provided evidence against a 'post-tubal ligation syndrome' that included dysmenorrhoea and menorrhagia, but could not address long-term outcomes, such as altered menopausal age (Pokoradi *et al*, 2011), symptoms (Whiteman *et al*, 2004; Wyshak, 2004; Nelson *et al*, 2005), or breast cancer risk.

A recent meta-analysis reported no association between tubal ligation and breast cancer (RR = 0.97); however, substantial heterogeneity between studies ($I^2 = 82.2\%$, $P < 0.001$) was observed. Effect estimates among eight studies ranged from RR = 0.37 (0.19, 0.68) to 1.20 (1.00, 1.30) (Gaudet *et al*, 2013). This variability may be partly due to incomplete information on subsequent gynaecologic surgeries and tumour subtypes. Women who have a tubal ligation are more likely to undergo hysterectomy (Hillis *et al*, 1998), which may include bilateral oophorectomy (Lowder *et al*, 2010), and thereby decrease breast cancer risk. Few studies have evaluated variation by tumours that express oestrogen receptor (ER) or progesterone receptor (PR) and may therefore be more sensitive to hormonal exposures (Eliassen *et al*, 2006; Press *et al*, 2011).

We studied tubal ligation in relation to menopausal age, symptoms, and ER/PR-defined breast cancer in the Sister Study.

MATERIALS AND METHODS

The Sister Study is an ongoing prospective cohort of US women who have a sister who was diagnosed with breast cancer (Godfrey *et al*, 2013; Xu *et al*, 2013). During 2003–2009, 50 884 women aged 35–74 years completed baseline telephone interviews including reproductive and medical history. All participants are asked to return brief annual health updates and comprehensive biennial questionnaires. Incident breast cancers are initially self-reported and later confirmed by medical record review. Response rates have been ⩾94% over follow-up. This research was approved by the Institutional Review Boards of the National Institute of Environmental Health Sciences, NIH, and the Copernicus Group. All participants provided informed consent.

Participants reported ever having a tubal ligation and at what age. We excluded 274 women with missing information on tubal ligation or age at tubal ligation, a breast cancer diagnosis preceding

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Table 1. PRs and 95% CIs for tubal ligation

	Tubal ligation		No tubal ligation		
	N	**%**	***N***	**%**	**PR (95% CI)[a]**
Total	14 802	100.0	35 512	100.0	N/A
Age at tubal ligation, mean years (s.d.)	32.7	(5.5)	N/A	N/A	N/A
Tubal ligation performed at last birth	4066	27.5	N/A	N/A	N/A
Age at study enrolment, mean years (s.d.)	55.9	(8.0)	54.9	(9.3)	1.01 (1.01, 1.01)
Education					
Less than HS	241	1.6	374	1.1	1.62 (1.47, 1.79)
HS diploma or equivalent	2614	17.7	4471	12.6	1.53 (1.47, 1.58)
Some college	5871	39.7	11 120	31.3	1.45 (1.40, 1.49)
4-Year college degree or higher	6076	41.0	19 547	55.0	1
Race					
Non-Hispanic White	11 802	79.7	30 352	85.5	1
Black	1910	12.9	2595	7.3	1.54 (1.48, 1.60)
Latina	667	4.5	1670	4.7	1.04 (0.97, 1.11)
Other	423	2.9	895	2.5	1.16 (1.07, 1.25)
Body mass index (kg m^{-2})					
<18.5	123	0.8	438	1.2	0.88 (0.75, 1.03)
18.5–24.9	4659	31.5	14 025	39.5	1
25.0–29.9	4939	33.4	11 036	31.1	1.22 (1.18, 1.27)
$\geqslant 30.0$	5081	34.3	10 013	28.2	1.34 (1.29, 1.38)
Smoking					
Never	7552	51.0	19 554	55.1	1
Social	300	2.0	843	2.4	0.95 (0.86, 1.04)
Former	5377	36.3	12571	35.4	1.05 (1.02, 1.08)
Current	1572	10.6	2541	7.2	1.39 (1.33. 1.45)
Missing	1	0.0	3	0.0	
Alcohol consumption					
Never	572	3.9	1344	3.8	1.00 (0.93, 1.08)
Former	2480	16.8	5151	14.5	1.11 (1.07, 1.15)
Current	11 750	79.4	29 017	81.7	1
Parity					
0	830	5.6	8296	23.4	0.41 (0.38, 0.45)
1	1591	10.7	5653	15.9	1
2–3	10 323	69.7	18 321	51.6	1.64 (1.56, 1.71)
$\geqslant 4$	2 058	13.9	3242	9.1	1.75 (1.65, 1.85)
Age at first birth, mean years (s.d.)	23.3	(4.7)	25.4	(5.4)	0.94 (0.94, 0.95)
Age at last birth, mean years (s.d.)	28.5	(5.2)	29.7	(5.4)	0.97 (0.97, 0.98)
Oral contraceptive use					
Never	1804	12.2	6239	17.6	1
Ever	12 998	87.8	29 273	82.4	1.45 (1.39, 1.51)
Hysterectomy					
Never	9646	65.2	24 897	70.1	1
Ever	5156	34.8	10 615	29.9	1.13 (1.10, 1.16)
Postmenopausal hormone use					
Never	7741	52.3	21 132	59.5	1
Unopposed oestrogens (E) only	3185	21.5	6758	19.0	1.16 (1.12, 1.21)
Combination of E and E + P	645	4.4	1354	3.8	1.16 (1.09, 1.25)
E plus P only	3189	21.5	6174	17.4	1.23 (1.19, 1.28)
Missing	42	0.3	94	0.3	

Table 1. (Continued)

	Tubal ligation		No tubal ligation		
	N	%	*N*	%	PR (95% CI)[a]
Mammogram screening					
Never	130	0.9	431	1.2	0.86 (0.74, 1.00)
Ever	14 672	99.1	35 080	98.8	N/A
Most recent <1 year ago	11 828	79.9	28 662	80.7	1
Most recent 1–2 years ago	2296	15.5	5109	14.4	1.07 (1.03, 1.11)
Most recent >2 years ago	546	3.7	1307	3.7	1.03 (0.96, 1.11)
Missing	2	0.0	2	0.0	

Abbreviations: 95% CI = 95% confidence interval; E = oestrogen; HS = high school; N/A = not applicable; P = progestin; PR = prevalence ratio.
[a]PRs and 95% CIs calculated from age-adjusted log-negative binomial regression models.

enrolment or with unknown date, or who reported tubal ligation after hysterectomy or menopause. Also excluded were 296 women (0.6%) with missing race, education, body mass index, alcohol consumption, oral contraceptive (OC) use, age at menarche, age at first birth, parity, marital status, hysterectomy, or menopausal status. Records from 50 314 women were analysed.

Women reported ever having hot flashes and at what age, and whether they ever had 'any other symptoms of menopause such as poor sleeping, night sweats, irritability, or depression' (yes/no) and at what age. Women were considered menopausal after 12 months of amenorrhoea not due to pregnancy or breastfeeding. Age at menopause was defined as a woman's age at last menstrual period.

Women who reported incident breast cancer were asked to provide diagnosis details and authorise the release of medical records. Approximately 10% declined medical record release or died before providing authorisation. Agreement was high between self-reports and medical records for ER status (95%) and invasiveness (81%) (Kim *et al*, 2011). When medical records were unavailable, self-reported data were used. At the time of this analysis, medical records were available for 77% of reported breast cancers.

Statistical analyses. Prevalence ratios (PRs) and 95% confidence intervals (CIs) were calculated from multivariate log-negative binomial regression. To evaluate tubal ligation in relation to menopausal characteristics, we calculated hazard ratios (HRs) and 95% CIs using Cox proportional hazards models. Women contributed person-time from the age of 30 years to the event of interest (menopause, hot flashes, other menopausal symptoms) or were censored at the age at interview, age at uterine ablation/embolisation, age at hysterectomy, age at oophorectomy, age at tamoxifen (for chemoprevention) initiation, age at ovarian cancer, or at the age of 60 years, whichever occurred first. Model covariates were selected *a priori* based on known associations with tubal ligation or menopausal characteristics. Final models adjusted for age at interview, race, education, marital status, body mass index (BMI) during ages 30–39 years, and two time-varying covariates: average number of daily cigarettes from the age of 30–60 years and average number of alcoholic drinks per week during each decade (1930s, 1940s, 1950s). In sensitivity analyses, we adjusted for parity and postmenopausal hormone use and stratified by OC use.

For breast cancer analyses, person-time was accrued from the age at study enrolment. In tumour subtype analyses, competing or undefined subtypes were censored at the date of diagnosis. Final models adjusted for the following covariates *a priori* as potential confounders: age (as the time scale), education, race, age at menarche, parity, OC use, age at first birth, age at last birth, BMI, and alcohol consumption at enrolment. In sensitivity analyses, we controlled for postmenopausal hormone use and stratified by mammography screening.

RESULTS

Overall, 14 802 women (29.4%) reported having a tubal ligation (mean age = 32.7 years; s.d. = 5.5); prevalence was highest among women who reported lower education, African-American race, overweight to obese BMI, current cigarette smoking, ever OC use, younger age at first birth, and having ⩾2 births. Tubal ligation was also more prevalent among women who reported hysterectomy, postmenopausal hormone use, and mammography screening (Table 1).

Menopause. Women who had a tubal ligation were 9% more likely to report hot flashes (95% CI: 1.06–1.12) and 10% more likely to have other symptoms of menopause (e.g., poor sleeping, night sweats, irritability, depression) (95% CI: 1.07–1.13) compared with women who did not have a tubal ligation (Table 2). Among those reporting symptoms, 71% had both hot flashes and other symptoms. Risk of hot flashes did not vary by age at tubal ligation, although other menopausal symptoms appeared more frequent at older ages (HR 1.15: 95% CI: 1.11–1.20 for tubal ligation ⩾35 years *vs* HR 1.07; 95% CI: 1.03–1.11 for <35; Table 2). In analyses among women who never used OCs or additionally adjusted for parity or postmenopausal hormone use, the results were virtually unchanged (data not shown).

Breast cancer. During 203 141 person-years (mean = 4.0 years), 1646 incident breast cancers were reported (1079 invasive, 422 *in situ*, 145 undefined). We observed no overall association between breast cancer and tubal ligation (HR 0.95; 95% CI: 0.85–1.06), or by timing of tubal ligation or subsequent gynaecologic surgery (Table 3).

Oestrogen receptor/PR status was available for 95% of invasive breast tumours. The HR for ER+/PR+ invasive disease after tubal ligation was 0.84 (95% CI: 0.70–1.01). Compared with women who reported no tubal ligation, hysterectomy, or bilateral oophorectomy, those who reported tubal ligation and hysterectomy with bilateral oophorectomy had a 42% decreased risk of ER+/PR+ invasive breast cancer (HR = 0.58; 95% CI: 0.38–0.89). Associations with ER+/PR+ invasive tumours were unchanged by adjustment for postmenopausal hormones (data not shown). Tubal ligation was not associated with ER−/PR− invasive breast cancer.

Table 2. HRs and 95% CIs for menopausal symptoms and menopause

	Hot flashes		Other menopausal symptoms[a]		Menopause[b]	
	N[c]/total	HR (95% CI)[d]	*N*[c]/total	HR (95% CI)[d]	*N*[c]/total	HR (95% CI)[d]
Tubal ligation						
No	21 472/33 265	1	19 921/34 038	1	20 746/34 148	1
Yes	10 346/3 898	1.09 (1.06, 1.12)	9569/14 246	1.10 (1.07, 1.13)	9843/14 395	0.99 (0.96, 1.02)
Age at tubal ligation (years)						
<35	6450/8555	1.10 (1.06, 1.14)	5950/8758	1.07 (1.03, 1.11)	5855/8879	0.99 (0.96, 1.03)
⩾35	3896/5343	1.08 (1.04, 1.13)	3619/5488	1.15 (1.11, 1.20)	3988/5516	0.99 (0.95, 1.02)

Abbreviations: 95% CI = 95% confidence interval; HR = hazard ratio.
[a]Other symptoms include, but are not limited to, ever experiencing 'poor sleeping, night sweats, irritability, and depression' (yes/no).
[b]The age-specific HR for postmenopausal status from the age of 30–60 years.
[c]At the baseline interview.
[d]Adjusted for age, race, education, marital status, body mass index, cigarette smoking, and alcohol consumption.

Table 3. HRs and 95% CIs for breast cancer

		Total breast cancer		ER+/PR+ invasive breast cancer		ER−/PR− invasive breast cancer		*In situ* breast cancer	
	Person-years	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a]	Cases	HR (95% CI)[a,b]
Overall									
Tubal ligation									
No	144 199	1192	1	534	1	109	1	293	1
Yes	58 942	454	0.95 (0.85, 1.06)	173	0.84 (0.70, 1.01)	47	0.98 (0.68, 1.40)	129	1.10 (0.88, 1.37)
Age at tubal ligation (years)									
<35	36 283	270	0.98 (0.85, 1.13)	110	0.93 (0.75, 1.16)	33	1.09 (0.72, 1.66)	66	0.95 (0.71, 1.26)
⩾35	22 658	184	0.92 (0.78, 1.08)	63	0.73 (0.56, 0.95)	14	0.81 (0.46, 1.42)	63	1.29 (0.98, 1.71)
Years since tubal ligation (years)									
<10	4498	35	1.30 (0.92, 1.84)	7	0.58 (0.27, 1.23)	3	1.37 (0.42, 4.48)	14	2.12 (1.20, 3.73)
10–19	14 304	103	1.02 (0.83, 1.26)	37	0.85 (0.60, 1.20)	12	1.20 (0.65, 2.23)	31	1.20 (0.81, 1.76)
20–29	26 399	186	0.86 (0.73, 1.01)	76	0.84 (0.65, 1.08)	21	0.91 (0.56, 1.48)	56	1.03 (0.76, 1.38)
⩾30	13 741	130	0.86 (0.80, 1.17)	53	0.90 (0.67, 1.22)	11	0.85 (0.44, 1.62)	28	0.88 (0.59, 1.33)
According to subsequent gynaecologic surgery									
No tubal ligation or hysterectomy/bilateral oophorectomy	97 027	766	1	354	1	60	1	193	1
Tubal ligation alone	36 742	294	1.01 (0.88, 1.17)	123	0.95 (0.76, 1.18)	32	1.38 (0.87, 2.18)	74	1.02 (0.77, 1.35)
Tubal ligation and hysterectomy alone	9080	73	1.02 (0.79, 1.31)	23	0.74 (0.48, 1.14)	6	0.95 (0.40, 2.28)	24	1.36 (0.87, 2.12)
Tubal ligation and hysterectomy with bilateral oophorectomy	11 034	76	0.83 (0.65, 1.06)	24	0.58 (0.38, 0.89)	8	1.01 (0.47, 2.20)	26	1.17 (0.76, 1.81)

Abbreviations: 95% CI = 95% confidence interval; ER = oestrogen receptor; HR = hazard ratio; PR = progesterone receptor.
[a]HRs and 95% CIs are calculated from multivariate Cox proportional hazards regression models and adjusted for age, age at menarche, education, race, body mass index, alcohol consumption, parity, age at first birth, age at last birth, and oral contraceptive use.
[b]Additionally adjusted for mammography screening.

We observed an increased risk of *in situ* breast cancer associated with tubal ligation within the past 10 years (HR 2.12; 95% CI: 1.20–3.73). Among women who reported having a screening mammogram within 12 months of enrolment, this association was no longer statistically significant (HR 1.87; 95% CI: 0.96–3.62; Supplementary Table).

DISCUSSION

Women who had a tubal ligation were ~10% more likely to report menopausal symptoms. Tubal ligation did not alter menopausal age or overall breast cancer risk. We observed a decreased risk of

ER+/PR+ invasive breast cancer associated with tubal ligation among women who also had a hysterectomy with bilateral oophorectomy.

In controlled studies, the majority report a higher prevalence of hot flashes among women with prior tubal ligation (Visvanathan and Wyshak, 2000; Whiteman *et al*, 2004; Wyshak, 2004). A study of 3650 postmenopausal women in the United Kingdom reported a 38% increase (95% CI: 1.02–1.87) in the odds of menopause before the age of 49 years among women who reported tubal ligation (Pokoradi *et al*, 2011); we did not observe an association between tubal ligation and menopausal age.

Our analysis is one of few to evaluate breast cancer risk according to ER/PR status (Eliassen *et al*, 2006; Press *et al*, 2011) or *in situ* disease. Previous studies were often unable to account for subsequent hysterectomy, which probably contributes to heterogeneity between reports (Gaudet *et al*, 2013). In our data, decreased breast cancer risk after tubal ligation appeared largely limited to women who also underwent bilateral oophorectomy and to hormonally responsive disease.

Strengths include our large sample and detailed reproductive and lifestyle information. We reconstructed life events from the age of 30 years to interview and used time-varying exposures. Limitations include potential misclassification based on self-reported information. However, in previous studies, hysterectomy and oophorectomy status have been reliably reported (Colditz *et al*, 1987; Phipps and Buist, 2009; Nichols *et al*, 2011). All exposure information was reported before diagnosis and was therefore unlikely to bias our results. Subgroup analyses of incident breast cancers were constrained by small numbers, and diagnoses not reported by participants would not have been captured. Our results were robust to covariate selection; however, we cannot exclude the possibility of residual confounding.

In our study, women who had a tubal ligation were more likely to report menopausal symptoms; however, tubal ligation alone did not influence menopausal age or breast cancer risk.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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