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Tubal ligation and ovarian cancer risk in African American women

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Abstract

Purpose—Tubal ligation has been associated with reduced risk of epithelial ovarian cancer (EOC) in studies of primarily white women, but less is known about the association in African

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American (AA) women. We sought to evaluate the associations among 597 invasive ovarian cancer cases and 742 controls of AA descent recruited from the African American Cancer Epidemiology Study, a population-based case–control study in 11 geographical areas in the US.

Methods—Multivariable logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) adjusted for potentially confounding factors.

Results—An inverse association between tubal ligation and EOC was observed that was not statistically significant (OR 0.88, 95% CI 0.68–1.14). However, an inverse association with EOC risk was observed among women who had a tubal ligation at age 35 years or older (OR 0.64; 95% CI 0.41–0.98), but not among those who had a tubal ligation before age 35 (OR 0.98; 95% CI 0.74–1.29) (*p* for interaction = 0.08). The association also varied considerably by tumor subtype. A strong inverse association was observed for endometrioid tumors (OR 0.31, 95% CI 0.14–0.70), whereas associations with mucinous (OR 0.87, 95% CI 0.36–2.12) and serous (OR 0.94, 95% CI 0.71–1.24) tumors were weaker and not statistically significant. A statistically non-significant positive association for clear cell tumors (OR 1.84, 95% CI 0.58–5.82) was based on a low number of cases.

Conclusions—Our findings show that tubal ligation may confer a reduced risk for EOC among AA women that is comparable to the associations that have been previously observed in primarily white populations.

Keywords

Ovarian cancer; Epidemiologic studies; Tubal ligation; African-American women

Introduction

Ovarian cancer is the most deadly of all gynecologic cancers, responsible for an expected 14,240 deaths among U.S. women in 2016 [1]. African American (AA) women have lower ovarian cancer incidence and mortality rates as compared with white women, but experience worse survival after diagnosis [2].

Tubal ligation has been shown to be associated with reduced risk of epithelial ovarian cancer (EOC) [3–20], the most commonly diagnosed type of ovarian cancer [21]. Tubal ligation is the most common method of contraception among AA women and it is performed more frequently and at an earlier age among AA women compared with any other racial/ethnic group in the U.S. [22]. AA women have been shown to have different prevalence rates of various biological and behavioral factors that could influence the association with tubal ligation [4, 23–31]. Yet, thus far, the largest study to analyze tubal ligation and EOC risk among AA women included both AA and white women and analyzed only 143 AA cases and 189 AA controls [12]. To date, no study has concentrated solely on the association between tubal ligation and EOC risk among AA women, a group that has historically been under-represented in studies of the etiology of EOC. Therefore, we examined the association between tubal ligation, various other identified EOC risk factors, and EOC incidence among 597 AA cases and 742 AA controls enrolled in the African American Cancer Epidemiology Study (AACES), a large, multi-center, population-based case–control study of AA women [32].

Methods

AACES is a population-based case–control study of invasive EOC among AA women in eleven locations across the United States (Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas). Study design and methods are described in full detail elsewhere [32]. Briefly, rapid case ascertainment was used to identify AA women between the ages of 20 and 79 years who were newly diagnosed with invasive EOC from 1 December, 2010 through 31 December, 2015. Controls were recruited through random-digit dialing, screened for eligibility (exclusions include self-identified race other than AA, a previous history of ovarian cancer, history of bilateral oophorectomy, and inability to complete an interview in English), and frequency matched to cases on 5 year age group and state of residence. Eligible and willing cases and controls were then contacted at an agreed-upon time to complete the computer-assisted telephone interview. The questionnaire included detailed questions on demographics, gynecologic and reproductive history, contraceptive and hormone use, personal and family medical history, insurance and access to care, social conditions, religious and cultural beliefs, and exposures such as radiation, talc, and smoking. Altogether, 602 cases and 751 controls have been enrolled. Tumor histotype was determined by a pathologist, usually at the diagnosing institution, and then centrally reviewed and verified by a study pathologist for AACES. This analysis included participants for whom tubal ligation status and all covariates were available, resulting in a sample size of 597 cases and 742 controls.

Personal history of tubal ligation

In the telephone interview, participants were asked “Have you ever used any method of birth control?” Those who answered “Yes” were then asked about methods used (tubal ligation is one of several options listed), age at first use, and length of use. An additional question in a later section of the questionnaire asked, “Have you ever had any of the following types of surgeries?” Those who answered “Yes” to “Tubal ligation (“tubes tied”)” were then asked, “How old were you when you had this surgery?” These two sets of questions were combined to determine whether the participant had a history of tubal ligation and the age at which it occurred. A positive history of tubal ligation was defined as having had the procedure more than two years prior to their reference age (age at diagnosis for cases or age at interview for controls). Participants were then grouped according to age at tubal ligation (<35 vs. 35+), consistent with previous studies [6, 7, 10].

Statistical analysis

The prevalence of demographic characteristics was calculated and t tests and χ^2 tests were performed to compare distributions between cases and controls (and by tubal ligation status among controls). Multivariable logistic regression was performed to calculate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between history of tubal ligation and risk of EOC, and age at tubal ligation (no tubal ligation, <35, 35+) and EOC risk. A number of potential confounders were identified in the literature and were considered for inclusion in the adjusted model, including body powder use [4, 7, 33]; smoking [3, 11, 13]; education [13, 15]; total household income [3, 15]; marital status [15];

parity [3, 4, 11–15, 18, 19, 32, 34–37]; oral contraceptive (OC) use [3, 4, 11–13, 15, 18, 19, 32, 34–37]; menopausal status [15]; hormone therapy (HT) use [3, 11, 12, 14, 18]; premenopausal hysterectomy [3, 6, 7, 10, 11, 36]; body mass index (BMI) [13, 15, 31, 32, 38]; age at menarche [12, 14]; family history of ovarian [4, 7, 11, 12, 19, 32, 34, 36] or breast [7, 11, 12, 32] cancer; breastfeeding [11–13, 18, 35, 37]; use of an intrauterine device (IUD) [14]; history of ovarian cysts [14]; history of infertility [12, 36]; and endometriosis [4, 12, 13, 34]. Of these potential confounders, parity was the only factor that changed the OR by 10% or more and was included in the final adjusted model. The crude model was adjusted for reference age and study site; the final adjusted model was adjusted for reference age, study site, and parity (0, 1, 2, 3+ live births). The final adjusted model was also examined across strata defined by histologic subtype (serous, mucinous, endometrioid, clear cell, other, unknown). Tests of statistical interaction were conducted for reference age, menopausal status, parity, OC use, HT use, body powder use, and smoking using a Wald hypothesis test for regression coefficients of the interaction term included in the model (e.g., variable × tubal ligation).

Results

Cases tended to be older than controls (mean age 58 years for cases and 55 years for controls; $p < 0.01$) (Table 1). Cases were also more likely than controls to report lower parity ($p = 0.05$); higher body powder use, especially in the genital area ($p < 0.01$); lower OC use ($p < 0.01$); lower educational attainment ($p = 0.02$); having been divorced, separated, or widowed ($p < 0.01$); a personal history of endometriosis ($p < 0.01$); and a family history of breast or ovarian cancer ($p < 0.01$). Most cases were diagnosed with high-grade serous ovarian cancer (70.7%); endometrioid tumors (11.1%) were the second most commonly diagnosed histologic subtype.

Controls (40.2%) were more likely than cases (35.9%) to have had tubal ligation, but this difference in proportions was not statistically significant ($p = 0.11$). Among women who had tubal ligation, a greater percentage of cases (80.8%) had the procedure before the age of 35 than did controls (75.2%); this difference was also not statistically significant ($p = 0.13$).

Among controls, women who had tubal ligation tended to be older than those who had not had the procedure (mean age 57 years for women with tubal ligation and 54 for women without; $p < 0.01$) (Supplemental Table 1). Women who had had tubal ligation were less educated ($p < 0.01$); were more likely to be married ($p = 0.02$); had a higher BMI ($p = 0.05$); reported higher parity ($p < 0.01$); experienced menarche at a later age ($p = 0.02$); were more likely to be postmenopausal ($p = 0.01$); and were more likely to have a family history of breast or ovarian cancer ($p = 0.03$).

In the minimally adjusted model (adjusted for age and study site), a statistically significant reduction in risk for EOC was observed among women with prior tubal ligation compared with women without tubal ligation (OR 0.76, 95% CI 0.61–0.96) (Table 2). The association observed in the fully adjusted model (adjusted for age, study site, and parity) was weaker and no longer statistically significant (OR 0.88, 95% CI 0.68–1.14). The association between tubal ligation and EOC risk was seen exclusively among women who had a tubal

ligation at age 35 years or older (OR 0.64; 95% CI 0.41–0.98), whereas no association between age at tubal ligation and EOC risk was found among those who had a tubal ligation before age 35 (OR 0.98; 95% CI 0.74–1.29). These ORs, however, were not statistically different from each other ($p = 0.08$). Adjustment for oral contraceptive use and other variables did not alter these findings. Women who had a tubal ligation at age 35 years or older had a significantly older mean age at last pregnancy (mean = 33.79, standard deviation (SD) = 6.95) than women who had a tubal ligation before age 35 (mean = 27.10, SD = 4.69), regardless of case–control status ($p < 0.0001$).

The association varied considerably by tumor subtype. A strong inverse association was observed for endometrioid tumors (OR 0.31, 95% CI 0.14–0.70). The associations for mucinous (OR 0.87, 95% CI 0.36–2.12) and high-grade serous (OR 0.95, 95% CI 0.71–1.25) tumors were in the protective direction but weak and not statistically significant. A positive association was observed for clear cell tumors in the fully adjusted model (OR 1.84, 95% CI 0.58–5.82) but the sample size was small ($n = 16$), making the confidence interval too wide for any meaningful interpretation.

The association between tubal ligation and EOC appeared to differ by age. There was an inverse association among women aged 50 years and older (OR 0.74, 95% CI 0.56–0.98) but no association among women under 50 years of age (OR 1.60, 95% CI 0.79–3.24), and the test for interaction was not significant ($p = 0.08$). Tubal ligation was inversely associated with EOC among ever smokers (OR 0.68, 95% CI 0.46–1.01), whereas no association was observed among never smokers (OR 1.06, 95% CI 0.75–1.49) (p for interaction = 0.24). No effect modification was seen between tubal ligation and menopausal status, parity, oral contraceptive use, hormone therapy use, or body powder use (data not shown).

Discussion

Our data suggest that the association between tubal ligation and invasive ovarian cancer risk in AA women is consistent with what has been shown in studies comprised predominantly of women of European ancestry that presented results stratified by histologic type (Table 3), with most ORs in the range of 0.7–0.9. In those studies, the associations by histologic type of EOC showed strong inverse associations for endometrioid tumors and weaker or null associations for serous and mucinous tumors, consistent with our data. A recent study [39] suggests that white women and AA women experience similar distributions of histologic type for EOC and fallopian tube cancers. The association with tubal ligation and EOC we observed was also consistent with the findings of previous smaller studies of EOC risk among AA women [4, 12, 16]. In contrast with previous studies, we observed no evidence of an inverse association between tubal ligation and clear cell carcinoma, although our result was based on very small sample size for that histological type of ovarian cancer.

Reference age, parity, and study site were found to be confounders and were included in the fully adjusted model. This is consistent with previous studies where age [5–8, 40–47], parity [5–8, 20, 40–47], and study site [6–8, 41, 45] were included in the adjusted models examining tubal ligation and ovarian cancer risk among predominantly white women. Despite its inclusion in the adjusted models of several previous studies [6–8, 20, 41, 43–45],

OC use was not found to be a confounder among AA women in this study. This was also the case for BMI [6, 7, 41, 43, 44], hysterectomy [5–7, 41, 44], and smoking status [6, 7, 41, 43, 44].

The mechanisms underlying an inverse association between tubal ligation and EOC risk are not entirely understood. [48] Two complementary theories dominate the current literature. One possible mechanism is prevention of the retrograde transport of malignant cells from tumors arising in the fallopian tubes, endometrium, and endocervix to the ovaries. [48] Another involves the prevention of passage of carcinogenic substances (such as talc or chemicals found in tobacco smoke) from the lower reproductive tract to the ovaries. [48] The results of the current study support both hypotheses such that tubal ligation may disrupt the pathway for cancerous cells and/or carcinogenic substances to reach the ovaries.

Recent studies suggest that EOC tumors may not arise in the ovary. EOC is a heterogeneous disease composed of different histologic subtypes that have varying underlying biology and associated risk factors [49]. Morphological evidence shows that cells of the most common subtypes of ovarian cancer (serous, endometrioid and clear cell, and mucinous) are not normally found in the ovary, but are identical to cells of the fallopian tubes, endometrium, and endocervix, respectively [50–53]. Epidemiologic studies have shown tubal ligation is inversely associated with risk of serous [3, 7, 8, 54], endometrioid [3, 5–8, 13, 54], clear cell [6–8], and mucinous [7, 8] ovarian cancers. The strong inverse association we observed between tubal ligation and risk for endometrioid tumors supports the theory that these tumors arise in the endometrium and that tubal ligation prevents ascent of malignant cells through the fallopian tubes to the ovaries.

An inverse association was observed between tubal ligation and EOC among ever smokers in our data, but there was no association among never smokers. This finding supports the hypothesis that tubal ligation disrupts the pathway for carcinogenic substances to travel through the reproductive tract to the ovaries. However, two previous studies of tubal ligation and EOC risk among mainly white women [41, 43] found no effect modification with smoking status. Given the number of tests we performed and the borderline statistical significance, we cannot rule out the role of chance as an explanation for our finding of effect modification by smoking status.

In our study, women who had a tubal ligation at age 35 or older showed a significant reduction in risk for EOC as compared with women who had no tubal ligation, whereas women who had the procedure before age 35 showed no altered risk. The limited research to date on age at tubal ligation and ovarian cancer risk shows mixed results. A 2014 Danish study [5] found a significantly reduced risk for EOC among women who had a tubal ligation after age 35 and no effect among women who had the procedure at a younger age. A 1997 UK study [43] and a 1996 multinational study [20] produced similar results. On the other hand, an analysis based on the U.S. Nurses' Health Studies published in 2014 [6] found a reduced risk for EOC among women who had a tubal ligation before age 35 and no effect for women who were older when they had the procedure. A 2013 analysis of the New England Case–Control Study [7] found a significant risk reduction for EOC among women who had a tubal ligation before the age of 40, especially among women who had the

procedure at 35–39 years of age, and no significant effect for women who had it at age 40 or older. The reasons for the disparate findings according to age are not yet clear.

A strength of this study is the relatively large number of AA women included in AACES compared to prior studies, as well as the robust individual data on known and potential confounders. AACES is the only study of ovarian cancer risk to focus solely on ovarian cancer in AA women. The large sample size allowed for stratification by histologic subtype, contributing to the growing discussion on the origin of EOC and tubal ligation's role in reducing risk for the disease, although sample sizes were still relatively small for some of the rarer subtypes. As with all retrospective case–control studies, there is the potential for recall bias. Overall, the literature shows good agreement between self-reported history of tubal ligation and medical record data [55], but we cannot rule out selective reporting in our study. There is also the potential for selection bias due to both the nature of random-digit dial surveys and the high fatality rate of EOC. Many women succumb to the disease before the survey can be administered, and it is often difficult to determine whether their risk factors differ from those women who survive long enough to participate in a study.

In summary, our findings suggest that tubal ligation may confer a reduced risk for invasive EOC among AA women that is comparable to the associations that have been previously observed in primarily white populations. Except for clear cell tumors, the associations observed by histologic type in the present study were comparable to the associations observed in largely white populations, particularly in showing a strong inverse association between tubal ligation and risk of endometrioid tumors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AA	African American
AACES	African American Cancer Epidemiology Study
BMI	Body mass index
CI	Confidence intervals
OR	Odds ratio

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Table 1

Characteristics of epithelial ovarian cancer cases and controls, AACES

	Cases (*n* = *597*)		Controls (*n* = *742*)		*p* value
	n	(%)	*n*	(%)	
Age at diagnosis/interview (years)					<0.01
<40	28	(4.7)	79	(10.7)	
40–49	96	(16.1)	120	(16.2)	
50–59	209	(35.0)	276	(37.2)	
60–69	167	(28.0)	194	(16.2)	
70–79	97	(16.3)	73	(9.8)	
Age at diagnosis/interview range (years)	20–79		20–79		
Mean age at diagnosis/interview (years) (SD)	58.0	(10.9)	55.0	(11.7)	
Education					0.02
High school or less	268	(44.9)	276	(37.2)	
Some post high school training	146	(24.5)	207	(27.9)	
College or graduate degree	183	(30.7)	259	(34.9)	
Marital status					<0.01
Never married	143	(24.0)	183	(24.7)	
Currently married/living with partner	193	(32.3)	308	(41.5)	
Divorced, separated, or widowed	261	(43.7)	251	(33.8)	
Body mass index (kg/m^2)					0.11
<25 (under- and normal weight)	88	(14.7)	140	(18.9)	
25–29.9 (overweight)	156	(26.1)	195	(26.3)	
30+ (obese)	353	(59.1)	407	(54.9)	
Parity (# of live births)					0.05
0	109	(18.3)	96	(12.9)	
1	108	(18.1)	139	(18.7)	
2	140	(23.5)	198	(26.7)	
3+	240	(40.2)	309	(41.6)	
Oral contraceptive use					<0.01
Never	185	(31.0)	156	(21.0)	

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	Cases (*n* = *597*)		Controls (*n* = *742*)		*p* value
	n	**(%)**	***n***	**(%)**	
<60 months	242	(40.5)	332	(44.7)	
60+ months	170	(28.5)	254	(34.2)	
History of endometriosis					<0.01
Yes	63	(10.6)	33	(4.5)	
No	534	(89.5)	709	(95.6)	
Premenopausal hysterectomy					0.64
Yes	140	(23.5)	166	(22.4)	
No	457	(76.6)	576	(77.6)	
Age at menarche (years)					0.13
<12	137	(23.0)	197	(26.6)	
12+	460	(77.1)	545	(73.5)	
Menopausal status					0.09
Premenopausal	155	(26.0)	224	(30.2)	
Postmenopausal	442	(74.0)	518	(69.8)	
Hormone Therapy[a]					0.29
Ever use	111	(25.1)	115	(22.2)	
Never use	331	(74.9)	403	(77.8)	
First-degree family history of breast or ovarian cancer					<0.01
Yes	148	(25.8)	129	(17.4)	
No	449	(75.2)	613	(82.6)	
Smoking					0.30
Ever	267	(44.7)	311	(41.9)	
Never	330	(55.3)	431	(58.1)	
Body powder use					<0.01
Never use	223	(37.4)	349	(47.0)	
Genital use	260	(43.6)	252	(34.0)	
Non-genital use	114	(19.1)	141	(19.0)	
Tubal ligation[b]					0.11
Yes	214	(35.9)	298	(40.2)	
No	383	(64.2)	444	(59.8)	

	Cases (*n* = *597*)		Controls (*n* = *742*)		*p* value
	n	**(%)**	***n***	**(%)**	
Age at tubal ligation (years)[c]					0.13
<35	173	(80.8)	224	(75.2)	
35+	41	(19.2)	74	(24.8)	
Histologic subtype					
Serous	422	(70.7)			
Mucinous	30	(5.0)			
Endometrioid	66	(11.1)			
Clear cell	16	(2.7)			
Other	37	(6.2)			
Unknown	26	(4.4)			

[a] Restricted to postmenopausal women

[b] Defined as having a tubal ligation >2 years prior to reference age. Women whose age was within 2 years of their reference age (*n* = 2) were excluded

[c] Among women who have had tubal ligation

Table 2

Odds ratios for the associations between epithelial ovarian cancer and tubal ligation by age at tubal ligation and by histologic subtypes, AACES

	Cases		Controls		Minimally adjusted OR[a]	95% CI	Fully adjusted OR[b]	95% CI
	Prior tubal ligation		Prior tubal ligation					
	n	*n* (%)	*n*	*n* (%)				
Overall	597	214 (35.9)	742	298 (40.2)	0.76	0.61, 0.96	0.88	0.68, 1.14
Age at tubal ligation								
No tubal ligation		383 (64.2)		444 (59.8)	1.00	Referent	1.00	Referent
Age <35		173 (29.0)		224 (30.2)	0.83	0.65, 1.07	0.98	0.74, 1.29
Age 35+		41 (6.9)		74 (10.0)	0.56	0.37, 0.85	0.64	0.41, 0.98
Serous	422	164 (38.9)			0.88	0.68, 1.13	0.94	0.71, 1.24
High grade	407	161 (39.6)			0.91	0.70, 1.17	0.95	0.71, 1.25
Low grade	15	3 (20.0)			0.45	0.12, 1.72	1.16	0.23, 5.84
Non-Serous[c]	175	50 (28.6)			0.55	0.38, 0.81	0.74	0.49, 1.13
Mucinous	30	10 (33.3)			0.71	0.32, 1.59	0.87	0.36, 2.12
Endometrioid	66	8 (12.1)			0.19	0.09, 0.40	0.31	0.14, 0.70
Clear Cell	16	8 (50.0)			1.32	0.48, 3.64	1.84	0.58, 5.82
Other/Unknown	63	24 (38.1)			0.84	0.48, 1.45	0.91	0.49, 1.67

[a] Adjusted for reference age (continuous) and study site

[b] Adjusted for reference age (continuous), study site, and parity (0, 1, 2, 3+)

[c] Includes mucinous, endometrioid, clear cell, other, and unknown subtypes

Table 3

Studies of tubal ligation and EOC risk by histologic subtypes, summary of relative risk findings

	Study design	Population characteristics	Total	Serous	Mucinous	Endometrioid	Clear Cell
AACES	Population-based case-control	AA women	0.88	0.94	0.87	0.31	1.84
Million women study (Gaitskell [3])	Prospective cohort	UK women aged 50+	0.80	0.84	0.99	0.54	0.55
Ovarian Cancer Cohort Consortium (Wentzensen [9])	Meta-analysis of 21 prospective cohort studies	Women in North America, Asia, and Europe	0.82	0.91	1.01	0.60	0.35
Denmark (Madsen et al. [5])	Population-based case-control	Danish women	0.87	0.92	1.25	0.66	1.03
Nurses' Health Study and Nurses' Health Study II (Rice et al. [6])	Two prospective cohorts	US female nurses	0.75	0.89	0.60	na	na
New England Case-Control Study (Rice et al. [7])	Case-control	Women in Boston, Eastern MA, and NH	0.82	0.93	0.47	0.46	0.87
Ovarian Cancer Association Consortium (Sieh [8])	Meta-analysis of 13 population-based case-control studies	Women in Australia, Canada, Denmark, Germany, and USA	0.71	0.81	0.68	0.48	0.52
Meta-analysis (Rice et al. [10])	Meta-analysis of 30 studies of various designs	Women in North America, Asia, Australia, and Europe	0.70	0.75	0.88	0.45	0.72
Austrailian ovarian cancer study (Nagle [13])	Population-based case-control	Australian women	na	na	na	0.4	0.7
Denmark (Kjaer [17])	Population-based cohort	Danish Women with Previous Tubal Ligation	0.82	0.72	1.49	na	na
Hawaii and Los Angeles (Tung et al. [18])	Population-based case-control	Women in Hawaii and Los Angeles	0.7	0.8	0.9	0.2	0.5
Delaware Valley (Modugno [19])	Population-based case-control	Delaware valley women aged 20–69	0.54	0.51	0.34	0.46	na
WHO collaborative study of neoplasia and steroid contraceptives (Rosenblatt and Thomas [20])	Hospital-based case- control	Women in Australia, Chile, China, Israel, Mexico, the Phillipines, and Thailand	0.71	0.98	0.88	0.21	0.33