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Past chlamydial infection is not associated with primary fallopian tube carcinoma

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ABSTRACT

We conducted a retrospective seroepidemiological study to evaluate the relationship between past chlamydial infection and primary fallopian tube carcinoma (PFTC). Postoperative serum samples were drawn from 79 consecutive patients treated for PFTC in 1985–2000. For each case two controls were selected. Serum samples were analysed for IgG antibodies to different *C. trachomatis* serotype pools and to *C. pneumoniae*. Seropositivity in general or serum antibody levels to different *C. trachomatis* serovars or *C. pneumoniae* did not differ between PFTC patients and controls. The lack of association between anti-chlamydial antibodies and PFTC suggests that past chlamydial infection does not play a role in the etiopathogenesis of PFTC. However, because chlamydial infection is common at young age and PFTC develops decades later, we cannot definitively exclude the possibility that *C.trachomatis* contributes to the development of PFTC.

1. Introduction

Primary fallopian tube carcinoma (PFTC) is a rare but aggressive disease, comprising 0.1–1.1% of female genital malignancies.[1] The age-adjusted annual incidence in Finland has increased from 1.2 per 1,000,000 women in 1953 to 5.4 per 1,000,000 women in 1997.[2] The incidence has increased especially among women in higher social classes and among those living in urban areas.[2] The aetiological factors are largely unknown, but may be similar to those of ovarian cancer.

Chlamydia trachomatis infection is the most common sexually transmitted bacterial infection (STI),[3] causing salpingitis and pelvic inflammatory disease (PID).[4,5] *Chlamydiae* are common intracellular bacteria and can cause chronic or persistent infections.[6] Chronic infections may predispose to malignant growth.[7] *C. trachomatis* has already been linked to cervical carcinoma.[8,9] History of PID has been linked to ovarian carcinoma.[10–12] Thus, an association between *C. trachomatis* and PFTC is biologically plausible. The purpose of this study was to evaluate the role of *C. trachomatis* in PFTC.

2. Patients and methods

The study population consisted of 79 consecutive patients treated for PFTC at the Department of Obstetrics and Gynaecology, University Hospital, Helsinki, between 1985 and 2000. Data were collected by systematic chart review. The patients had not received chemotherapy prior to surgery. Staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) criteria. Pelvic and

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para-aortic lymphadenectomy was performed whenever possible. Stage, grade, histological findings, tumour size, and size of the residual tumour were recorded. Serum samples were drawn at a median of 36 d (interquartile range 28–55 d) after primary surgery. For each case, two controls were selected randomly from women matched for age at serum sampling (±5 years), and who had no cancer diagnosis. For the five youngest patients the age criterion had to be somewhat relaxed due to lack of suitable controls. Because two blood samples were drawn from the same control subject by mistake, two cases had only one control. Thus, the total number of controls was 156. Ninety-one serum samples were from control patients from the Helsinki City Maternity Hospital, operated for a benign gynaecological disease. Sixty-one control archival serum samples were from patients coming to an examination for a benign colon disease (30 controls) or were female employees at Helsinki University Hospital (35 controls). The time periods were on average 4 years apart. Collection of control serum samples was performed with the approval of the Ethics Committee of the Department of Obstetrics and Gynaecology, Helsinki University Hospital. All samples were stored at −25 °C and analysed simultaneously.

The mean ages of the patients and controls were 61.2 years (range 40.0–82.8 years) and 61.5 years (range 24.5–87.0 years), respectively. Clinical and histopathological characteristics are shown in Table 1.

Table 1 – Clinical characteristics of 79 patients with primary fallopian tube carcinoma (PFTC)

Parameter	*n*	(%)
Stage		
I	11	(14)
II	12	(15)
III	40	(51)
IV	15	(19)
No data	1	(1)
Grade		
1	7	(9)
2	20	(25)
3	45	(57)
No data	7	(9)
Histological type		
Serous	57	(72)
Anaplastic	13	(16)
Carcinosarcoma	5	(7)
Endometrioid	1	(1)
Clear cell	1	(1)
Unknown	2	(3)
Tumour size (cm)		
<2	7	(9)
2–5	14	(18)
5–10	19	(24)
>10	36	(45)
No data	3	(4)
Residual tumour size (cm)		
None	28	(35)
<0.5	2	(3)
0.5–1.0	1	(1)
1–2	4	(5)
>2	30	(38)
Peritoneal carcinosis	10	(13)
No data	4	(5)

2.1. *Chlamydia* serology

Chlamydia trachomatis- and *C. pneumoniae*-specific IgG antibodies were assayed by a micro-immunofluorescence method (MIF)[13] using pooled serovars (GFK, CJHI, BED) of *C. trachomatis* (Washington Research Foundation, Seattle, WA, United States of America (USA)) and serovar Kajaani 6 for *C. pneumoniae* as control antigens, and fluorescein isothiocyanate (FITC)-conjugated anti-human IgG (Kallestad, Chaska, MO, USA) as conjugate.[13] The serum samples were analysed at two-fold dilutions for *C. trachomatis* and at four-fold dilutions for *C. pneumoniae*. Titres of $\geqslant$16 were considered positive for *C. trachomatis*. Titres of $\geqslant$32 were considered positive for *C. pneumoniae*.

2.2. Statistical analysis

A statistical power of 80% was planned to detect a hypothesised difference at a two-tailed significance of $P < 0.05$. The power calculations were based on a hypothesised odds ratio (OR) of 2.8[8] and a prevalence of *C. trachomatis* antibodies of 14% in the general population.[14] Thus, 135 controls would be needed for the cases. Univariate and multivariate ORs with 95% confidence intervals (CIs) and two-sided *P*-values were estimated by conditional logistic regression.[15] Statistical calculations were performed using Stata 8.0 (Stata Corp, College Station, Tex) and SPSS 12.0 (SPSS Inc, Chicago, III) software.

3. Results

Seropositivity to the different *C. trachomatis* serovars and to *C. pneumoniae* in PFTC patients varied from 13.9% to 21.5%. In control subjects seropositivity varied from 10.3% to 21.8% (Table 2). The overall prevalence of *C. trachomatis* IgG antibodies to one or more serotype pools in PFTC patients and controls was 20% and 16%, respectively ($P = 0.42$). Serum IgG antibodies to the different *C. trachomatis* serovars or to *C. pneumoniae* were not associated with PFTC (Table 3). The presence of serum IgG antibodies to more than one serotype pool did not increase the risk of PFTC (Table 4). The study population was divided into age quintiles to study the effect of age on seropositivity, but again there was no correlation. However, patients with elevated *C. trachomatis* IgG titres to serotypes BED were younger than control subjects, 39 years versus 56 years ($P = 0.038$). When comparing PFTC patients and con-

Table 2 – Seropositivity to different *chlamydia trachomatis* serovars and to *chlamydia pneumoniae* in PFTC (*N* = 79) and control patients (*N* = 156)

	Cases, *n* (%)	Controls, *n* (%)	
C. trachomatis			
CJHI	13 (16)	17 (11)	$p = 0.2$
GFK	13 (16)	23 (15)	$p = 0.7$
BED	11 (14)	16 (10)	$p = 0.4$
C. pneumoniae	17 (21)	34 (22)	$p = 0.9$

Table 3 – Odds ratios calculated by conditional logistic regression analysis of PFTC associated with different *chlamydia trachomatis* serovars and with *chlamydia pneumoniae*

	Odds ratio	95% CI[a]
Chlamydia trachomatis		
CHIJ	1.6	0.7–3.5
BED	1.4	0.6–3.2
GFK	1.1	0.5–2.4
Chlamydia pneumoniae	1.0	0.5–1.9

a CI = Confidence interval.

trols, a trend towards elevated *C. trachomatis* IgG antibody titres to one or more serotype pools was seen among younger PFTC patients, whereas such trend was not seen among young controls, but this did not reach statistical significance ($P = 0.115$). Stage, histology or grade showed no association with seropositivity to *C. trachomatis* or *C. pneumoniae* and PFTC.

4. Discussion

This study is the first of an association between exposure to *C. trachomatis* and subsequent PFTC. The potential role of specific infectious agents as risk factors of PFTC is unknown. There have been some case reports of tuberculous salpingitis being a possible promoter of PFTC.[16] No evidence was found of the role of past history of chlamydial infection as a risk factor of PFTC. Thus, the results of this study were somewhat disappointing and unexpected. *C. trachomatis* is an intracellular bacterium and a major cause of salpingitis and PID. PID may lead to pyosalpinx, sactosalpinx, fallopian tube adhesions and obstruction, leading to ectopic pregnancy or tubal factor infertility.[17,18] One of the mechanisms by which chlamydia may be involved in carcinogenesis is through chronic persistent inflammation. Inflammation involves rapid cell division, DNA repair, oxidative stress, and high tissue concentrations of cytokines and prostaglandins, all of which can play a role in carcinogenesis.[19] Another important factor in carcinogenesis may be the anti-apoptotic effect of chlamydia.[20] Koskela and colleagues[8] have published sero-epidemiological evidence that infection with *C. trachomatis* confers an increased risk of subsequent development of invasive squamous cell carcinoma of the uterine cervix. The presence of serum IgG antibodies to serotype G increased the risk 6.6-fold. In addition, antibodies to more than one serotype tended to further increase the risk.[9] A number of investigators have found an elevated risk of ovarian carcinoma associated with a past history of PID.[10,11,19] Risch and Howe found an increased risk of ovarian carcinoma among women who had prior PID (OR 1.5).[11] The relationship between PID and ovarian carcinoma was strongest in women who had had PID at an early age, and in nulliparous or infertile women. The risk of ovarian cancer increased with the number of PID episodes. In contrast, Parazzini and colleagues found no link between ovarian carcinoma and history of PID.[21] However, cancer incidence correlations suggest common aetiological factors for cervical and ovarian cancer.[22] Furthermore, tubal ligation and hysterectomy protect against ovarian cancer, supporting the theory of ascending aetiological factors.[23] In the present study the risk of PFTC was not increased among those with chlamydial antibodies. This is difficult to explain. If there is an inflammatory agent ascending from the cervix to the ovaries, one would expect to see an association with fallopian tube carcinoma.

Data on the natural history and kinetics of *C. trachomatis* antibodies are limited. Puolakkainen and colleagues showed that *C. trachomatis* IgG antibodies measured by means of an indirect immunofluorescence technique persisted at stable levels in 43% of the women involved for up to 6 years; 43% of the women showed a decrease in IgG titres, and 13% showed an increase.[24] Chlamydial infections are rare among older women. In the present study, the mean age of the patients was 61.2 years. Chlamydial IgG antibodies were measured by MIF, which is considered the gold standard.[22] It is not known whether the negative results in the present study can be explained by decreasing serum chlamydial antibody titres. There are no studies on the possible protective effect of tubal ligation or hysterectomy on PFTC. If tubal ligation does not protect women from PFTC, this would support the negative results of the present study.

In conclusion, the presence of serum anti-chlamydial antibodies was not associated with PFTC. However, because chlamydial infection is common in young women and PFTC develops several decades later, one cannot exclude the possibility that it contributes to the development of PFTC.

Conflict of interest statement

None declared.

Table 4 – Risk by number of positive *C. trachomatis* serotype pools in PFTC patients and controls, univariate analysis

	Percent positive				
Number of serotype pools	Cases *n* (%)	Controls *n* (%)	Odds ratio	95%CI	*p*-value
0	63 (80)	131 (84)	1.0		
1	3 (4)	5 (3)	1.2	0.3–5.4	0.7
2	5 (6)	9 (6)	1.1	0.4–3.6	0.8
3	8 (10)	11 (7)	1.5	0.6–3.9	0.4
Total	79 (100)	156 (100)			

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