

Discussion

Of these 11 women with perihepatitis or diffuse peritonitis, nine had excellent serological evidence of acute recent chlamydial infections. Five of the patients had no evidence of gonococcal infection. The age, sexual activity, symptoms, and the laparoscopic findings typical of Fitz-Hugh-Curtis syndrome in three of the women suggested that a genital tract infection may have spread to the peritoneum. Chlamydiae, increasingly found to be responsible for various non-gonococcal sexually transmitted diseases in men and women, are plausible candidates for this type of infection. Five women in our series had evidence of past or current gonococcal infection. Local genital tract infections with more than one agent are frequent,⁹ and the invading organisms are not necessarily identical with those cultivated from the cervical mucosa. Unless agents are cultured directly from the inflamed peritoneum, it is impossible in such cases to determine whether the peritonitis may have been due to one or the other agent or both. Nevertheless, the extremely high *C trachomatis* antibody titres in many of our patients was suggestive of an aetiological association.

Only two of our 11 patients with peritonitis had signs of salpingitis on gynaecological examination. If the assumption that our patients had genitally acquired infections is correct, probably the infectious agent ascending from the cervical canal often reaches the peritoneum without causing salpingitis. Equally, perihepatitis does not seem to be an invariable feature of the disease. Two patients (cases 1 and 4), both of whom had very high titres to chlamydiae, had neither salpingitis nor perihepatitis. These two cases show that evidence for genitally transmitted infections should be sought in all women with apparent "spontaneous" peritonitis.

Four of the nine women with signs of chlamydial infections were not treated with tetracycline but with antibiotics not thought to be active against chlamydiae (two with ampicillin, two with spectinomycin), yet their disease subsided within one to two weeks. Nevertheless, one patient (case 2) continued to be ill for weeks when taking ampicillin alone, but rapidly improved after receiving tetracycline. Hence chlamydial peritonitis may follow a benign course, but tetracyclines can accelerate recovery.

In sexually active women with various partners multiple *C*

trachomatis antibody types may be found. Studies on monkeys¹⁰ and experience with patients attending venereal-disease clinics showed that the original infecting type was often recalled after infection with a new type, and in the screening microimmuno-fluorescence test or with IgG conjugate the highest antibody titre was found against a previous immunotype rather than the current infecting type.⁷ If the organism cannot be isolated the use of the IgM conjugate helps to determine the current infecting type when multiple antibody types are present. Thus in three of our patients (cases 5, 6, and 8) the antibody type measured with IgM conjugate was probably the current infecting type.

We hope that our report will encourage clinicians and microbiologists to look for direct evidence of chlamydial infections in similar cases by culturing the agents from the inflamed sites.

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Contraceptive steroids and breast cancer

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Summary and conclusions

The prognosis and pathological findings in 44 patients with breast cancer who had taken contraceptive steroids during the year before diagnosis were compared with those in 44 controls matched for age and parity. No significant differences between the two groups were

found in the histological features of the tumour or extent of axillary lymph-node disease. In patients with axillary node disease the recurrence rate in the controls was significantly higher than in the study group and more of the control patients had died.

It is concluded that oral contraceptives have no untoward effect on the prognosis of breast cancer.

Introduction

It has been suggested that steroidal oral contraceptives may affect the pathogenesis and rate of growth of breast cancers. Most of these agents contain small amounts of oestrogenic steroids and it is widely believed that low doses of oestrogen may accelerate the rate of growth of breast tumours, though this assumption is based only on experiments with laboratory animals and on a few anecdotal cases concerning women with the disease.¹⁻³ Indeed, a trial using small doses of stilboestrol

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(1.5 mg) to treat postmenopausal women with advanced breast cancer showed no evidence of enhancement of growth.⁴ Nevertheless, many surgeons believe that patients who are using steroidal contraceptives when they present with breast cancer have a poor prognosis, and it is almost universal practice to advise women who have had breast cancer not to use these products.^{5, 6}

Most studies on the relation between steroidal contraceptives and breast cancer have been concerned with whether the incidence of the disease is increased in premenopausal women who have taken these products. Vessey *et al.*,⁷ in a study of premenopausal patients, found no evidence that the use of oral contraceptives was associated with an increased incidence of breast cancer, but they suggested that many years of observation would be required before the question of whether there was a positive relation between oral contraceptives and breast cancer was finally resolved. Fasal and Paffenbarger⁸ reported an increased incidence of breast cancer in women who had been taking the products for between two and four years.

The question whether taking contraceptive steroids affects the progress of established breast cancer has not been fully investigated. Fechner⁹ described the pathological and histological findings in five patients with breast cancer who had been taking oral contraceptives and compared them with 11 controls. He noted no morphological differences between tumours in the two groups of patients, but the analysis and follow-up were limited. Vessey *et al.*¹⁰ stated that histological review of the material excised from their patients with breast cancer who had taken contraceptive steroids was unrewarding, but they gave no details of the analysis.

Our paper primarily concerns the pathological findings in 44 patients with breast cancer who had been taking contraceptive pills during the year before diagnosis and in 44 matched controls. Preliminary results on recurrence and survival rates are also described.

Patients and methods

The study group comprised patients who either were using steroidal contraceptives when cancer was diagnosed or had been taking these products during the previous year. One year was chosen because the reported doubling times of breast tumours are such that the lesions must have been present in these patients for at least that length of time. The mean duration of contraceptive use was four years (range three months to 11 years) and all patients had been using products containing 50 µg of oestrogen or less. At diagnosis contraceptive steroids were withdrawn and patients were advised not to take them again. Forty-four patients who stated that they had never used contraceptive steroids served as controls. They were matched for age and parity with patients in the study group. All patients had presented to the Breast Unit at Guy's Hospital during 1970-6. Comparisons between the two groups were made in respect of related history; clinical findings at diagnosis; histological findings in the primary tumour (tumour type, grade, lymphoplasmacytic reaction, lymphatic disease); number of axillary nodes affected and degree of sinus histiocytosis in unaffected nodes; and recurrence rate and survival.

Tumour size was measured clinically at the patient's first attendance

TABLE I—Clinical features in study group and controls. Groups were matched for age and parity. Ranges given in parentheses

	Study group	Controls
No of patients	44	44
Mean age (years)	37 (25-55)	38 (25-49)
Mean No of pregnancies ..	2 (0-5)	2 (0-5)
No of nulliparae	6	5
No of patients with family history of breast cancer:		
In mothers	9	0
In sisters	1	1
Mean age (years) at first pregnancy	24 (18-32)	26 (17-36)
Mean age (years) at menarche ..	13 (10-17)	13 (10-18)
Median duration of history of breast cancer (weeks) ..	5.5 (1 day-208 weeks)	3.0 (1 day-500 weeks)

TABLE II—Clinical assessment of breast tumours at first examination in study group and controls, according to TNM classification

	T0	T1	T2	T3	T4	Tumour diameter (maximum)		N0	N1a	N1b	M1
						Mean (cm)	Range (cm)				
Study group	1	25	17	1	0	2.1	0-6	40		4	1
Controls	2	20	20	1	1	2.3	0-6.5	37		7	1

TABLE III—Histological types of primary tumour in study group and controls. Figures are numbers of patients

Histological type of tumour	Study group	Controls
Infiltrating duct	32	33
Infiltrating lobular	4	2
Infiltrating duct and lobular ..	1	0
Medullary with lymphoid stroma	0	1
Mucoid	3	1
Tubular	2	2
Intracystic papillary	0	1
In-situ intraduct	2	3
In-situ lobular	0	1

and the original slide of the biopsy specimen of the breast tumour was used to define the histological characteristics. The tumours were graded by the method of Bloom and Richardson.¹¹ The degree of lymphoplasmacytic reaction was assessed subjectively and graded 0-3, 3 representing the greatest reaction. In each case in which radical mastectomy was the primary treatment all detectable lymph nodes were dissected out in the unfixed specimen and examined microscopically for secondary deposits. Sinus histiocytosis was assessed using the criteria described by Black and Speer¹² and modified by Cutler *et al.*¹³ The pathological examination was undertaken without knowledge of whether the patient was in the study or control group. After surgery all patients were examined three-monthly for three years, then six-monthly until the fifth postoperative year, and thence yearly. No patients were lost to follow-up.

Results

Related history—Clinical features of patients in the two groups are compared in table I. The only notable difference between the two groups was the excess of patients in the study group whose mothers had had breast cancer. No obvious reason could be found to explain this considerable difference.

Clinical findings—Table II shows the clinical findings at first examination, categorised according to the TNM classification. Thirty patients in each group were treated by radical mastectomy, and those with deposits in lymph nodes were given postoperative radiotherapy to the node fields only. Twenty-three patients (11 in the study group and 12 controls) were treated initially by wide excision followed by radiotherapy to the residual breast and node fields. This treatment was chosen by random sample as part of a clinical trial comparing radical mastectomy with wide excision.¹⁴ Five patients (three in the study group and two controls) who had advanced tumours at first diagnosis received radiotherapy to the breast and node fields without surgical intervention other than an initial biopsy. The study and control groups were comparable in terms of clinical presentation.

Histological findings—Table III shows the histological types of the primary tumour. Tumour grade, degree of lymphoplasmacytic reaction round both the tumour and related blood vessels, and the number in each group with local lymph-node disease are shown in table IV. There were no appreciable differences between study and control groups in any of the histological characteristics.

Axillary nodes—Data from examination of the axillary nodes in patients and controls who had a radical mastectomy are shown in table V. The differences between the two groups in the number with axillary node disease and the mean number of nodes per positive axilla were not significant.

Recurrence and survival—The extent of nodal infiltration was greater in controls than in the study group, and we allowed for this when comparing recurrence and survival rates. The rates were therefore calculated separately for patients in pathological stages 1 and

TABLE IV—Related histological features of primary tumour in study group and controls. Figures are numbers of patients

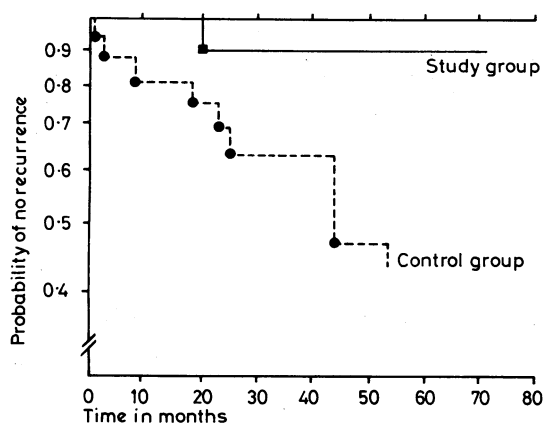
	Tumour grade				Lymphoplasmacytic reaction†				Perivascular lymphoplasmacytic cuffing*				Lymphatic invasion
	I	II	III	In situ	0	1	2	3	0	1	2	3	
Study group	9	22	10	3	19	14	10	1	24	14	5	1	8
Controls	7	22	12	3	15	17	10	2	23	14	7	0	8

*Graded 0-3 in ascending order of severity.

TABLE V—Data from pathological examination of axillary lymph nodes in 30 patients in study group and 30 controls who underwent radical mastectomy

	Study group	Controls
Total No of nodes examined	427	394
No of patients with axillary node disease	13	16
Mean No of positive nodes per positive axilla	2.3	3.4
Proportion of unaffected lymph nodes showing moderate and severe sinus histiocytosis	2/30 (7%)	2/27 (7%)

2. There was no significant difference between the two groups in the recurrence rate among patients with pathological stage 1 tumours. The figure shows a life-table analysis of the recurrence rate in patients with pathological stage 2 tumours. The recurrence rate was significantly higher in controls than in the study group (log-rank test: $\chi^2=5.416$; $0.025 > P > 0.01$). So far seven patients (16%) in the control group and four (9%) in the study group have died. This difference is not significant nor is any significant difference apparent when stage is taken into account.



Life table showing recurrence rates in patients in study and control groups with pathological stage 2 tumours of breast.

Discussion

No appreciable difference in tumour size, histological type, grade of malignancy, or lymphoplasmacytic infiltration was found in women who had taken contraceptive steroids during the year before diagnosis when compared with a control group matched for age and parity. Moreover, the degree of sinus histiocytosis in unaffected lymph nodes was similar. Each of these features is considered to be correlated with prognosis. Contrary to expectation, fewer patients in the study group had

axillary lymph-node infiltration and the mean number of affected nodes in these patients was less than that of the controls, a feature also noted by Fechner.⁹ The difference was not significant. One interesting and unexplained finding was that the mothers of nine patients in the study group (20%) had had breast cancer compared with none in the control group. This difference merits further investigation in a larger series.

The numbers were too small and the follow-up was too short to attach much importance to the significant difference in recurrence rates in patients with pathological stage 2 disease. In addition, the patients with stage 2 tumours in the control group had more affected nodes, and this might have influenced their recurrence and survival rates. Nevertheless, our findings suggest that recurrence rate and mortality are unlikely to be increased in patients who have taken contraceptive pills before breast cancer is diagnosed—indeed, the opposite seems to be the case.

The assumption that contraceptive steroids exert a deleterious effect on the progress of breast cancer has not been substantiated. If our findings are supported by larger studies, in which the chances of detecting real differences would be greater, it might be argued that taking contraceptive steroids might improve prognosis in premenopausal women with breast cancer.

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