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A case control study of carcinoma of the ovary

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SUMMARY There is increased concern over the apparent rise in incidence of patients with carcinoma of the ovary, particularly in older women. In an attempt to identify aetiological factors 300 women with cancer of the ovary diagnosed at laparatomy were studied. A questionnaire was administered to these women (Group A) and to two control groups matched by age. The first control group (Group B) comprised patients in a gynaecological ward and the second (Group C) comprised women on the lists of general practitioners living in the same areas as the index cases. Differences were shown in the obstetric history of the three groups. Fewer of the women in Group A had married and fewer had ever been pregnant and the family size was smaller. Significantly fewer of them recollected an attack of mumps, measles, or rubella. In all, only 81 of the whole series of 900 had used oral contraceptives, 19 of Group A and 31 in each of the control groups, a statistically significant deficiency. These findings support those of other investigations and suggest lines of further inquiry.

During the past decade there has been increased interest in the epidemiology of cancer of the ovary. This condition causes over 3000 deaths each year in the United Kingdom and is a more common cause of death than cancer of the cervix. Since 1950 the mortality rate both in the United Kingdom and the United States of America has steadily increased. Detailed analysis of the figures for England and Wales (Registrar General) show that the main increase in death rates for carcinoma of the ovary was in those of 65 years and older (Figure), in contrast to cancer of cervix uteri, for which the rates in this age group appear to be declining.

West (1966) reported a study of 175 women with ovarian cancer, compared with the same number of patients with non-malignant conditions of the ovary. He commented that the study by Dorn and Cutler (1959) showed that there was a higher morbidity among never-married women. The only positive finding of West was of a lower incidence of mumps-parotitis among the patients with malignant ovarian tumours. Wynder *et al.* (1969) also studied 150 women with ovarian cancers and compared them with 300 age-matched hospital controls, 25% of whom had cancer of other sites. He did not find a relationship with pregnancy or marital state, but he did find that the women with ovarian cancer had a less frequent history of mumps than his control groups. The women with ovarian cancer more frequently had an earlier menarche, heavier periods, and dysmenorrhoea. But apart from this the results were negative. In 1974, Joly *et al.*, reported a study of over 400 women with suspected ovarian cancer admitted to one hospital between 1957 and 1965.

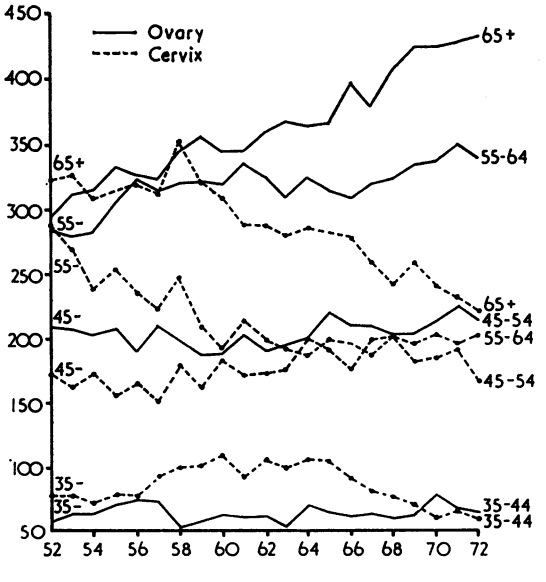

Figure *Death rates per 1 000 000 women from carcinoma of cervix (ICD 171) and carcinoma of ovary (ICD 175), 1952–72.*

They found there was a reduced number of pregnancies and lower parity in women suffering from ovarian cancer, and a higher risk among those who had been married but had not had children, than among single women with no children.

Method

The present study was a joint project of the Medical Women's Federation (MWF) and the 20 members of the Women's Visiting Gynaecologists Club (WVGC). Because of the limited membership, colleagues were co-opted to augment the number of cases; 17 centres contributed (Table 1). It was designed as a case control study and its aim was to identify factors in the personal history that might be of aetiological significance in the occurrence of carcinoma of the ovary. It was not possible to study environmental factors because of the uneven scatter of cases.

The diagnosis of primary carcinoma of the ovary was confirmed by the gynaecologists at laparatomy; subsequently a structured questionnaire was administered by the gynaecologist or another member of the medical staff. In approximately two-thirds of the patients the questionnaire was completed as soon as practical after operation; in the rest it was completed during treatment at one of three radiotherapeutic centres, usually within three months of operation.

The first control series (Group B) comprised postoperative patients currently in hospital. Their ages were within 2½ years of the index cases, and they were suffering from a gynaecological complaint other than an ovarian tumour or cyst. The cases from the radiotherapy centres were similarly matched with patients at that time in the hospital to which the centre was attached. Thirty-nine per cent of them had been admitted for perineal repair operations: 23% for abdominal hysterectomies, the remainder for a variety of conditions including 5% for treatment of various cancers and 5% for investigation of postmenopausal bleeding.

The second control series (Group C) comprised women whose ages were also within 2½ years of the index cases. They were obtained from the lists of general practitioners, domiciled in the same neighbourhood as the index cases. In fewer than 20 cases, area matching was not possible and the control was then obtained from a locality as nearly similar to the original domicile as could be arranged. They were interviewed either by the practitioner himself or a member of the MWF. The control was chosen by the practitioner searching his files under the initial of the surname of the index case and continuing until a patient within the required age group was found.

The eight-page questionnaire asked for details of identification, age, and residence. The height and the weight at 20 years and the heaviest known weight were recorded. A full occupational history was not taken but each woman was asked if she had ever worked in a factory; the husband's main occupation, and his current one if not retired, was also recorded. It also sought information about diagnostic *x* rays, acute infectious illnesses, chronic illnesses, operations, smoking, menstrual cycles, pregnancies, miscarriages, endocrine disorders and endocrine therapy including the contraceptive pill. Details of the operation and the pathology report were entered on the last page for index cases only.

Relative risks of ovarian cancer according to the presence (as compared with absence) of selected factors were calculated. Each set of controls was used in turn for this comparison. The analysis was performed using the method of matched controls (Mantel and Haenszel, 1959).

Table 1 *Centres contributing a group of 300 women with ovarian cancers*

No. of cases and centre	*Hospital cases*	*Radiotherapy centres*
21+		
London	34	71 (Chester Beatty Research Unit)
Bristol	50	36
10–20		
Cheltenham		8
Barnet		
Cambridge	57	
Carlisle		
York		
5–9		
Dorking		
Dundee		
Esher	25	
Newcastle		
<5		
Birmingham		
Brighton		
Littlehampton		
Lewisham	19	
Manchester		
Margate		
Total no. of cases	185	115

NUMBERS OF PAIRS BY PRESENCE OR ABSENCE OF FACTOR IN CASE OR CONTROL

Controls	*Cases*	
	Factor present	*Factor absent*
Factor present	a	b
Factor absent	c	d

Only those pairs in which the factor is present in one of the pair and absent in the other are considered. These are b and c in the diagram. The relative risk of ovarian cancer when the factor is present compared with when the factor is absent is c/b.

PATHOLOGICAL DIAGNOSIS

Histological sections or paraffin blocks were examined except in the cases of 11 patients for whom the sections or blocks were not available; however these were included in the series as the surgical operation report was consistent with the pathologist's report at time of laparatomy. Sections were stained with haematoxylin and eosin but occasionally Van Geissen and mucin stains were used. Ten cases were rejected as the surgical findings were indefinite ('frozen pelvis' or 'gross' malignant spread) and pelvic organs were not identified; the histology in these 10 cases was of carcinoma which could have developed from any one of the following primary sites: stomach and large bowel, uterine body, pancreas or bile duct; two were of classical Krunkenberg pattern. A further six cases were rejected because no pathological material was received and the reports from the hospital were inconclusive (Table 2).

Table 2 *Material in study*

Accepted	
By JMF	289
On other pathologists' report	11
Rejected	
By JMF not primary ovarian tumour	10
No histology report or material available	6
Total	316

Results

The tumours were classified (Table 3) as suggested by Fox (1970). This classification is based on the hypothesis that certain components of the mature ovary retain a competence to develop along the lines which are available to their tissue of origin. Table 3 also shows the age distribution at the time of interview. Few tumours were present in the younger age groups, the main incidence was in the decade between 45 and 54 years. Two hundred and seventy-five of the tumours were classified as those arising from germinal epithelium. Papillary cystadenocarcinoma, endometroid carcinoma, and cystadenocarcinoma were the most common. As a preliminary step, the experience of groups of women with tumours of different pathological types was compared. The five patients with tumours classified as clear-celled adenocarcinoma were grouped with the 70 women suffering from serous cystadenoma, making four groups of patients with tumours derived from germinal epithelium. The remaining 25 patients were grouped together, among whom there were seven separate pathological diagnoses. There were 10 granulosa cell tumours in this group.

The results of the analysis are shown in Table 4. The mean ages at interview did not show any statistically significant differences, although the mean age of the group of patients with endometroid cancer was the highest at 57·5 years, while that of the rather smaller group of mucinous cystadenoma was some eight years younger at 48·7. The main landmarks in the reproductive history including the proportion of women marrying and the mean number of pregnancies were similar. Nor did the experience of the five groups in relation to common infectious diseases, mumps in particular, and to diagnostic *x* ray of the trunk differ significantly. Significantly fewer ($P<0·05$) of the group suffering from papillary adenocarcinoma admitted to smoking but little reliance can be placed on this in a comparatively small series.

The five main pathological groups were therefore combined into one group of 300 women and their responses to the questionnaire were compared with the responses of the women in the two control groups. There were no significant differences in the mean heights of the three groups; Quetelet's index (W/H^2), a measure of obesity, was calculated for the weight at 20 years and for the heaviest known weight and it also showed no significant difference between groups.

Table 3 *Age distribution of tumours according to pathological type*

Tissue of origin	*Tumour type*	*Age (years)*					*Total*
		<44	45–54	55–64	65+	*All ages*	
Germinal epithelium	Papillary cystadenocarcinoma	12	31	28	22	93	
	Endometroid carcinoma*	11	18	22	22	73	
	Serous cystadenocarcinoma	15	27	16	12	70	
	Mucinous cystadenocarcinoma	10	12	10	2	34	
	Clear-celled adenocarcinoma	1	0	4	0	5	275
Sex cord mesenchyme	Granulosa celled tumour	1	1	3	5	10	10
Mesonephric origin	Mesonephroma	2	2	1	1	6	6
Germ cell origin	Dysgerminoma	1	0	0	0	1	
	Squamous carcinoma	1	1	1	0	3	
	Brenner	1	0	0	0	1	
	Mixed mesenchymal sarcoma	1	1	0	1	3	8
Non-specialised stroma	Fibrosarcoma	0	1	0	0	1	1
Total		56	94	85	65	300	300

*Including adenocarcinoma, columnar-celled, and cuboidal-celled carcinoma.

Table 4 *Comparison of experience of patients with different types of ovarian cancer (Group A)*

Details	*Pathological type*				
	Papillary cystadenocarcinoma	*Serous* cystadenocarcinoma*	*Endometrial carcinoma*	*Mucinous cystadenocarcinoma*	*Other tumours*
No. of cases	93	75	73	34	25
Mean age at interview (years)	55·9	52·7	57·5	48·7	52·8
Mean age at catamenia (years)	13·8	13·5	13·6	13·5	13·1
Mean age at birth of first child (years)	25·8	24·9	25·2	25·7	25·9
Irregular periods (%)	11	8	4	9	8
Mean age at menopause (years)	49·1	46·4	47·0	50·6	48·3
Percentage married	81	84	88	74	64
Mean no. of pregnancies	1·66	1·32	1·67	1·44	1·32
Positive history					
Of mumps, measles, chicken pox, or German measles (%)	87	84	85	82	100
Of mumps (%)	41	41	47	35	36
Of *x* ray of trunk (%)	53	53	42	50	48
Of smoking (%)	38	61	48	59	52

*Includes five clear-celled adenocarcinomas.

Smoking habits of each group were similar, approximately 50% of each group were current smokers. Their experience of major illness and endocrine disease—such as, diabetes or thyroid disease—was essentially similar. The three groups were well matched for age. Nor was there any significant difference in the age of catamenia, the menstrual history, the age of bearing the first child, or the age at menopause (Table 5) and approximately 90% of the women in each group claimed to have had regular periods with a cycle of 21–30 days.

Table 5 *Gynaecological history in the three groups (mean age at specific events)*

Mean age (years)	*Ovarian cancer (Group A)*	*Hospital controls (Group B)*	*GP controls (Group C)*
At interview	54·4 (300)	54·4 (300)	55·1 (300)
At catamenia	13·6 (300)	13·3 (300)	13·4 (300)
At birth of first child (parous women) (excludes miscarriages)	26·1 (175)	25·8 (263)	26·0 (235)
At menopause (natural)	47·8 (153)	48·9 (155)	48·6 (170)
At menopause (artificial)	41·2 (29)	42·8 (13)	42·6 (26)

Figures in brackets indicate number of women in category.

All the women were asked questions about *x* ray; approximately half the women in each group remembered an *x* ray investigation of the abdominal organs or the spine. There was no evidence that Group A had received more radiation than the others. More women in Group B had received hormones to regulate the periods or control hot flushes but the differences were not significant.

Differences, however, were shown in the obstetric history of these women: fewer of the women in Group A had married, fewer had ever been pregnant, and among those ever pregnant the mean number of pregnancies was lower (Table 6). When comparing the three it must be remembered that the women in Group B were selected from patients in a gynaecological ward of whom more than one-third had been admitted for treatment of uterine prolapse and other conditions which are often late complications of child bearing. However, this did not apply to Group C compared to whom the difference was still marked. Table 7 demonstrates that as well as a higher proportion of nulliparous women among those in Group A there was a marked deficit of women who had two or more children. There was little difference in the number of pregnancies terminating in miscarriage—20% among the women in Group A, 17% in Group B, and 15% in Group C. The relative risk of ovarian cancer among those

Table 6 *Marital and pregnancy history in the three groups (number and percentage of cases)*

Category	*Ovarian cancer (Group A)*	*Hospital controls (Group B)*	*GP controls (Group C)*
Ever married	243 (81·0%)	277 (92·3%)	269 (89 7%)
Never married	57 (19·0%)	23 (7·7%)	31 (10·3%)
Number of parous women*	186 (62·0%)	267 (89·0%)	240 (80·0%)
Mean no. of children (whole series)	1·25	2·17	2·12
Mean no. of children among women ever pregnant	2·10	2·46	2·70

*Includes miscarriages.

Table 7 *Number of children in the three groups*

No. of children	*Ovarian cancer (Group A)*	*Hospital controls (Group B)*	*GP controls (Group C)*
None	121 (40·3%)	35 (11·7%)	64 (21·3%)
1	64 (21·3%)	67 (22·3%)	53 (17·7%)
2	66 (22·0%)	97 (32·3%)	83 (27·7%)
3	32 (10·6%)	55 (18·3%)	48 (16·0%)
4 or more	17 (5·7%)	46 (15·3%)	52 (17·3%)

never pregnant is shown in Table 8. Those who had been pregnant appeared to have approximately one-quarter of the risk of developing the tumour.

Table 8 *Relative risks of ovarian cancer in those with history of pregnancy and pill use*

Risk factor	*Group B*	*Group C*
Ever pregnant	0·25 ***	0·27 ***
Used pill	0·59 (NS)	0·33 *

Fewer women in Group A could recollect an attack of mumps than could those in either control group, and the consequential reduction in the relative risk of developing ovarian cancer in the presence of a history of mumps was statistically significant for both groups (Table 9). However, for

Table 9 *Percentage recalling a common infectious disease*

Infectious disease	*Group A (300)*	*Group B (300)*	*Group C (300)*
Mumps	42·6	52·7	53·3
Measles	76·3	79·7	86·7
German measles	30·3	33·7	40·0
Chicken pox	50·3	54·3	59·0

measles, German measles, and chicken pox, Group A also recalled fewer attacks than did either control group and in the case of Group C the reduction in relative risk associated with these acute infections was statistically significant (Table 10). A separate analysis of those who recalled an attack of mumps before and after puberty failed to detect any significant differences.

Table 10 *Relative risks of ovarian cancer in those with positive history of infective disease*

Infection	*Group B*	*Group C*
Mumps	0·68 *	0·61 **
Measles	0·82 (NS)	0·47 ***
German measles	0·86 (NS)	0·62 **
Chicken pox	0·83 (NS)	0·66 *

In all, only 81 of the 900 women had used oral contraceptives, 19 of these were in Group A and 31 in each of the other two groups. The relative risk among those who had used the contraceptive pill was markedly reduced in both groups, being statistically significant at the 5% level for Group C (Table 8).

Each woman was asked if she had ever worked in a factory or an industrial concern. None gave a history of work in an asbestos factory; a number of women in the Bristol area had worked in chocolate or cigarette factories, two of the main industries in that area, but there was no evidence of an association of ovarian cancer with any particular industry where either the women or their husbands had worked. Social class could only be assessed among married women as full occupational histories had not been requested and the occupation (apart from employment in a factory of unmarried women) was not recorded. In each group the social class of the married woman showed the usual distribution with the majority of the women in social class III. There was no evidence of increased incidence of tumours in women of social class IV and V.

Discussion

The outstanding differences in the experience of the women who completed the questionnaire relate to marriage and pregnancy; 57 (19%) of the women in Group A compared with 23 (7·6%) and 31 (10·3%) of the women in the other two groups had not married (Table 6). Among those in Group A there were many more women (40%) who had never been pregnant, even after allowing for differences in marital state, and fewer had large families (Table 7). In common with other authors it was found that an attack of mumps was less common in patients suffering from ovarian cancer than in women in the control groups; to a lesser extent past attacks of measles, chicken pox, and German measles were also less often reported. This finding should be treated with caution. The number of siblings in the respondent's family was not recorded but the patients in Group A tended to have small families; small family size may be a familial characteristic and children in small families tend to have fewer attacks of infectious diseases.

Although this study does not provide any new clear-cut epidemiological leads to the factors associated with the development of this tumour, it at least provokes further speculation on its aetiology.

It is likely that aetiological factors operate for some years before a tumour presents. The incidence of carcinoma of the ovary increases rapidly after the early menopausal years (Dorn and Cutler, 1959; Doll *et al.*, 1966). Ovarian abnormalities, possibly hormonally induced, may be triggered or enhanced at the time of the menopause.

Ovarian carcinoma is more common in unmarried and childless women and there is a trend in these patients to have fewer pregnancies, which may reflect a lower fertility. Although this could be interpreted as suggesting that an ovary which later develops a malignant lesion will have functioned poorly throughout life, there is no evidence to support this and the hypothesis does not account for the higher risk of tumours in unmarried women. These facts may be more easily interpreted by

suggesting that childbearing protects against ovarian carcinoma. In contrast to breast cancer, youth at first pregnancy does not appear to reduce the incidence of ovarian cancer (Lingeman, 1974) although Joly *et al.* (1974) found there was a longer interval between marriage and conception in their patients compared with controls. It has been suggested that incessant ovulation without physiological rest periods may be a factor in ovarian carcinogenesis (Fathalla, 1972). Although this may be a factor, the rest from ovulation during pregnancy is short in relation to the years of fertile life and it is likely that additional factors are involved. However, it is of great interest that, although the numbers involved are small, there is evidence that the contraceptive pill, which prevents ovulation, may protect against ovarian cancer.

In our study there is no evidence of a higher incidence of thyroid disease in patients with ovarian cancer. This contrasts with the findings in other series (Bergren, 1964). No evidence was obtained regarding dietary iodine (Stadel, 1976) or Vitamin A (Zuckerman, 1962) in our series, but there is no reason to suspect any difference between index cases and controls.

Thus in our patients, as in other series, two protective factors against ovarian carcinoma appear to be operative, a history of pregnancy and of infection by mumps, measles, rubella, or chicken pox. It might have been expected that a virus affecting the ovary would increase the risk of initiating changes resulting in tumour growth therein. Also paradoxically mumps is thought to be associated with decreased fertility.

Future studies to confirm these findings and to elucidate the relationship of the contraceptive pill to ovarian carcinoma will be of great interest.

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References

Bergren, O. G. (1964). Female genital carcinoma and thyroid disease. *Acta obstetricia et gynecologica Scandinavica*, **42**, 425-437.

Doll, R., Payne, P., and Waterhouse, J. (1966). *Cancer Incidence in Five Continents. A Technical Report.* Springer-Verlag: Berlin.

Dorn, H. F., and Cutler, S. (1959). *Morbidity from Cancer in the United States.* Public Health Monograph No. 56. US Government Printing Office: Washington DC.

Fathalla, M. F. (1972). Factors in causation and incidence of ovarian cancer. *Obstetrical and Gynecological Survey*, **27**, 751-768.

Fox, H. (1970). Tumours of the ovary. *British Journal of Hospital Medicine*, **3**, 255-258.

Joly, D. J., Lilienfield, A. M., Diamond, E. L., and Bross, I. D. J. (1974). An epidemiologic study of the relationship of reproductive experience to cancer of the ovary. *American Journal of Epidemiology*, **99**, 190-209.

Lingeman, C. H. (1974). Etiology of cancer of the human ovary: A review. *Journal of the National Cancer Institute*, **53**, 1603-1618.

Mantel, N., and Haenszel, W. (1959). Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute*, **22**, 719-748.

Registrar General. *Statistical Review* (various dates). HMSO: London.

Stadel, B. V. (1976). Dietary iodine and risk of breast, endometrial, and ovarian cancer. *Lancet*, **1**, 890-891.

West, R. O. (1966). Epidemiological study of malignancies of the ovaries. *Cancer*, **19**, 1001-1007.

Wynder, E. L., Dodo, H., and Barber, H. R. (1969). Epidemiology of cancer of the ovary. *Cancer*, **23**, 352-370.

Zuckerman, S. (1962). *The Ovary*, volume 2, p. 291. Academic Press: New York.