EPIDEMIOLOGIC STUDY OF MALIGNANCIES OF THE OVARIES

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The descriptive epidemiology of ovarian malignancies, including age, marital status and race, is discussed. A study of 97 cases of ovarian malignancies compared to 97 cases of benign ovarian tumors is analyzed. Between most of the variables there are no statistically significant differences. Three variables, however, are of special importance: (1) history of x-irradiation, (2) history of internalization of hormones and (3) history of mumps parotitis. In the first 2 variables no statistically significant differences were found. The conclusion is that exposure to x-irradiation and the internalization of hormones did not influence the onset of ovarian malignancies. With the third variable a p value of 0.007 was encountered. The difference favored having mumps. The benign controls gave a history of mumps parotitis far more often than did the patients with ovarian malignancies. A causal association with a possible protective value is suggested.

THE EPIDEMIOLOGIC METHODS OF TODAY ARE far advanced. In the hope that they would reveal variables that are statistically associated with malignancies of the ovary and which may elucidate etiology thereof, I planned and executed this study. My reasons for being interested in ovarian malignancies are two-fold: (1) a careful survey of the literature failed to reveal any similar study and (2) there appears to be a secular increase in malignancies of the ovary. Case[3] has reported this in England and Wales (Fig. 1). Also, descriptive epidemiology has raised a number of interesting questions and has provided some clues as to cause.

VARIATION FACTORS

Age: The United States' 10-city morbidity survey of 1947[7] reveals an interesting age distribution. Age incidence curves for most forms of carcinoma morbidity sweep upward from youth until the end of the lifespan. Ovarian malignancies are one exception to this. Also, there appears to be a critical era near age 40, when the rate of increase is dramatic (Fig. 2). The morbidity rate increases until approximately age 70, when it declines. Similar morbidity rates have been reported by Clemmeson,[5] using data from the Danish cancer registry.

Marital status: The 10-city morbidity survey[7] reveals that never-married females have considerably higher morbidity rates than ever-married; this is especially true during the reproductive and menopausal years (Fig. 3).

Race: The same survey demonstrates morbidity differences between Caucasians and non-Caucasians (Fig. 2). The rate and magnitude of increase is almost identical in the 2 racial groups until about the age of menopause, when the non-Caucasian rate levels off and then declines around age 60 to 65. The rate for Caucasians continues to rise sharply for another decade.

Segi[10] has provided data from the Miyagi prefecture, located on the north-eastern Pacific coast of the Japanese Island of Honshu. His survey was guided by methods used in the U.S. 10-metropolis study. When Japan's mortality rates are compared with morbidity rates of the United States, it is clear that in Japan malignancies of the ovary are much less common than in the United States.

Because of the Japanese experience, R. L. Smith[11] has provided statistical data by comparing mortality rates with the Japanese of the United States and Hawaii. His method was to compare observed deaths among these people with that expected if they had been subject to the same mortality rates prevailing among the Caucasian and non-Caucasian populations of the United States. He concludes that the incidence of ovarian malignancies in Japanese of the United States and Hawaii is significantly less than the incidence in Caucasian females in the U.S.

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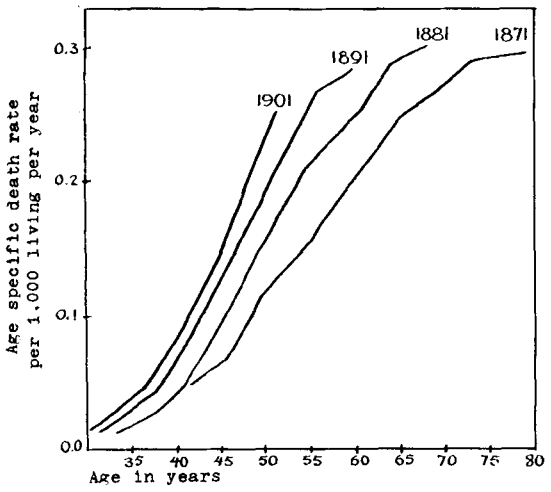

FIG. 1. Cohort Analysis of mortality from cancer of the ovary in England and Wales, 1911-1954, rates per 1,000 living population (adapted from Case[3]).

Socio-economic status: In the 10-metropolitan-area morbidity study of 1947[7] classification into socio-economic status was based entirely on family income and the results were inconclusive. In England and Wales, where socio-economic status is determined by occupation, this is not the case. Stocks[13] found a consistent trend in which standard mortality ratios were highest in professional classes and diminished directly with the socio-economic level.

Urban-rural differences: Data from several sources are not consistent. In the State of Iowa cancer study[2] of 1950 ovarian morbidity rates were higher in urban than rural especially after the years of reproduction, but only inconsistently before. The data from Connecticut[1] give higher morbidity rates in the metropolitan areas. In Denmark Clemmeson[4] found the same to be true after the age of menopause (based on 175 cases) but Stocks,[12] working with mortality data, found no consistent urban excess outside London.

Certain clinical facts concerning ovarian malignancies are striking. The signs and symptoms are few and, unfortunately, too late. The duration of symptoms has little effect on the prognosis. Patients found to possess advanced inoperable lesions have reported symptoms of only a few days' duration. The commonest symptoms are abdominal pain and abdominal enlargement. Concerning survival rates, there has been only modest progress in 2 decades of treatment.[15]

Wheelock[14] compared the prognosis of cases from 1901 to 1934 with that from 1935 to 1943. In the former years the 5-year survival rate was 15.5%. In the latter years it was 26.6%. He attributes this improvement to more aggressive surgery and to the therapeutic use of x-irradiation. All authors are agreed that exploration should be done if there is doubt as to whether the mass is an ovarian tumor or a fibroid.

This study attempts to answer 2 major questions: (1) What is the reason for the ap-

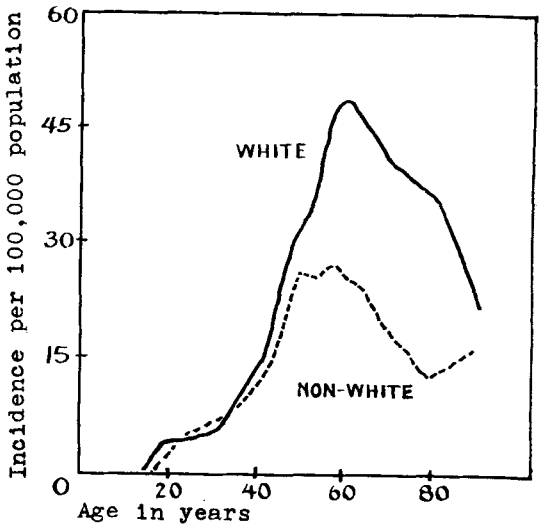

FIG. 2. Incidence rates (ovarian cancer) per 100,000 population, U.S. 10-city survey, 1947, by age and race.

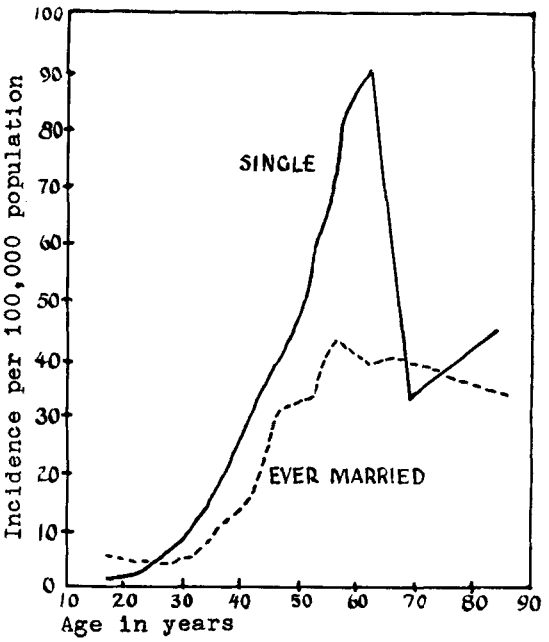

FIG. 3. Incidence rates (ovarian cancer) per 100,000 population. Ten-city survey, 1947, by marital status.

TABLE 1. Ovarian Malignancies and Benign Controls Lost to the Study

	Refused						Ineligible									
	By physician		By patient		By relative of patient		Wrong age		Wrong residence		De-ceased		None exists		Total	
Status	M*	C	M	C	M	C	M	C	M	C	M	C	M	C	M	C
Eligible but incomplete	4	4	8	9	3	0	0	0	0	4	11	0	—	0	26	17
Eligible, complete	—	—	—	—	—	—	—	—	—	—	—	—	—	—	97	91
TOTAL															123	108

* M stands for ovarian malignancies; C stands for benign controls.

parent secular increase in morbidity rates of cancer of the ovary? (2) What statistical associations can be found with cancer of the ovary and are they causal?

When considering this morbidity increase, one is concerned with the possible effect of diagnostic and therapeutic x-irradiation. Deringer and co-workers[6] produced ovarian tumors in hybrid mice by exposing them to 300 to 500 R. Can modern diagnostic techniques be duplicating this in human females?

Another question is the possible role of therapeutic hormones in producing ovarian malignancies. The work of Peckham[9] stimulated this interest. He and his co-workers produced hormonal imbalances in mice by transplanting the ovaries into the spleen. Since the liver destroys estrogens and venous drainage from the spleen passes through the liver, the ovarian transplants thus were exposed to continuous hypophyseal gonadotropic stimulation. Tumors were produced consistently that resembled the human granulosathecal-cell type.

MATERIALS AND METHODS

Study design: This is a controlled case-history study. The study population was defined as every case of malignancy of the ovary incident within a 50-mile radius of Boston within Massachusetts from January 1, 1959 until March 31, 1960. The only exclusions were cases older than 75 years at the time of diagnosis, those cases having a co-existent malignancy of another organ that was not metastatic from the ovary and recurrent cases. Thus, all cases included had their origin within the ovary. The date of incidence was defined as the day of surgery. Case finding was accomplished through the cooperation of the pathologists of most of the hospitals in the area outlined above. I interviewed each patient as soon as possible after the diagnosis was made. Some cases had to be excluded because of death following surgery or because the physician or patient refused to permit the interview (Table 1).

Definition of controls: The controls were selected from female hospital patients matched

TABLE 2. Analysis of Cases and Controls by Age Groups

Age groups	Patient		Benign control	
	No.	%	No.	%
20–24	0	0	1	1.1
25–29	3	3.3	2	2.2
30–34	2	2.2	3	3.3
35–39	6	6.6	4	4.4
40–44	9	9.9	19	20.85
45–49	17	18.65	19	20.85
50–54	17	18.65	17	18.7
55–59	15	16.5	11	12.1
60–64	12	13.2	6	6.6
65–69	8	8.8	6	6.6
70–74	2	2.2	1	1.1
75+	0	0.0	2	2.2
TOTALS	91	100.0	91	100.0

TABLE 3. Analysis of Cases and Controls According to Education

Education	Patient		Benign control	
	Absolute no.	%	Absolute no.	%
Elementary only	14	14.4	13	14.3
High school				
Began but did not complete	4	4.1	6	6.6
Completed	48	50.0	53	58.2
College				
Began but did not complete	19	19.6	10	11.0
Graduated	7	7.2	7	7.7
Postgraduate	4	4.1	1	1.1
Unknown	1	1.0	1	1.1
TOTAL	97	100.0	91	100.0

TABLE 4. Analysis of Interviews by Study Group and Religion

Study group	Protestant		Catholic		Hebrew		Other		Unknown		Totals	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Patient	39	48.1	46	52.8	9	64.3	1	50.0	2	50.0	97	51.6
Benign control	42	51.9	41	47.2	5	35.7	1	50.0	2	50.0	91	48.4
TOTALS	81	100.0	87	100.0	14	100.0	2	100.0	4	100.0	188	100.0

for age, residence and date of surgery. Each control was the next operated case of a benign ovarian neoplasm from the same hospital as the original case having the malignancy. These, likewise, were interviewed as soon after diagnosis as possible. Cases and benign-tumor controls came from 50 different hospitals in the Boston and greater Boston area.

Because the selection of controls is probably the most critical part of a case-history study, the cases and the controls were as comparable as possible in every respect except for the illness being investigated. A major assumption of this study is that the patient and the controls will remember or forget approximately to the same degree. Thereby, no bias because of memory defect will occur.

RESULTS

One hundred, twenty-three eligible cases with malignancy were located from January 1, 1959 to March 31, 1960. Twenty-six of these were not interviewed; reasons for this are shown in Table 1. The statistics of the malignant cases compare favorably with those with benign tumors with the exception that there were 7 deaths in the patient group and no deaths in the control group.

Comparison of patients and controls: Age is probably the most important single variable. Table 2 indicates that the larger percentages in the control group cluster around ages 40 to 59 whereas those in the patient group cluster about the ages 45 to 64.

Age matching, one of the criteria for controls, was done on a range of plus or minus 5 years. It is evident that within the scope of this study benign ovarian tumors tend to occur about 5 years earlier than malignancies (when considering the mode rather than the mean). This must be remembered when interpretations of differences are made. The mean ages for patients and benign controls are 52.6 and 50.0 years, respectively.

When analyzing the cases and the controls by hospital and medical care, I divided the hospitals into teaching, nonteaching, urban and suburban. The patients were classified as private and service. Proportionately, there were a few more controls than malignant cases taken from service care. This suggests that the cases and controls may not be quite comparable socio-economically.

Cases and controls were compared according to education (Table 3). Fifty percent of the patient group and 58.2% of the control group completed high school whereas 19.6% of the patient group and 11% of the benign-tumor group began but did not complete college. No other obvious differences occur between the 2 groups at various educational levels.

When studying the groups from the stand-

TABLE 5. Comparison of Cases and Controls by Marital Status

Marital status	Patient		Control	
	No.	%	No.	%
Married	63	69.2	74	81.3
Widowed	10	11.0	8	8.8
Single	15	16.5	7	7.7
Divorced	3	3.3	2	2.2
TOTAL	91	100.0	91	100.0

TABLE 6. Ovarian Malignancies Reported by Diagnosis and Eligibility*

Diagnosis	Eligible complete	Eligible incomplete	Total
Pseudo mucinous cystadenocarcinoma	23	4	27
Serous cystadenocarcinoma	16	6	22
Cystadenocarcinoma and adenocarcinoma	43	13	56
Carcinoma	6	1	7
Granulosa cell	5	1	6
Teratoma (malignant)	1	—	1
Dysgerminoma	1	—	1
Meso-meta-nephroma	1	1	2
Unclassified	1	—	1
TOTAL	97	26	123

* Hospitals of Greater Boston Area, January 1, 1959 to March 31, 1960.

TABLE 7. Results of Variables Measured by Interview for Cases of Ovarian Malignancies and Controls

Variable	Scale used*	Significance test used†	No. of matched pairs	P level	Mean values for internal data	
					Patient	Benign control
Duration of marriage (yr.)	I	t	67	>0.3	26.1	23.1
Age at menarche (yr.)	I	t	92	>0.3	13.0	13.1
Menstrual cycle (days)	I	t	86	>0.3	28.4	29.1
Menstrual irregularity	O	Si	86	0.04		
Duration of period (days)	I	t	90	>0.3	4.6	5.1
Dysmenorrhea	O	Si	89	0.3		
Menorrhagia	N	χ^2	90	0.1		
Metrorrhagia	N	χ^2	89	0.2		
Leucorrhea	N	χ^2	88	0.3		
Parity, excluding abortions (ever married only)	I	t	74	>0.3	1.9	2.2
Abortions and miscarriage	I	t	91	>0.3	0.27	0.50
Total known pregnancies	I	t	74	>0.3	2.2	2.5
Lactation (mo.)	I	t	76	>0.3	6.6	5.8
Age onset of menopause (yr.); excludes those not of *menopause age*	I	t	36	>0.3	45.0	46.4
Need medical help with menopause	N	χ^2	38	0.01		
Medicines (probably hormones) given to prevent abortion	N	χ^2	91	0.15		
Medicines (probably hormones) given for menopause	N	χ^2	39	0.1		
Medicines (which were probably female hormones), ever	N	χ^2	86	0.09		
Medicines (probably female hormones) for menopause	N	χ^2	90	0.3		
Cortisone	N	χ^2	89	0.2		
Thyroid	N	χ^2	86	0.30		
Any endocrines ever	N	χ^2	80	0.2		
Mumps	N	χ^2	78	0.007		
Roseola (9-day measles)	N	χ^2	70	0.3		
Rubella (3-day measles)	N	χ^2	56	0.02		
Other neoplasm	N	χ^2	90	0.3		
Tonsillectomy	N	χ^2	79	0.08		
Appendectomy	N	χ^2	70	0.16		
Obesity (treated for)	N	χ^2	91	0.3		
Underweight (treated for)	N	χ^2	91	0.3		
Hemorrhoids	N	χ^2	87	0.3		
Varicose veins	N	χ^2	89	0.3		
Constipation	N	χ^2	89	0.3		
X-rays (diagnostic) all areas	O	Si	90	0.3		
X-rays (diagnostic) abdominal only	N	χ^2	89	0.3		
X-ray (therapy)	N	χ^2	90	0.3		
X-ray (shoe fitting)	N	χ^2	92	0.3		
Use of tobacco	N	χ^2	91	0.16		
Use of alcohol	N	χ^2	92	0.28		
Education	O	Si	90	0.3		
Family size	I	t	90	>0.3	3.8	5.1

* I—interval; O—ordinal; N—nominal.
† Si—sign; χ^2—marginal chi square, t—student t test.

point of religion (Table 4) I did not observe any significant differences between cases and controls. Analysis by marital status (Table 5) revealed a higher proportion of single cases than benign controls. Differences otherwise were not remarkable.

Table 6 is a tabulation of the diagnostic categories of the 97 cases as taken from the pathologists' files in the various hospitals. No attempt was made in this study to extend or improve the variety of classifications found in the literature for *ovarian malignancies. Adenocarcinoma, cystic* and noncystic, were the most frequent, accounting for approximately two-fifths of all. Pseudomucinous cyst adenocarcinoma and serous cyst adenocarcinoma, having 23 and 16 cases respectively perhaps should be grouped together.

The control cases were much more varied: There were 25 seperate diagnoses, the commonest being endometriosis ovari—19 cases; simple cyst—10 cases; pseudomucinous cystadenoma—9 cases; dermoid cyst—8 cases.

Analysis of data: The interview protocol

was the same for patient and controls. It consisted of questions concerning approximately 50 variables. Several variables which were assessed are not reported here because they did not occur frequently enough in either patient or control to make a statistical analysis feasible. Examples are cesarean sections, toxemias of pregnancy, diabetes and tuberculosis.

All of the variables that were tested for statistical significance are summarized in Table 7. If differences found could have occurred by chance one time in 100 or less, they were considered to be significant. Thus, a p level of 0.01 is the level chosen for significance.

As is customary in data collected by interview, an occasional irrelevant question is included. Although irrelevance is difficult to define when one is searching for etiologic clues in a malignant disorder, I chose tonsillectomy (item 27) as being irrelevant to the development of an ovarian malignancy; this was proven because there was no significant difference and the "p" value was greater than 0.01.

For most of the variables, it was not possible to elicit the necessary data from every patient and every control. If either the patient or the control did not know the answer, or was not quite confident of the answer, the matched pair was dropped from the analysis of that particular variable. For example, data concerning tonsillectomy almost certainly could be elicited and, if necessary, one could check to see if tonsils were absent. Where measles or mumps were concerned, the interviewer had to be content with relegating the patient–control pair into the unknown column if either member was not quite certain of the answer. Because these pairs have been matched on the basis of age, sex and geographic residence, they are considered to be dependent and thus are paired in calculations.

INTERPRETATION

Of all the variables examined 3 are of special interest:

1. Milliroentgens delivered to ovaries by diagnostic and therapeutic x-irradiation;

2. Therapeutic use of hormones;

3. Clinically recognizable case of mumps parotitis.

Volumes have been written concerning the ability of x-irradiation to produce malignancies. The results of this study (Table 7, items 34 through 37) do not warrant the conclusion that exposure to x-ray, particularly diagnostic x-ray, influences the production of ovarian malignancies. Calculations were done on both nominal and ordinal scales. On the nominal scale, calculations were based only on whether or not the patient and the control had received x-irradiation over the abdomen; the question of who may have had more was not considered. On this scale there was no significant difference between the patient and benign ovarian-tumor group.

This data was placed on an ordinal scale when each procedure that the patient and control could recall having had done was given a value in milliroentgens. The values for this were based on those published by Norwood.[8] The sign test was used as the test of significance. There were 40 patients who had had more x-irradiation than benign tumor controls and 48 benign tumor controls who had more x-irradiation than patients with malignancies. There were 2 ties. The "p" level is not significant.

Ten patients reported having had x-irradiation as a therapeutic measure for one of several reasons. The commonest reasons given for therapeutic x-irradiation were skin lesions and bursitis.

Unfortunately, we have no way of estimating the milliroentgens delivered to the ovaries in any of these cases. We can deal with this deficiency by making 2 assumptions:

1. That therapeutic x-irradiation is overwhelming in the amount of milliroentgens delivered to the ovary and that each case (or control) giving a history thereof has thus had more exposure than her match; under this assumption $p = 0.3$ for patient and benign tumor control group and 0.23 for patient and relative control;

2. That x-irradiation was distributed fairly evenly between patient and control and thus affects them about equally; 8 patients and 13 controls gave histories of therapeutic x-irradiation.

Another potential source of ovarian exposure to x-rays was the fitting of shoes by x-irradiation. Because of a total lack of standardization, no attempt is made to ascertain the usual dosage of milliroentgens delivered to the ovaries by this morality. The use of this method for shoe fitting was fairly

evenly distributed between patient and control groups. Twelve of the patient group (12.4%) and 10 of the benign ovarian tumor control group (11%), gave a history of one or more shoe fittings with the help of an x-ray unit.

The second variable of unusual interest is the therapeutic use of hormones. Repeated attempts were made during each interview to elicit any history of natural or synthetic hormones including estrogen, progesterone, testosterone, thyroid, ACTH, and cortisone or its derivatives. Patients generally are unaware of the kind of medicines they are receiving or have received. Because of this, a great many pairs had to be discarded simply because the patient was unable to recollect whether or not medicine had been given. A few did know that they had been given estrogenic substance and occasionally one was able to produce from the medicine cabinet remnants of prescriptions they had taken. Items 16 through 22 of Table 7 show the breakdown of all questions pertaining to hormones included in the interview. In items 18, 19 and 20 no statistical difference is seen between patient and control group. No significant differences were found in the use of cortisone or thyroid and, when all endocrines are considered together, significant differences are not apparent.

The third variable of particular interest is that of having had a clinically recognizable case of mumps parotitis. Here (item 23) differences occur between patient group and benign controls and these are statistically significant. Can a patient recall if she has had a clinically evident case of mumps? This is speculative. But, as mentioned before, if patient and control pairs are chosen carefully, both groups should remember and forget in a random way and thus memory defect should not bias the outcome of this variable. The difference is in the direction of the patient having had mumps less often than control. This can be interpreted in at least 2 ways:

1. Having mumps in childhood may have a protective value against getting an ovarian malignancy in later years;

2. Some unknown factor that gives a patient resistance against developing a clinically recognizable case of mumps at the same time decreases one's resistance to development of ovarian malignancy.

The use of tobacco has been considered in connection with the etiology of several chronic and noninfectious diseases in recent years. In this study there was no significant difference in the use of tobacco between patient and control groups.

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