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Perspectives in Cancer Research

The Clinical Relevance of the Epidemiology of Ovarian Cancer*

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Abstract—*This paper reviews some clinically relevant aspects of the epidemiology of ovarian cancer. The items presented and discussed are:* (1) *incidence and mortality data: they show substantial stability in all Western countries over the last few decades;* (2) *risk factors: the relationships with child-bearing patterns and other reproductive variables (age at menarche and at menopause; oral contraceptives) appear well established but no risk factor is sufficiently strong to be of practical value in prevention or early diagnosis:* (3) *long-term survival: in spite of the large number of clinical studies that have claimed 'more effective' treatments, no improvement of long-term survival in the population as a whole has been established. Some discrepancies and drawbacks in published trials are discussed, and a different approach towards clinical studies is suggested.*

INTRODUCTION

IN PRINCIPLE, various factors might be relevant to the control of a disease such as ovarian cancer. Ideally, causative factors might be discovered that it would be practicable to modify in a population. Alternatively, if women at extremely high risk could be identified, then regular screening or prophylactic oophorectomy might be offered. Finally, the approach that has been most vigorously pursued has been the search for effective forms of therapy. In practice, however, ovarian cancer has remained a largely unresolved challenge to epidemiologists and clinicians, and the disease remains a major cause of death among women.

Epithelial ovarian cancers are related to the pattern of childbearing, but the mechanism underlying the increased risk associated with few and late pregnancies has not yet been settled, although current studies of hormonal correlates of the risk of disease onset may help in this respect. There are large differences in incidence, and hence in mortality, between different countries, but their chief causes are not known (and appear to involve important factors other than reproductive patterns). Thus no practicable measures of prevention (other than oophorectomy) or early diagnosis are yet available. Furthermore, though many clinical studies have been carried out since the early 1970s, many of these were poorly designed and there is still little reliably known of the effects of various forms of treatment on long-term survival.

This paper briefly reviews current knowledge on ovarian cancer trends over time, geographical variations, risk factors and the effects of therapy on long-term survival.

DESCRIPTIVE EPIDEMIOLOGY: INCIDENCE AND MORTALITY

One opinion that appears to be widespread is that an epidemic increase of ovarian cancer is currently in progress. Woodruff, who recently reviewed historical sources of medical data in the U.S.A., even concluded that ovarian neoplasms

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(or intra-abdominal malignancies, including the ovary) may be a disease of the present century [1] and an otherwise authoritative review published a few years ago in a leading medical journal began with the statement that 'the death rate from this disease has tripled in the past 40 years' [2].

These views are, however, grossly at variance with readily available data, at least as regards Western developed countries. The absolute number of deaths has indeed increased, but among individuals of any given age the death rates from ovarian cancer have over the last 40 yr shown only irregular fluctuations and no clear-cut trend. Indeed, in middle age both incidence and mortality have been decreasing slightly in the U.S.A. for at least the past quarter of a century. The age-standardized death rates among U.S. women aged under 65 yr were 57/million in 1953–1957 and 50/million in 1978, while the corresponding incidence rates were 124/million in 1947–1948 and 101/million in 1969–1971 [3]. (This gentle decrease in mortality existed through the 1950s and 1960s, before chemotherapy could have had any material effect on national death rates, and exhibited no apparent interruption during the 1970s.)

The general stability of the incidence of cancer of the ovary in 22 different populations in the period 1960–1975 is evident from Table 1. Available evidence therefore makes the hypothesis of any important new causal agent having been introduced extremely unlikely. On the other hand, although any comparison with mortality rates going back 50–80 yr must be done with the utmost caution, the age-standardized death certification rates actually seem to have doubled in this century.* An original critical analysis of these data [4] has shown that the increase may well

Table 1. *Geographic incidence of cancer of the ovary** (*truncated,* 35–64 yr, *standardized incidence rates/*100,000 *females*)

Geographic location	Approximate year of observation				% change, 1960–1975
	1960†	1965‡	1970§	1975‖	
Nigeria, Ibadan	21.1	20.8	19.4	—	—
Canada, Alberta	19.3	23.8	19.6	22.3	+16
Canada, Manitoba	34.3	31.5	22.5	23.2	-32
Columbia, Cali	29.4	21.8	22.0	22.6	-23
Jamaica, Kingston	16.3	16.8	16.7	12.1	-26
Puerto Rico	10.4	11.8	10.8	10.7	+ 3
U.S.A., Connecticut	27.5	24.3	26.4	24.3	-12
U.S.A., N.Y. State	22.0	—	24.0	27.1	+23
Israel, all Jews	26.3	24.6	27.6	25.7	- 2
Japan, Miyagi	4.2	3.8	5.1	6.9	+64
Singapore (Chinese)	6.1	—	13.4	12.0	+97
Denmark	30.2	29.4	31.0	30.1	0
U.K., Birmingham	22.7	24.4	25.0	25.0	+10
U.K., Liverpool	21.3	22.4	22.1	22.0	+ 3
Finland	18.2	21.2	21.6	22.3	+23
Iceland	24.1	—	26.2	—	—
Norway	24.4	23.7	30.4	31.9	+31
Sweden	28.7	30.6	31.3	33.2	+16
Yugoslavia, Slovenia	18.9	20.3	23.2	24.1	+28
Hawaii (Caucasian)	25.5	32.0	27.4	21.0	-18
Hawaii (Japanese)	19.6	24.5	16.0	15.0	-23
Hawaii (Hawaiian)	32.6	37.4	29.0	24.4	-25
Mean (excluding Nigeria and Iceland)	21.9	22.9	22.3	21.8	0

*ICD 175 (7th revision) or 183 (8th revision): ovary, tube and broad ligament.

Data from: † DOLL R, PAYNE P, WATERHOUSE J, eds. *Cancer Incidence in Five Continents.* UICC, 1966, Vol. I; ‡ DOLL R, MUIR C, WATERHOUSE J, eds. *Cancer Incidence in Five Continents.* UICC, 1970, Vol. II; §WATERHOUSE J, MUIR C, CORREA P, POWELL J, eds. *Cancer Incidence in Five Continents.* IARC, 1976, Vol. III; ‖WATERHOUSE J, MUIR C, SHANMUGARATNAM K, POWELL J, eds. *Cancer Incidence in Five Continents.* IARC, 1982, Vol. IV.

Interpolated values used for U.S.A. (N.Y. State) and Singapore (Chinese).

*A general overview is given by Beral *et al.* [4], where age standardized (on the average age-structure of the population of England and Wales and the U.S.A. from 1931–1973) cohort death certification rates for women 30–74 from 1931 to 1975 in England and Wales and from 1931 to 1973 in the U.S.A. are presented.

be referred to a historical decrease in average parity.The magnitude of the increased risk between generations born since 1861 in England, Wales and the U.S.A. shows a strong negative correlation with the average completed family size ($r = -0.97$; $P < 0.001$), but no clear secular trend [4]. In those countries the age-standardized mortality rate, for instance, is low for the generations born at the end of the last century, with high average parity (3–3.5 children/woman), high in the cohorts born during the first decade of this century, with low average parity (1.5–2 being of child-bearing age during the depression of the '30s), and decreasing again in the generation born in the '30s, whose fertility peak occurred in the so-called post-war 'baby-boom' [4]. This inverse relationship between parity and ovarian cancer will be considered in more detail in the analysis of etiologic studies.

Differences between geographical areas may be interesting as well [5]: all the Western countries, like the U.S.A., England, Sweden or Israel, have incidence rates higher than 20/100,000, while less-developed countries (and Japan) report 2–5 times lower figures (Table 1). Although such geographical variations may be partially artifactual, they do suggest that some 'environmental' factors, including general life-style habits, may be responsible for the apparent differences and, consequently, that a large number of such tumors are, at least in principle, preventable.

ETIOLOGICAL STUDIES

Relatively few studies have been published on the etiology of ovarian cancer considering the amount of epidemiological work that has been carried out on other gynecological malignancies (e.g. endometrial cancer and the oestrogen controversy). The 11 major case-control studies [6–16] have identified reproductive variables as the most consistent risk factors for this malignancy: nine [6, 9–16] of them found that women with ovarian cancer had had fewer pregnancies and births that controls. It is still controversial whether these data reflect a real protection conferred by pregnancy or, rather, prior subfertility in women predisposed to gonadal malignancies. Five studies [6, 9, 14–16] found later age at first pregnancy in cases than in controls, and it is of interest that this association appeared to be independent of parity [16]—indeed, unpublished data from one study [16] indicated that early age at first pregnancy, and not parity, may well be the most important (and, perhaps, the only relevant) protective factor among the reproductive variables that were recorded. In that study the relative risk, comparing parous with nulliparous women, is extremely low (RR = 0.2) for women who had their first pregnancy when less than 20, but not (RR = 0.9) for women who had their first pregnancy when aged 25 or more, independently of the total number of pregnancies (Table 2). Moreover, the protection conferred by young age at first pregnancy (RR = 0.5) was not modified after adjustment for parity (Table 3). Like pregnancy, the use of oral contraceptives appears to reduce the risk of ovarian cancer: six studies [6, 9, 14–17] have reported a protective effect of the pill, though the relationship with age and duration of exposure has not yet been adequately characterised.

Cases of ovarian cancer also differed from controls as regards age at menarche and at menopause: earlier menarche and delay of menopause were more commonly identified among cases, thus indicating an increased risk [6, 8, 12, 15, 16].

Other risk factors emerged less consistently: four reports [6, 9, 10, 13] suggested that single women were at increased risk, but nulliparity, generally linked with unmarried status, may well account for this finding. Cases appeared somewhat more educated than controls, probably as a consequence of a socioeconomic gradient also seen in vital statistics [6, 8–10, 13]. For the time being, however, this finding appears controversial and might also be related to the pattern of child-bearing.

The relationship of ovarian cancer with other sporadically reported factors ('ovulatory years'

Table 2. Distribution of 161 cases of ovarian cancer and 561 controls according to age at first pregnancy, Milan, Italy, 1979–1980

	Ovarian cancer		Controls		Relative risk
	No.	(%)	No.	(%)	estimate (95% C.I.)
Nulligravidae	50	(31)	127	(23)	(1)*
<20 yr	4	(2)	58	(10)	0.2 (0.1–0.5)
20–24 yr	34	(21)	165	(29)	0.5 (0.3–0.9)
≥25 yr	73	(45)	211	(38)	0.9 (0.6–1.3)†

*Reference category.

†Test for trend (nulligravidae excluded): $\chi^2_1 = 13.62$; $P < 0.001$.

Table 3. Relative risks for the onset of epithelial ovarian cancer according to various characteristics, Milan, Italy, 1979–1980; 161 cases and 561 controls [16]

	Relative risk estimate	(95% C.I.)
Parity		
0	(1)*	
1–2	0.8	(0.5–1.1)
⩾3	0.5	(0.3–0.8)
Age at first pregnancy (yr)		
⩾25	(1)*	
<25	0.5	(0.3–0.8)†
Age at menarche (yr)		
⩾15	(1)*	
12–14	1.3	(0.8–2.1)
⩽11	1.5	(0.8–2.7)
Age at menopause (yr)		
<45	(1)*	
45–49	2.9	(1.1–7.9)
⩾50	4.6	(1.8–11.5)
Past use of oral contraceptives		
No	(1)*	
Yes	0.7	(0.4–1.1)

*Reference category.

†Relative risk after adjusting for parity: 0.5 (95% C.I. = 0.3–0.8).

[27], oestrogen replacement therapy [18], childhood infectious diseases [7, 10, 14], talcum powder, asbestos and other industrial pollutants [19, 20], cigarette smoking [20] and coffee [21] still lacks biological or biostatistical consistency, and even the established risk factors tend not to confer any very extreme relative risks.

The one apparent exception is the familial clustering of a small proportion of ovarian neoplasms [22, 23]. About thirty families have now been reported with *three or more* cases of ovarian cancer and, although it is difficult to make due allowance for reporting biases in assessing these findings, they do appear to be far too extreme to be ascribable merely to the play of chance. Familial neoplasms occupy a curious position in the control of ovarian cancer, for although genetic factors *per se* are largely or wholly unavoidable, the identification of a cluster may well have immediate preventive implications, as in these rare families prophylactic oophorectomy at the end of the child-bearing period may be advisable [23].

LONG-TERM SURVIVAL

Since the 1950s, when standards of surgery fairly similar to those of today were already available, long-term survival ('cure') of about one in three ovarian cancer cases has been obtained [24]. The 5-yr survival in countries for which reliable data are available has improved only slightly in the last 30 yr. In the United States, for example, the estimated 5-yr relative survival percentages have risen from 30% during the period 1950–1954 to 34% in 1960–1964 and to 36% in 1970–1973 (U.S. population, whites only) [3], while in Norway the 5-yr relative survival has risen from 33% in 1963–1967 to 36% in 1968–1971 and to 37% in 1972–1975 [25]. These figures represent upper limits on the degree of improvement that has actually occurred, since more complete case registration may account for part of these differences. (The 5-yr survival data derive in part from cancer registries, and in the 1950s a larger proportion of cases than now were registered only via the monitoring of death certificates.)

This substantial evidence of only slight improvement in curative therapy during the past few decades stands in striking contrast to the numerous optimistic descriptions of 'highly' or 'more' effective treatments in clinical trial reports.

Most such studies, however, report only 'response' rates (which do not imply cure, and which may be affected by subjective or instrumental variation), rather than (long-term) survival figures. For instance, among the 32 trials [26–57] of medical treatments of ovarian cancer published during the years 1979–1980 in three of the more authoritative journals in the field (*The American Journal of Obstetrics and Gynecology, Cancer, Cancer Treatment Reports*) (Table 4), only 11 [26, 28, 29, 39–43, 46, 49, 54] gave a simple, standard life table, and in only three cases was the life table analysis based on three or more years of observation. Most of these studies (23/32, 72%) did not directly compare different regimens, since they were merely 'phase II' studies (although considering the variability in the reported response rates with traditional alkylating agents, it might well be advisable to randomize many phase II studies in the future [58]).

Other major drawbacks in ovarian cancer trials that make it extremely difficult to draw definite conclusions include: (1) the small size (median about 30 patients), which, by itself, greatly

*Table 4. Distribution of various characteristics in 25 clinical trials on epithelial ovarian cancer**

Characteristic	No. of studies (%)
No. of patients ⩾50 yr	10 (40)
Life-table analysis	10 (40)
Comparison of two or more treatments	9 (36)
Randomization	7 (28)
All the above	3 (12)

Derives from: *The American Journal of Obstetrics and Gynecology, Cancer, Cancer Treatment Reports* 1978–1980), phase II studies (whenever clearly stated) excluded.

reduces their scientific value, even when the most sophisticated monitoring (or data analysis) is employed; (2) the frequent use of 'data dredging' (*a posteriori* identification of subgroups of patients, according to age, histopathological features etc., in which one of the treatments is *apparently* more effective while the overall results of the study are negative). Although such subgroup analyses might be informative in a really large study (e.g. of several hundreds, or even some thousands, of cases), in small studies they are far less reliable than is commonly supposed [59]; and (3) the well-known tendency to publish positive results rather than negative ones, reflected in the large proportion of 'preliminary reports'.

CONCLUDING REMARKS

The general stability of incidence and mortality data in Western countries over the last few decades and the nature of the risk factors thus far identified suggest that major changes in the onset rate and natural history of ovarian cancer cannot be expected in the near future.The preventable fraction seems at present to be limited to the few cases where familial factors can be identified that are sufficiently strong to justify prophylactic oophorectomy. This has implications for future strategies in both epidemiologic and therapeutic experimentation. Epidemiologically, the chief need appears to be for more precise data as to exactly what are the key hormonal (and other) correlates of disease outset. Clinically, one thing that is needed is to plan trials in a more scientific fashion with due attention to the recruitment of adequate numbers of patients and to the assessment of end-points capable of measuring not only short- and medium-term 'responses' but also long-term survival. As in other fields of solid tumor chemotherapy, current treatment schemes should not engender undue optimism as to their capacity for inducing anything more than *moderate* improvements in the outcome. If this is accepted, then a major revision is clearly needed of the strategies that are currently adopted in the organization of clinical trials. Larger scale collaborative studies, considering long-term outcome, will be needed if treatments are to be assessed sufficiently reliably for ordinary clinical purposes.

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