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A POPULATION-BASED SURVEY OF OVARIAN MALIGNANCIES IN THE SOUTHEAST HEALTH CARE REGION OF SWEDEN 1984–1987

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All 426 patients with ovarian malignancies registered in the population-based Tumor Registry of the Southeast region of Sweden during 1984 to 1987 were analyzed by survey of the hospital records and population registry data. After comparison with other population-based materials, it seems that the overall survival figures have improved in ovarian cancer. Excluding patients diagnosed at autopsy a 5-year corrected survival of 43% was recorded. Among patients aged under 45 years the corrected 5-year survival was 72%. In a Cox's regression analysis age and stage were significant predictors of cancer death while histology (epithelial vs. non-epithelial), although significant in the univariate analysis, did not add prognostic information in the multivariate model. The relative cancer death rate was 6.4 for patients aged over 74 years compared with those aged under 45 ($p < 0.0001$), and 13.8 for FIGO stage IV compared to stage I ($p < 0.0001$). For patients with advanced stage tumors (FIGO stage III or IV) postoperative residual tumor, stage, and age were independent prognostic factors in a multivariate analysis. The corrected cancer death rate was 2.0 for patients with >1 cm relative to $\leqslant 1$ cm postoperative residual tumor nodule(s) ($p < 0.0001$).

Ovarian cancer ranks as the fourth most common malignancy in females in Sweden (1). Sweden has been running national and regional population based cancer registries since 1958. The treatment of patients with gynecological cancer is centralized to seven Departments of Gynecologic Oncology at the University Hospitals, each serving a defined geographical area. This, together with a low migration and a national population registry, makes possible population based surveys of different malignant diseases with an almost complete coverage of the diagnosis and the follow-up. Reports on treatment results in population-based patient materials complement hospital-based reports, which are usually subject to selection mechanisms which can be difficult to describe and evaluate. The present study is a population-based survey of all cases of ovarian malignancies reported to the Regional Cancer Registry in the Southeast Health Care Region of Sweden during the years 1984 to 1987. The emphasis is on the survival results. These results are compared with survival results reported from other population based materials

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Material and Methods

Case identification and data recording. The Regional Tumor Registry in the Southeast Health Care Region of Sweden was searched for the code 175.0 (malignant) in the ICD-7 nomenclature (International Classification of Diseases, seventh revision). The date of diagnosis ranged from January 1, 1984 to December 31, 1987. These time limits were chosen because the treatment regimens were consistent from the beginning of 1984. The cut-off at December 31, 1987 allows sufficient observation time to make the estimations of 5-year survival reliable. The search resulted in an output of 451 patients. The hospital records were obtained and reviewed by one of the authors (T.H.). To be eligible for this study an unequivocal diagnosis of a primary ovarian malignancy was required. Diagnosis solely

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Table 1

The reasons for the exclusion of 25 cases from the material after review of the hospital records

Endometrical cancer	3
Metastatic cancer	6
Uncertain clinical diagnosis without histology	6
Uncertain histology	7
Wrong registration[1]	3
Total	25

[1] The three patients labelled as wrongly registered were rejected for the following reasons: The first patient was registered in the Stockholm region at the time of the diagnosis and should only have been registered in the Stockholm Cancer Registry, nothing was found in the hospital records to indicate that the second patient actually had an ovarian cancer diagnosed, and the diagnosis for the third patient was changed to benign serous cystomas at pathological review.

by clinical examination or certain ancillary methods (e.g. ultrasound) was not accepted. In cases with uncertain histology but with clinical evidence of an ovarian tumor the cases were only included if the pathologist suggested an ovarian primary as the most likely alternative. At the time of referral most biopsies were reviewed by pathologists at the University Hospital of Linköping. Twenty-five patients were excluded after the review of the hospital records (Table 1), leaving 426 patients for the present study. Since 19 patients were diagnosed by an autopsy, the study population for the survival analyses consisted of 407 patients. The following data were registered: age, diagnostic procedure, FIGO stage, histology, amount of residual tumor after primary surgery, therapy after second-look surgery, and survival time.

Treatment and staging. The primary operation was performed by specialized gynecologists at the local hospitals and was aimed at staging and maximal tumor reduction. Most patients, 364/407 (89%), were then referred to the Department of Gynecologic Oncology, University Hospital of Linköping. Patients requiring further treatment came to the University Hospital for their treatment and follow-up. The patients were substaged according to the latest revision of the FIGO staging (2) of ovarian cancer. The actual clinical staging was based on surgical findings and histopathologic results, even though staging procedures were sometimes incomplete, which of course means that some patients were understaged (3). In 9 cases staging was not possible. The treatment policy for the epithelial ovarian malignancies was defined on the basis of clinical FIGO stage. Stage IA and IB patients were treated with only surgery. Patients with stage IC disease had adjuvant chemotherapy with an anthracycline and cisplatinum (AP × 4). Patients with stage II–IV disease were given six, or in the later part of the study, four courses of postoperative cytoreductive or adjuvant chemotherapy (AP × 4–6). Second-look or secondary tumor reduction surgery was usually performed four weeks after the last chemotherapy treatment in stage IC–IV patients. The therapy after the secondary operation was somewhat more varied; the same chemotherapy given for another four to six cycles (43%), intraperitoneal chemotherapy with cisplatinum or cisplatinum and etoposide (16%), whole abdominal external radiotherapy (5%), no further treatment (21%) (mostly in the early stages), and other treatment (14%). The treatment of non-epithelial tumors was less standardized.

Statistics. The survival curves and the survival probabilities were calculated by the Kaplan-Meier method (4). Crude survival included all causes of death. Corrected survival included only deaths from cancer or from treatment complications. Relative survival (the ratio of the crude survival probability to that 'expected' for demographically similar individuals in a reference population) (5) was calculated according to the method based on individual records in Ederer et al. (6). The mean death rates for the Swedish female population divided into 5-year age intervals during the period 1983–1986 were used. The death rate tables were supplied by the Swedish National Central Bureau of Statistics. Differences in the survival between groups were tested with the log-rank test (7). For three or more groups a modified log-rank test for trend in survival across the groups was applied (8). The relative survival comparisons were done using the methods described by Buckley (5). This paper describes a means of generating scores analogous to the log-rank scores. The 95% confidence intervals (CI) for the survival rates were calculated according to Machin & Gardner (9). The prognostic factors were further analyzed with univariate and multivariate Cox analysis (10). Very few (15%) patients in stage I and II had postoperative residual macroscopic tumor. Therefore the analyses pertaining to residual tumor after primary surgery were restricted to stages III and IV. The cut-off date for the survival analysis was May 13, 1991. The median potential observation time (time from the date of diagnosis to the cut-off date) was 64 months (range 37–88). The date of diagnosis was used as entry date. When corrected survival was used, the cause of death was obtained from the hospital records or from death certificates. No patient was lost to follow-up.

Results

The population at risk was computed by adding together the mean female population in the area for each year, which resulted in 1 881 024 woman-years. The number of patients on whom the incidence calculations were made was 426. The crude yearly incidence of ovarian malignancies was 22.7/100 000 woman-years. The age-standardized incidence to the world population was 14.2/100 000, and to the Swedish 1970 census population 20.1/100 000. Fig. 1 shows the age distribution and the age-specific incidence.

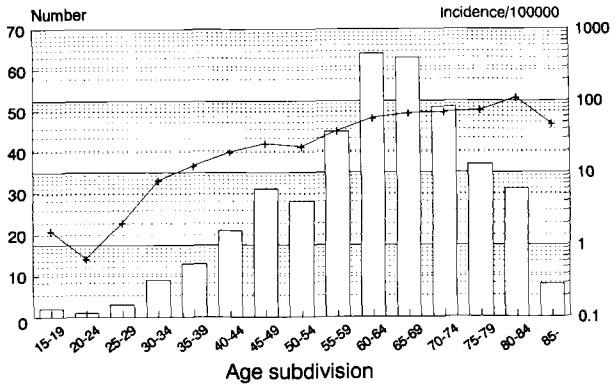

Fig. 1. Age distribution (bars) and log age-specific incidence (line).

The most commonly used diagnostic method was histological biopsy which was registered in 392/426 (92%) of the cases, 14 (3%) were diagnosed by fine-needle aspiration cytology. Nineteen (5%) cases were diagnosed by autopsy and one patient was clinically diagnosed with later verification by autopsy. A total of 384/407 patients (94%) had a primary diagnostic laparotomy. The distribution of the patients according to stage and histology respectively by age is given in Table 2, and the distribution according to stage by histology in Table 3. The old patients more often presented with a metastasizing disease (stage II–IV); 79% of patients aged over 74 years were in stage II–IV versus 61% if aged under 45 (χ^2, $p = 0.02$) (Table 2). Tables 2 and 3 also show that the patients with non-epithelial tumors were younger and had earlier stage disease.

Fig. 2 shows the survival curves for all patients with ovarian malignancies ($n = 407$; 19 autopsy cases excluded). The estimated corrected 5-year survival was 43% (95% CI: 38–48%), relative 5-year survival was also 43% (CI 37–48%), and the crude 5-year survival 40% (CI 35–45%). Fig. 2 shows that, in this material, there was a very close match between the relative and corrected survival curves. Therefore all the succeeding analyses were made utilizing corrected survival.

The corrected survival according to stage (Fig. 3) was 84% (CI 77–92%), 60% (CI 49–72%), 19% (CI 13–25%), and 16% (CI 5–27%) in stage I, II, III, and IV respectively

Table 3

Distribution of patients according to stage by histology

Histology	Stage					
	I	II	III	IV	N.A.*	All
Epithelial	75	77	171	52	9	384
Non-epithelial	28	4	7	3	0	42
All	103	81	178	55	9	426

* not assigned

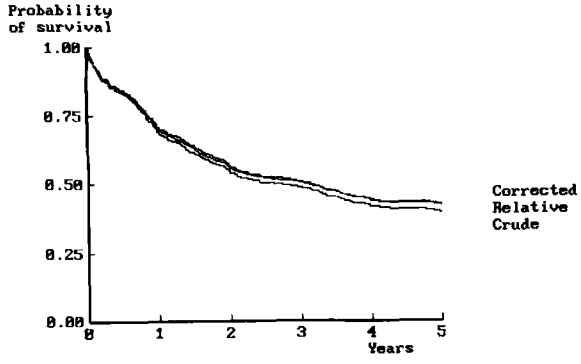

Fig. 2. The overall corrected, relative and crude survival curves for the 407 patients.

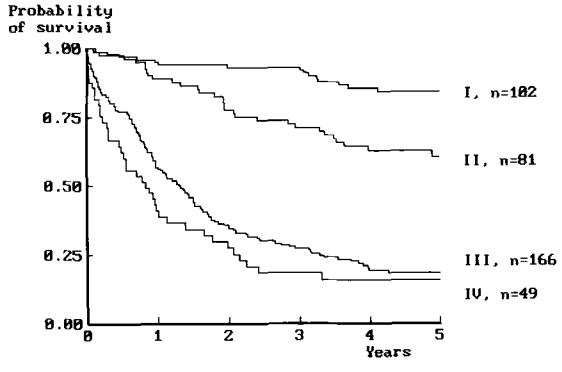

Fig. 3. The corrected survival according to stage ($n = 398$; 9 unstaged patients rejected).

Table 2

The distribution of patients according to stage and histology respectively by age

Age, years	Stage					Histology		
	I	II	III	IV	N.A.*	Epithelial	Non-epithelial	All
<45	19	9	18	3	0	41	8	49
45–74	73	63	111	39	1	257	30	287
>74	11	9	49	13	8	86	4	90
All	103	81	178	55	9	384	42	426

* not assigned

Table 4

Corrected 5-year survival rates (%) according to stage by age (n = 398; 9 unstaged patients rejected)

Age	Stage					
	I	II	III	IV	All	p (trend)
<45	100	78	41	67	72	0.0002
45–74	83	63	20	16	45	<0.0001
>74	64	25	0	0	14	<0.0001
All	84	61	19	16		<0.0001
p (trend)	0.005	0.06	<0.0001	0.007	<0.0001	

($p < 0.0001$, trend). The corrected survival in stage II–IV (metastasized) was 30% (CI 24–36%). With stratification for age stage was a significant predictor of survival in all three age categories (Table 4). The age of the patient at the time of diagnosis was also important for the corrected survival (Fig. 3). If the patient was aged < 45 years, 45–74 years, or > 74 years it was 72% (CI 59–85%), 45% (CI 39–51%), and 13% (CI 5–22%) respectively ($p < 0.0001$ for trend). With stratification for stage, age was still a significant predictor of survival in all stages (borderline significance for stage II, $p = 0.06$) (Table 4). The patients with non-epithelial malignancies constituted 41/426 (10%) and had a better survival than those with epithelial malignancies (75% (CI 61–88%) versus 39% (CI 34–45%) corrected 5-year survival; $p = 0.0001$).

Macroscopic radical operation could be performed in 154/182 (85%) of the patients allotted to FIGO stages I and II. Of the patients with FIGO stages III and IV disease (n = 200 eligible for recording of postoperative residual tumor) 22 (11%) underwent total tumor reduction and 25 (13%), 33 (17%), and 120 (60%) were left with ≤1, 1–3 or >3 cm postoperative residual tumor nodule(s). The corrected survival according to residual tumor in stages III and IV (Fig. 4) was 38% (CI 17–59%), 40% (CI 21–59%), 16% (CI 3–29%), and 12% (CI 6–18%) respectively ($p < 0.0001$ trend).

The following variables were introduced into the Cox analyses: age (<45 years, 45–74 years, or >74 years),

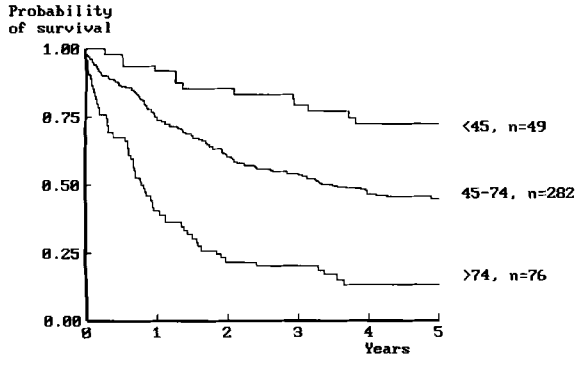

Fig. 4. The corrected survival according to age (n = 407).

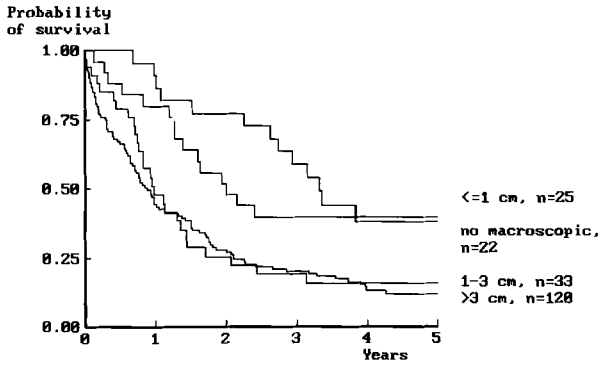

Fig. 5. The corrected survival according to postoperative residual tumor in patients with stage III and IV disease (n = 200; 9 unstaged patients and 15 patients undefined for postoperative residual tumor rejected).

FIGO stage (I, II, III, IV), histology (epithelial, non-epithelial), and for patients allotted to FIGO stages III and IV amount of postoperative residual tumor (≤1 cm, and >1 cm) (Table 5). In the multivariate models (Table 6) age and stage were independent prognostic factors in patients with stage I and II disease. Histology was not significant in any of the multivariate models. For patients in stage III and IV postoperative residual tumor and age retained their significance while stage was not significant. For patients in all stages age and stage were significant. We could not disclose any significant interactions between the variables.

Discussion

The age distribution was very similar to what was described by SEER (Surveillance, Epidemiology and End Results Program of the National Cancer Institute) (11) with a peak between 60 to 69 years of age. The age-specific incidence was under 10/100 000 per year before 40 years of age after which it steeply rose with increasing age. The figures are in close agreement with those pertaining to Sweden during the period from 1980 to 1984 (12).

The incidence of ovarian cancer in Sweden has been fairly stable. Adami et al. (12) analyzed the trend in Sweden during the period 1960–1984 and found an initial increase followed by a stabilization and later a decline, especially in the younger birth cohorts. They proposed that the decline could be caused by a high population exposure to oral contraceptives. The same trend has been found in the USA (13). A generally decreasing trend has lately been found in Finland and Denmark, whereas in Norway there has been an increasing incidence up to 1980 (14). Our region has an average risk for the Nordic countries (15) which are known to carry the highest incidence of ovarian cancer in the world (16). The reason for this is unknown. Page & Asire (17), however, stated that ovarian cancer carries one of the lowest ranges of incidence rates (the

Table 5

Univariate Cox's analyses summaries

Variable	Relative death rate	95% confidence interval	p-value
FIGO stage I and II			
Age, years			
<45	1.0		
45–74	3.9	0.9–16.1	0.06
>74	11.2	2.4–51.1	0.002
Epithelial vs. non-epithelial			
Epithelial	1.0		
Non-epithelial	0.3	0.09–0.9	0.04
FIGO stage			
I	1.0		
II	2.7	1.5–5.0	0.001
FIGO stage III and IV			
Postoperative residual tumor			
≤1 cm	1.0		
>1 cm	2.4	1.6–3.6	<0.0001
Age, years			
<45	1.0		
45–74	2.5	1.4–4.6	0.003
>74	5.8	3.0–11.1	<0.0001
Epithelial vs. non-epithelial			
Epithelial	1.0		
Non-epithelial	1.3	0.6–2.7	NS*
FIGO stage			
III	1.0		
IV	1.3	0.9–1.9	NS*
All FIGO stages			
Age, years			
<45	1.0		
45–74	2.5	1.4–4.3	0.001
>74	6.7	3.7–12.0	<0.0001
Epithelial vs. non-epithelial			
Epithelial	1.0		
Non-epithelial	0.3	0.2–0.6	0.0004
FIGO stage			
I	1.0		
II	2.7	1.5–4.9	0.001
III	10.3	6.1–17.3	<0.0001
IV	13.8	7.7–24.6	<0.0001

* not significant

ratio of the highest rate to the lowest rate) among all types of cancer. Around 1975 this rate was 8.2 (17).

The diagnosis of ovarian cancer was, however, very often made at an advanced stage of the disease; 55% (233/426) of the patients in our material were in FIGO clinical stage III or IV. This is comparable to Balvert-Locht et al. (18) who found 60% in stage III–IV in their population-based material from the Netherlands during the years 1975–1985. In the SEER material 71% were in stage III–IV (11). During our study period the surgical staging procedures in the early stages have been unsatisfactorily conducted in our region. None of the stage I and II patients were subjected to retroperitoneal lymph node sampling and only in very few cases were an omental resection or a peritoneal lavage performed. This makes understaging probable in a proportion of the early stage patients (3). A higher awareness of the insidious nature of the symptoms and signs of ovarian cancer and better diagnostic equipment (e.g. gynecologic ultrasound) may have contributed to earlier diagnosis. Better surgical staging procedures might result in a relative increase in the number of patients allotted to higher stages (3). Although the staging procedures in the early cases were unsatisfactory, we do have a very high proportion (92%) of patients diagnosed and staged by laparotomy. The factors mentioned might all be operating at the same time, making the interpretation of stage distributions difficult.

The estimated corrected 5-year survival of all patients was 43% (CI 38–48%). Balvert-Locht et al. (18) reported an overall relative survival of 42% in patients diagnosed in

Table 6

Multivariate Cox's analyses summaries. No significant interactions could be detected

Variable	Relative death rate	95% confidence interval	p-value
FIGO stage I and II			
Age, years			
<45	1.0		
45–74	3.3	0.8–13.9	NS*
>74	9.6	2.1–44.0	0.004
FIGO stage			
I	1.0		
II	2.5	1.4–4.6	0.003
Epithelial vs. non-epithelial			
NS*			
FIGO stage III and IV			
Postoperative residual tumor			
≤1 cm	1.0		
>1 cm	2.0	1.4–3.1	<0.0007
Age, years			
<45	1.0		
45–74	2.1	1.1–3.8	0.02
>74	4.7	2.4–9.3	<0.0001
FIGO stage			NS*
NS*			
Epithelial vs. non-epithelial			
NS*			
ALL FIGO stages			
Age, years			
<45	1.0		
45–74	2.6	1.5–4.4	0.0009
>74	6.4	3.5–11.6	<0.0001
FIGO stage			
I	1.0		
II	2.5	1.4–4.7	0.003
III	9.9	5.9–16.8	<0.0001
IV	13.8	7.7–24.8	<0.0001
Epithelial vs. non-epithelial			
NS*			

* not significant

1981–1985 and 28% in patients diagnosed in 1975–1980. According to a compilation, prepared by Hanai (14), the 5-year survival in Norway during the years 1975–1979 was 41% and in Finland during the same period 39%, while in England and Wales during the years 1976–1979 it was 25%. In the SEER material for whites it was 34% both during the years 1967–1973 and 1973–1979.

Hanai (14) reported the survival according to stage by dividing the stages into localized (stage I) and others (stages II–IV, referred to as metastasized in this study). In our material the corrected survival was 84% with localized disease and 30% (CI 24–35%) in metastasized disease. For Norway Hanai (14) reports that the relative survival figures in 1975–1979 were 83% and 21%, in Finland during the same period 82% and 12%, and in the USA (SEER, white) 78% and 18%. In all materials, reported by Hanai (14), there was a tendency towards better treatment results in the later periods for the localized cases. Hanai (14) suggested that the reason for that was partly caused by better staging procedures. In some countries (Norway and USA) there was also an improvement in the treatment results for the metastasized cases, which was probably due to better chemotherapy. Our material suggests a further improvement of the results for the advanced stages. However, one has to be aware of the effect of changing staging procedures. Moving cases from stage I (localized) to stages II–IV (metastasized) might have the effect of improving the survival figures in both categories while the overall survival remains unchanged.

The prognosis in ovarian cancer is worse in the older patient groups (11). A gradual increase over time in the age of the patients might conceal better treatment results. In our material the median age was 63.5 years (mean 61.3). Balvert-Locht et al. (18) observed a mean age of 57 years during the period 1975–1980 and 59 years 1981–1985. A trend towards better 5-year survival in younger age groups has been observed in several materials, e.g. in Norway from 63% to 71% between the periods 1968–1975 and

1975–1979 and in the USA (SEER) from 55% to 61% between the periods 1967–1973 and 1973–1979 (14). In our material patients aged under 45 years had an estimated corrected 5-year survival of 72%. In their multivariate analysis Balvert-Locht et al. (18) found that the improvement in survival between the periods 1975–1980 and 1981–1985 was greatest in younger patients and was no longer present for patients with advanced age at diagnosis. They did not report the survival separately for the different periods for age subgroups, but the relative 5-year survival was 66% for all patients aged under 45 including both periods.

Age, stage, and, in the advanced stages, amount of postoperative residual tumor were highly significant prognostic factors (Tables 5 and 6). If the cancer death rate for patients in FIGO stage III or IV with residual tumor after the primary operation amounting to ≤ 1 cm was considered as 1.0, patients with greater residual tumor burdens had a doubled cancer death rate. Considering all stages, patients aged >74 years ran 6–7 times greater risk of dying of cancer compared to those aged <45, and patients with stage IV disease had 14 times greater risk of dying of cancer relative to patients with stage I disease. Whether the tumor was epithelial or non-epithelial was highly significant in the univariate analyses (Table 5), but had no prognostic significance in the multivariate models (Table 6). This agrees with Balvert-Locht et al. (18) who found a crude 5-year survival of 65% and 63% in stromal and germ-cell tumors respectively, compared to 32% in epithelial tumors. When they corrected for stage and age, however, there were no statistically significant differences.

After comparing our material with those of others, it seems that the overall survival figures have improved in ovarian cancer. The improvement has been most pronounced in the younger age groups. The corrected 5-year survival for patients under 45 years of age was 72% in our material. This is an impressive figure in a disease traditionally regarded as having a dismal prognosis. However, this is not unique to our material, but is supported by other population-based materials (14, 18). This study has been performed on a population-based material from a well defined geographical region and the treatment regimens have been consistent. Since comparisons with other materials are very difficult to evaluate we will in the future perform repeated surveys from this region to follow possible trends in the treatment results.

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