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Ovarian cancer: an institutional review of patterns of care, health insurance and prognosis

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Abstract

The purpose of this study was to investigate the prognostic importance of the health insurance status in 145 consecutive patients with ovarian cancer diagnosed between 1984 and 1996. All patients had basic (Type III) insurance to cover outpatient treatment and hospital expenses for a *per diem* flat fee; some patients had one of two types of supplemental private insurance (Type I and Type II) to cover the treatment by physicians of their choice and fee-for-service hospital treatment. The prognostic impact of health insurance was evaluated by multivariate statistical methods. The median follow-up was 81.9 months (range: 21–181); the 5-year probability of survival was 72% (standard error of the mean (SEM) 9.8%) for stage I, 53% (SEM 16.2%) for stage II, 17% (SEM 5.9%) for stage III and 11% (SEM 5.5%) for stage IV cancer. Age, stage, histological grade and debulking surgery were independent predictors of survival in multivariate proportional hazards regression analysis. Patients with private insurance were younger and received more chemotherapy than patients with basic insurance. In multivariate analysis, insurance was an independent predictor of survival: patients with Type II insurance had a hazard ratio of 2.31 (95% confidence interval (CI): 1.05–5.04), and patients with Type III insurance had a hazard ratio of 3.30 (95% CI 1.52–7.17) compared with the reference group of Type I insured patients. Health insurance status was an independent predictor of survival in ovarian cancer. Research is needed to devise strategies to improve the medical care of patients with basic insurance. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Ovarian neoplasms; Insurance; Health; Prognosis; Factor; Age

1. Introduction

Ovarian cancer has the highest mortality rate of malignant neoplasms of the female genital tract [1]. The incidence (17.4/100 000 women/year), and the mortality (8.1/100 000/year) in Switzerland [2] is similar to other Western countries. Most patients are diagnosed with advanced stage disease, and the prognosis depends on the stage, the biological properties of the tumour, and on treatment: patients with optimal debulking surgery survive longer than patients with bulky residual tumour [3]. In addition, the expertise of the treating surgeon [4], and the choice of chemotherapy appear to be critical determinants of survival. For instance, the introduction of paclitaxel into clinical practice improved the median survival of advanced stage ovarian cancer patients by 10 to 14 months [5]. The prognosis of certain cancers depends on social and economic factors [6]. In contrast to other tumours, the prognostic impact of socio-economic factors has rarely been investigated in ovarian cancer.

The Swiss health insurance system has two components: all inhabitants (>97% in 1984, 100% in 1996 [7]) are covered by basic health insurance (Type III insurance); this insurance covers 90% of all outpatient treatment expenses on a fee-for-service basis and all inpatient treatments for a *per diem* flat fee in public hospitals. The physicians involved in the care of patients with type III insurance receive no additional salary for their services. As a supplement to basic coverage, patients can buy so-called private insurance (Type II and Type I insurance) to cover the treatment by private physicians of their choice in private hospitals and direct care by senior physicians in public hospitals. Type I insurance pays for the hospital stay in single bed rooms,

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whereas Type II insurance guarantees two-bed rooms. Patients with Type I insurance are usually treated by the directors of the respective departments. The services and materials used by patients with private insurance (Type I and II) are charged on a fee-for-service basis, and the treating physicians are reimbursed separately for their work. All types of insurance premiums are paid by the insured persons and are not part of a benefits package from the employer. Type I and Type II insurance coverage is considerably more expensive than basic insurance. The Swiss system of health insurance is believed to guarantee equal access to medical care for all patients and to affect the comfort, but not the quality of care during in-patient treatment.

The present retrospective analysis of patients who had both surgical and medical treatment at the University Hospital of Berne was intended to gain information on the patterns of therapy and prognosis and whether they were influenced by the insurance status of patients with adenocarcinoma of the ovary.

2. Patients and methods

Between 1984 and 1996, 255 consecutive patients were treated at the University Hospital of Berne for a malignant primary tumour of the ovaries. The clinical records of the departments of medical oncology and of gynaecology were reviewed. 172 of these patients had both the initial surgical and the medical treatment at this hospital. The study was approved by the local institutional ethics review committee.

2.1. Demographic and clinical data

Information was collected from clinical records. In addition to the data shown in Table 1, the following variables were assembled: date and age at diagnosis; date of surgery; surgical findings and procedures; initial chemotherapy (drugs, duration); haematological toxicity; CA125 after three chemotherapy cycles and at the end of treatment; clinical response; time to relapse; and survival. A clinical complete remission was defined as the absence of any clinical or radiological evidence of disease and a serum CA125 concentration within normal limits. Partial remissions, stable and progressive disease were defined according to standard World Health Organization (WHO) criteria [8].

2.2. Statistical methods

Categorical variables were analysed with cross-tables, and associations were tested for statistical significance by χ^2 or Fisher's exact tests, respectively. Multivariate logistic regression analysis was used to assess prognostic factors for the achievement of a complete remission. Survival was estimated according to the Kaplan–Meier method [9], and differences between survival curves were evaluated by the logrank test [10]. Multivariate proportional hazards models [11] were used to evaluate the contribution of different prognostic factors. The appropriateness of the assumption of proportional hazards was tested visually by constructing log-minus-log plots of the most important covariates; no violation of this assumption was detected (data not shown). Age was treated as a categorical variable in all (univariate and logistical regression) analyses except in the multivariate proportional regression analysis of survival, where age was treated as a continuous (numerical) covariate. All P values reported are two-sided, and P values of < 0.05 were considered statistically significant. The statistical analyses were performed using the SPSS 8.0 for Windows software (SPSS Inc. 1997, Chicago, IL, USA).

3. Results

Between 1984 and 1996, 172 patients were treated for malignant primary ovarian neoplasms at the departments of gynaecology and medical oncology of the University Hospital in Berne. 12 patients (7%) did not have epithelial ovarian cancer (sarcoma, 1; malignant

Table 1
Patient characteristics

	n (%)
Number of patients	145 (100)[a]
WHO performance status	
0	97 (67)
1	20 (14)
2	3 (2)
3	22 (15)
4	3 (2)
Insurance status	
I	18 (12)
II	60 (41)
III	67 (46)
Histology	
Serous	62 (43)
Mucinous	17 (12)
Undifferentiated	27 (19)
Other	39 (27)
Histological grade	
1	15 (10)
2	36 (25)
3	94 (65)
FIGO stages	
I	27 (19)
II	13 (9)
III	68 (47)
IV	37 (26)

[a] The per cent figures may not add up to 100 due to rounding errors.

teratoma, 4; dysgerminoma, 1; mixed mesodermal tumour, 2; granulosa cell carcinoma 4). 15 of the remaining 160 patients (9%) with epithelial ovarian cancer had low-malignant potential ('borderline') carcinoma. The median age of these patients was 55 years (range: 25–74). 10 patients had FIGO stage I, 1 stage II and 4 stage III disease. After a median follow-up period of 70 months, 3 patients with borderline tumours have died. The 145 patients with invasive epithelial ovarian cancer form the basis of the subsequent analysis. The median age at diagnosis was 61 years (range: 18–84 years). The main characteristics of the patients are summarised in Table 1. The median follow-up period was 81.9 months (range: 21–181). Most patients presented with poorly differentiated (grade 3, 65%) FIGO stage III (47%) or IV (26%) cancer. The relationship of the insurance type with numerous prognostic and demographic variables is summarised in Table 2.

Primary surgery resulted in so-called 'optimal' tumour debulking to cancer residues of <2 cm in 63% of the patients with stage III and in 25% of patients with stage IV disease. For patients with stage III disease, cross-tabulation revealed that the amount of postoperative residual tumour did not depend on any of the variables investigated; specifically, the residual tumour size was independent of performance status and histological grade (data not shown), as well as the insurance category (Table 2). We observed a trend towards more successful debulking surgery in more recent years (1992–1996 22% no macroscopic residuals, 50% <2 cm; 1984–1991 14% no macroscopic residuals, 40% <2 cm).

Eighty per cent of patients (116/145) were treated with chemotherapy. Of the 29 patients who did not receive chemotherapy, 18 had stage I disease; chemotherapy was withheld in the remaining 11 patients for various medical reasons. The majority of the patients (85%; 99/116) had platinum-based chemotherapy, and 12/17 patients who did not receive a platinum compound were treated before 1988. Only 13 patients (9%) received

Table 2
Associations of insurance status and age, stage, surgery and chemotherapy

	Insurance type			P[a] value
	I ($n=18$)	II ($n=60$)	III ($n=67$)	
All patients ($n=145$)	*n* (%)	*n* (%)	*n* (%)	
Age				0.0062
$\leqslant 50$	4 (22)	22 (37)	9 (13)	
51–65	10 (56)	19 (32)	23 (34)	
>65	4 (22)	19 (32)	35 (52)	
FIGO stage				0.48
I	1 (6)	10 (17)	16 (24)	
II	1 (6)	7 (12)	5 (7)	
III	12 (67)	27 (45)	29 (43)	
IV	4 (22)	16 (27)	17 (25)	
Residual tumour after surgery				0.20
None	4 (22)	23 (38)	25 (37)	
<2 cm	9 (50)	15 (25)	14 (21)	
$\geqslant 2$ cm	5 (28)	22 (37)	25 (37)	
Unknown	0	0	3 (4)	
Chemotherapy				0.045
No	1 (6)	9 (15)	19 (28)	
Yes	17 (94)	51 (85)	48 (72)	
Patients with chemotherapy ($n=116$)	$n=17$	$n=51$	$n=48$	
	n (%)	*n* (%)	*n* (%)	
Chemotherapy				0.0061
Single drug	2 (12)	9 (18)	19 (40)	
Multiple drugs	15 (88)	42 (82)	29 (60)	
Platinum-based chemotherapy				0.0022
No	0	6 (12)	11 (23)	
Yes	17 (100)	45 (88)	37 (77)	
Duration of chemotherapy				0.44
<90 days	3 (18)	16 (31)	20 (42)	
90–180 days	10 (59)	27 (53)	22 (46)	
>180 days	4 (24)	8 (16)	6 (13)	

[a] χ^2-test.

paclitaxel as part of their initial chemotherapy regimen. The proportion of patients with chemotherapy was similar in patients treated between 1984 and 1991 and between 1992 and 1996 (59/75, 79% versus 57/70, 81%), but the proportion of patients receiving platinum-based chemotherapy (cisplatin or carboplatin) was significantly higher in patients diagnosed between 1992 and 1996 (43/59, 73% versus 56/57, 98%, $P < 0.001$).

The primary treatment strategy (initial surgery, chemotherapy, and interval surgery after three cycles of chemotherapy in selected patients who could not receive optimal debulking at primary surgery) resulted in a complete remission in 70 patients (48%) and in a partial remission (PR) in 36 patients (25%). The remaining patients had either stable (5; 3%) or progressive (29; 20%) disease. The clinical record was inadequate to define the response of 5 patients (3%). The analysis of predictors of complete remission was restricted to patients with stage $\geqslant$ II disease. Significant predictors of complete remission in univariate analysis were the FIGO stage, the amount of postoperative residual tumour and the type of insurance (Table 3): patients with class I (private) insurance coverage had a higher probability (70%) of obtaining a complete remission than the other patients (34% for class II, 29% for class III). When the analysis was limited to the patients who had received chemotherapy, the above factors remained statistically significant. The predictors of complete remission were further analysed by multivariate logistic regression analysis. The stage obviously predicts the results of debulking surgery; therefore, stage was not an independent predictor of complete remission when the

Table 3
Predictors of complete remission (CR) as a result of primary treatment (surgery and chemotherapy) in patients with FIGO stage $\geqslant$ II ovarian cancer

	Proportion of patients in CR (%)	Univariate P value[a]	Multivariate P value
All patients ($n = 145$)			
WHO performance status (0–4)		0.31	
FIGO stage (II, III, IV)		0.004	0.083
Stage II	77		
Stage III	38		
Stage IV	22		
Histological grade (1, 2, 3)		0.32	
Residual tumour (none, <2 cm, $\geqslant 2$ cm)		<0.001	0.019
No macroscopic tumour	64		
<2 cm	47		
$\geqslant 2$ cm	19		
Age ($\leqslant 50$, 51–65, >65 years)		0.67	
Date of diagnosis (1984–1991, 1992–1996)		0.51[b]	
Chemotherapy versus no chemotherapy		0.052[b]	0.11
Chemotherapy	9		
No chemotherapy	40		
Insurance type (I, II, III)		0.013	0.025
I	70		
II	34		
III	29		
Patients with chemotherapy			
WHO performance status (0–4)		0.36	
FIGO stage (II, III, IV)		0.008	0.015
Histological grade (1, 2, 3)		0.40	
Residual tumour (none, <2 cm, $\geqslant 2$ cm)		0.001	0.019
Age ($\leqslant 50$, 51–65, >65 years)		0.68	
Date of diagnosis (1984–1991, 1992–1996)		0.35[b]	
Insurance type (I, II, III)		0.029	0.082
Chemotherapy with single versus multiple drugs		0.002[b]	0.24
Single drug	17		
Combination chemotherapy	49		
Platinum-based versus non-platinum chemotherapy		0.001[b]	0.056
Non-platinum	6		
Platinum	47		
Duration of chemotherapy ($\leqslant 90$, 90–180, >180 days)		0.17	

[a] χ^2-test.
[b] Fisher's exact test.

result of surgery was taken into account. When the analysis was limited to patients who received chemotherapy, the favourable effect of the insurance status on the result of the initial treatment was not formally statistically significant ($P = 0.082$); this may result from a lack of statistical power due to the lower number of patients in this analysis.

At the cut-off date (median follow-up 81.9 months), 92 women (63%) had died, and 39 of the 70 patients with complete remission (56%) had relapsed. The median survival of the whole cohort was 32.8 months with a probability of survival at 5 years of 31%. The 5-year probability of survival was 72% (standard error of the mean (SEM) 9.8%) for stage I, 53% (SEM 16.2%) for stage II, 17% (SEM 5.9%) for stage III and 11% (SEM 5.5%) for stage IV cancer. Between 1984 and 1991, the median survival was 27.4 (95% confidence interval (CI) 17.2 to 37.6) months; in the more recent period (1992–1996) the median survival was 48.5 (95% CI 29.4–67.6) months ($P = 0.056$) although there was no shift in the

Table 4
Univariate analysis of prognostic factors for overall survival

	Median survival (months)[a]	*P* value[b]
All patients ($n = 145$)		
WHO performance status (0–4)		0.52
FIGO stage		< 0.0001
I	95.4	
II	> 130	
III	30.2	
IV	12.5	
Histological grade		0.0003
1	95.4	
2	38.2	
3	21.0	
Residual tumour		< 0.0001
none	74.0	
< 2 cm	40.0	
⩾ 2 cm	12.5	
Age		0.0045
⩽ 50 years	63.3	
51–65 years	40.0	
> 65 years	18.9	
Date of diagnosis		0.056
1984–1991	27.4	
1992–1996	48.5	
Insurance type		0.18
Type I	50.5	
Type II	38.2	
Type III	28.4	
Patients with chemotherapy ($n = 116$)		
WHO performance status (0–4)		0.89
FIGO stage (I, II, III, IV)		0.003
Histological grade		0.28
Residual tumour (none, < 2 cm, ⩾ 2 cm)		0.0007
Age (⩽ 50, 51–65, > 65 years)		0.017
Date of diagnosis (1984–1991, 1992–1996)		0.016
Insurance type		0.0084
Type I	47.5	
Type II	33.4	
Type III	21.7	
Chemotherapy with single versus multiple drugs		0.011
Platinum based versus non-platinum chemotherapy		< 0.0001
Duration of chemotherapy (⩽ 90, 90–180, > 180 days)		0.49
Haematological toxicity grade 3 or 4 in any cycle		0.16

[a] Kaplan-Meier estimates.
[b] Logrank test.

stage or age distribution and in the distribution of the different types of insurance coverage (data not shown): this improvement was more pronounced when the analysis was restricted to patients receiving chemotherapy (23.5 versus 40.0 months; $P = 0.016$).

The impact of demographic and biological factors on survival is summarised in Table 4. In univariate analyses of all 145 patients, the stage, the amount of residual cancer after debulking surgery, the date of diagnosis and the histological grade were predictors of survival; in addition, we found that the median survival of older patients was substantially shorter than younger patients. When only patients with chemotherapy were considered, the histological grade was no longer statistically significant, but the type of insurance coverage was a significant predictor of survival; for instance, the median survival of patients with basic (Type III) coverage was 21.7 (95% CI 12.2–31.2) months compared with 47.5 (95% CI 24.6–70.4) months and 33.4 (95% CI 5.4–61.4) months for patients with Type I or Type II coverage, respectively ($P = 0.0084$).

The association between insurance coverage and survival was not anticipated: there was no significant correlation between stage (Table 2) or histological grade (data not shown) and insurance status. This led us to investigate the correlation of insurance type, use of

Table 5
Cox multivariate analysis of prognostic factors for survival

		HR (95% CI)	*P* value
All patients ($n = 145$)			
Age		1.03 (1.00–1.05)	0.019
Insurance type[a]			
	II	2.31 (1.05–5.04)	0.037
	III	3.30 (1.52–7.17)	0.003
Grade[b]			
	II	4.03 (1.22–13.2)	0.022
	III	7.02 (2.13–23.2)	0.001
FIGO[c]			
	II	2.96 (0.72–12.2)	0.134
	III	8.74 (2.31–33.1)	0.001
	IV	18.29 (4.77–70.2)	< 0.001
Residual tumour[d]			
	< 2 cm	0.80 (0.46–1.39)	0.427
Chemotherapy[e]	None	0.18 (0.06–0.51)	0.001
Date of diagnosis (1984–1991, 1992–1996)[f]	1992–1996	0.72 (0.45–1.16)	0.178
Patients with chemotherapy ($n = 116$)			
Age		1.03 (1.01–1.06)	0.012
Insurance type[a]			
	II	1.92 (0.83–4.40)	0.126
	III	3.40 (1.51–7.69)	0.003
Grade[b]			
	II	1.75 (0.49–6.34)	0.392
	III	2.91 (0.83–10.2)	0.096
FIGO[c]			
	II	0.65 (0.15–2.86)	0.570
	III	1.54 (0.47–5.02)	0.476
	IV	3.22 (0.93–11.2)	0.066
Residual tumour[d]			
	None	0.63 (0.30–1.30)	0.208
	< 2 cm	0.99 (0.56–1.77)	0.984
Date of diagnosis (1984–1991, 1992–1996)[f]	1992–1996	0.85 (0.47–1.53)	0.593
Chemotherapy with single versus multiple drugs[g]	Multiple	0.56 (0.24–1.32)	0.185
Platinum versus non-platinum chemotherapy[h]	Non-platinum	3.05 (1.13–8.25)	0.028

HR, hazard ratio; CI, confidence interval.

[a] The comparison was made with patients with Type I insurance.

[b] The comparison was made with grade 1 tumours.

[c] The comparison was made with patients with FIGO stage I tumours.

[d] The comparison was made with postoperative residuals $\geqslant 2$ cm.

[e] The comparison was made with patients requiring chemotherapy.

[f] The comparison was made with patients diagnosed between 1984 and 1991.

[g] The comparison was made with patients receiving single drug chemotherapy.

[h] The comparison was made with patients receiving platinum-based chemotherapy.

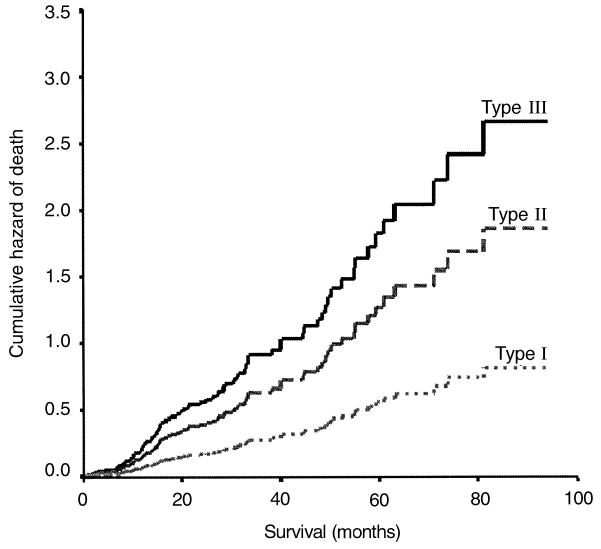

Fig. 1. Cumulative hazard of death according to the type of insurance (the other significant covariates have been set to their respective mean values) Patients with Type I and II insurance had a significantly lower hazard ratio of death than patients with Type III insurance coverage (see Table 5).

chemotherapy and age. Table 2 illustrates that older patients had Type III insurance coverage more frequently than younger patients; in addition, chemotherapy was used slightly less often in patients with Type III insurance. When the analysis was limited to patients who received chemotherapy, it appeared that patients with basic coverage (Type III) more frequently received single drug rather than combination chemotherapy compared with those with Type I or II insurance and had a higher probability of receiving non-platinum-based treatment. A Cox proportional hazards model was used to assess the independent contribution of the prognostic factors (Table 5). The insurance status remained a statistically significant even after adjusting for age, stage and chemotherapy. Fig. 1 illustrates the theoretical cumulative hazard of death for patients with the different types of insurance after adjustment for age, stage and treatment. Although the insurance status was correlated with age (Table 2), the interaction term between insurance and age was not statistically significant in an additional Cox model (data not shown).

4. Discussion

This review of patients with invasive epithelial carcinoma of the ovary treated in a Swiss tertiary care hospital revealed that although all patients were covered by basic health insurance, those with additional private insurance had a better prognosis.

All operated patients had exploratory laparotomy and staging procedures according to current standards to establish the correct stage. During the study period, we observed a steady increase of the proportion of patients with optimally debulked disease. This improvement did not depend on the insurance category and coincided with a heightened awareness of the prognostic importance of surgical cytoreduction in ovarian cancer. This finding might reflect an increasingly aggressive surgical attitude [3], as well as the informal specialisation of gynaecological oncologists [4,12]. The surgical advances combined with the more widespread use of platinum-based chemotherapy prompted an increase in the median survival of the patients by 21.1 months between the periods of 1984–1991 and 1992–1996. The overall efficacy of the initial therapy and the survival of the patients treated for ovarian cancer at the University Hospital in Berne between 1984 and 1996 is similar to published data [5,13]; only a small minority (9%) of the patients received paclitaxel as part of the initial chemotherapy.

The multivariate analysis of potential prognostic factors revealed stage, postsurgical residual tumour and chemotherapy as independent predictors of achieving a complete response. The same factors, the histological grade and age were significant predictors of survival. Thus, the prognostic factors in our cohort are similar to previously published prognosticators [14]. In addition to the classical prognostic factors, the type of insurance was predictive of response and survival even after adjusting for age, stage, histological grade and chemotherapy. Patients with private (Type I or Type II) insurance coverage had a significantly more favourable outcome than patients with basic insurance coverage; in a univariate analysis, this effect was statistically significant only in patients who received chemotherapy. This is easily explained by the fact that patients who did not receive chemotherapy had either an excellent or a particularly dismal prognosis; thus, their exclusion from the analysis eliminates an important confounding factor. This interpretation is strengthened by the significance of insurance type in the multivariate models that allow for the prognostic importance of chemotherapy. The finding of insurance type as a significant independent predictor of survival is surprising in view of the fact that all patients had equal access to outpatient medical care, and that drugs were reimbursed equally for all types of insurance coverage. Differences in patient age and in the medical treatment were nevertheless obvious: patients with private insurance were younger and received more platinum-based and combination chemotherapy; however, even after adjusting for these and other factors in a multivariate proportional hazards regression analysis, the patients with private insurance had a more favourable prognosis. Insurance status is an important predictor of mortality in the USA with uninsured persons having a significantly higher mortality than patients with health insurance [15]. More limited access to healthcare is an explanation for the

poor outcome in African American compared with white American women with breast [16] and ovarian [17] cancers and for the poorer prognosis of patients without insurance coverage in the USA [18,19]. As the FIGO stages in this study were similarly distributed, the differences in outcome can not be explained by an earlier detection of cancer in patients with better insurance coverage. Since private insurance is substantially more expensive than basic insurance, the insurance status may correlate with the income of the patients; studies of the correlation of insurance status and income are under way in Switzerland, but are not currently available. Large differences have been observed in the outcome of certain cancers between poor and affluent patients [6,20], as well as between high and low community incomes in the USA, Canada [21] and Great Britain [22]. Such differences were not observed for ovarian cancer in Canada and the USA [21]. For patients with adequate access to screening and therapy, as is the case in the patients in this study, the published information of the impact of insurance on outcome is scarce: patients with breast cancer and fee-for-service insurance had a slightly less favourable outcome than patients with HMO-type insurance, but the difference in outcome failed to reach statistical significance [23].

In summary, the present review is the first to address the impact of different insurance models on the outcome of therapy in patients with ovarian cancer; it revealed that although the overall results of treatment between 1984 and 1996 were excellent, patients with private insurance had a better prognosis than patients with basic insurance. Further research is needed to define the reasons for the observed inequality and to establish processes of medical care that improve the outcome of patients without private insurance coverage.

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