

Societal costs of ovarian cancer in a population-based cohort – a cost of illness analysis

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ABSTRACT

Background: The societal cost associated with ovarian cancer (OC) is not well known. Increasing costs for new treatments and/or the impact of organizational changes motivates these costs to be described and communicated. This study aims to evaluate the cost of illness of OC in a population-based cohort.

Material and methods: All patients diagnosed with ovarian, fallopian tube, primary peritoneal cancer, and serous cancer of undesignated primary site (UPS) in 2011–2012 were followed for six years. Direct costs, i.e., costs for health care expenditures, were gathered from the regional healthcare database. Information on indirect costs, i.e., costs of loss of production due to sick leave, was retrieved from Statistics Sweden. Sub-group analyses were conducted regarding stage, income levels, residential area, and diagnosis.

Results: The cost of illness for all stages during the six years of follow-up was €201,086 per patient, where indirect costs constituted 43.7%. The mean cost of illness per year per patient for all stages was €33,514. Direct costs were higher in advanced stages compared to early stages for every year from diagnosis. During the first two years, there were no differences in indirect costs between early and advanced stages. However, during the third year there was a difference with higher indirect costs in advanced stages. There was no difference in direct costs depending on income levels. Regarding residential area, there was a difference in the outpatient cost during the index and second year with higher costs when chemotherapy and follow-up were provided at county hospitals, compared to at the tertiary hospital.

Conclusions: Indirect costs constituted a large part of the cost of illness over 6 years from diagnosis. This could indicate that even though treatment costs can be expected to rise with the introduction of new therapies, the societal cost may decrease when survival increase.

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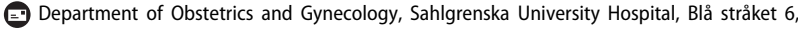
Cost of illness; direct cost; indirect cost; societal cost; ovarian cancer

Background

Treatment of ovarian cancer (OC) is costly, both for the women affected and for society. OC is often diagnosed in advanced stages and has a high mortality rate with a 5-year survival of less than 45% [1]. Most women with advanced disease have a relapse within two years and many patients therefore receive multiple treatment lines, mainly with chemotherapy [2]. New targeted therapies have shown encouraging results, delaying relapse and increasing survival [3–6]. With new promising therapies, the treatment costs can be expected to rise, but the societal cost may fall due to longer progression-free survival together with increased overall survival.

Cost of illness is a method used to describe the economic consequences of diseases. The method was developed by

Dorothy Rice [7] and includes both health care expenditures, the so-called *direct costs*, and the cost of loss of production due to sick leave and premature death, the so-called *indirect costs*. In other words, direct costs are those for which payments are made and indirect costs are those for which resources are lost [8]. There are some publications on cost of illness related to cancer diseases. For example, a large population-based cost-of-illness study on breast cancer in Sweden showed that the direct costs of the disease only constituted 30% of the total cost of illness, whereas 70% were indirect costs with the main cost driver (52%) being the loss of production caused by premature mortality [9]. This finding was supported by a cost-of-illness study on pancreatic cancer where premature mortality constituted 79% of the cost of loss of productivity [10]. In terms of OC, there are multiple studies on the costs connected to the introduction of new

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treatments [11–16], but, to our knowledge, only one estimating the societal cost including cost of productivity loss [17]. The cost of illness of OC is therefore less known and hence it is difficult to correctly evaluate the societal cost of new medical treatments.

This study aimed at measuring the cost of illness of OC in a complete population-based cohort. Additionally, we sought to analyze whether there were differences in the cost of illness related to income levels and residential area. The study was performed at the time after centralization of primary surgical treatment in advanced stages in our region, but before the introduction of new medical targeted therapies, such as angiogenesis inhibitors and poly(ADP-ribose) polymerase inhibitors (PARPi).

Material and methods

Study population

This is a population-based cohort study from the county of Western Sweden, i.e., the Region Västra Götaland, with 1.7 million inhabitants. The Swedish Quality Register for Gynecological Cancer (SQRGC) was used to identify all women ≥ 18 years in the region diagnosed with ovarian, fallopian tube, primary peritoneal cancer, or serous cancer of undesignated primary site (UPS) from 1 January 2011 to 31 December 2012. Patients were followed for six years. The study was approved by the regional ethical review board in Gothenburg (Dnr 867–16).

Data collection

Detailed information concerning cancer diagnosis, age at diagnosis, received treatment, and FIGO stage was retrieved from the SQRGC. The SQRGC has been validated as previously described and has close to 100% coverage every year in the Region Västra Götaland compared to the Swedish National Cancer Registry [18]. Reporting all new cancer diagnoses to the Swedish National Cancer Registry is mandatory. All included patients have approved participation in the SQRGC. The study was conducted by linking Swedish registry data based on unique personal identity numbers available for each member of the Swedish population [19]. In Sweden, all cancers are treated in public care. Staging was performed by the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) classification from 1988.

The Longitudinal Integration Database for Health Insurance and Labor Market Studies from Statistics Sweden (the LISA registry), was used to obtain socioeconomic status, including income, employment, sick leave, and marital status. Individual information on inpatient and outpatient healthcare for six years following diagnosis was retrieved from the health-care database VEGA in Region Västra Götaland. Ovarian, fallopian tube, and primary peritoneal cancer were together categorized into one group, named 'ovarian cancer and other'.

Treatment setting

The region has one tertiary hospital and three county hospitals. Inhabitants in areas where basic gynecological inpatient care was provided at the tertiary hospital were considered urban residents, hereafter referred to as 'urban', and women living elsewhere in the Region Västra Götaland were considered 'region' residents. There is a combination of urban and rural areas around both the tertiary hospital and the county hospitals. Primary surgery of advanced OC, including extensive surgery, such as upper abdomen surgery, was centralized to the tertiary hospital 1 January 2011. Women with presumed FIGO Stage I disease had pelvic and paraaortic lymphadenectomies for staging performed at the tertiary hospital. The following outpatient adjuvant chemotherapy was administered at either the tertiary hospital for urban residents or at the local county hospital for region residents.

Standard adjuvant treatment

The main treatment of choice was carboplatin AUC 5 and paclitaxel 175 mg/m² intravenously every third week for six cycles. Women treated with neoadjuvant chemotherapy generally had interval debulking surgery performed after three or four cycles of chemotherapy. Treatment was planned according to regional guidelines introduced in 2011, and since 2012 the very similar Swedish national guidelines [20]. The angiogenesis inhibitor bevacizumab was not implemented in Sweden until 2013. Patients had clinical follow-ups at fixed time-points if no recurrence occurred; every third to fourth month during the first two years after primary treatment; every six months for the following three years until a total follow-up time of five years. At first recurrence, a majority were treated with carboplatin combinations and at further recurrences patients were treated with various chemotherapy regimens.

Cost analysis

The cost analyses were conducted from a societal perspective and are presented in Euro (€). Thus, both healthcare utilization from inpatient and outpatient care and cost from loss of production were included in the analyses. An approximate exchange rate of 0.10 was used when converting from Swedish krona (SEK) to €, however the actual average exchange rate was 0.093 during 2011–2018 (range 0.086–0.103) [21]. The data were structured by hospitalization episode and outpatient visit, i.e., one hospitalization episode or visit had one cost connected to it, but could contain several ICD-10 codes and procedure codes. Thus, costs were differentiated on care setting, such as inpatient or outpatient. Healthcare utilizations due to other conditions not related to OC were extracted from the cost analyses. All costs are presented in one-year periods for every individual starting at the date of diagnosis. Costs for primary care services and prescription medication were not included in this study.

Annual cost for loss of productivity was estimated as a function of individual annual days of sick leave multiplied

with each woman's individual daily income. Loss of production was only accounted for women of working age, i.e., up to 67 years old and not for women older than 67 years.

Statistical analysis

Descriptive statistics of patient characteristics were presented as frequencies with percentage, mean with standard deviation, or median with minimum and maximum values.

The statistical analyses included three dependent variables: outpatient costs; inpatient costs; and cost of production loss. These dependent variables were positively skewed. Thus, generalized linear models (GLMs) with Gamma-distribution of the dependent variables and with robust variance and 95% confidence level were used to estimate the inpatient and outpatient healthcare cost and cost of loss of production. The regression models were run for each year separately and were adjusted with the following covariates: age at diagnosis (discrete variable), residence (coded as 'urban' or 'region'), cancer type (coded as 'ovarian cancer and other' or 'cancer of undesignated site'), FIGO stage (coded as 'FIGO I-II' or 'FIGO III-VI, X'), and income at index year (categorized into three equal groups of mean annual income from work for women up to 67 years old).

All analyses were carried out in Stata version 16.1 (Stata, College Station, TX). The 'glm' was used to fit the regression models with 'amly(gamma)' and 'link(log)', while the 'margins' command was used for predictions.

Results

There were 283 women diagnosed with ovarian, fallopian tube and primary peritoneal cancer, together hereafter

Table 1. Demographic features.

	Total
Number of patients, <i>n</i> (%)	283 (100)
Index year 2011, <i>n</i> (%)	137 (48)
Index year 2012, <i>n</i> (%)	146 (52)
Age at diagnosis, median years (range)	67 (20–92)
Mean years (SD)	66 (13)
Residence, <i>n</i> (%)	
Urban	171 (61)
Region	111 (39)
Missing	1 (0)
Marital status, <i>n</i> (%)	
Married/partner	144 (51)
Single	122 (43)
Missing	17 (6)
Annual income at index year (€) ^a , mean (SD)	
Low income (range < 3000, <i>n</i> = 51)	122 (500)
Middle income (range 3000–25,000, <i>n</i> = 51)	15,631 (5622)
High income (range > 25,000, <i>n</i> = 51)	34,564 (12,272)
FIGO stage, <i>n</i> (%)	
I–II	76 (27)
III–VI, X	207 (73)
Cancer type, <i>n</i> (%)	
Ovarian cancer and other ^b	243 (86)
Serous cancer of undesignated primary site	40 (14)

^aCategorized into three equal groups based on annual income from work for women up to 67 years old; ^bOvarian, fallopian tube, and primary peritoneal cancer.

n: number; €: Euro; SD: standard deviation; FIGO: Federation Internationale de Gynecologie d'Obstetrique

named OC, and UPS during the study period, 2011–2012 (Table 1). No patients were excluded. One patient was missing in the analysis of residency due to hidden identity and unknown area of residency. There were 153 out of 283 women (54%) aged 67 years or younger at diagnosis, with a median age in the cohort of 67 years. Detailed demographic features of all women are presented in Table 1.

In total, one patient was treated with bevacizumab at first recurrence and three patients at later recurrences. Patients received up to eight lines of oncological treatment during the six years of follow-up.

Costs

The total cost of illness during six years for all stages was €201,086 per patient where the indirect cost constituted 43.7% (€87,843) (Table 2). The mean cost of illness per year for all stages was €33,514 per patient. The indirect cost from diagnosis for all FIGO stages constituted 28.7%, 53.2%, 49.3%, 47.2%, 43.1%, and 59.1% of the cost of illness for every year, respectively. The cost of illness was €22,677 per patient in FIGO Stages I and II and €37,519 per patient in FIGO Stages III and IV and X during the index year. The mean cost of illness per year in FIGO Stages I and II was €9082 per patient and €24,433 per patient in FIGO Stages III and IV and X, where indirect cost constituted 47.8% and 42.2%, respectively (Table 2).

Both the inpatient and outpatient costs per patient were significantly higher in advanced stages compared to early stages for every year from diagnosis (Figure 1). The highest inpatient cost per patient was during the index year for all FIGO stages, €11,737 (95% CI: €9683–13,792) in early stages and €25,453 (95% CI: €23,134–27,772) in advanced stages. The highest outpatient cost per patient was during the second year in early stages, €2621 (95% CI: €2033–3210), and during the third year in advanced stages, €7211 (95% CI: €5767–8656) (Figure 1).

There was no statistically significant difference in the indirect cost per patient, i.e., the cost of production loss, for women of working age, ≤67 years (*n* = 153) at diagnosis, comparing early stages with advanced stages during the first 2 years after diagnosis (Figure 2). However, during the third year there was a statistically significant difference with a higher cost of production loss for women in advanced stages. During the third year the cost of production loss for women diagnosed with FIGO Stages I and II was €4156 per patient (95% CI: €1735–6578) compared with €13,134 per patient (95% CI: €7049–19,220) for women with FIGO Stages III and IV or X. During the fourth, fifth, and sixth year after diagnosis the CIs were wide and overlapping and no statistically significant difference was found (Figure 2).

In regard to inpatient and outpatient costs per patient compared to income levels, no statistically significant difference was found (Figure 3(a)). Inpatient and outpatient costs were calculated per residential area, with no statistically significant difference in inpatient cost per patient during the first or second year (Figure 3(b)). There was a statistically significant difference in outpatient cost per patient during the

Table 2. Cost of illness of ovarian cancer and serous cancer of undesignated primary site.

	Index year <i>n</i> = 283	Second year <i>n</i> = 254	Third year <i>n</i> = 210	Fourth year <i>n</i> = 183	Fifth year <i>n</i> = 158	Sixth year <i>n</i> = 126	Total cost all years	Mean cost/year
All FIGO stages								
Cost of illness, €	60,196	43,205	35,045	24,983	23,324	14,334	201,086	33,514
direct costs, € (%)	42,947 (71.3)	20,213 (46.8)	17,755 (50.7)	13,194 (52.8)	13,277 (56.9)	5858 (40.9)	113,243 (56.3)	18,874 (56.3)
indirect cost ^a , € (%)	17,249 (28.7) <i>n</i> = 153	22,991 (53.2) <i>n</i> = 148	17,290 (49.3) <i>n</i> = 127	11,789 (47.2) <i>n</i> = 117	10,047 (43.1) <i>n</i> = 103	8476 (59.1) <i>n</i> = 87	87,843 (43.7)	14,640 (43.7)
FIGO I-II	<i>n</i> = 76	<i>n</i> = 74	<i>n</i> = 71	<i>n</i> = 67	<i>n</i> = 62	<i>n</i> = 58		
Cost of illness, €	22,677	13,966	7854	3677	4356	1960	54,490	9082
direct costs, € (%)	13,961 (61.6)	5010 (35.9)	3699 (47.1)	1922 (52.3)	2785 (63.9)	1074 (54.8)	28,451 (52.2)	4742 (52.2)
indirect cost ^a , € (%)	8716 (38.4) <i>n</i> = 50	8956 (64.1) <i>n</i> = 50	4156 (52.9) <i>n</i> = 48	1755 (47.7) <i>n</i> = 47	1571 (36.1) <i>n</i> = 43	887 (45.2) <i>n</i> = 41	26,041 (47.8)	4340 (47.8)
FIGO III-IV + X	<i>n</i> = 207	<i>n</i> = 180	<i>n</i> = 139	<i>n</i> = 116	<i>n</i> = 96	<i>n</i> = 68		
Cost of illness, €	37,519	29,239	27,190	21,306	18,968	12,374	146,596	24,433
direct costs, € (%)	28,986 (77.2)	15,204 (52.0)	14,056 (51.7)	11,272 (52.9)	10,492 (55.3)	4784 (38.7)	84,794 (57.8)	14,132 (57.8)
indirect cost ^a , € (%)	8534 (22.7) <i>n</i> = 103	14,035 (48.0) <i>n</i> = 98	13,134 (48.3) <i>n</i> = 79	10,034 (47.1) <i>n</i> = 70	8476 (44.7) <i>n</i> = 60	7590 (61.3) <i>n</i> = 46	61,803 (42.2)	10,301 (42.2)

All costs are estimated numbers per patient. ^aIndirect cost only includes women ≤ 67 years; *n*: numbers alive; FIGO: Federation Internationale de Gynecologie d'Obstetrique; €: Euro.

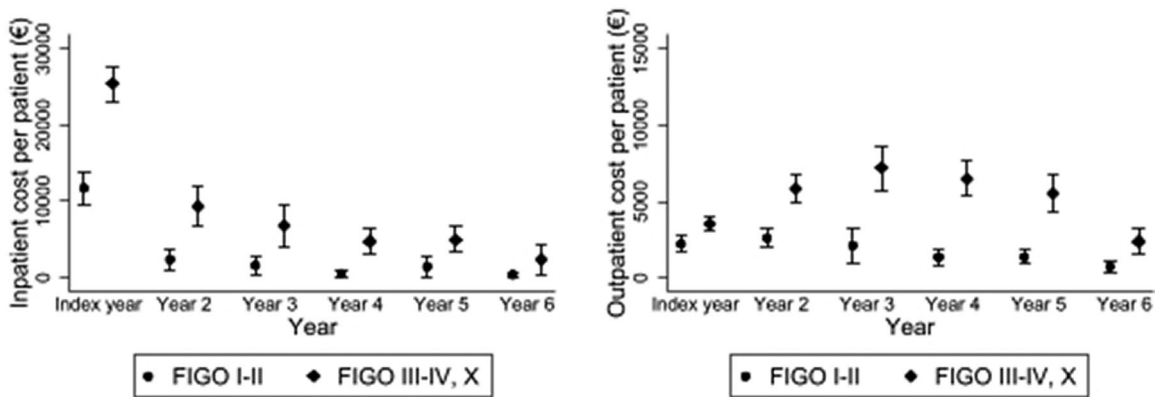


Figure 1. Direct costs shown as inpatient and outpatient costs per year per FIGO category (95% confidence interval). FIGO: Federation Internationale de Gynecologie d'Obstetrique.

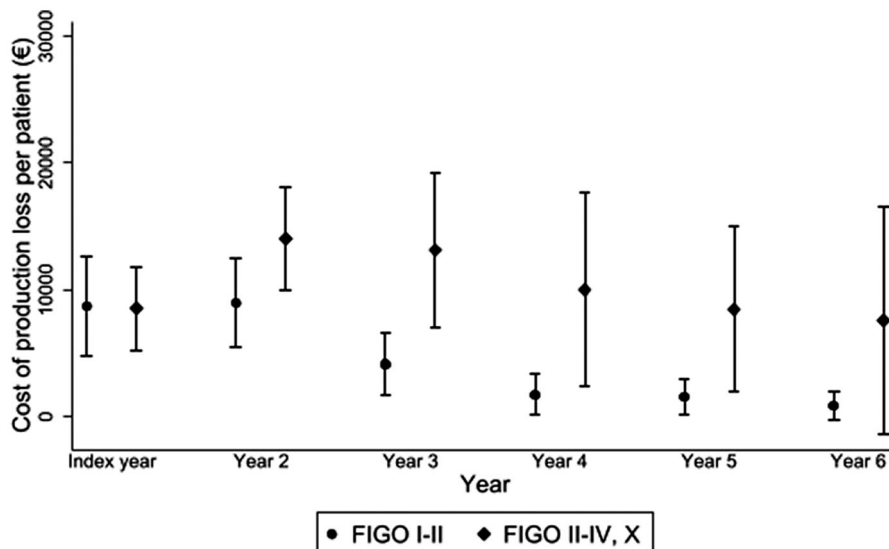


Figure 2. Indirect cost of production loss for working-age women (≤67 years) per year per FIGO category (95% confidence interval). FIGO: Federation Internationale de Gynecologie d'Obstetrique.

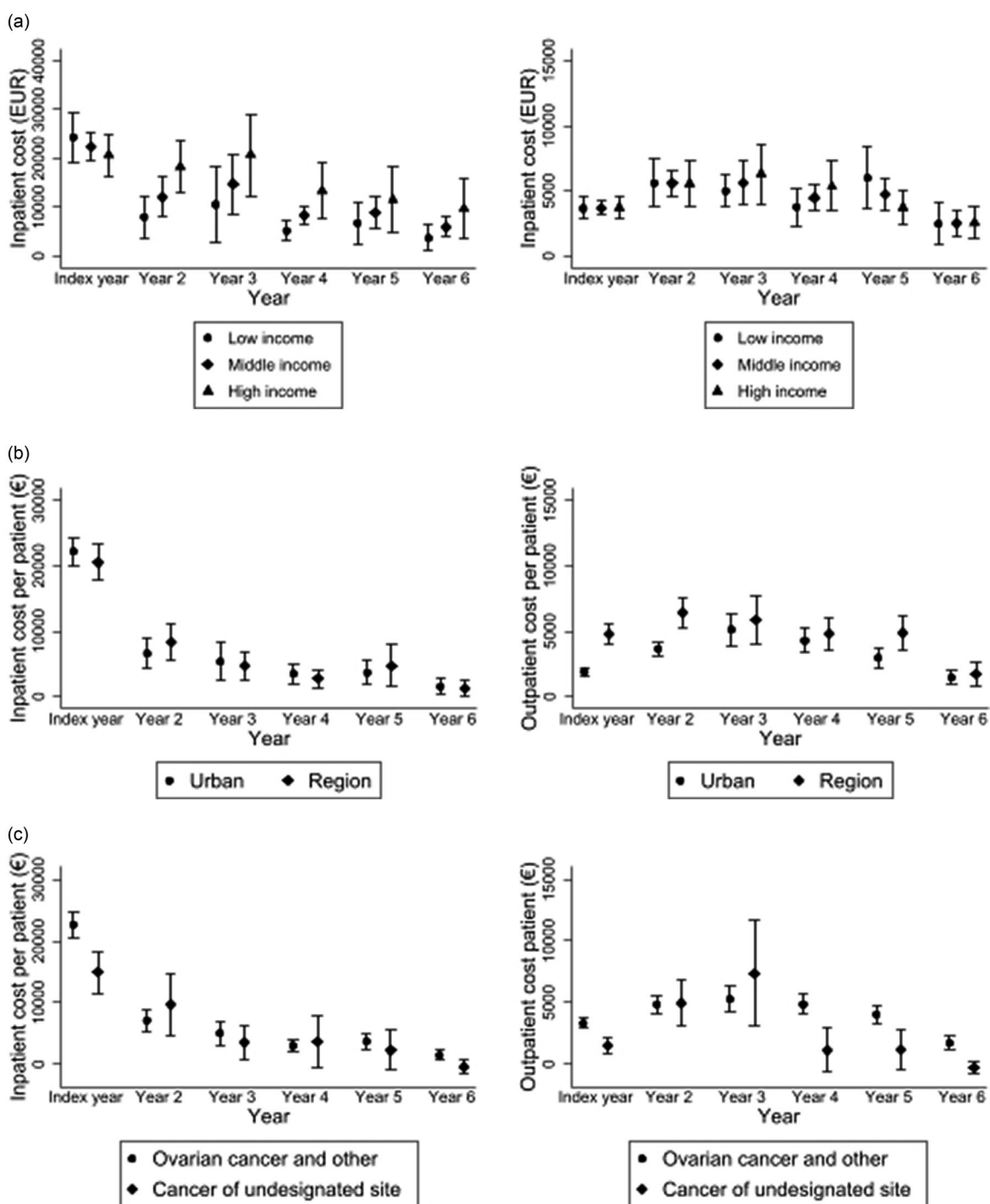


Figure 3. a) Direct costs shown as inpatient and outpatient costs per year per income group (95% confidence interval (CI)). Categorized into three groups based on annual income from work. Includes women up to 67 years old. b) Direct costs shown as inpatient and outpatient costs per year per residential area (95% CI). Numbers alive; Index year, Urban (U): 171, Region (R): 111. Second year, U: 146, R: 108. Third year, U: 118, R: 92. Fourth year, U: 106, R: 77. Fifth year, U: 91, R: 67. Sixth year U: 70, R: 56. c) Direct costs shown as inpatient and outpatient costs per year per cancer type (95% CI). Ovarian, fallopian tube, and primary peritoneal cancer categorized as 'Ovarian cancer and other'. Numbers alive; Index year, Ovarian cancer and other (OC): 243, Serous cancer of undesignated primary site (UPS): 40. Second year, OC: 226, UPS: 28. Third year, OC: 191, UPS: 19. Fourth year, OC: 169, UPS: 14. Fifth year, OC: 147, UPS: 11. Sixth year, OC: 120, UPS: 6.

first and second year after diagnosis. The outpatient cost per patient for urban residents during the index year was €1893 (95% CI: €1614–2172) and for region residents €4786 (95% CI: €3994–5578). During the second year the outpatient cost per patient for urban residents was €3638 (95% CI: €3039–4236) and for region residents €6400 (95% CI:

€5217–7584). In the third to sixth year, no statistically significant difference was observed (Figure 3(b)).

The inpatient cost per patient was significantly higher for OC than for UPS during the index year, €22,591(95% CI: €20,610–24,572) and €15,853 (95% CI: €12,993–18,712), respectively, but then similar and lower for the following

years (Figure 3(c)). The highest outpatient cost per patient occurred during the third year, €5254 (95% CI: €4233–6274) in the OC cohort and €7289 (95% CI: €3690–10,887) in the UPS cohort. During the index year and the fourth, fifth, and sixth year after diagnosis there were higher outpatient costs per patient in the OC group than in the UPS group (Figure 3(c)).

Discussion

There are, to our knowledge, no previous population-based studies on the cost of illness of OC and UPS. The concept of cost of illness includes both direct costs, i.e., health care expenditures including inpatient and outpatient costs and indirect costs, i.e., the cost of loss of production due to illness. Moreover, cost of illness is an important basis for further health economic evaluations of new treatments and organizational changes. In our complete population-based cohort of 283 women with OC and UPS the indirect cost constituted 43.7% of the cost of illness over 6 years from diagnosis. Direct costs were significantly higher in advanced stages compared to early stages for every year. During the first two years, there were no differences in indirect costs between early and advanced stages. There was no significant difference in direct costs depending on income levels but there was a significant difference in outpatient cost during the first two years after diagnosis toward more costly care for regional residents compared to urban residents.

The cost of illness of OC in Spain has been evaluated in a model where the total annual average cost was estimated to €24,111 per patient regardless of stage [17], a cost that is lower than our calculated median yearly cost per patient, but covering 10 years instead of 6 and costs are reduced for every year after diagnosis. In the Spanish study, the direct costs constituted 71.2%, direct non-healthcare costs (including formal and informal care) 24.7%, and indirect costs only 4.1%, a major difference compared to our study where indirect costs constituted 43.7% of the mean cost of illness per year. However, the Spanish study estimated that the cost per patient was higher the higher the stage, a finding that was confirmed by our study. Their study differs from ours in that they built a model from data collected from Spanish and international literature reviews and included estimated patients from 2017 to 2026, whereas the data in our study is based on population-based registered data.

Authors of previous studies on cost of illness in breast and pancreatic cancer reason that the great cost of production loss is caused by many patients being not yet retired when diagnosed, thus losing many years of income because of sick leave and premature death [9,10]. This argument is valid also for women diagnosed with advanced OC and UPS, diseases with high mortality. In our study, 153 out of 283 women were 67 years of age or younger at diagnosis and the median age in the cohort was 67 years, the recommended retirement age in Sweden. The indirect cost constituted 70% of the cost of illness of breast cancer [9] and 67% in human papillomavirus-related precancers and cancers [22] compared to 44% in our study. In prostate cancer, where

most patients are retired at diagnosis, the direct cost constituted 62%, informal care 28%, and productivity loss 10% [23,24]. The cost of production loss is significantly higher in advanced stages of OC compared to earlier stages after the second year from diagnosis in our study, most likely due to the high risk of recurrence. Hopefully, new treatment options will not only enhance progression-free survival but also decrease the cost associated with loss of production.

Interestingly, we found no difference in cost of illness depending on income levels. The median yearly income for all women 18–67 years of age in urban area of the tertiary hospital was €19,280 in 2011 and €19,800 in 2012, compared with €17,700 in 2011 and €18,510 in 2012 in the complete Region of Västra Götaland including the urban area of the tertiary hospital [24], and agrees well with our middle-income group. Our finding is in contrast to previous studies from the US, where they have shown a difference in mortality in OC depending on income level and geographical accessibility of healthcare [25–29]. In the US studies, the health care was not centralized and the individual cost of treatment depended on patients' individual economic resources and/or insurance.

We found a difference in cost depending on residential area in our study, but not the one expected. Our results demonstrated that women living in the urban area of the tertiary hospital had lower outpatient cost per patient compared to the region residents. We expected no difference or the opposite, based on the hypothesis that living closer to the tertiary hospital, where treatment decisions are made, would be beneficial and possibly lead to a higher consumption of healthcare.

The cost of aggressive and complex surgery has been studied by Aletti *et al.* with the conclusion that complex surgery was expensive, but cost-effective with an increased survival gain of 1.32 years with complex vs. simple surgery [30]. The increased survival after advanced surgery has been shown in multiple studies [31–33] and has prompted centralized care in many regions and countries. Moreover, we have previously shown an increased survival for all women with OC after centralized care in our region in 2011 and after the introduction of national guidelines in Sweden in 2012 [34–36]. We are not aware of any cost of illness studies on organizational changes for cancer patients in any country or region. The cost of major system change in providing specialist surgery for prostate, bladder, renal, and esophagogastric cancers in London and West Essex was ambitiously studied in regard to organizational healthcare costs, but the possible cost-benefits of prolonged survival were not estimated [37].

The introduction of PARPi in the treatment of advanced OC has excited patients and clinicians with promising results, but the treatment comes with increased costs [38,39]. Researchers have analyzed if these new treatments can be considered cost effective. Studies on out-of-pocket spending in the US suggest a high cost for the patients as the treatment may continue for years [15,40]. Cost-effectiveness studies have focused on costs of treatment and adverse events and the results are diverging where some show that

maintenance therapy with PARPi or bevacizumab may not be cost effective at the present time [13,14], whereas others show cost-effectiveness [41]. These studies differ in patient selection which may explain some of the differences. However, we found no studies on the total cost of illness including treatment with PARPi or bevacizumab. Our study analyses the cost of illness in a complete population-based cohort before the introduction of bevacizumab and PARPi and hopefully our results may enable health economic studies of new therapies in a future context.

One strength of our study is that we were able to include a close to complete population-based cohort of women with OC and UPS. Also, we were able to extract information on treatment, socioeconomic factors, and sick leave about every single patient since all Swedish citizens have a personal identification number. Furthermore, another strength of our study is that the care of advanced OC and UPS is centralized in the studied region since 1 January 2011 and thereafter the majority of women with advanced disease have been evaluated at a multidisciplinary board, deciding on the best treatment choice for each individual. Additionally, all women with OC regardless of stage have been treated according to the national guidelines for OC [36]. All these factors should ensure minimal bias. However, a possible weakness of our study may be the retrospective design. The cost of illness may have changed over time not only because of treatment changes but also due to societal changes. The median income in our study is considerably lower than the median national income of approximately €22,500 [24]. This may affect the outcome, and a national population may have higher indirect costs. However, the median income group of our study relates well to the median income of women in the complete region. Also, we do not have any information about the household income for women that are married or cohabitants.

Treatment of OC is costly to society. With the introduction of new targeted pharmacological therapies, the treatment costs can be expected to rise, but the societal cost may actually decrease when progression-free and overall survival increase. We hope that our study can inspire cost-of-illness studies on OC that may enable valuable evaluation of new treatments and reorganization of healthcare, which in turn may contribute to a sound use of public funds and equal healthcare for all women.

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Disclosure statement

The authors declare no conflicts of interest.

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Data availability statement

The data that support the findings of this study are available from the corresponding author (CP), upon reasonable request.

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