Societal costs of ovarian cancer 2018

NÄTVERKET MOT GYNEKOLOGISK CANCER

NordIQ ANALYTICS

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Abstract

Background

Ovarian cancer constitutes about 3% of all female cancers and is the most severe form of gynecological cancer given its high mortality. This is mainly due to difficulties in establishing diagnosis, as symptoms are difficult to identify, resulting in detection at an advanced stage when it is more difficult to treat. In addition to human suffering, ovarian cancer also results in significant healthcare consumption and productivity losses.

Aim

To estimate the prevalence and disease burden of ovarian cancer in Sweden in 2018, including cancer in the ovaries, fallopian tubes and peritoneum. Additionally, the study aimed to estimate the societal costs of ovarian cancer, including costs related to the healthcare sector and productivity losses.

Methods

A cost of illness study was conducted, where resource use was estimated based on data from the Swedish National Board of Health and Welfare, the Swedish Social Insurance Agency, scientific literature and the National Care Program for ovarian cancer in Sweden. A valuation of resource use was made based on cost data from the Swedish Association of Local Authorities and Regions, Statistics Sweden and the Swedish Dental and Pharmaceutical Benefits Agency.

Result

In 2018, 730 women were diagnosed with ovarian cancer, representing approximately 0.5% of the total disease burden in Sweden. Total costs related to the disease were estimated at SEK 824 million. Direct costs related to healthcare amounted to SEK 230 million. Indirect costs related to sick leave and early retirement were estimated at SEK 55 million, while early mortality resulted in productivity losses of SEK 539 million.

Conclusion

The disease burden and societal costs of ovarian cancer are significant, with a majority of costs related to productivity losses. Future research should aim at finding effective screening and treatment methods to reduce human suffering and the economic burden to society.

DISCLAIMER

This report was commissioned by the Swedish Network against Gynecological Cancer. The views expressed in this report are solely those of the authors and do not reflect the views of the Swedish Network against Gynecological Cancer. The Swedish Network against Gynecological Cancer had no influence on study design, data collection, statistical analyses, drafting the manuscript and drawing conclusions, which was solely done by the authors. The Swedish Network against Gynecological Cancer did not have any influence on this.

Preface

This report was produced by NordIQ Analytics on behalf of the Swedish Network against Gynecological Cancer and through financial support from the Swedish Cancer Foundation. The aim was to estimate the societal costs of ovarian cancer, both related to the burden on the healthcare sector and on other sectors. The Network against Gynecological Cancer consists of patients, relatives and other individuals who collectively work towards spreading knowledge, pushing for improvement in the treatment and care of ovarian cancer patients, and creating debate related to gynecological cancer diseases. An important part of this work stems from the belief that all affected women should have access to timely and optimal care, treatment and rehabilitation, and that more research should be conducted within the subject area.

The Swedish Network against Gynecological Cancer did not have any influence on study design, statistical analyses, drafting the manuscript or the conclusions of this report. However, we would like to thank the network for valuable views and feedback that improved and led the work towards the final product. Many thanks to Roshan Tofighi (Board Member of the Network), Barbro Sjölander (Chairman of the Network) and Christer Borgfeldt (Professor at the Department of Obstetrics and Gynaecology, Lund University).

Stockholm, February 2020

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Abbreviations

BRCA1/2	Breast cancer susceptibility genes 1/2
COI	Cost of illness
DALY	Disability-adjusted life-years
DRG	Diagnosis-related group
ICD-7/10	International Classification of Diseases 7th to 10th Revision
CPP	Cost per patient
SIA	Swedish Social Insurance Agency
SKR	The Swedish Association of Local Authorities and Regions
SQRGC	Swedish Quality Register for Gynecologic Cancer
NBHW	The Swedish National Board of Health and Welfare
DPBA	The Dental and Pharmaceutical Benefits Agency
Ovarian cancer	Cancer in the ovaries, fallopian tubes and peritoneum
Broad ligament	A broad fold of peritoneum that extends from the side of the uterus to the wall of the pelvis, which the fallopian tubes are attached to

Summary

In the last few decades, the proportion of women suffering from ovarian cancer has decreased, partly because of the protective effect of birth control pills. However, about 700 women contract ovarian cancer in Sweden annually and the mortality is high, largely due to detection of the cancer at a late stage. Thus, ovarian cancer contributes to a high disease burden as well as significant societal consequences, including substantial healthcare costs and lost productivity due to illness and premature death. This report presents the prevalence of ovarian cancer in Sweden in 2018, its related disease burden and societal costs. Ovarian cancer includes cancer in the ovaries, fallopian tubes and peritoneum.

The report follows a cost of illness design. Healthcare consumption consisting of inpatient and specialized outpatient care, including medical diagnosis and treatment, were estimated using the Patient Register from the Swedish National Board of Health and Welfare and the Cost per Patient database from the Swedish Association of Local Authorities and Regions. Estimates of productivity loss related to sick leave, early retirement and premature death were based on statistics from the Swedish Social Insurance Agency and the National Board of Health and Welfare. Productivity losses were valued using cost estimates from Statistics Sweden. The burden of disease related to ovarian cancer was estimated using data from the Global Burden of Disease Study.

The total cost of ovarian cancer in Sweden in 2018 amounted to approximately SEK 824 million. Direct costs related to outpatient care accounted for 28% of total costs. Expenses for outpatient and inpatient care amounted to SEK 230 million. Productivity losses (indirect costs) amounted to 72% of total costs. Sick leave and early retirement cost just under SEK 55 million, while early mortality resulted in productivity losses of SEK 539 million. The disease burden amounted to 12,000 disability-adjusted life-years, approximately 0.5% of the total disease burden in Sweden.

Ovarian cancer is related to large morbidity and mortality, and consequently large societal costs. In order to avoid human suffering and substantial costs to individuals and society, resources should be prioritized towards further research in areas such as early detection and effective treatment.

1. Introduction

Ovarian cancer is the seventh most common form of cancer among women, with nearly 240,000 women diagnosed annually on a global scale [1]. Cancer in the ovaries and the fallopian tubes accounts for about 3% of all female cancers, and in 2018, 680 new cases were discovered in Sweden [2]. If cancer in the peritoneum is included, the number increases to 730 cases. Cancer in the ovaries, fallopian tubes and peritoneum are included in the concept of ovarian cancer, with estimates based on individuals with malignant cancerous tumors only.

Ovarian cancer includes many subgroups, but epithelial ovarian cancer is the most common and difficult to treat. Non-epithelial ovarian cancer is uncommon and mainly affects younger women, usually with a very good prognosis. Borderline tumors in the ovaries also primarily affect younger women and have a very good prognosis, where many can be treated with a fertility-preserving procedure. Ovarian cancer can affect women of all ages, but rarely occurs before the age of 30 [2]. It is the most serious gynecological cancer based on its high mortality rate, which is mainly due to the difficulty in detecting the disease at an early stage and women often developing resistance to treatment [3]. In Sweden, the 1-year survival rate is around 90%while the 5-year survival rate drops to around 56% [4]. The number of diagnosed women in Sweden has decreased in the last decades. Today, approximately 13 out of 100,000 women are diagnosed, as compared to 26 per 100,000 women annually in 1975 (see Figure 1) [2]. One likely explanation may be the increased use of birth control, a protective factor against ovarian cancer [5]. Another factor may be the increased number of relatives to ovarian cancer patients being tested for mutations in the hereditary BRCA1 and BRCA2 genes. These genes increase the risk of ovarian cancer [6]. Testing for ovarian cancer introduces a possibility for preventive measures at an earlier stage, such as prophylactic removal of ovaries and fallopian tubes after childbearing age (about 38-42 years of age).

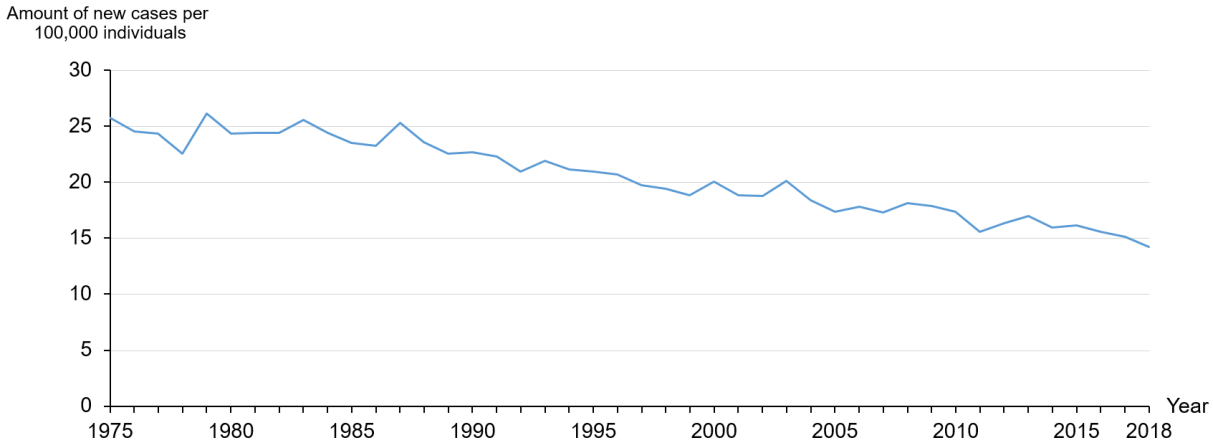

Figure 1. Incidence of cancer in the ovaries, fallopian tubes and peritoneum between 1975-2018 for all ages in Sweden [2]

It is not clear what causes ovarian cancer, other than the reasons being multifactorial. The greatest risk arises if people in the genetic family have had the disease [7]. This may be due to a change in the DNA of the cells, especially the BRCA1 or BRCA2 genes. About 3-27% of all ovarian cancers are inherited and linked to these gene mutations, as well as to the Lynch syndrome (another type of gene mutation) [6]. Other factors that increase the risk of ovarian cancer include prolonged hormonal substitution therapy with estrogen, polycystic ovarian syndrome (PCOS), endometriosis and age [7].

Our increased knowledge of underlying factors and mechanisms has resulted in a breakthrough, with the first maintenance therapy for ovarian cancer approved a few years ago [8] and with another recently approved maintenance therapy [9, 10] in Sweden. Intensive research is underway with different types of targeted treatments and immunotherapy. This also increases the prerequisite for primary and secondary prevention of the different types of ovarian cancer. In the UK, a long-term follow-up is currently underway to investigate whether it is worthwhile to screen for ovarian cancer [11, 12]. However, based on the first published results, screening could not effectively reduce the mortality rate among ovarian cancer patients. What the long-term results will show remains to be seen. In Sweden, research is being conducted on the possibility of using biomarkers to improve diagnosis and identify women for referral to specialized examination for ovarian cancer [13, 14], hopefully improving the prognosis of affected individuals. Despite this, ovarian cancer contributes to a significant burden for individuals and society at large, with a large impact on the affected individuals and their families. Resource use within the healthcare sector and the effect on the individuals' ability to work may also contribute to substantial societal costs. However, the economic burden to society has not previously been estimated, thus limiting the economic arguments to substantiate a push for further research.

1.1 Aim

The aim of this report was to estimate the societal cost consequences and the burden of disease related to ovarian cancer, consisting of cancer in the ovaries, the fallopian tubes and peritoneum. The report focused on women with an ovarian cancer diagnosis in Sweden in 2018.

1.2 Method

This report used a cost of illness study design, where costs related to resource use and loss of productivity were estimated for the year 2018.

Two methods were used to estimate total costs: the incidence and the prevalence method. Costs for medication which were not included in resource consumption estimates within specialized outpatient care (in this case, only maintenance therapy with Olaparib) were estimated according to the incidence method, which means that it was based on all diagnosed cases in 2018. Although treatment for ovarian cancer often extends over a year, it was assumed that this cost component occurred for women who were diagnosed in previous years but received maintenance therapy in 2018. This method was used as the number of new cases of ovarian cancer has been stable over the recent years. For other valuations, the prevalence method was used, since total costs were based on all ongoing cases of ovarian cancer, regardless of the year the individual was diagnosed. Both methods are commonly used in research. As the number of new cases have been stable over the last years, these methods can be used simultaneously. These methods are more thoroughly explained in Chapter 3.

The diagnoses included in "ovarian cancer" are presented in the table below, with associated disease classifications according to the International Classification of Diseases 7th to 10th Revision (ICD-7/10) [15]. The number of individuals diagnosed with ovarian cancer annually was based on information from the Swedish Cancer Registry, which is based on ICD-7 classifications. Cancer in the ovaries, fallopian tubes and peritoneum are often included within the concept of ovarian cancer. In this report, a decision was made to include these diagnoses (ICD-7 disease code 158 and 175). This categorization is broad, especially based on the inclusion of peritoneal cancer. The reason for this inclusion is that the tissues in

the affected areas and symptoms are similar, whereby peritoneal cancer is handled and managed in the same way as cancer in the ovaries or fallopian tubes.

The report only included women with malignant cancer tumors. There are also benign and borderline tumors that originate from the ovaries. These types were not included in this overview. The aim was to report costs categorized by type of cancer, although this has not always been possible.

Table 1. Diagnoses included in the report

Disease code ICD-7	Disease code ICD-10	Disease group
175	C56-C57	Malignant neoplasm of ovary, fallopian tube and broad ligament
including		
1750		Ovary (ovarium)
1751		Fallopian tube and broad ligament
1758		Fallopian tube and broad ligament, specified parts
1759		Fallopian tube and broad ligament, unspecified parts
158	C48	Malignant neoplasm of retroperitoneum

Clarification: Broad ligament - the wide fold of peritoneum that connects the sides of the uterus to the walls and floor of the pelvis.

Information about the recommended treatment regimen in Sweden for ovarian cancer patients was retrieved from different sources. These included the National Care program for ovarian cancer in Sweden [1], as well as the latest report from the Swedish Quality Register for Gynecologic Cancer (SQRGC), which includes statistics until 2018 [4]. The SQRGC is based on four sub-registers, one of them for ovarian cancer. The register collects statistics and information about ovarian cancer to contribute to improvement and quality development at local clinics, in care settings regionally and nationally, and to provide data for international comparisons and research. In a peer reviewed article, the register was deemed as having high validity and reliability, thus of good use for research purposes [16]. The register was used to estimate the number of women diagnosed with ovarian cancer in 2018, subdivided by stage. The register was also used to assess how many women underwent surgery, medical treatment or both, based on stage subdivisions, for the year 2018.

Direct costs, which include healthcare resource use and medications, were calculated based on the Swedish National Board of Health and Welfare's (NBHW) Patient Register, the Swedish Association of Local Authorities and Regions (SKR) Cost Per Patient (CPP) database, the National Care program for ovarian cancer and the Swedish Dental and Pharmaceutical Benefits Agency (DPBA). These are explained in more detail in later chapters.

Indirect costs, including the value of lost productivity, were estimated using the human capital approach, described in more detail in Chapter 3. These costs were categorized into short and long-term sick leave, permanent sick leave (early retirement) and early mortality. The cost of sick leave was estimated based on statistics from the Swedish Social Insurance Agency (SIA) and national averages of gross income, estimated with data from Statistics Sweden. These calculations included social fees and holiday allowance and were estimated for women between the ages 20-65. The same average gross salary was used to estimate the cost of early mortality, both for the year 2018 and forecasted until retirement age. Since information on an individual level was not available for this population, it was not possible to estimate the cost for lost household production.

Ovarian cancer patients also experience impaired functioning due to pain, suffering and discomfort associated with the disease and treatment. We estimated the burden of disease for people diagnosed with ovarian cancer using statistics from the Global Burden of Disease Study [17] with specific data for Sweden.

Some costs were not possible to estimate in this report. Among them are outpatient data from primary care, which is not routinely collected in Sweden. This data also varies widely among Regions. Therefore, no aggregated statistics were available to estimate resource consumption in primary care. In addition, end of life palliative care could be a major contribution to the total costs, for which reliable statistics were also lacking. We were also not able to include costs for genetic screening of hereditary ovarian cancer, eg. tests for BRCA1 or BRCA2 mutation, as potential absence (negative test) of ovarian cancer means that this cost item would not be found in cancer-specific outpatient registries. Other types of care, such as municipal provided care through home visits could not be estimated based on the absence of aggregated data for Sweden. Additionally, individual suffering and care provided by family members or relatives were also not included.

1.2.1 Data on resource use, productivity losses and disease burden

In order to estimate the frequency of healthcare resource use, data was collected from the NBHW on inpatient and specialized outpatient care and cause of death [18, 19]. To estimate productivity losses, statistics from SIA [20], which in some cases were combined with evidence from the scientific literature [21], were used. Use of medication for cancer treatment is generally included in specialized outpatient care if administered to patients during their visit. Consumption of medication that can be administered outside the visit (at home) was estimated based on information from the National Care program for ovarian cancer [1].

1.2.1.1 Inpatient and specialized outpatient care

Resources used in inpatient and specialized outpatient care were retrieved from national statistics from the NBHW's Patient Register. After each completed healthcare visit, the care provider is obliged to report information regarding the patient, including, for instance, age, gender, current diagnoses and surgeries. This means that there are reliable statistics for all patients who have been in contact with healthcare (inpatient and specialized outpatient) for diagnoses associated with ovarian cancer. The ICD-10 disease codes used to collect data from the Patient Register were: C48, C56 and C57.

1.2.1.2 Medication

Statistics on pharmaceuticals can be found in the Prescribed Drug Register from the NBHW. This register is categorized by substances, rather than based on disease codes. Since most cytostatic treatments (chemotherapy treatments) recommended for ovarian cancer are also prescribed for other types of cancer, it was not possible to estimate the proportion of the drugs that could be attributed to ovarian cancer. This register was therefore not chosen as a basis for calculating drug use. In addition, no information was available on indirect drug use outside of treatment, such as pain-relieving medication or other drugs used to reduce the occurrence of side effects due to treatment. Thus, the estimation of drug consumption is most likely underestimated.

Direct costs associated with the use of drugs related to the treatment of ovarian cancer are included in the estimate of specialized outpatient care. This is because many of the drugs are registered as requisition medicines. These are purchased directly by the clinics or hospital departments and administered during the care visit. These include both chemotherapy and other drugs that counteract side effects and relieve pain during treatment. After a complete chemotherapy regimen, Olaparib may be prescribed as maintenance therapy to patients with a BRCA1 or BRCA2 mutation (approximately 10% of the total patient population). This is the only drug included in the treatment regimen for ovarian cancer that is not included in the specialized outpatient care register, as these are prescribed directly to the patients and administered at home. Therefore, the consumption of Olaparib was estimated separately on the basis of recommendations from the National Care program for ovarian cancer [1]. However, one should keep in mind that drugs can be distributed in different ways, i.e. be requested by or prescribed to the patient, which may vary between geographical areas or units and over time [22]. This means that the estimation of drug consumption was not fully captured by the cost item 'specialized outpatient care'. However, it is not known to what extent. Thus, as mentioned earlier, the estimation of drug costs is probably underestimated.

Medication varies depending on the stage of the cancer. Recommendations for treatment of ovarian cancer stem from the National Care program. This care program is based on the latest evidence and distinguishes between primary care, primary treatment, maintenance treatment and relapse treatment. Recommended medical treatments and the options if patients cannot undergo treatment with the recommended regimen, are described in detail in this care program. In Table 2, it is summarized which drugs are most commonly administered for treatment of ovarian cancer.

Table 2. Drugs (substances) often administered for management of ovarian cancer

Primary treatment	**Description/assumptions**
Carboplatin	Dose based on height and weight
Paclitaxel	Dose based on height and weight
Bevacizumab	Administered for phase III-V patients. Initiation during the second cycle of treatment
Maintenance treatment	
Olaparib	For patients with BRCA1/2-mutation (approx. 10% of the total patient population). Daily dose initiated 8 weeks post treatment and used on average for 9 months for patients with relapse>6 months post treatment (approx. 70% of the total population)
Niraparib	Approved by DPBA on December 1st, 2019 [11]. This report is based on treatment recommendations from the National Care program for ovarian cancer from 2018/2019. Updated recommendations based on this approval have not yet been released, and there is no data on usage. Niraparib was therefore excluded from the total estimation of costs. An estimated cost per day for Niraparib per individual was thus reported in the results section, allowing future users to make estimations on the use of Niraparib, when data is available.
Bevacizumab	For patients with a relapse>6 months post treatment (approx. 70%)
Relapse treatment	
Carboplatin	Only for relapse>6 months (platinum sensitive cases) post treatment (approx. 70%). Non-sensitive cases with relapse<6 months are recommended Paclitaxel in combination with Bevacizumab*
Paclitaxel	Same as for primary treatment
Bevacizumab	Same as for primary treatment

Abbreviations: DPBA - The Swedish Dental and Pharmaceutical Benefits Agency

All information is based on recommendations from the National Care program for ovarian cancer. Data on how many patients are treated with specific drugs are not available.

* Women who relapse and cannot tolerate cytostatics or who do not respond to cytostatics may in selected cases be offered palliative endocrine care, including tamoxifen or aromatase inhibitors. There is currently no aggregated data on how many patients are affected by this.

1.2.1.3 Productivity losses

Indirect costs were based on data from the SIA, including financial compensation due to illness and early retirement, as well as information from the NBHW's Cause of Death Register. This register includes all individuals deceased by calendar year and cause of death, regardless of the country of death. In 2018, the number of deaths in Sweden amounted to 92,254 [19]. The SIA provides statistics on the amount of days of financial compensation related to illness lasting longer than 14 days (long-term sick leave). Compensation up to 14 days (short-term sick leave) is paid by the employer and is therefore not included in the SIA register. To a large extent, it is possible to obtain data on financial compensation distributed per diagnosis, but if there are fewer than 10 individuals in the sub-category, the SIA cannot disclose this information for reasons of confidentiality. Productivity losses were estimated for the proportion of ongoing cases of financial compensation due to any of the ovarian cancer diagnoses in December 2018.

The value of production was estimated according to the human capital method. In this method, the valuation of production is usually based on the assumption that production can be valued at a market price. This price may be set as the average gross income including social fees and holiday allowance,

which refers to the costs that the employer would have incurred had the individual been in full employment. The result is a value of lost productivity, estimated from a societal perspective.

When an employee is ill and is thus absent from work, the employer is obliged to pay an amount to the employee for the first 2-14 days (short-term sick leave), corresponding to 80% of the salary. Day one is a qualifying deduction corresponding to 20% of the average weekly working time.

Since 2003, early retirement is not included in the pension system, but rather belongs to the universal social insurance coverage, and is categorized into activity compensation and sickness benefits. Both sickness benefits and activity compensation are paid to individuals who will probably never work full time again as a result of illness, where the difference is that the activity allowance applies to individuals between 19 and 30 years.

1.2.1.4 Disease burden

Disability-adjusted life years (DALYs) is a composite measure of the disease burden in a population. DALYs are calculated by combining estimates of life expectancy and quality of life for various illnesses or health-related disability. While quality-adjusted life years (QALYs), which are most commonly used within the healthcare setting in Sweden, are used to estimate the individual health effects of interventions, DALYs measure the total disease burden for a population, for example the population of Sweden.

DALYs partly take into account that disease leads to impaired functioning in everyday life (years lived with disability - YLD), as well as mortality linked to the disease (years of life lost - YLL). The higher the amount of DALYs in a population, the higher the burden of disease. How much a specific disease affects a person is called a disability weight. These weights are measured on a scale between 0-1, where 0 means no functional impairment, i.e. the best of the cases. A disease of weight 1 represents the worst possible condition. These disability weights have been estimated through population surveys globally, including Sweden. In these surveys, 15 different health conditions have been compared in relation to each other, and respondents have been asked which of the states they prefer. The respondents were randomly asked questions where the conditions were described as chronic or temporary (up to one week). The result of these surveys are over 300 disability weights for different diseases and health conditions, including ovarian cancer.

The burden of disease for people diagnosed with cancer in the ovaries is based on statistics from the Global burden of Disease study [17], categorized by country. The most recent European survey on disability weights was carried out by the WHO in the autumn of 2013. These estimates were used in the estimation of total DALYs related to cancer in the ovaries in Sweden. The remaining parameters included in the DALY calculation, such as disease incidence and the number of new cases, are from 2017. A description of DALYs is shown in the figure below. DALY weights were only available for cancer in the ovaries, hence there is no information regarding the disease burden for cancer in the fallopian tubes or peritoneal cancer.

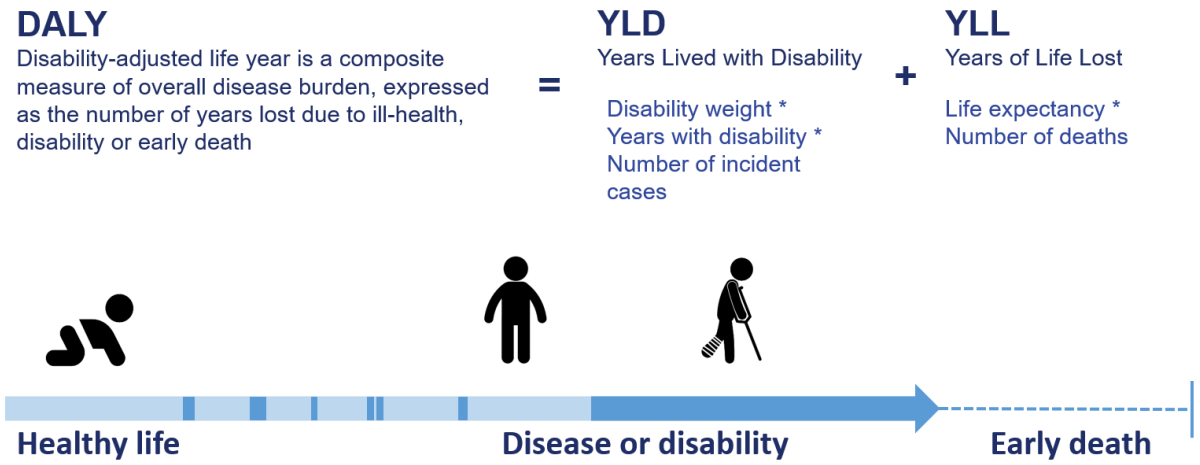

Figure 2. Figure explaining disability-adjusted life years (DALYs)

In Sweden, the total burden of disease was estimated at approximately 2,615,600 DALYs in 2017, representing about 0.1% of the total disease burden worldwide.

1.2.2 Valuation of resource use and productivity losses

The use of healthcare resources and productivity loss were valued using the CPP-database for inpatient and specialized outpatient care [23], the DPBA's price list for approved drugs [24], pharmacy retail prices [25] and salary estimates from Statistics Sweden [26].

1.2.2.1 Inpatient and specialized outpatient care

The CPP-database contains data on the actual cost for each patient visit and is based on each individual's healthcare utilization. The CPP is an accounting system that is primarily used to monitor the volume of resources used in healthcare. The calculations in the CPP database are therefore based on costs recorded in connection with each visit within healthcare [27], registered with a so-called DRG code. Cost per visit was calculated by dividing the total cost per visit by the frequency of each DRG code (number of visits registered with the same DRG code). The cost per visit estimated in this report was an average cost based on the total cost per visit for the DRG codes; C48, C56, C57 (related to ovarian cancer).

Today, most regions in Sweden are represented in the database [23]. In 2018, 1,269,239 somatic care cases were registered, which corresponds to approximately 93% of all somatic inpatient care in the NBHW Patient Register. The CPP-database for outpatient care comprises a total of 15.5 million visits and includes visits to all types of medical professions. The database covers approximately 70% of all medical visits. Average cost estimates from the CPP-database can therefore be considered a reliable estimate of the actual costs related to healthcare visits in Sweden [28], although not all types of visits within healthcare are registered in the CPP-database.

1.2.2.2 Medication

In order to estimate the cost of medications not included in the cost per visit estimate within specialized outpatient care (only Olaparib), pharmacy retail prices (AUP) were used, based on list prices from the DPBA [24].

1.2.2.3 Productivity losses

The cost related to individuals´ inability to work (until the age of retirement) due to illness or premature death was estimated based on the average gross income in Sweden in 2018 for women between 20 and 64 years. This information was retrieved from Statistics Sweden [26]. The estimate included social fees estimated at 43.3% and holiday allowance [29].

2. Ovarian cancer – a significant health problem

2.1 Prevalence

The ovaries produce the female sex hormone estrogen and progesterone. They also produce female germ cells - eggs, which are transported to the uterus for fertilization. Millions of pre-follicular germ cells are found in each ovary. Ovarian cancer is a collective name for a group of tumor diseases that originate from the ovaries and its nearby structures. Fallopian tube and peritoneal cancer are similar to cancer in the ovaries and are therefore managed, classified and treated as ovarian cancer. Just over 500 women are diagnosed with cancer in the ovaries annually in Sweden. If fallopian tube and peritoneal cancer is included, this figure increases to 730 women. The disease can be divided into four stages, I-IV, depending on its spread. As the symptoms of these cancer types are diffuse and mimic other diseases of the abdomen, ovarian cancer is usually detected at a late stage. About 60% of all cases are detected in stages III-IV, meaning that the tumor has spread to the abdominal cavity and/or other organs.

Table 3. Number of diagnosed cases categorized by stage in years 2014-2018.

Stage	Number	Frequency
I	808	33%
II	197	8%
IIIA-IIIB	213	9%
IIIC	713	29%
IV-X	515	21%
Total	**2,446**	**100%**

Sample: Cancer in the ovaries. Source: Report from the Swedish Quality Register for Gynecologic Cancer (SQRGC), 2019 [4]

Estimates of the number of women diagnosed with ovarian cancer annually include only tumors that have been diagnosed on the basis of vaginal ultrasound and blood tests or surgery to examine the cancer cells. This means that women who never undergo surgery or sampling of the tumor cells in the ovaries, fallopian tubes or peritoneum are not included in these estimates. Reasons for this may be that the cancer is detected at a late stage or that the origin of the tumor in, for instance, the pelvis or the abdomen, is unclear. Cancer in the pelvis or abdomen may have developed from an ovarian cancer tumor or independently.

2.2 Age and stage distributions

The median age for an incident case is 66 years, with a range between 12-100 years [4]. The age distribution is illustrated in Figure 3, based on data from the Patient Register from the NBHW.

Table 4 shows the number of diagnosed cases between the years 2015-2018. Since 1975, the number of incident cases has decreased by about 50% [2]. It should be noted that the diagnostic criteria has changed, and a diagnosis of ovarian cancer today requires assessment of the tumor [1].

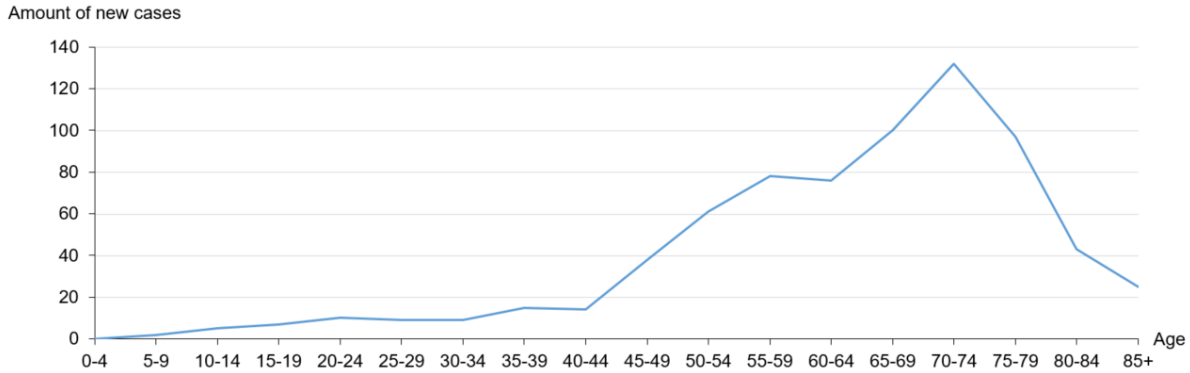

Figure 3. Number of incident cases of cancer in the ovaries, fallopian tubes and peritoneum for women in Sweden, year 2018.

Table 4. Amount and frequency of individuals based on cancer stages between the years 2015-2018

Cancer type	**Number (Proportion)**			
	2015	**2016**	**2017**	**2018**
Cancer in the ovaries	585 (79%)	558 (73%)	514 (72%)	516 (71%)
Cancer in the fallopian tubes	106 (14%)	159 (21%)	159 (22%)	164 (22%)
Cancer in peritoneum	49 (7%)	48 (6%)	45 (6%)	50 (7%)
Total	**740**	**765**	**718**	**730**

2.3 Mortality

Ovarian cancer is the most fatal type of gynecological cancer. The number of deaths due to ovarian cancer in Sweden in 2018 amounted to 687 [19]. Between the years 2010 and 2018, the number of deaths decreased from 728 individuals, i.e. just over 6%. The five-year survival increased from 44% in the years 2004-2009 to 50% for the years 2010-2015 [1]. In a European study where 5-year survival rates were compared between different cancer types, Sweden showed the highest survival rate for ovarian cancer out of all countries [30]. Today, the relative 1-year survival rate for patients with ovarian cancer in Sweden is 90%, while the 5-year survival rate is 56%, a clear improvement since previous years. The earlier the stage in which the cancer is detected, the higher the rate of survival. Between 2014 and 2018, the 5-year survival for stage I was 90%, stage II 85%, stage III 39% and stage IV 22% [4].

2.4 Risk factors

The cause of ovarian cancer development is multifactorial, including between 3 and 27% of all cases being hereditary [6] with about 65-85% of these attributed to the BRCA1 and BRCA2 genes, while the remaining proportion is based on pathogenic variants in other genes [7, 31]. Hereditary ovarian cancer can be suspected if there is a history of ovarian or breast cancer in the family at early age, if there have

been several cases of ovarian or breast cancer in the family, among other factors. However, new evidence suggests that approximately 40% of women with hereditary cancer have no family history [1]. Therefore, it is recommended for all women with ovarian cancer, regardless of family history, to be offered genetic screening. Other risk factors for ovarian cancer include age, not having given birth, endometriosis and hormonal substitution therapy with estrogen.

2.5 Surgery - complete tumor resection

If a diagnosis of advanced stage ovarian cancer (stages III-IV) is established, there is strong scientific evidence that as much as possible of the cancer tumor should be removed to achieve complete tumor resection (i.e. the tumor not being visible to the eye). This is recommended to increase the chance of survival. The average five-year survival rate between years 2013-2017 for women with a complete resection was 53%, whereas women without complete resection had a five-year survival rate of 20% [4].

Although it is often difficult to detect ovarian cancer, there is usually a short time between detection and surgery. In 2018, in Sweden, 80% of patients had completed surgery within 25.8 days after the decision to proceed with surgery was made.

For some women, surgery is performed after the initiation of cytostatic therapy, often after three cytostatic cycles. This may be because of comorbidity or spreading of the tumor, which may make it difficult to remove the tumor before medical treatment. The average five-year survival of women who underwent delayed surgery and achieved complete tumor resection was 43% between 2013-2017, while for women not achieving complete tumor resection survival was 10% [4].

2.6 Medical treatment

Regardless of the stage in which cancer in the ovaries, fallopian tubes or peritoneum is detected, cytostatic therapy is the recommended medical approach, with the exception of stage I. The recommendation is platinum-based therapy, administered as either single therapy with carboplatin, or in combination with paclitaxel, depending on the type of cancer and stage at diagnosis.

The time between surgery and initiation of cytostatic therapy has improved in Sweden between the years 2014 and 2017 [4]. According to the National Care Program for ovarian cancer, women respond differently to treatment. Of those with an advanced tumor, about 30% are platinum resistant. This means that the tumor does not stop in its development during ongoing treatment with platinum or within 6 months of discontinuing therapy. For these women, the prognosis is poor, as it means that platinum treatment is ineffective. A majority of those who respond to platinum therapy with advanced cancer relapse within 18 months (median 12-18 months after discontinuation of treatment, depending on study).

3. Cost of illness

This chapter gives an overview of the theoretical underpinnings of the methodology used in the costing analysis in this report, and in a more detailed manner, describe the assumptions behind the cost estimates.

The fundamental goal with cost of illness (COI) studies is to evaluate the economic burden that illness imposes on society. Estimates from COI studies serve different purposes. They can be used to inform decision-makers and stakeholders of the magnitude of a certain disease by describing all medical and societal costs related to that disease. COI can help argue that policies targeting certain diseases should be given high priority in a policy agenda setting. Additionally, COI estimates can drive stakeholders towards a need to investigate the cost-effectiveness of new healthcare programs, therapies, or drugs. Estimates of societal costs can also facilitate cross-national comparisons of disease consequences and various approaches that are available to confront those consequences. COI studies do not, however, provide guidance on what or how we should optimally allocate societal resources. They rather show the potential (economic) benefits that can be achieved by a certain intervention or policy if it can successfully prevent the use of societal resources related to a certain disease, given the intervention is cheaper than status quo. In this vein, COI studies generally include a metric of 'health loss' and try to measure the resource costs incurred in treating a specific disease. It is important, however, that costs are estimated using similar methodology across medical areas to allow for fair comparisons of economic burden of illnesses and strategies to combat them [32, 33].

COI studies are based on the assumption that every resource has an alternative use. This may imply that all types of resources can be measured, even if not in monetary terms. There are three steps in a cost analysis: (1) *identification,* (2) *quantification* and (3) *valuation*. Additionally, future costs should be discounted to present value to reflect individuals´ positive time preferences.

3.1 Identification

The first step in a cost analysis is to identify all the relevant resources that will be consumed in relation to a particular disease. This requires deep knowledge about the illness being investigated to ensure validity, as well as clear and well-defined diagnosis codes to ensure transparency.

COI studies may be carried out from a variety of perspectives, each including slightly different cost items, which may lead to different results for the same illness. These perspectives may measure costs to a particular society, the healthcare system, third-party payers, the government, and the patients and their families. It is, therefore, important to define the perspective from which costs will be estimated.

In general, the broader societal perspective is preferred, because it reflects the full range of opportunity costs attributable to a disease regardless of which sector they occur in. A third-party payer perspective, for instance a region’s or municipality’s perspective, takes a narrower financial perspective, and would only include the costs that would influence their own budget.

The definition of a societal cost can be divided into three different aspects [34]. The first aspect (1) requires that a cost cannot be incurred as an income in another sector of society. Redistributions or transfer costs can therefore not be seen as a cost, for instance, rehabilitation benefits. Such may be a cost for the SIA, but an income to the individual. In the second aspect (2), only external costs constitute a societal cost, not internal costs. An internal cost is what a consumer pays for a good or a service. This cost

only affects the consumer, whereas an external cost has a wider impact. This is because an internal cost is usually offset against the value of the good or the service being consumed, and the cost would not have arisen had the consumer refrained from consumption. The third aspect (3) says that sometimes one can refrain from the second aspect if the consumer does not consume the goods or services voluntarily or deliberately. Discomfort and deterioration of one's standard of living due to illness can therefore be regarded as a cost to society.

Economic costs fall into three categories: direct, indirect and intangible costs. *Direct costs* are tangible, monetary costs that can be determined by observing immediate expenditure on health services, social care and other services. They consist of both medical and non-medical costs. Medical costs are costs related to medical care expenses for diagnosis, treatment and rehabilitation, such as outpatient and inpatient care and medication. If we were to estimate costs from the healthcare payer perspective, only medical costs would be included. Non-medical costs relate to the consumption of other resources by patients and families, including transportation costs and informal care (often given by relatives).

Indirect costs are opportunity costs that represent societal output forgone as a consequence of a disease or illness and are measured in terms of lost productivity. These can, for instance, include short and long-term sick leave and early retirement. Indirect costs therefore include resources that are not produced by individuals due to reduced work capacity because of their illness. Indirect costs include sectors other than the healthcare sector, such as the educational sector. An example would be costs for additional support in school due to a disability or disease. These costs would only be relevant from a societal perspective.

Intangible costs are not resources *per se,* rather a valuation of the wider impacts associated with early mortality or pain and suffering. These are usually considered subjective, as they are not associated with any real cost, and their value is usually determined or estimated by a decision-maker.

3.2 Quantification

Upon identification of the relevant cost items from the costing perspective chosen, the extent of resource consumption must be assessed. Resource use can be estimated quantifying, for instance, number of days of care, time spent on each healthcare visit, medication used or number of days of sick leave. When quantifying the resources used, the level of detail will depend on the availability of information. Costs can be obtained by means of micro-costing or simply using a gross cost. When micro-costing, every component of a larger cost, such as hospitalization, transportation or overheads should be estimated. This is, however, time-consuming, especially when dealing with complex data. Importantly, resource use between individuals differs, thus generalizing estimates based on a few individuals to a larger population inevitably carries large bias. Additionally, it is usually difficult to have access to individual-level data pertaining to different sectors of society. Gross-costing is generally easier, where aggregated costs are usually obtained from a single source such as electronic databases or the medical literature. For instance, hospitalization costs can be obtained for specific diagnosis codes from registers.

Two different methodological approaches can be used to estimate costs in COI studies - the *prevalence-based* and the *incidence-based* approach. In the *prevalence-based* approach, all resource use related to the disease under study is identified and quantified over a specific year. Productivity losses related to, for instance, early mortality, are summed and attributed to the year in which the deaths occurred. The prevalence-based approach thus constitutes a combination of actual resource use over a year and future expected resource use attributed to a particular year.

The *incidence-based* approach estimates the number of cases of death or hospitalization in a given year and applies a lifetime cost estimate to these new cases. The choice of method depends on data availability and the purpose of the study, and can be combined to strengthen the results [35].

Two methods can be used when quantifying resource consumption, a 'top-down' and a 'bottom-up' approach, based on what type of data is available. In the 'top-down' approach, all relevant expenditure is added and then divided by the corresponding unit of activity. This approach is simple to apply, often using routinely collected data for the whole population, and is most appropriate where an average cost, such as the average cost per person receiving treatment for ovarian cancer, is required. However, this approach does not allow analysis of variation in costs, for example for patients requiring additional support beyond a standard intervention or variation by patient characteristics. In contrast, in the 'bottom-up' approach, all resources required to provide a specific intervention or service are described and quantified. One departs from a sub-group of individuals from a population of interest, for instance a sub-group of women with a diagnosis of ovarian cancer, and estimates the resource use for every individual in that sample. The average estimates are later applied to all individuals in the population studied. The monetary value of those resources is linked to the specific resource item. This approach tends to be more accurate and versatile, as it can be linked to individuals, thus retaining variability between patients and between sites [36].

3.3 Valuation

Upon the selection of costing perspective, and thereby the identification and quantification of the relevant resources, these should be valued in monetary terms. According to economic theory, resources should be valued according to their 'opportunity cost' – the benefit forgone from not investing in the next best alternative. Under the assumption of perfect markets, market prices may reflect opportunity costs. Perfect markets are free from competition, there is full information on goods and services for consumers and sellers, and there are no external effects that can affect pricing or trading. Since we usually do not trade in perfect markets, resource use must be valued in a different manner other than through market prices.

Direct medical costs, i.e. healthcare related costs, are usually not considered to come from perfect markets, therefore different tariffs and standard prices are used to value such costs, including price lists for different healthcare visits or treatments. Such established price lists are usually based on time spent during visits, resources used (materials, etc.) and overheads (rent, administration, etc.).

Indirect costs can be valued using a human capital approach [37] or a friction cost approach [38]. The human capital approach is most often used to value indirect costs. This method is based on the assumption that markets are perfect, that there is free movement of goods and people, and that there is no unemployment, which means that nobody can replace a person who is unable to work. In short, this method places a value on lost output by calculating the sum of discounted expected future income, which equals the individual´s gross income including social fees. On the other hand, the friction cost approach takes into account unemployment, and the fact that people can be replaced after a certain number of months or years depending on the type of work. However, information at the individual level is required to perform a friction cost analysis, thus the human capital method is most often used.

Estimating the value of intangible costs is complicated because they are not valued within a market, but usually by decision-makers. Most COI studies report the prevalence of disease burden, but refrain from quantifying it. Within healthcare, there has long been an unwillingness to quantify human suffering in

monetary terms, which has contributed to the use of generic measures of health-related quality of life, such as QALYs or DALYs [36]. The use of QALYs or DALYs in the evaluation of different treatments across different medical areas allows for the possibility of comparing alternatives and relative cost-effectiveness, since disease-specific measures cannot be compared outside their specific medical areas. It also enables decision-makers to put a price tag on a QALY or a DALY, and therefore make a monetary assessment of the burden of disease and quality of life.

3.4 Discounting

Costs that incur in the future should be adjusted in order to be comparable to costs that incur in the present. This is because, according to common economic assumptions, most individuals exhibit positive time preference, and would rather consume goods in the present than in the future. Additionally, opportunity costs also play a role, and there are other potential uses for resources. Thus, money can be invested and, at a given interest rate, increase in value over time. Discounting makes current costs and benefits worth more than those incurring in the future because there is an opportunity cost to spending money now, as well as a desire to enjoy benefits today rather than in the future.

Future costs in economic analyses should therefore be discounted to its present value by applying a yearly discount factor. The discount factor increases over time, based on an underlying discount rate. A discount rate of 3% is recommended by the DPBA [39], but these rates may vary between countries and settings. The formula below demonstrates how the present value of future costs can be estimated.

NVC = Present value of future costs; Ct = cost year t, r = discounting factor and t = time period (years).

$$NVC = \sum_{t=0}^{t=\infty} \frac{Ct}{(1+r)^t}$$

Example: a cost of SEK 10,000 incurs in four years. This cost discounted according to the equation above becomes $10{,}000/1.03^4$ = SEK 8,849.

Overall, different methodologies can be used to estimate the economic burden of various diseases in COI studies. Therefore, it is important that a clear description of the methodology used is provided to enable comparison between studies.

4. Societal costs and burden of ovarian cancer

This chapter presents the societal costs and burden of disease of ovarian cancer. The first part of the chapter presents the societal costs, which are categorized into direct and indirect costs. The second part of the chapter presents a brief description of the burden of disease associated with ovarian cancer.

4.1 Direct costs

Direct costs pertain to costs related to the use of healthcare resources including inpatient and specialized outpatient care, as well as costs related to pharmacological treatment (medication).

4.1.1 Inpatient care

The NBHW Patient Register contains information on all public inpatient care delivered as a public service in Sweden, including completed visits, average length of care, number of days of care, and number of patients. All inpatient care usage is reported per main diagnosis. The number of visits due to ovarian cancer amounted to 2,029 in 2018 (Table 5), which resulted in 16,422 days of care (Table 6). The number of days of inpatient care decreased by 13% between 2014 and 2018.

Table 5. Number of inpatient care visits, 2014-2018

Diagnosis	2014	2015	2016	2017	2018
Cancer in the peritoneum	232	193	226	212	214
Cancer in the ovaries	1,885	1,842	1,740	1,713	1,567
Cancer in the fallopian tubes	227	208	237	296	248
Total	**2,344**	**2,243**	**2,203**	**2,221**	**2,029**

Table 6. Number of inpatient care days, 2014-2018

Diagnosis	2014	2015	2016	2017	2018
Cancer in the peritoneum	1,935	1,802	2,122	1,656	2,165
Cancer in the ovaries	15,159	14,012	14,060	13,810	12,151
Cancer in the fallopian tubes	1,896	1,665	1,883	2,598	2,106
Total	**18,990**	**17,479**	**18,065**	**18,064**	**16,422**

The average cost per hospital visit and diagnosis are expressed as 2018 Swedish krona (SEK). Table 7 summarizes the average costs per inpatient care visit for all diagnoses of ovarian cancer. The average cost per hospital visit for patients diagnosed with cancer in the peritoneum was SEK 88,931, which was based on 56 episodes in the CPP database. The average cost per visit to inpatient care with a diagnosis of cancer in the ovaries was SEK 91,014, which was based on 1,286 episodes. The average cost per visit to inpatient care for cancer in the fallopian tubes was estimated at SEK 119,099, based on 132 episodes.

The total cost of inpatient care for ovarian cancer was estimated by multiplying the number of visits by the average cost per episode for all diagnosis categories. The total cost of inpatient care was estimated at

SEK 191 million (see table 7). Costs were highest among patients with cancer in the ovaries, SEK 142 million. Inpatient care costs amongst patients with cancer in the fallopian tubes amounted to SEK 29 million, and costs among patients with cancer in the peritoneum amounted to SEK 19 million. The distribution of inpatient care costs is illustrated in Figure 4.

Table 7. Inpatient care cost of ovarian cancer in 2018

Diagnosis	Number of visits[a]	Number of episodes DRG[b]	Cost per visit (SEK)	Total (SEK)
Cancer in the peritoneum	214	56	88,931	19,031,180
Cancer in the ovaries	1,567	1,286	91,014	142,619,440
Cancer in the fallopian tubes	248	132	119,099	29,536,606
Total	**2,029**	**1,474**		**191,187,227**

DRG - Diagnosis Related Groups

[a] The National Board of Health and Welfare's Patient Register

[b] The Swedish Association of Local Authorities and Regions' Cost Per Patient-database

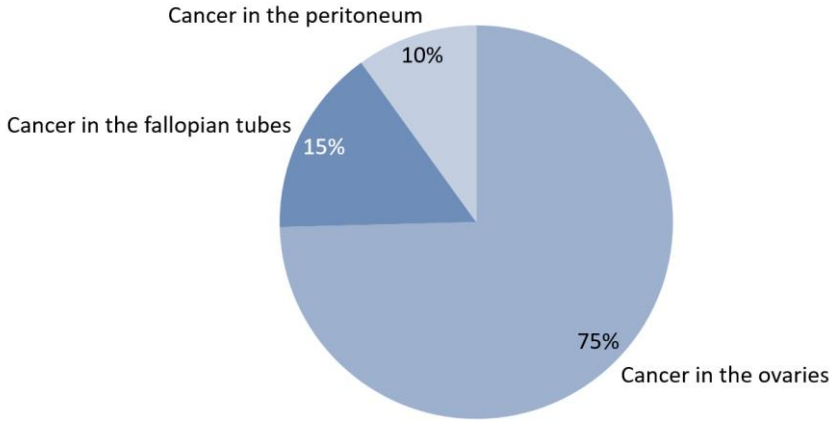

Figure 4. Inpatient care cost of ovarian cancer in 2018

4.2.2 Specialized outpatient care

The NBHW CPP-database also contains information on patients who have received specialized outpatient care since 2001. Outpatient care refers to the type of care that does not require overnight hospitalization. Specialized outpatient care can include both less resource-intensive services such as visits to clinics or welfare officers and more resource-intensive services such as day surgery. Medication administered to patients during outpatient visits, such as chemotherapy is included in the cost of specialized outpatient care.

The number of specialized outpatient care visits due to ovarian cancer amounted to 7,294 in 2018 (Table 8). The number of visits to outpatient care due to ovarian cancer decreased by 14% between 2014 and 2018.

Table 8. Number of specialized outpatient care visits, 2014-2018

Diagnosis	2014	2015	2016	2017	2018
Cancer in the peritoneum	640	628	664	690	669
Cancer in the ovaries	7,066	5,186	4,907	5,198	5,401
Cancer in the fallopian tubes	770	858	880	953	1,224
Total	**8,476**	**6,672**	**6,451**	**6,841**	**7,294**

The number of specialized outpatient care visits was multiplied by the average cost per visit for each diagnosis category to estimate the total cost of specialized outpatient care. This was estimated at nearly SEK 26 million (see Table 9). Costs were highest among patients with cancer in the ovaries, nearly SEK 20 million. Specialized outpatient care costs amongst patients with cancer in the fallopian tubes amounted to SEK 3.7 million, and costs among patients with cancer in the peritoneum amounted to roughly SEK 2 million. Figure 5 shows the distribution of outpatient care costs among the different diagnoses.

Table 9. Specialized outpatient care cost of ovarian cancer in 2018

Diagnosis	Number of visits	Number of episodes DRG[b]	Cost per visit (SEK)	Total (SEK)
Cancer in the peritoneum	669	403	3,173	2,122,441
Cancer in the ovaries	5,401	8,399	3,703	19,999,437
Cancer in the fallopian tubes	1,224	1,596	3,049	3,732,442
Total	**7,294**	**10,398**		**25,854,320**

DRG - Diagnosis Related Groups

[b] The Swedish Association of Local Authorities and Regions' Cost Per Patient-database

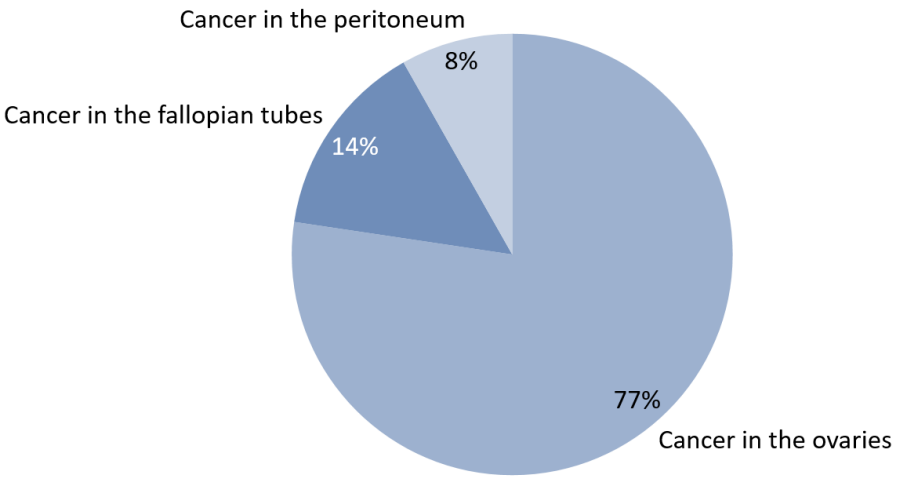

Figure 5. Specialized outpatient care cost of ovarian cancer in 2018

4.2.3 Medication

A majority of costs related to the consumption of medication for treatment of ovarian cancer were included in the cost estimates for specialized outpatient care, described in section 4.2.2. The only drug not registered during the outpatient visit is Olaparib, a maintenance treatment drug for patients with advanced ovarian cancer with a BRCA1 or BRCA2 mutation. The estimates of resource use were based on treatment recommendations [1] and information sourced from the SQRGC [4]. Costs were sourced from the DPBA national price lists [24].

Based on information from the SQRGC, in 2018, 21% of diagnosed women underwent surgery, 6% medication only, and the remaining 73% received both medication and surgical treatment. These are average estimates based on all disease stages of ovarian cancer. Consequently, it was estimated that 79% of the population of women diagnosed with ovarian cancer in 2018 received pharmacological treatment (557 out of 730 women).

Given a relative 1-year survival in Sweden of 90%, it was assumed that 10% of women would not initiate treatment with Olaparib. Of the most advanced stages of ovarian cancer (stage III-V - approximately 59% of women), it was assumed that about 70% of cases would respond to primary treatment with cytostatics (platinum sensitive cases) [1], whereas the majority would relapse within two years [1]. The consumption of Olaparib was estimated for those patients (given a BRCA1 or BRCA2 mutation) for a period of nine months (average number of months after treatment completion and two years, which is the maximum time limit of using Olaparib). The estimates are presented in Table 10.

It was not possible to estimate consumption of the drug Niraparib, as maintenance treatment with this drug was approved by the DPBA on the 1st of December 2019. Niraparib will be subsidized for patients with platinum sensitive relapse who have responded (partial or complete remission) to platinum-based cytostatic treatment for late relapse (>6 months after treatment completion) of advanced stage ovarian cancer. According to the published decision from the DPBA, the recommended daily dose of Niraparib is 3x100mg and would cost SEK 2,440 per patient [9].

Table 10. Costs for use of Olaparib as maintenance treatment for ovarian cancer for patients with a BRCA1 or BRCA2 mutation, in 2018 SEK

Drug	Cancer in the peritoneum	Cancer in the ovaries	Cancer in the fallopian tubes	Total cost
Olaparib	866,183	8,939,011	2,841,081	12,646,275

It was assumed that 70% of women with advanced cancer (59%) relapse < 6 months after primary treatment. Since 2015, patients with a BRCA1/2 mutation are offered Olaparib as maintenance treatment. The recommendations for maintenance treatment apply to patients with platinum sensitive relapse that respond to (partial or complete remission) platinum-based chemotherapy for late relapse (> 6 months after treatment completion) of advanced stage ovarian cancer. Given that between 3-27% of the proportion of women diagnosed with ovarian cancer has a BRCA1/2 mutation, it was assumed that 10% of the patient population uses Olaparib, thus costs were estimated for this population.

4.3 Indirect costs

Indirect costs included illness-related productivity losses that are borne by the community at large, such as for instance, costs of reduced working capacity due to morbidity.

In this report, productivity losses have been divided into those accruing due to short- and long-term sick leave, early retirement and early mortality. Productivity losses were estimated based on the human capital approach.

The average disposable income in Sweden in 2018 among women aged between 20-64 was SEK 300,883, according to Statistics Sweden [26]. Including 43,3% social charges [29], the average societal cost of one year of lost productivity amounts to SEK 431,165. Since sickness and rehabilitation benefits are calendar-day allowances, individuals receive allowance seven days a week. Therefore, one year of lost productivity corresponds to 365 days of sick leave.

Since short- and long-term sickness benefits as well as disability pension are transfer costs (state allowances), the actual transfer cost estimates were not included in the present analysis. Including such costs would involve a double count of costs when taking into account the loss of production that occurs due to the individual's absence from work. However, the extra cost that arises when processing these payments could be costly. Such costs vary widely between individuals, and we have therefore chosen to exclude it from the analysis.

4.3.1 Productivity loss due to short-term sick leave

Short-term sick leave refers to sickness absence that is shorter than 14 days, hence qualifying for sickness benefits paid by the employer. During 2018, the number of sick days for women was estimated at 4,166,781. This estimate was based on the average number of women employed in Sweden during 2018, estimated at 2,216,373 [40] and the average number of sick days per employee of 1.88 [41].

Under the simplified assumption that the proportion of ovarian cancer-related short-term sick leave is the same as for long-term sick leave (0.084% of total sick leave), the number of sick days as a result of ovarian cancer was 30,710, which corresponded to a total of 84.14 lost years of productivity for the population of women with ovarian cancer in 2018. The cost related to short-term sick leave due to ovarian cancer was therefore estimated at SEK 4,135,753.

4.3.2 Productivity loss due to long-term sick leave

Long-term sick leave refers to the sick leave from work that lasts longer than 14 days, and thus entails sickness and rehabilitation allowance from the SIA. According to statistics from the SIA, the number of female recipients for sickness and rehabilitation benefits in Sweden in 2018 amounted to 603,146 individuals, and the number of net days amounted to 36,549,112. The number of ongoing cases at the SIA due to ovarian cancer in 2018 amounted to 370. Information on the number of net days related to specific diagnoses is not included in the public statistics, hence this data was not available.

Based on the number of ongoing cases due to ovarian cancer, the number of net days with sickness benefits was calculated, which corresponded to 30,710 (0.084% of total net days of sickness benefits among women in Sweden in 2018). It was assumed that women with ovarian cancer were absent from work due to the disease for an average of 83 days, based on scientific literature [21]. The total number of days with sickness benefits due to ovarian cancer in Sweden was estimated at 84.14 years. The monetary value of productivity loss due to long-term sick leave amounted to just over SEK 36 million (presented in Table 11).

The number of cases at the SIA due to cancer in the ovaries was 295, which corresponded to 24,485 days and approximately 67 years with a cost of approximately SEK 29 million. Cancer in the ovaries accounted for nearly 80% of the costs related to loss of productivity due to long-term sick leave. The distribution among the different types of cancer is illustrated in Figure 6.

Table 11. Number of paid sickness benefits and productivity losses in 2018

Diagnosis	Number of cases in progress	Sickness benefits (in days)	Sickness benefits (in years)	Total productivity loss (SEK)
Cancer in the peritoneum	27	2,241	6.14	2,647,237
Cancer in the ovaries	295	24,485	67.08	28,923,511
Cancer in the fallopian tubes	48	3,984	10.92	4,706,198
Total	**370**	**30,710**	**84.14**	**36,276,947**

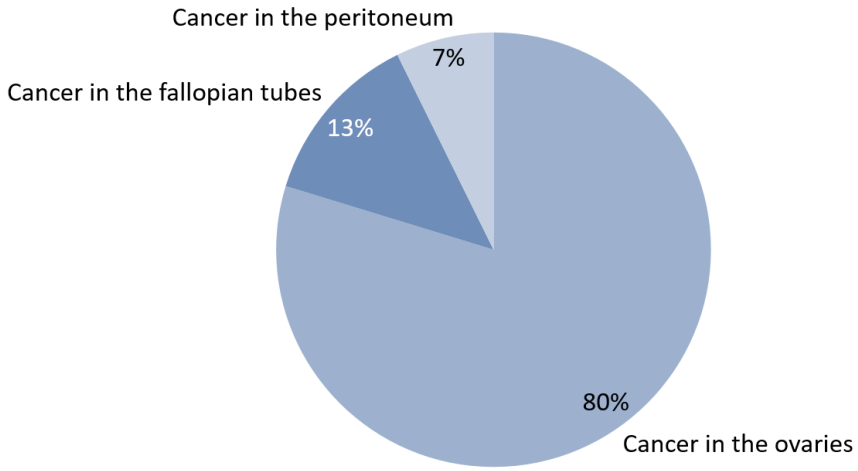

Figure 6. Productivity losses due to long-term sick leave, 2018

4.3.3 Productivity loss due to early retirement

Early retirement due to sickness refers to those individuals who receive financial disability benefits. To be eligible for disability benefits, the individual's ability to work must be reduced by at least a quarter for at least one year.

In 2018, according to the SIA, 41 women with ovarian cancer were granted disability benefits, including 31 with a diagnosis of cancer in the ovaries and 10 with a diagnosis of cancer in the fallopian tubes. Disability benefits can be granted to varying degrees (25, 50, 75 and 100%) depending on how much work capacity is considered to be reduced. Of the 31 people diagnosed with cancer in the ovaries, 20 received full compensation. The number of individuals with a different degree of benefits could not be ascertained due to data confidentiality, hence it was assumed that the remaining 11 individuals with a diagnosis of cancer in the ovaries received half (50%) of the full amount of disability compensation. The 10 women diagnosed with cancer in the fallopian tubes were divided between full (100%) and half (50%) compensation based on the same proportion estimated for the individuals diagnosed with cancer in the ovaries.

In 2018, the cost of early retirement due to cancer in the ovaries amounted to almost SEK 11 million. The corresponding cost for cancer in the fallopian tubes was SEK 3.5 million. The distribution between different types of cancer is illustrated in Figure 7.

Table 12. Productivity losses due to early retirement in 2018

Diagnosis	N. of people with full compensation	N. of people with half compensation	Production years (full compensation)	Production years (half compensation)	Productivity loss (SEK)
Cancer in the ovaries	20	11	20	5.5	10,994,714
Cancer in the fallopian tubes	6	4	6	2	3,546,682
Total	**26**	**15**	**26**	**7**	**14,541,397**

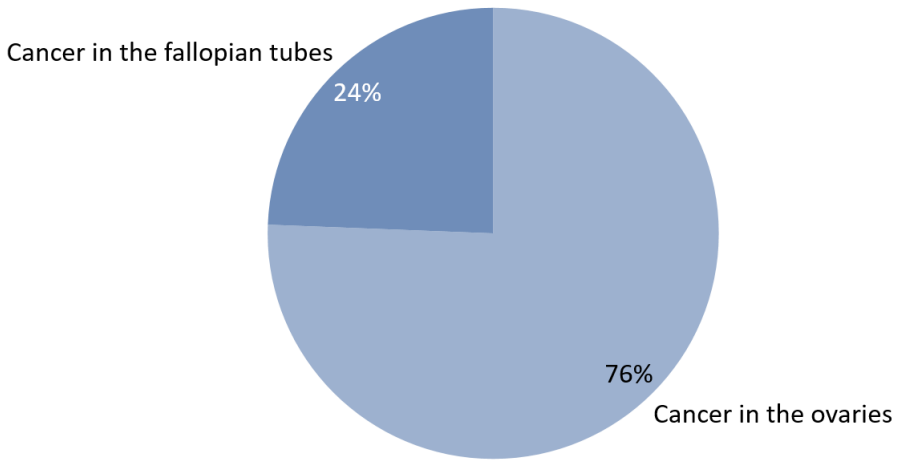

Figure 7. Productivity losses due to early retirement, 2018

4.3.4 Productivity losses due to early mortality (years of life lost)

Productivity losses due to early mortality refer to years of lost production that arise because an individual dies before reaching retirement age.

According to the NBHW's official Cause of Death Register, 687 people died due to ovarian cancer in 2018. Cancer in the ovaries accounted for over 82% of these deaths. The vast majority of deaths occurred in individuals over the age of 65. Of the deaths that occurred in the 2018 population, only 159 occurred in adults (older than 20 years of age) and before retirement age (see Table 13). These 159 deaths result in productivity losses due to years of life lost. However, this means that the real cost to society is underestimated, as older individuals are not expected to contribute any production to society.

Table 13. Number of deaths due to ovarian cancer in 2018

Age	Cancer in the peritoneum	Cancer in the ovaries	Cancer in the fallopian tubes	Total
0-14	0	0	0	0
15-19	0	1	0	1
20-24	0	1	0	1
25-29	0	2	0	2
30-34	0	0	0	0
35-39	0	5	0	5
40-44	0	4	1	5
45-49	0	5	4	9
50-54	0	24	5	29
55-59	2	34	6	42
60-64	1	61	4	66
65-69	1	64	7	72
70-74	4	129	14	147
75-79	4	93	21	118
80-84	4	72	13	89
85+	3	73	25	101
Total	**19**	**568**	**100**	**687**

* The number of deaths is based on all individuals with the diagnosis of ovarian cancer, regardless of the year the diagnosis was given.

Productivity losses due to early mortality (years of life lost) due to ovarian were estimated based on two different scenarios: (1) productivity losses due to premature death were calculated only for the year 2018, and (2) productivity losses were aggregated until the Swedish retirement age of 65. This is because future changes in the labor market may affect potential production, therefore scenario two includes a more uncertain estimate.

The first scenario was based on the number of deaths multiplied by the average disposable income for women in 2018, including social fees. A correction factor of 0.5 (corresponding to 6 months) was applied to the estimates to take into account that individuals can die at different times during the year.

Table 14 shows productivity losses in 2018. Productivity losses related to early mortality due ovarian cancer and related diagnoses amounted to over SEK 34 million.

Table 14. Productivity losses due to mortality (based on scenario 1) for ovarian cancer in 2018

Age	Number of deaths	Productivity loss (SEK)
20-24	1	215,583
25-29	2	431,165
30-34	0	0
35-39	5	1,077,913
40-44	5	1,077,913
45-49	9	1,940,244
50-54	29	6,251,896
55-59	42	9,054,471
60-64	66	14,228,454
Total	**159**	**34,277,639**

The cost for 2018 has not been discounted.

Table 15 shows the cost categorized by diagnosis. The cost of cancer in the ovaries amounted to over SEK 29 million, approximately 86% of the total productivity losses due to early mortality. The cost of cancer in the fallopian tubes was estimated at SEK 4.3 million. The distribution of costs between different types of cancer is illustrated in Figure 8.

Table 15. Productivity losses due to early mortality (based on scenario 1) for ovarian cancer, per diagnosis, in 2018

Age	Cancer in the peritoneum	Productivity loss (SEK)	Cancer in the ovaries	Productivity loss (SEK)	Cancer in the fallopian tubes	Productivity loss (SEK)
20-24	0	-	1	215,583	0	-
25-29	0	-	2	431,165	0	-
30-34	0	-	0	-	0	-
35-39	0	-	5	1,077,913	0	-
40-44	0	-	4	862,331	1	215,583
45-49	0	-	5	1,077,913	4	862,331
50-54	0	-	24	5,173,983	5	1,077,913
55-59	2	431,165	34	7,329,810	6	1,293,496
60-64	1	215,583	61	13,150,541	4	862,331
Total	**3**	**646,748**	**136**	**29,319,238**	**20**	**4,311,653**

The cost for 2018 has not been discounted.

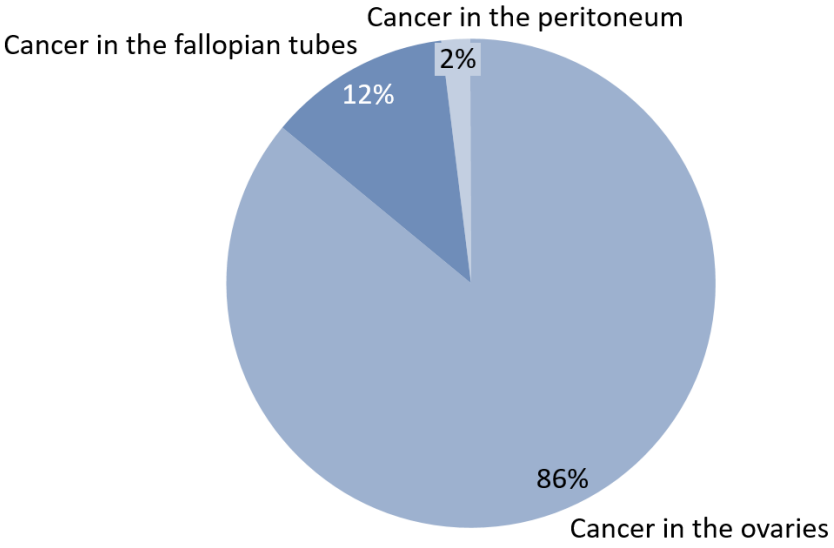

Figure 8. Productivity loss due to early mortality (based on scenario 1) for ovarian cancer, per diagnosis, in 2018

Scenario two was based on the number of deaths multiplied by the number of years to the Swedish retirement age and the average disposable income for women in 2018, including social fees. It was assumed that all individuals would continue to work full time (without any kind of allowance) and without considering potential changes in the labor market.

Table 16 shows the costs of future productivity losses discounted with 3% or 5%. All estimates are gross costs and exclude deductions for the expected future consumption of deceased individuals.

The choice of discount rate had an impact on the cost estimates. When productivity losses related to early mortality were discounted by 3%, losses amounted to SEK 539 million. When a discount rate of 5% was applied, these were reduced to SEK 413 million.

Table 16. Productivity losses due to early mortality (based on scenario 2) for ovarian cancer, in 2018

Age	Number of deaths	Productivity loss (undiscounted, SEK)	Productivity loss (3% discount, SEK)	Productivity loss (5% discount, SEK)
20-24	1	19,537,672	5,118,837	2,141,452
25-29	2	34,814,733	10,555,720	4,856,137
30-34	0	-	-	-
35-39	5	65,759,150	26,692,082	14,846,334
40-44	5	55,200,300	25,896,563	15,826,535
45-49	9	80,551,818	43,611,202	29,256,628
50-54	29	199,897,762	124,617,664	91,633,704
55-59	42	204,633,573	146,525,918	117,905,711
60-64	66	190,467,492	156,278,372	137,403,203
Total	**159**	**850,862,500**	**539,296,357**	**413,869,704**

Table 17 shows productivity losses broken down by diagnosis. Productivity losses due to cancer in the ovaries alone amounted to SEK 453 million, about 84% of the total productivity losses due to early mortality. The cost of cancer in the fallopian tubes was approximately SEK 76 million. The distribution of productivity losses due to early mortality between different types of cancer is illustrated in Figure 9.

Table 17. Productivity losses due to mortality (based on scenario 2) for ovarian cancer, per diagnosis, in 2018

Age	Cancer in the peritoneum	Productivity loss (3% discount, SEK)	Cancer in the ovaries	Productivity loss (3% discount, SEK)	Cancer in the fallopian tubes	Productivity loss (3% discount, SEK)
20-24	0	-	1	5,118,837	0	-
25-29	0	-	2	10,555,720	0	-
30-34	0	-	0	-	0	-
35-39	0	-	5	26,692,082	0	-
40-44	0	-	4	20,717,250	1	5,179,313
45-49	0	-	5	24,228,445	4	19,382,756
50-54	0	-	24	103,131,860	5	21,485,804
55-59	2	6,977,425	34	118,616,219	6	20,932,274
60-64	1	2,367,854	61	144,439,101	4	9,471,416
Total	**3**	**9,345,279**	**136**	**453,499,515**	**20**	**76,451,563**

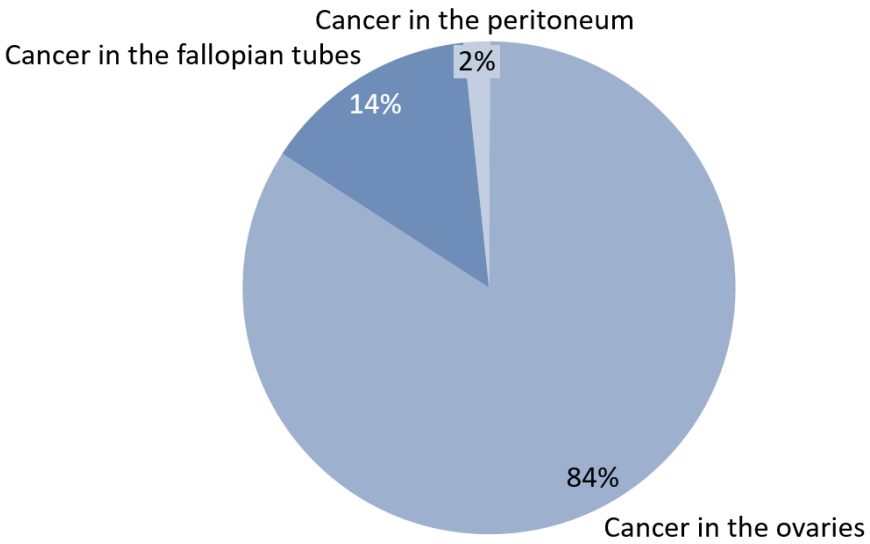

Figure 9. Productivity loss due to mortality (based on scenario 2) for ovarian cancer, per diagnosis, in 2018

4.4 Total societal costs for ovarian cancer

Table 18 and figure 10 show the total societal costs of ovarian cancer. Total societal costs amounted to over SEK 824 million. Direct healthcare costs including both outpatient and inpatient care, diagnosis and treatment amounted to approximately SEK 230 million. The largest cost items were those linked to inpatient care, which accounted for 83% of the direct costs related to ovarian cancer. Overall, direct healthcare costs accounted for nearly 28% of total societal costs.

Indirect costs amounted to over SEK 594 million, in 2018. The largest indirect costs were productivity losses due to early mortality (which were calculated based on a scenario where individuals would continue to work full time without any compensation until retirement age), which accounted for 65% of the total societal costs of ovarian cancer. Overall, indirect costs accounted for 72% of total societal costs.

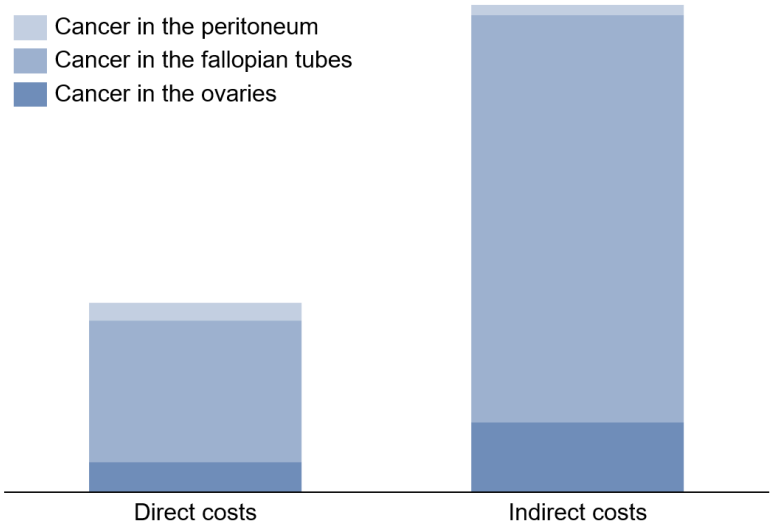

Figure 10. Total societal costs of ovarian cancer in 2018, SEK

Table 18. Total societal costs of ovarian cancer in 2018, SEK

	Cancer in the peritoneum	Cancer in the ovaries	Cancer in the fallopian tubes	Total
Direct costs	**22,019,804**	**171,557,888**	**36,110,129**	**229,687,822**
Inpatient care	19,031,180	142,619,440	29,536,606	191,187,227
Specialized outpatient care	2,122,441	19,999,437	3,732,442	25,854,320
Medication	866,183	8,939,011	2,841,081	12,646,275
Indirect costs	**11,992,515**	**493,417,741**	**84,704,444**	**594,250,453**
Morbidity	**2,647,237**	**39,918,226**	**8,252,881**	**54,954,096**
Short-term sick leave	-	-	-	4,135,753
Long-term sick leave	2,647,237	28,923,511	4,706,198	36,276,947
Early retirement	-	10,994,714	3,546,682	14,541,397
Mortality*	**9,345,279**	**453,499,515**	**76,451,563**	**539,296,357**
Total costs	**34,012,319**	**664,975,629**	**120,814,573**	**823,938,275**

*Productivity losses due to early mortality discounted with 3%.

Cancer in the ovaries accounted for the largest societal costs, approximately SEK 665 million, which corresponded to over 80% of the total societal costs for ovarian cancer. Costs related to productivity losses due to early mortality primarily contributed to this financial burden.

4.5 Burden of disease

The table below shows the total burden of disease both globally and in Sweden, as well as the burden of disease related to ovarian cancer and the proportion it constitutes of the total disease burden. Burden of disease is based on disability-adjusted life years (DALYs), which take into account both years lost to disability, also known as years lived with a disability/disease, as well as early mortality related to the disease.

Ovarian cancer in Sweden is responsible for, approximately, 12,000 DALYs, which corresponds to 0.5% of the total burden of disease in Sweden.

Table 19. Burden of disease expressed as Disability Adjusted Life Years (DALY)

Burden of disease	Setting	Disability Adjusted Life Years (DALY)	Proportion of total burden of disease
Total	Globally	2,499,292,055	
Total	Sweden	2,615,621	
Ovarian cancer	Globally	4,673,034	0.19%
Ovarian cancer	Sweden	12,035	0.46%

5. Discussion

This report aimed to identify, quantify and value the socioeconomic consequences related to cancer in the ovaries, the fallopian tubes and the peritoneum (ovarian cancer), as well as to estimate their disease burden. The total societal costs related to ovarian cancer amounted to approximately SEK 824 million. Direct healthcare costs amounted to SEK 230 million. The largest direct cost items were those related to inpatient care, which accounted for 83% of the direct costs of ovarian cancer. Indirect costs related to loss of production due to sick leave, early retirement and early mortality amounted to SEK 594 million. The burden of disease related to cancer in the ovaries was approximately 12,000 disability-adjusted life years, which constitutes approximately 0.5% of the total disease burden in Sweden.

In addition to being the seventh most common form of cancer among women and constituting about 3% of all female cancers, ovarian cancer is the most severe gynecological cancer given its high mortality. To date, the scientific literature does not indicate that there are effective screening methods for detecting ovarian cancer [14]. It is therefore of great importance that additional resources are invested toward research on early detection and effective treatments for ovarian cancer to alleviate human suffering and reduce its societal burden.

The results of the present report should be interpreted with caution, as they are based on multiple assumptions. First, data limitations made it challenging to fully quantify medical related resource use. The CPP-database does not have 100% coverage of all healthcare visits in the country, nor are all contacts with the healthcare services recorded in this database by healthcare professionals. Cost per visit, which is an estimate based on the total number of care visits, is likely underestimated. In addition, the costs related to medication use were probably grossly underestimated. Since data at the aggregate level was not available per diagnostic category, these costs were estimated from the literature. We chose to include pharmacological treatment, although individuals use, for instance, pain relieving drugs and drugs to reduce side effects. It was also not possible to estimate how many individuals that will use the recently approved substance Niraparib in the future.

Another limitation pertained to the estimation of indirect costs. Short-term sick leave (up to 14 days) was calculated based on several assumptions (the same number of individuals registered for long-term sick leave was assumed in this estimation). Although this estimate is conservative, it should be interpreted with caution. Additionally, no information was available on the number of days individuals with ovarian cancer were on long-term sick leave (which affected sickness benefits beyond the first 14 days). An average estimate was sourced from the published literature. However, the study this estimate was sourced from was neither from Sweden nor solely based on patients with ovarian cancer, hence the impact of this assumption on the results is difficult to assess.

Importantly, two different methods were employed to estimate societal costs related to ovarian cancer, namely both the prevalence and the incidence-based approach. The prevalence-based approach means that all those who received treatment based on an ovarian cancer diagnosis in 2018 were captured, not only the number of cases diagnosed that year. The report therefore estimates the annual cost of diagnosed cases, rather than the cost of those diagnosed in 2018.

6. Conclusion

Total societal costs of ovarian cancer amounted to approximately SEK 824 million, with direct healthcare costs estimated at SEK 230 million and indirect costs related to productivity losses amounting to SEK 594 million. Despite limitations in finding reliable data regarding resource use for individuals with ovarian cancer, the disease burden and its related societal costs are undeniably significant. Priority should be given to resource allocation towards further research on prevention, early detection and effective treatment methods for ovarian cancer.

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