Incidence, treatment, and survival trends in older versus younger women with epithelial ovarian cancer from 2005 to 2018: A nationwide Danish study

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HIGHLIGHTS
- Incidence of EOC in Denmark decreased among women <70 years of age but was stable for women ≥70 years during 2005–2018.
- The proportion of patients with advanced EOC not undergoing primary debulking surgery increased from 2005 to 2018.
- During the same period, the proportion of patients having no residual disease after primary debulking surgery increased.
- During the same period, cancer-specific survival increased for both younger and older EOC patients.

ABSTRACT

Objective. To examine clinical trends in Denmark for younger and older epithelial ovarian cancer (EOC) patients, focusing on incidence, treatment, and survival changes.

Methods. We included a nationwide cohort diagnosed with EOC from 2005 to 2018. We described age-standardized incidence, surgical patterns, and residual disease trends, and cancer-specific survival stratified by age (<70 and ≥70 years), stage, and period (2005–09, 2010–13, 2014–18).

Results. We included 7522 patients. The incidence decreased from 16.3 (2005) to 11.4 (2018) per 100,000 woman-years, driven by the younger cohort. While the proportion of patients with stage IIIC-IV disease undergoing primary debulking surgery (PDS) decreased, the proportion of patients having interval debulking surgery (IDS) and no debulking surgery increased significantly. In 2014–18, 36% and 24% had PDS for younger and older patients, respectively, compared to 72% and 62% in 2005–09. In both age cohorts, the proportion of patients debulked to no residual disease increased significantly among patients with stage IIIC-IV and in the total cohort.

Two-year cancer-specific survival increased from 75% (2005–09) to 84% (2014–18) for younger patients and from 53% to 66% for older patients. After adjusting for potential confounders, age ≥70 was associated with a 1.4-fold increased risk of cancer-specific death (95% confidence interval: 1.2, 1.5).

Conclusions. The proportion of patients with advanced EOC not undergoing PDS or IDS increased significantly. During the same period, patients debulked to no residual disease, and cancer-specific survival increased. However, a survival gap in favor of the younger patients remains after adjusting for potential confounders.

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1. Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecological malignancy in the Western world, and the prognosis worsens markedly with age [1,2]. Although survival is increasing, this trend appears to be driven mainly by improved survival among the younger patients [3]. Thus, growing attention has focused on inequality in the treatment of EOC.
younger versus older cancer patients. Older EOC patients are less likely to receive curatively intended treatment [4], although it has been shown that these patients and their younger counterparts benefit equally from standard treatment regimens [3]. Most recently, studies have reported increasing rates of older patients not having curatively intended treatment. Therefore, it is crucial to address real-world evidence of changing treatment strategies for older patients to understand these gaps between age groups and eventually improve outcomes.

The age composition of patients is expected to change due to aging populations and increased life expectancy globally [5], highlighting the importance of knowledge on older women with EOC. Describing the temporal trends and knowing the current epidemiology of EOC is crucial to understand the present and future disease burden and consequences of treatment approaches.

Although a wide variety of changes in the treatment pathway have been implemented in Denmark during the last decades to successively increase the survival of EOC patients, we speculated if these changes had influenced the younger and older patient population equally. Thus, we aimed to describe time trends in incidence, treatment, and survival in a Danish nationwide cohort of EOC patients for younger and older patients diagnosed between 2005 and 2018.

2. Materials and methods

2.1. Study population and data sources

In this nationwide cohort study, we included all patients in Denmark aged 18 years or older diagnosed with EOC (including primary cancer in the ovaries, fallopian tubes, or peritoneum) between January 1, 2005, and December 31, 2018. We excluded patients with borderline or non-epithelial tumors.

Patients were identified in the Danish Gynecological Cancer Database (DGCD). The DGCD is a nationwide multidisciplinary database containing detailed information about gynecological malignancies [6]. In Denmark, cancer treatment is tax-financed, and it is mandatory for all gynecological and pathological departments that take part in the diagnosis and treatment of gynecological malignancies to report to the DGCD. The DGCD has yielded high coverage rates since its establishment in 2005, and from 2014 to 2018, coverage rates were 97–99% [6]. The DGCD has linked annually with the Danish Register of Causes of Death and the National Patient Registry to enhance the completeness of registration. The Danish Register of Causes of Death collects information regarding all deaths in Denmark. Data originates from mandatory death certificates, including date and cause of death, coded according to the ICD-10 [7]. The most used comorbidity index, the Charlson Comorbidity Index (CCI), was supplemented from the National Patient Registry for this study [8]. Data on whether the patients had received chemotherapy (yes/no) in the frontline setting was added from the National Patient Registry.

We divided the study population into two cohorts according to age at diagnosis: a younger cohort of patients <70 years and an older cohort of patients ≥70 years. In the last decade, most international studies on aging and EOC agree on a limit between younger and older patients of 70 years [9]. Furthermore, previous age-specific incidence rates for ovarian cancer have shown different rates over time for women aged < and ≥ 70 years of age [10] why it is relevant to report incidence rates for these two groups separately.

To study time trends, we divided the two age cohorts into three periods; T1 = 2005 to 2009, T2 = 2010 to 2013, T3 = 2014 to 2018, equivalent in length of time (4–5 years), and population size. Further, treatment modalities were grouped into three categories based on surgical treatment: (1) primary debulking surgery (PDS), (2) interval debulking surgery (IDS), and (3) no debulking surgery (NDS), including palliative surgery, chemotherapy only, or absence of any surgical or oncological treatment.

2.2. Statistical analysis

Age-standardized incidence (world standard population) rate was calculated for 1-year intervals and reported as the number of new cases per 100,000 woman-years for EOC. An age restriction of 18 years was applied. We obtained person-time at risk from the NORDCAN database [11]. To investigate incidence trends over time, we calculated the annual percentage change (APC) and corresponding 95% confidence intervals (CI) from 1-year standardized rates under the assumption of a log-linear Poisson distribution.

We performed descriptive statistics to describe baseline characteristics and treatment changes stratified by age cohorts and periods. Treatment characteristics were described for patients with FIGO stage IIIC-IV. Comparisons between groups were performed using fitted tests for categorical data and Mann-Whitney U tests for continuous variables.

We conducted two-year cancer-specific survival analyses stratified by age cohort, stage, and period since we had at least two years of follow-up on patients. For this, we used data from the Danish Register of Causes of Death. The date of death was available for 7201 patients (96%), and the cause of death was accessible for 7198 patients; thus, we excluded 324 patients from cancer-specific survival analyses. We estimated cancer-specific survival probabilities for EOC patients with stage IIIC-IV disease using the Kaplan-Meier method, assessing the time from the date of diagnosis until death of EOC or end of follow-up. A multivariate Cox regression analysis was performed to estimate hazard ratios and to adjust for possible confounders. We tested the proportional hazards assumption using Schoenfeld residuals, and the model was found fit for use. Follow-up ended on February 11, 2021, or date of death, whichever came first.

Statistical analyses were performed using R version 3.5 (The R Foundation for Statistical Computing). Two-sided p-values of <0.05 were considered statistically significant.

2.3. Ethics

The Danish Data Protection Agency (File number: P-2019-738) and The Danish Clinical Quality Program – National Clinical Registries approved access to registry data. No ethical approval was required.

3. Results

3.1. Age-standardized incidence rate

We included 7522 patients diagnosed with EOC between 2005 and 2018, 4539 (60%) patients <70 years, and 2983 (40%) ≥ 70 years. Throughout the study period, the age-standardized incidence rate varied between 16.3 (2005) and 11.4 (2018) per 100,000 woman-years with a significant decrease of 2.1% per year (APC = −2.1; 95% CI: −2.8, −1.5) (Supplementary Table S1). Fig. 1 presents the age-standardized incidence rates by age cohort in a semi-logarithmic scale. In the younger patients, we observed a significant decrease in the age-standardized incidence rate from 14.3 per 100,000 woman-years in 2005 to 9.0 per 100,000 woman-years in 2018 (APC = −2.8; 95% CI: −3.6, −2.1). In contrast, the age-standardized incidence rate of the older patients ranged from 1.8 (2009) to 2.6 (2016) per 100,000 woman-years with no significant change throughout the study period (APC = +1.5; 95% CI: −0.2, 3.3).

3.2. Trends of age

The median age of the study population was 66 years (interquartile range (IQR): 57, 74), and age ranged from 19 to 101 years. In the younger cohort of patients, the median age was 60 years, and in the older cohort of patients, the median age was 76 years. The median age for the total study population increased by 2.5 months per year from 2005 to 2018 (Supplementary Fig. S2). Accordingly, we found a significant


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increase in median age at diagnosis in the total cohort in the three periods, T1 (n = 2742, median age = 65 years), T2 (n = 2190, median age = 66 years) and T3 (n = 2589, median age = 68 years) (p < 0.001).

3.3. Baseline characteristics

Table 1 displays the baseline characteristics of the younger and the older cohort in the three periods. Older patients scored higher in CCI and performance status than the younger patients. Regarding histological subtypes, the number of younger patients with high-grade serous carcinomas decreased, while for the older patients, the number increased. For both age cohorts, however, the proportion of high-grade serous carcinomas increased. For the younger patients, the proportion of low-grade serous, endometrioid and clear cell carcinomas decreased. While, for the older patients, the proportion of mucinous and endometrioid carcinomas decreased. In addition, a lower proportion of patients ≥70 years had FIGO stage I disease, and a higher proportion had stage IIIC and IV disease than their younger counterparts throughout all three periods. In the most recent period, we observed a shift towards stage IV instead of stage IIIC disease in both age cohorts.

3.4. Trends of treatment modality and surgical outcome

In the analyses of treatment modality and residual disease after surgery, we included EOC patients of stages IIIC-IV (n = 4486). For both the younger and older patients, the percentage of patients undergoing PDS declined in the three periods (Table 2 and Fig. 2). At the same time, we observed an increase in patients undergoing IDS and NDS in both age cohorts, although this was most pronounced in the older patients. Thus, in the most recent period, 45% of the older patients with stage IIIC-IV disease had NDS versus 18% of the younger patients compared to 30% and 12%, respectively, during 2005–2009. IDS was the most performed surgical modality in the younger patients <70 years (46%) in T3. In both age cohorts, we found a remarkable increase in the proportion of patients with no residual disease after PDS or IDS over time (Table 2). Accordingly, the proportion of patients with no residual disease after surgery tripled between T1 and T3 for the older cohort.

For both age cohorts and within all three treatment modalities (PDS, IDS, and NDS), the use of chemotherapy has increased during the three periods (Table 2). The greatest leap is seen in the older cohort having NDS, from 49% treated with chemotherapy in 2005–09 to 76% in 2014–18.

3.5. Survival analyses

Two-year cancer-specific survival for patients of all stages increased significantly during the study period (from 75% (95% CI: 74, 78) in T1 to 84% (95% CI: 82, 86) in T3 in the younger cohort and from 53% (95% CI: 49, 56) in T1 to 66% (95% CI: 63, 69) in T3 in the older cohort). For both age groups, the two-year cancer-specific survival and median cancer-specific survival increased between T1 and T3 (Figs. 3 and 4).

We adjusted for Charlson comorbidity score, performance status, histology, stage, surgical modality, and residual disease after surgery in the multivariate Cox regression model for patients with advanced-stage disease (Supplementary Table S3). All variables except CCI and histological subtype were significantly associated with cancer-specific survival. A late time period was significantly associated with decreased risk of cancer-specific death. The hazard rate of T2 versus T1 was 0.8 (95% CI: 0.8–0.9), and the hazard rate of T3 versus T1 was 0.5 (95% CI: 0.4, 0.6). High age was associated with a higher risk of cancer-specific death. The hazard rate of the older cohort versus the younger was 1.4 (95% CI: 1.2, 1.5).
The overall incidence of EOC has decreased from 2005 to 2018, predominantly driven by a significant decrease for younger women. This trend aligns with international studies [12,13], and previously published Danish data has shown the same tendency; however, the study lacked data on peritoneal cancer [10]. It is speculated that the trend might be attributed to the steady increase in oral contraceptive use known to reduce the risk of EOC [14]. Oral contraceptives were released in Denmark in 1966, giving both the younger and older cohort of the present study equal access thereaf-

4.2. Interpretation

Thus, even though the risk reduction might persist for more than 30 years after the use has ceased, risk reduction diminishes over time [16]. Therefore, the risk reduction in the older cohort may be less than in the younger cohort. This might explain why we observe a decrease in incidence among younger women but not in older women.
Bilateral salpingo-oophorectomy as a risk-reducing strategy in patients with Breast Cancer Gene (BRCA) mutations may potentially affect the incidence of EOC in the future. However, surgical implications may extend beyond prophylactic surgery in high-risk patients. Due to the role of the fallopian tube in the development of EOC, procedures such as tubal ligation, bilateral salpingectomy, and oophorectomy performed for various benign reasons could potentially impact the incidence [17]. These procedures are mainly performed on women between 40 and 60 years; yet, they may affect the development of EOC in both younger and older women. The NORDCAN woman-time at risk used to estimate incidence rates does not account for previous risk-reducing procedures why the incidence might be underestimated due to an overestimation of the population at risk.

During the three periods, histological patterns have changed. We observed an increase in the proportion of patients with high-grade serous carcinomas for both younger and older patients. Patients with high-grade serous carcinomas are often older with advanced-stage disease at diagnosis and an unfavorable histotype-specific survival [18,19]. The change in histological pattern might reflect the changes in age distribution towards a more aging population of EOC patients observed in our cohort.

We also observed stage migration for both age cohorts, with a shift towards a larger proportion of patients diagnosed with a more advanced stage over time. This is in line with a Dutch study showing an increase in advanced-stage patients from 1989 to 2014 [20]. In Denmark, PET-CT has slowly been incorporated in the diagnostic workup for patients suspected of EOC since 2007, and it is now fully implemented nationwide. This seems to cause stage migration by increasing the proportion of patients diagnosed with stage IV due to better detection and staging [21]. Expectantly, stage migration may improve survival within stages IIIC and IV; however, it does not affect survival in the total cohort [22].

During the study period, surgical treatment of EOC changed immensely due to three large randomized controlled trials demonstrating that PDS followed by adjuvant chemotherapy and neoadjuvant chemotherapy followed by IDS have similar efficacy [23–25]. Although debatable, the introduction of IDS has increased the ability to individualize treatment, and IDS primarily serves as an alternative for patients not

### Table 2

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<th>Surgical treatment (%)</th>
<th>EOC patients &lt;70 years</th>
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<td><strong>PDS</strong></td>
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Residual disease after PDS or IDS (%)

### Fig. 2.

Trends in surgical treatment modality from 2005 to 2018 for stage IIIC-IV epithelial ovarian cancer patients by age cohorts.
Fig. 3. Two-year cancer-specific survival (%) for epithelial ovarian cancer patients according to age cohorts, stage, and period.

Fig. 4. Cancer-specific survival of stages III-IV epithelial ovarian cancer patients by age cohort and period.
suitable for PDS due to unresectable disease, severe comorbidities, or high age [26]. Our results reflect these treatment changes; IDS has increased in both age cohorts. This is in line with a study by Horner et al. reporting trends of treatment modality between 2004 and 2015 [27]. They found a decrease in PDS and an increase in IDS, and, interestingly, an increase in surgical complexity for both approaches. Furthermore, they reported a reduction in 30-day mortality and an increase in 5-year survival.

Strikingly, NDS has increased significantly in our data, from 30% in T1 to 45% in T3 in older patients. It has long been hypothesized that undertreatment of older cancer patients is one of the primary reasons for poorer survival. Several studies have assessed this persistent inequality in the treatment between older and younger patients [4,28]. However, international studies on the proportion of patients with advanced-stage EOC having NDS are scarce. Shalowitz et al. explored non-surgically managed EOC patients in the United States between 2003 and 2011 [29]. Similar to our results, they found 44% of FIGO stage III-IV patients >75 years receiving systemic treatment only or no treatment at all. A more recent study from the Netherlands describes an increase in the proportion of patients of all ages with advanced-stage disease not receiving combined cytoreductive surgery and chemotherapy from 30% to 37% between 2008 and 2016 [30]. Further, they report that patient’s choice was the main reason for not having treatment, whereas the patient’s poor condition was the second most common reason.

Patient preferences balancing the treatment burden, quality of life, and expected survival benefits are vital elements of patient-centered care, and patient involvement in the decision-making process combined with careful selection of patients for treatment is therefore essential. Kitson et al. have assessed three central concepts behind patient-centered care: patient participation and involvement, the relationship between the patient and the health professional, and the context of care delivery [31]. Our results contribute to future evidence-based decisions, taking into account the current treatment practice in addition to patient preferences and the organizational context. Being well-informed represents a key criterion for being involved in decisions. However, the severe diagnosis and rather acute context of the initial planning of surgery might impact patients’ capability of taking in comprehensive information regarding complex surgery, chemotherapy, and complications [32], while the more chronic setting during chemotherapy might facilitate shared decision-making.

Studies report that older women desire active treatment and cure just as much as their younger counterparts and do not perceive their age as a barrier to this [33,34]. Thus, while shared-decision making has been gaining ground in recent years, this might not explain the increase in NDS in our results. Yet, a central question emerging from our findings is how and by whom treatment decisions are made. The relatively large proportion of older patients having NDS in recent years may reflect an increasing awareness among physicians of selecting which patients to offer debulking surgery since there is likely a subgroup of frail patients for whom the benefits of aggressive debulking do not balance the risks.

Our results show a significant increase in the proportion of patients debulked to no residual disease, and during the same period, cancer-specific survival increased. It is striking that NDS increases during the same period. Thus, despite the reduction in debulked patients, the cancer-specific survival increases, which may be ascribed to the vast increase in patients debulked to no residual disease or rather the correct selection of patients.

However, a factor that also plays a vital role in improved survival is the increased use of chemotherapy across both age cohorts and all treatment modalities throughout the study period. Noteworthy, chemotherapy only (NDS) has increased by 55% from T1 to T3 within the older cohort. The introduction of IDS might explain a part of the increase in both NDS and NDS + chemotherapy during the study period since, expectantly, IDS may not be feasible for various reasons in a subgroup of the patients initially treated with neoadjuvant chemotherapy.

For decades, the systemic treatment has involved platinum-based chemotherapy and a taxane; however, in 2012, an antiangiogenic strategy (bevacizumab) was added to the treatment of patients with advanced-stage EOC [26]. Unfortunately, the DGCD does not contain specified data on systemic treatments, but we suspect that around 1845 patients in our study cohort would have been eligible for bevacizumab treatment based on stage and postoperative residual disease status only. Thus, the introduction of bevacizumab might also impact cancer-specific survival in advanced-stage patients.

Paradigmatic changes and improvements in the clinical management of EOC in Denmark have likely also contributed to the increased cancer-specific survival. A centralization of treatment was slowly implemented from 2001 to 2007, and the positive effect of this centralized and specialized treatment on survival is well-documented [35]. However, it is hypothesized that specialization not only leads to better surgical outcomes. Physicians may also have become more experienced in identifying the patients who may benefit most from debulking surgery and, equally important, the patients who may not.

Yet, although it seems the cancer-specific survival has increased more in the older cohort of patients than in the younger, survival remains higher for younger patients with EOC, as estimated by the multivariate model. Notably, this is after adjusting for potential confounders. Differences between the two age cohorts other than the ones described in this study may thus exist.

Geriatric screening, comprehensive geriatric assessment, and prehabilitation are relatively new approaches to assess and improve older patients’ conditions. Optimizing old and frail patients with tailored geriatric interventions to ultimately enable surgery might narrow the survival gap between the older patients and their younger counterparts [36,37]. Although results from randomized controlled trials regarding the benefit of such approaches in EOC patients lack, both the American Society of Clinical Oncology and the International Society of Geriatric Oncology recommend geriatric assessment in all patients ≥65 years receiving oncologic treatment [38,39]. Our results show that patients are getting older at diagnosis, highlighting the need to explore these approaches further. Additionally, studies support that this patient population is positive towards supported and supervised prehabilitation [40].

4.3. Strengths and limitations

The present study is based on nationwide prospectively collected data on EOC patients registered in the DGCD. Data represent around 97% of all patients treated for EOC throughout the period. Thus, the risk of selection bias is minimal. Furthermore, linkage to other national registers secures life-long follow-up. This ensures high power in all statistical analyses.

The information on the cause of death from the Danish Register of Causes of Death made it possible to analyze cancer-specific survival. Due to the aggressive nature of EOC, death is most often ascribed to the disease, and cancer-specific survival is thought to be identical to all-cause survival. However, older patients have more comorbidities than younger patients and might be at greater risk of dying for other reasons than their cancer disease. Accordingly, we found it relevant to study the cancer-specific survival when comparing the two age cohorts. This method might introduce information bias due to misclassification of cancer-specific causes of death on death certificates. However, the Danish Register of Causes of Death ensures accuracy by manually validating around 20–25% of all death certificates annually [7].

A common limitation to register-based studies is missing data. Yet, our key variables only had small proportions of missing data. Since a large proportion of the older patients in our cohort have NDS, a
pathological examination of surgical tissue may not have been performed, explaining the proportion of "undetermined" cancer sites reported by pathologists specialized in gynecological oncology. Thus, we do not consider this missing data. Patients not eligible for surgical staging will at present be diagnosed with an undetermined origin of cancer site, while in earlier periods, a diagnosis of ovarian cancer was registered in many cases without a specific biopsy of the adnexa. During the study period, it has become widely accepted that EOC evolves during the past decades have likely played an important role.

5. Conclusions

In conclusion, we demonstrate an overall positive development in epidemiological trends in EOC in Denmark from 2005 to 2018 with decreasing incidence and increasing survival rates. The decrease in incidence is primarily driven by fewer women <70 years diagnosed with EOC. In addition, cancer-specific survival has improved for EOC patients across age cohorts regardless of fewer patients undergoing PDS or IADS. A vast increase in the proportion of patients having complete tumor debulking and the proportion of particularly older patients receiving chemotherapy during the past decades have likely played an important role. Furthermore, we speculate whether the selection of patients to PDS/IADS has improved due to a more patient-centered approach and the establishment of gynecological cancer centers, thus refining the balance between the expected survival benefit, the surgical burden, and postoperative morbidity.

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Declaration of Competing Interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgyno.2021.10.081.

References


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