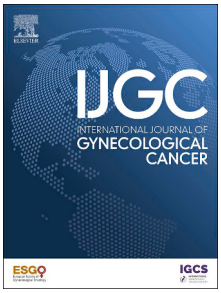
ORIGINAL RESEARCH

Ovarian cancer survival in Germany: a nationwide analysis by stage and histotype



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HIGHLIGHTS

- Marked differences in survival by stage across ovarian cancer histotypes
- Excess mortality hazard patterns show histotype-specific profiles over time
- Effect of stage decreased over follow-up; largest during the first year after diagnosis

ABSTRACT

Objective: Previous population-based studies on ovarian cancer survival have evaluated less granular disease staging categories and histologic sub-types than are in current use, and there is a need to assess survival in the context of more contemporary treatment practices and histotype classifications.

Methods: Using flexible parametric models, we assessed the 1-, 3-, 5-, and 10-year net survival and excess mortality hazards of 54,267 incident invasive ovarian cancer cases by stage and histology and 9478 borderline cases diagnosed between January 1, 2010 and December 31, 2021 recorded in Germany.

Results: Net survival differed markedly by stage, with consistently favorable long-term survival for early-stage (I to II) and poor outcomes for advanced-stage (III to IV) disease across histotypes. Although most stage I tumors showed high 10-year net survival ($\geq$ 77%), carcinosarcomas represented a notable exception. Net survival declined with advancing stage, with 10-year estimates ranging from 46% to 76% for stage II, 18% to 55% for stage III, and poor 5-year survival for stage IV tumors (15% to 41%). Considering patterns by time since diagnosis, the excess mortality hazard was the highest across all histotype-stage groups during the first 3 years with variability suggestive of histotype-specific treatment resistance and disease recurrence. The influence of stage decreased over the follow-up, with the largest impact mostly observed during the first year after diagnosis. Net survival for borderline tumors was high (10-year survival = 92.9%).

Conclusions: Net survival was favorable for patients with early-stage disease. Variability was observed across histotypes by stage. The early post-diagnosis period is a critical window for excess mortality, and the development of histotype-specific treatments is needed.

Keywords:
Ovarian Cancer; Net Survival; Histotype; Stage

WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous population-based studies in the United States, Germany, and Norway have assessed ovarian cancer survival with less detailed staging and histotype categories and with lower counts of diagnoses during less recent time periods. A larger-scale, contemporary analysis of ovarian cancer survival is needed in light of the development of newer treatments for and classifications of this disease.

WHAT THIS STUDY ADDS

For all histology groups, including the largely diagnosed high-grade serous histotype, more favorable survival was observed for stages I and II. Within 1 year of diagnosis and mostly for stages III and IV group comparisons versus stage I, the highest time-varying excess hazard ratio was observed for the high-grade serous, endometrioid, mucinous, clear cell, and carcinosarcoma groups. The impact of stage on survival declined over the follow-up time.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

This study shows the early post-diagnosis period as a period with high mortality for individuals with ovarian cancer and motivates the continued development of more targeted treatment options by disease histotypes and the potential benefits of earlier detection.

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INTRODUCTION

Epithelial ovarian/tube/peritoneal carcinoma is a lethal gynecologic malignancy, diagnosed predominantly at late stage and with poor long-term survival. In Germany, the 5-year relative survival has been reported to be approximately 44% (as of 2019/2020), with poorer survival observed for more aggressive histotypes and tumors diagnosed at advanced stages.[1] Given the heterogeneity of ovarian cancer, with histotypes originating from different sites, and the different associated somatic mutations, progression profiles, and treatment responses, there is a need for population-based survival analyses stratified by histotype. International data on ovarian cancer survival by histotype and stage within the context of contemporary histotype classification and treatment remain limited.

The most recent German cancer registry study included diagnoses through 2006,[2] with more recent studies in Norway[3] (diagnoses through 2021) and the United States (diagnoses through 2014)[4] using more contemporary histotype classifications. The study in Norway had a relatively limited number of cases in sub-groups of stage and histology, and the study in the United States lacked detailed data on disease stage and more recent diagnoses. Thus, this study aimed to provide further population-based data on survival by histotype and stage to characterize the contemporary survival profile of patients with this lethal disease. Furthermore, we describe the characteristics of women diagnosed with incident ovarian cancer from 2010 to 2021 in Germany. The European Medicines Agency approved bevacizumab for the treatment of advanced ovarian cancer in 2011 and poly adenosine diphosphate-ribose polymerase (PARP) inhibitors for the treatment of recurrent BRCA-mutated, recurrent ovarian cancer in 2014;[5] thus, our study also allows the assessment of survival during this period of targeted therapy.

METHODS

Data from the Center for Cancer Registry Data at the Robert Koch Institute[6] and the Federal Statistical Office of Germany were used. The Zentrum für Krebsregisterdaten is responsible for the aggregation of data from each of the population-based cancer registries of the 16 German federal states.[7] Data from the Zentrum für Krebsregisterdaten includes tumor stage and histology, with data availability from 1999 for some federal states. Tumor topography and morphology were classified by the International Classification of Diseases for Oncology, third edition. The Federal Statistical Office of Germany provided national mortality tables needed to calculate yearly expected mortality rates by age and federal state.[8] In accordance with the journal's guidelines, we will provide our analytic code for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested. The data are available by application from the Center for Cancer Registry Data.

Study Population

Individuals with a diagnosis of incident ovarian (International Classification of Diseases for Oncology, third edition: C569), fallopian tube (C570), or primary peritoneal (C480, C481, C482, C488) cancer between January 1, 2010 and December 31, 2021 recorded in a German federal state registry were included in this study. We restricted the study population to patients diagnosed between 2010 and 2021 to ensure sufficient data coverage across federal states.[1] A total of 103,312 patients with invasive and 16,473 borderline tumors met these criteria. Diagnoses on an autopsy or death certificate ($n = 11{,}199$), patients aged < 18 or > 80 years ($n = 15{,}603$), duplicate registrations ($n = 5$), patients with missing diagnosis date in months ($n = 65$), with only year or month of death registered ($n = 2$), patients with tumors of unknown stage ($n = 23{,}177$), tumors not classified as epithelial or non-epithelial ($n = 970$), and carcinomas not otherwise specified and mixed tumors not classified as high-grade ($n = 5019$) were excluded, which resulted in final data set of 54,267 patients with invasive and 9478 borderline tumors for analyses.

Histology Classification

Using the fourth (2014) edition of the World Health Organization classification for female reproductive tumors, International Classification of Diseases for Oncology, third edition morphology codes were classified into histotype groups, with some exceptions (Table S1); this edition covers the majority of the study period. For tumors diagnosed in 2016-2021, morphology code 8461/3 was classified as high-grade serous and 8460/3 was classified as low-grade serous, and, for those diagnosed in 2010-2015, the sixth digit was used (low-grade = 1 or high-grade = 2, 3, 4). Endometroid and mixed histologies, along with some carcinomas, with a high grade (3 or 4) were classified as high-grade serous, based on data suggesting historical misclassification of high-grade serous tumors as high-grade endometrioid,[9] and, for all other serous and carcinoma cases, a grade of 1 was defined as low-grade serous and a grade of 2 to 4 was defined as high-grade serous, as has been done previously.[3,4]

Statistical Analysis

Survival time was calculated as the time from cancer diagnosis until death or December 31, 2021. Patients with identical dates for diagnosis and death were assigned 1 day of survival time. Net survival was estimated in a relative survival framework using flexible parametric models.[10] Kaplan—Meier curves were generated to evaluate overall survival (Fig. S1 and Table S2). The expected mortality rate was calculated from national morality tables stratified by age, year, and federal state, provided by the Federal Statistical Office of Germany. Initial flexible parametric models stratified by histotype and stage, where the baseline log-cumulative excess hazard was modeled with 5 degrees of freedom (and allowed to vary by 2 degrees) using B-splines, were developed to obtain 1-, 3-, 5-, and 10-year net survival and excess mortality hazard predictions for women with a mean age at diagnosis of 62 years from 2010 to 2021. Net survival was estimated for histotype and stage groups with at least 20 cases and 20 events (deaths) across the follow-up period, and no predictions beyond the last event were made. Flexible parametric models were used to evaluate histotype adjusted for stage and histotype and stage combinations as the main effect to estimate the excess mortality hazard and excess mortality hazard ratios (Supplementary Methods). Statistical significance evaluated at the 0.05 α level and all analyses were performed in R (4.3.0) for Windows,[11] using the rstpm2 package.

Table 1 Descriptive Characteristics of Women Diagnosed With Incident Ovarian Cancer From 2010-2021 in Germany, by Tumor Behavior

	Overall, $N = 63{,}745$[a]	Invasive, $n = 54{,}267$[a]	Borderline, $n = 9478$[a]
Age at diagnosis	61 (13)	62 (12)	53 (15)
Age at death	68 (10)	68 (10)	69 (12)
Cause of death			
Ovarian, fallopian, peritoneal	6681 (10%)	6643 (12%)	38 (0.4%)
Non ovarian, fallopian, peritoneal	3614 (5.7%)	3350 (6.2%)	264 (2.8%)
Alive	36,874 (58%)	28,108 (52%)	8766 (92%)
Unknown	16,576 (26%)	16,166 (30%)	410 (4.3%)
Histology			
High-grade serous	38,905 (61%)	38,905 (72%)	0 (0%)
Low-grade serous	2405 (3.8%)	2405 (4.4%)	0 (0%)
Endometrioid	3189 (5.0%)	3189 (5.9%)	0 (0%)
Mucinous	3190 (5.0%)	3190 (5.9%)	0 (0%)
Clear cell	1822 (2.9%)	1822 (3.4%)	0 (0%)
Carcinosarcoma	891 (1.4%)	891 (1.6%)	0 (0%)
Borderline	9478 (15%)	0 (0%)	9,478 (100%)
Non-epithelial	1583 (2.5%)	1583 (2.9%)	0 (0%)
Malignant Brenner	134 (0.2%)	134 (0.2%)	0 (0%)
Serous - missing grade	2148 (3.4%)	2148 (4.0%)	0 (0%)
Stage			
I	22,069 (35%)	13,620 (25%)	8449 (89%)
II	5860 (9.2%)	5321 (9.8%)	539 (5.7%)
III	23,339 (37%)	22,866 (42%)	473 (5.0%)
IV	12,477 (20%)	12,460 (23%)	17 (0.2%)
Localization			
On both sides	22,545 (40%)	20,911 (44%)	1634 (18%)
Right	17,239 (31%)	13,321 (28%)	3918 (44%)
Left	15,780 (28%)	12,409 (26%)	3371 (38%)
Does not apply	620 (1.1%)	617 (1.3%)	3 (<0.1%)
Center	1 (<0.1%)	1 (<0.1%)	0 (0%)
Unknown	7560	7008	552
Type of diagnostic confirmation			
Histology primary tumor	61,416 (98%)	52,208 (98%)	9208 (99%)
Histology metastasis	422 (0.7%)	421 (0.8%)	1 (<0.1%)
Cytology	371 (0.6%)	339 (0.6%)	32 (0.3%)
Clinical diagnostics	185 (0.3%)	164 (0.3%)	21 (0.2%)
Other	114 (0.2%)	112 (0.2%)	2 (<0.1%)
Not defined	40 (<0.1%)	28 (<0.1%)	12 (0.1%)
Clinical without specific diagnostics	27 (<0.1%)	26 (<0.1%)	1 (<0.1%)
Unknown	1,170	969	201
Topography/localization according to ICD-O-3			
Ovary	58,038 (91%)	48,594 (90%)	9444 (100%)
Fallopian tube	4133 (6.5%)	4112 (7.6%)	21 (0.2%)
Specified parts of peritoneum	960 (1.5%)	953 (1.8%)	7 (<0.1%)
Peritoneum, NOS	442 (0.7%)	439 (0.8%)	3 (<0.1%)
Overlapping lesion of retroperitoneum and peritoneum	140 (0.2%)	139 (0.3%)	1 (<0.1%)
Retroperitoneum	32 (<0.1%)	30 (<0.1%)	2 (<0.1%)

Abbreviations: ICD-O-3, International Classification of Diseases for Oncology, Third Edition; NOS, not otherwise specified; SD, standard deviation.
[a] Mean (SD); *n* (%).

RESULTS

Of the 54,267 included patients with invasive disease, the majority were diagnosed with a tumor of high-grade serous histology (72%), followed by mucinous (5.9%), endometrioid (5.9%), and low-grade serous (4.4%) (Table 1). The majority of patients were diagnosed with advanced disease (stage III: 42%; stage IV: 23%), with differences observed by histotype. High- and low-grade serous tumors were largely diagnosed at advanced stage (high-grade stage III: 49% and low-grade stage III: 40%; high-grade stage IV: 27% and low-grade stage IV: 16%) (Fig. 1 and Table S3), whereas endometrioid, mucinous, and clear cell tumors were mostly diagnosed at an earlier stage (stage I range 64% to 73%). The majority of carcinosarcomas (73%) were diagnosed at advanced stage (stage III or IV). Borderline and invasive non-epithelial tumors were largely diagnosed as stage I (89% and 78%, respectively), as were the majority of malignant Brenner tumors (54%).

Net survival by histotype and stage at 1, 3, 5, and 10 years after diagnosis and excess hazard rates per 1000 person-years were estimated (Table 2 and Fig. 2B).

The 10-year net survival for stage I tumors was at least 77.0%, with the exception of carcinosarcomas, where survival was poor (56.9% 10-year net survival) (Table 2; Fig. 2A). Survival decreased stepwise for all histotypes with more advanced stage at diagnosis (eg, 10-year net survival range, stage II: 46.2% [mucinous] to 76.2% [endometrioid]; stage III: 18.1% [mucinous] to 55.0% [non-epithelial]). For stage IV tumors, the last event for many histotypes occurred before the 10-year follow-up time, and 5-year net survival ranged from 15.3% (carcinosarcoma) to 40.6% (endometrioid). Substantial variability in excess hazard rates by stage was observed in the first 3 years post-cancer diagnosis across and within histotypes. When considering excess mortality hazards by time since diagnosis, the mucinous, carcinosarcoma, clear cell, and non-epithelial histotypes displayed a very high excess mortality hazard for stages III and IV disease directly after diagnosis, and this rapidly declined over the follow-up time. More specifically, the stage III and IV mucinous, clear cell, and carcinosarcoma groups demonstrated an initial decrease in excess hazard immediately after diagnosis, followed by an increase approximately 1 to 2 years later. For the stage III and IV high-grade serous groups, the excess hazard decreased until 1 year after diagnosis, and then a pronounced increase was observed approximately 3 years after diagnosis.

We further evaluated the excess mortality hazard ratios by time since diagnosis, comparing stages II, III, and IV disease with stage I disease (Fig. 3) to evaluate the impact of stage by time since diagnosis. Stages III and IV endometrioid, mucinous, clear cell, and carcinosarcoma tumors had the highest excess mortality hazard ratio values within 1 year of diagnosis, after which the excess mortality hazard ratios decreased with time; this suggests a diminishing impact of advanced stage with longer time from diagnosis. This pattern was also observed for stage IV high-grade serous tumors.

Survival for the malignant Brenner histotype could not be calculated by individual stage due to insufficient sample size; for stages I to II and III to IV, the 5-year net survival was 88.3% and 42.6%, respectively (Table S4; Fig. S2). For borderline tumors and across all stages, net survival was excellent with a range of 98.8% (1 year) to 92.9% (10 years).

The patterns of overall survival probabilities estimated from Kaplan–Meier curves were similar to the net survival estimates mentioned previously (Table S2).

Finally, we evaluated excess mortality hazard due to invasive epithelial ovarian cancer from models evaluating histotype adjusted for stage and histotype and stage combinations. In the model adjusted for stage and compared with the high-grade serous group, the excess mortality hazard was significantly higher among the mucinous, carcinosarcoma, and clear cell groups (all excess mortality hazard ratios $\geq$ 1.4 [clear cell; 95% confidence interval {CI} 1.27 to 1.53; Table S5]) and lower among the low-grade serous and endometrioid groups (excess mortality hazard ratios $\leq$ 0.62 [endometrioid; 95% CI 0.56 to 0.69]). In the model including individual combinations of all stages and histotypes and relative to stage I high-grade serous tumors, the excess mortality hazard ratio was significantly lower for individuals with tumors of low-grade serous or endometrioid histotypes (excess mortality hazard ratios $\leq$ 0.49 [low-grade serous; 95% CI 0.34 to 0.67]) and higher for carcinosarcomas. Within the high-grade serous histotype, the excess mortality hazards for stages II, III, and IV tumors were significantly higher than that for stage I (ie, stage IV excess mortality hazard ratio 7.56, 95% CI 7.38 to 7.75). Among the other histotype-stage combinations, the stage IV mucinous, carcinosarcoma, and clear cell groups demonstrated substantially higher excess mortality hazards than the stage I high-grade serous group (all excess mortality hazard ratios $\geq$ 12.8 [carcinosarcoma IV; 95% CI 10.96 to 14.83]).

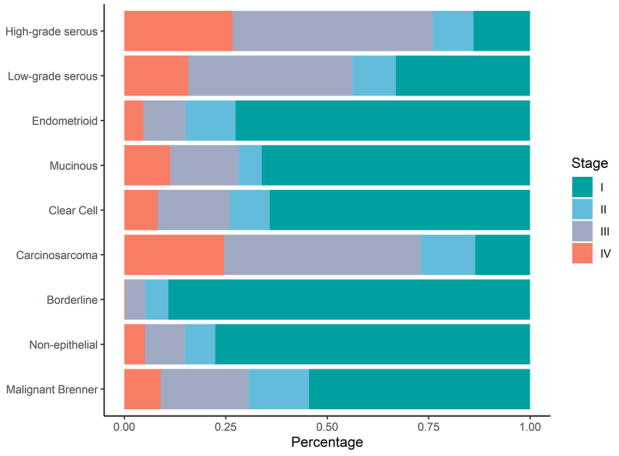

Figure 1 Distribution of stage at diagnosis, stratified by histotype.

DISCUSSION

Summary of Main Results

In this nationwide, population-based study including ovarian cancer diagnoses from the years 2010-2021 in Germany, using contemporary histotype classifications, we present the largest study to date (n = 54,267 invasive cases) to evaluate survival by histotype and stage. These findings add to the sparse literature on population-based survival profiles of patients with ovarian cancer diagnosed during more recent periods with more contemporary treatment practices. We observed a moderate 5-year net survival for high-grade serous stage I and II tumors (at least 72.2%),

Table 2 NS Estimates[a] With 95% CIs by Ovarian Cancer Histotype and Stage Predicted From Flexible Parametric Models for Women With a Mean Age of Diagnosis of 62 Years From 2010 to 2021 in Germany

Histotype	Stage	Cases	1-year NS (95% CI)	3-year NS (95% CI)	5-year NS (95% CI)	10-year NS (95% CI)
High-grade serous	I	5424	96.7% (96.3% to 97.2%)	91.4% (90.5% to 92.2%)	85.8% (84.7% to 87.0%)	77.0% (75.1% to 78.9%)
Low-grade serous	I	795	98.0% (96.9% to 99.2%)	95.4% (93.6% to 97.2%)	93.0% (90.6% to 95.6%)	87.9% (83.1% to 92.9%)
Endometrioid	I	2314	98.6% (98.0% to 99.2%)	96.4% (95.3% to 97.4%)	94.4% (93.0% to 95.9%)	91.2% (88.9% to 93.6%)
Mucinous	I	2109	96.1% (95.2% to 97.0%)	89.9% (88.3% to 91.5%)	86.2% (84.2% to 88.2%)	79.8% (76.8% to 83.0%)
Clear cell	I	1169	97.7% (96.8% to 98.6%)	91.7% (89.7% to 93.7%)	88.5% (85.9% to 91.2%)	85.3% (81.5% to 89.2%)
Carcinosarcoma	I	120	91.0% (86.3% to 95.8%)	70.1% (61.8% to 79.6%)	60.9% (51.5% to 72.0%)	56.9% (45.2% to 71.6%)
Non-epithelial	I	1228	98.0% (96.9% to 99.0%)	96.6% (95.0% to 98.2%)	95.4% (93.3% to 97.6%)	92.9% (87.9% to 98.1%)
High-grade serous	II	3905	93.8% (93.1% to 94.6%)	82.9% (81.6% to 84.2%)	72.2% (70.5% to 73.8%)	56.1% (53.7% to 58.6%)
Low-grade serous	II	259	95.8% (93.3% to 98.4%)	91.7% (87.9% to 95.8%)	86.9% (81.7% to 92.4%)	70.4% (59.9% to 82.7%)
Endometrioid	II	397	94.3% (92.1% to 96.6%)	86.9% (83.3% to 90.8%)	81.3% (76.6% to 86.2%)	76.2% (69.6% to 83.5%)
Mucinous	II	182	80.6% (75.2% to 86.3%)	63.0% (56.1% to 70.8%)	55.5% (48.2% to 63.8%)	46.2% (37.1% to 57.5%)
Clear cell	II	179	91.5% (87.4% to 95.8%)	73.4% (66.6% to 81.0%)	65.4% (57.5% to 74.4%)	58.6% (47.9% to 71.6%)
Carcinosarcoma	II	120	71.7% (64.0% to 80.2%)	46.4% (37.3% to 57.8%)	37.1% (28.1% to 49.0%)	After last event
Non-epithelial	II	119	93.3% (88.3% to 98.6%)	84.8% (76.6% to 93.7%)	80.5% (70.1% to 92.5%)	After last event
High-grade serous	III	19215	87.2% (86.7% to 87.6%)	61.6% (60.8% to 62.3%)	42.3% (41.4% to 43.1%)	25.3% (24.3% to 26.2%)
Low-grade serous	III	972	92.5% (90.9% to 94.2%)	78.6% (75.8% to 81.5%)	63.8% (60.1% to 67.9%)	45.6% (39.8% to 52.3%)
Endometrioid	III	329	87.9% (84.6% to 91.3%)	68.5% (63.4% to 73.9%)	57.0% (51.5% to 63.2%)	42.4% (35.2% to 50.9%)
Mucinous	III	538	61.6% (58.0% to 65.4%)	33.7% (29.9% to 38.0%)	25.6% (22.0% to 29.8%)	18.1% (14.1% to 23.3%)
Clear cell	III	324	74.9% (70.7% to 79.3%)	41.6% (36.4% to 47.6%)	32.3% (27.2% to 38.3%)	25.1% (19.1% to 32.9%)
Carcinosarcoma	III	432	65.4% (60.6% to 70.5%)	37.8% (32.5% to 44.0%)	29.6% (24.4% to 35.9%)	22.2% (16.4% to 30.0%)
Non-epithelial	III	156	77.8% (71.4% to 84.9%)	64.4% (56.2% to 73.8%)	59.9% (51.2% to 70.2%)	55.0% (43.7% to 69.3%)
High-grade serous	IV	10361	79.8% (79.1% to 80.6%)	46.8% (45.8% to 47.8%)	30.1% (29.1% to 31.1%)	16.3% (15.2% to 17.5%)
Low-grade serous	IV	379	80.0% (76.3% to 83.9%)	56.7% (51.7% to 62.3%)	39.8% (34.7% to 45.7%)	15.8% (10.5% to 24.0%)
Endometrioid	IV	149	75.8% (69.6% to 82.5%)	52.7% (45.1% to 61.5%)	40.6% (33.1% to 49.8%)	After last event
Mucinous	IV	361	48.7% (44.3% to 53.6%)	23.3% (19.5% to 27.9%)	16.9% (13.5% to 21.2%)	After last event
Clear cell	IV	150	48.6% (41.9% to 56.5%)	23.9% (18.0% to 31.9%)	19.5% (13.7% to 27.8%)	After last event
Carcinosarcoma	IV	219	57.7% (51.2% to 65.1%)	21.9% (16.5% to 29.1%)	15.3% (10.6% to 22.1%)	After last event
Non-epithelial	IV	80	58.8% (48.9% to 70.7%)	38.6% (28.8% to 51.8%)	30.9% (21.4% to 44.6%)	21.8% (11.7% to 40.7%)

Abbreviation: CI, confidence interval; NS, net survival.

[a] The baseline hazard was estimated with B-splines with 5 degrees of freedom. For the following histotype-stage sub-groups, the baseline hazard was allowed to vary: carcinosarcoma III and IV, clear cell I, mucinous I, endometrioid II, low-grade serous III (all estimated with 4 degrees of freedom) and carcinosarcoma I and II; clear cell II, III, and IV; non-epithelial I to IV; mucinous II, III, and IV; endometrioid I, III, and IV; low-grade serous I, II, and IV (all estimated with 3 degrees of freedom). NS was not estimated for histotype-stage groups with fewer than 20 cases at the start of follow-up and those with less than 20 events (deaths) across follow-up.

although this comprised of a small proportion of invasive cases. The 5-year net survival for high-grade serous stage III and IV tumors was poor, and, for the smaller sub-set of mucinous and clear cell tumors also diagnosed at these stages, the survival was worse than that for the high-grade serous group. Endometroid and low-grade serous tumors generally exhibited more favorable survival across all stages. Additional variability in survival was observed across histotype by stage. Across all histotype-stage groups, the excess morality hazard was highest during the first 3 years after diagnosis, and variability in survival was observed during this period as well. In our assessment of the histotype-specific time-varying impact of stage of diagnosis across follow-up time, the most substantial differences between more versus less advanced disease were found within 1 year after diagnosis for the majority of the histotypes, with the highest excess mortality hazard for the stage IV to stage I comparison.

Results in the Context of Published Literature:

Previous population-based registry studies on ovarian cancer survival have been published since 2013, including those from the United States,[4] Norway,[3] and Germany[2] (diagnoses through 2006), although differing statistical analysis methods across studies limits the direct comparably of these studies. The 5-year net survival was the maximum survival period evaluated across all of the aforementioned studies. On balance, qualitatively similar findings were observed across these studies for this follow-up period. Our findings regarding the poor survival profiles of stage III and IV mucinous and clear cell tumors are consistent with 2 recent

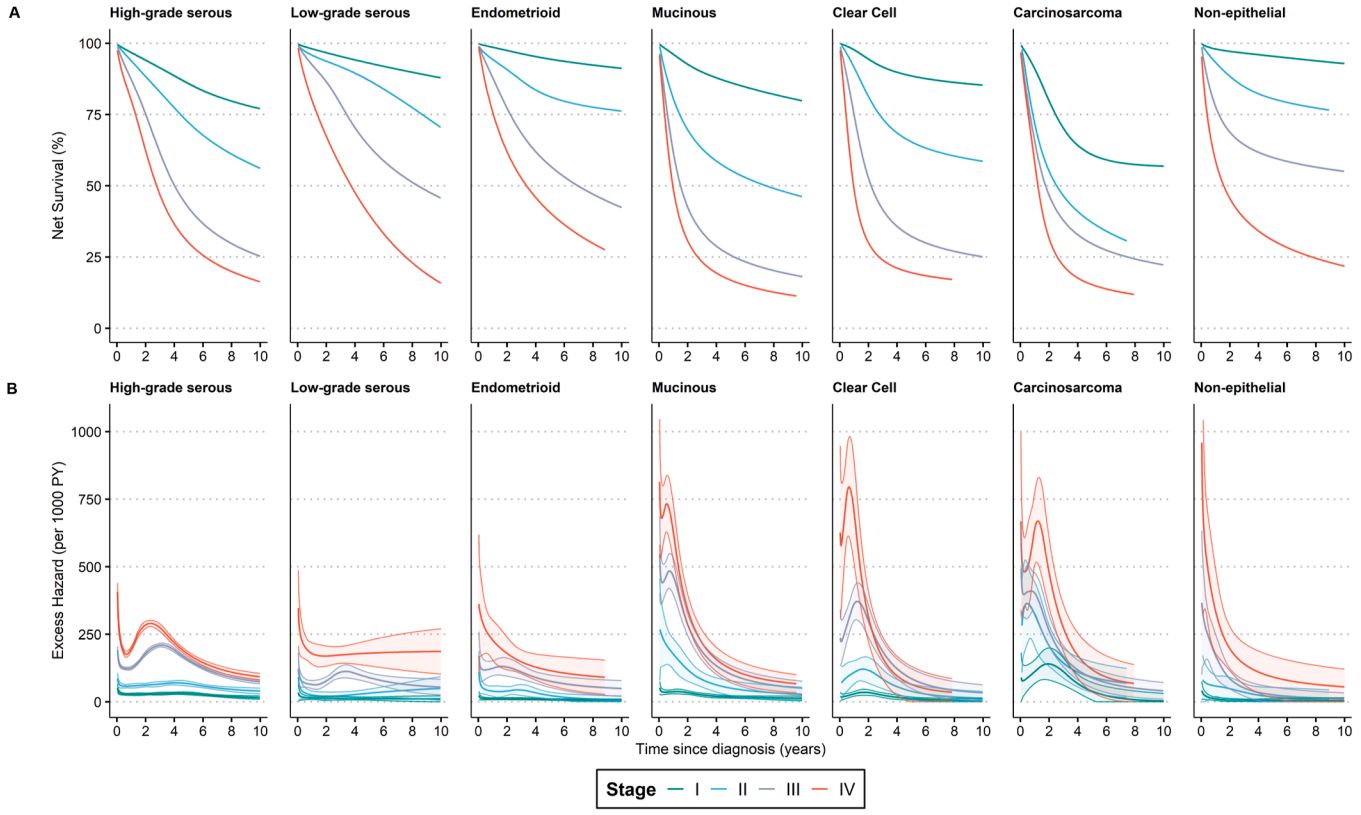

Figure 2 Ovarian cancer net survival probabilities (**A**) and excess hazard rates (**B**) across time since diagnosis for women with a mean age of diagnosis of 62 years from 2010 to 2021 in Germany. The baseline hazard was estimated with B-splines with 5 degrees of freedom. For the following histotype-stage sub-groups, the baseline hazard was allowed to vary: carcinosarcoma III and IV, clear cell I, mucinous I, endometrioid II, and low-grade serous III (all estimated with 4 degrees of freedom) and carcinosarcoma I and II; clear cell II, III, and IV; non-epithelial I to IV, mucinous II, III, and IV; endometrioid I, III, and IV; low-grade serous I, II, and IV (all estimated with 3 degrees of freedom). PY, person-year.

reviews[12,13] where the prognosis for women with stage II to IV mucinous[14,15] and stage III/IV clear cell[16,17] disease were highlighted as having worse survival than those with (high-grade) serous tumors for patients undergoing similar treatment regimens. Our stage-independent observation of more desirable survival for endometroid and low-grade serous tumors is in line with the studies in the United States[4] and Norway[3] (and in Germany[2] for endometroid tumors). The poor net survival observed for the carcinosarcomas[3,4,18] and favorable survival observed for stages I to II (and less favorable for stages III to IV) for the non-epithelial histotypes is in line with previous findings.[19]

Previous studies have emphasized the importance of stage as a strong predictor of ovarian cancer survival during the years immediately after diagnosis, after which a waning effect is observed.[20] The impact of stage generally declined over the follow-up period, and the discrepancy between the stage IV and stages III and II groups also became less pronounced as time progressed. This diminishing impact of stage over time in the longer-term survivors may be attributed to the experience of a longer progression-free interval (high-grade serous)[21] or complete remission after cytoreductive surgery in combination with platinum- and taxane-based chemotherapy.[22]

Strengths and Weaknesses

Given that ovarian cancer is a heterogenous disease arising from different cell and tissues types, survival analyses stratified by histotype and stage are necessary to better understand disease progression. With our sufficiently large number of cases and events in each histotype-stage stratum, we were able to evaluate the net survival in most of these sub-groups. Furthermore, such a comprehensive population-based analysis in Germany has not been completed since 2013, where diagnoses through 2006 were included, ahead of the introduction of the 2014 World Health Organization guidelines and the initiation of the PARP inhibitor era. Since the publication of this previous study, substantial progress has been made in the completeness and the attainment of the federal state-specific cancer registry data in Germany, with the majority of states demonstrating coverage of greater than 90% during 2010-2021. Such improvements enable a more accurate and updated characterization of the ovarian cancer survival landscape in Germany. However, we did not have access to data regarding detailed treatment and surgical information, including timing, scope, and outcome of debulking surgery; complications; co-morbidity; general performance status; and molecular information such as BRCA or homologous recombination deficiency

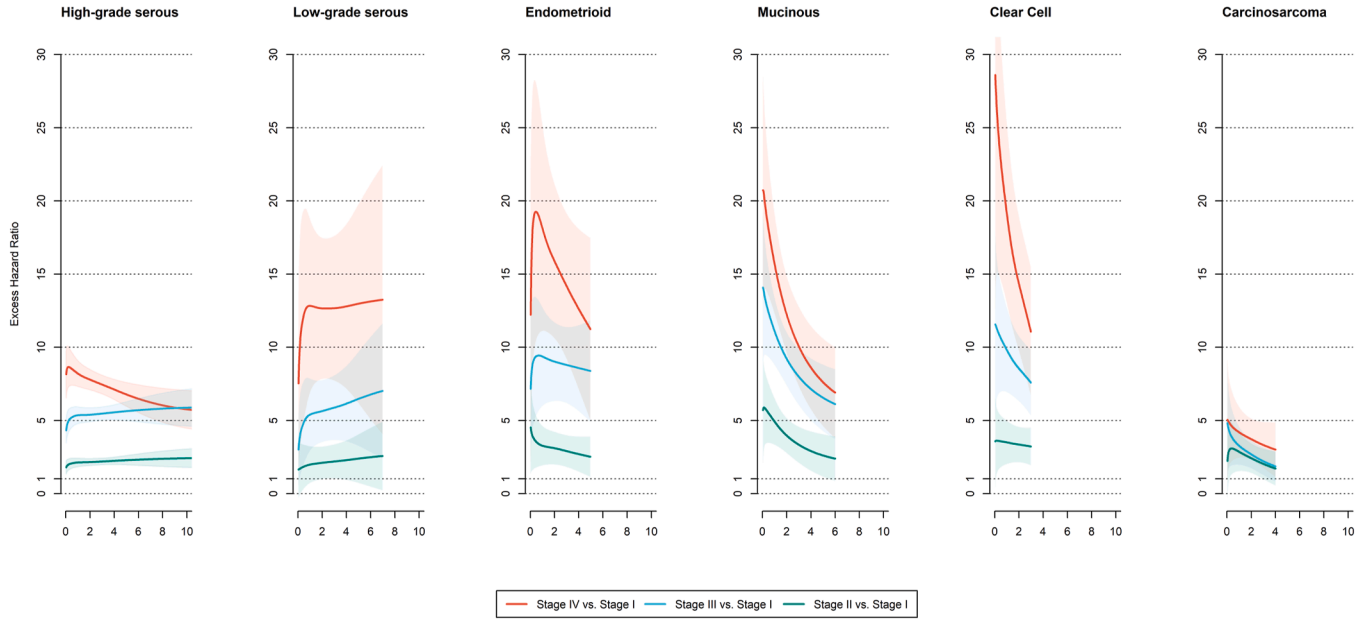

Figure 3 Time-varying excess hazard ratios predicted from flexible parametric models for stage at diagnosis, stratified by histology. Models additionally adjusted for age at diagnosis, year of diagnosis, and region. The baseline hazard was estimated with 5 degrees of freedom using B-splines. Age of diagnosis was modeled using B-splines with 3 degrees of freedom. Stage was modeled as a time varying effect using B-splines with 2 degrees of freedom. Excess hazard ratios are predicted throughout time since diagnosis where at least 10 events (deaths) are observed.

status and we were unable to assess the impact of medications (chemotherapy, PARP inhibitors, etc.) or access to care on net survival.

Implications for Practice and Future Research

The markedly poor net survival of the mucinous, clear cell, and carcinosarcoma histotype groups is in line with the clinical behavior, treatment response profiles, and limited effective treatment options of these groups. Although the proportion of patients attaining no residual disease after debulking surgery for mucinous and clear cell tumors has been shown to be higher than the serous and carcinosarcoma groups,[3,23] the mucinous and clear cell groups are less responsive to standard cytotoxic chemotherapy with platinum and taxane regimens.[12,13] This relative chemoresistance is reflected in the increase in excess mortality hazard observed for stages III and IV approximately 1 year after cancer diagnosis. The initial high mortality during the first year post-diagnosis may also be attributed to the presentation of surgical and treatment complications; tumor; or the patient's comorbidities, frailty, and performance status. Carcinosarcomas, although relatively rare, are highly aggressive, and their biphasic nature (malignant epithelial and mesenchymal components) pose a serious challenge to understanding the clinical, histopathologic, and treatment response characteristics of this histotype.[24,25] Moreover, compared with the other histotypes, there is a lack of research and representation of the mucinous, clear cell, and carcinosarcoma histotypes in clinical trials, and targeted therapy options are limited and largely in the developmental phase.[12,13,25]

Many patients diagnosed with high-grade serous ovarian cancer initially respond to platinum-based therapies, with over 70% attaining remission.[26-28] A substantial (~80%) proportion develop resistance to platinum-based therapies, with subsequent progression.[26,29,30] This initial, favorable sensitivity to such therapies is reflected in the decrease in the excess mortality hazard we observed until 1 year post-diagnosis. The subsequent peak that we observed 3-years post-diagnosis is indicative of the development of a potential resistance to platinum therapy. These findings are also consistent with the previous study in Norway,[3] and previous studies in patients with advanced ovarian cancer reported a median time to recurrence of 18.2 months (and 10.2 months after the first relapse) for those eligible for a second-line therapy and 13.8 months in those with a platinum sensitivity and treated with the PARP inhibitor Niraparib.[31] Although molecular heterogeneity could not be analyzed in this study, this topic serves as an important point of investigation in future research. Our observation of more desirable survival for the high-grade serous stage I and II groups helps to motivate continued early detection efforts. Authors of a recent study used a natural history model using data from the UK Collaborative Trial of Ovarian Cancer Screening to estimate a preclinical detectable phase of 2.2 years for high-grade serous tumors in the multi-modal screening arm.[32] There is a need to extend this time window through the improvement of screening technologies (identification of more sensitive biomarkers) to more successfully detect smaller, early stage tumors[32] and develop histotype-specific treatments to help combat treatment resistance and disease recurrence.

Bevacizumab was approved by the European Medicines Agency and introduced in Germany for treatment of advanced ovarian cancer in 2011. The PARP inhibitor olaparib was first approved for treatment of recurrent BRCA-mutated, recurrent ovarian cancer in 2014,[5] with the German Guideline Program in Oncology including the recommendation of first-line treatment with a PARP inhibitor in the context of a BRCA mutation in 2019 and the extension to tumors with homologous recombination deficiency in 2021.[33]

Despite our study being conducted during the availability of PARP inhibitors in Germany, the guidelines for their use changed over the study period. Surgical treatment of patients with primary and recurrent ovarian cancer is recommended to be carried out in centers certified in gynecologic oncology and the majority of patients with ovarian cancer undergo surgery in certified centers. Although there is substantial variability in the volume of surgical procedures among these centers, the certification process allows a standard evidence-based quality control.[34] The surgical treatment of patients included in this study represents the generalizable surgical care of patients among certified centers in Germany.

CONCLUSIONS

In this large-scale population-based study including ovarian cancer diagnoses from 2010 until 2021, we examined the net survival by histology and stage in the context of contemporary targeted treatment within a relatively recent timespan. The more favorable survival observed for the smaller sub-set of women diagnosed at stages I and II, notably, the high-grade serous histotype, helps to support the potential of early detection efforts to identify this disease at an earlier, more treatable stage. However, we could not characterize systematic within-histotype differences in tumor behavior (ie, impacting aggressiveness) between cases diagnosed at earlier and later stage. We observed considerable survival variability across histotype by stage, and the initial years post-diagnosis demonstrated a crucial time window for excess mortality, with the impact of stage declining over time. If this lethal disease is detected before dissemination, prognosis may be substantially improved. In the meantime, continued efforts need to be directed toward the development and optimization of histotype-specific treatment regimens and targeted therapies.

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Declaration of Competing Interests None declared.

Data Availability The data that support the findings of this study are available from the Zentrum für Krebsregisterdaten (Center for Cancer Registry Data) at the Robert Koch Institute (https://www.krebsdaten.de/).

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