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A Binary Histologic Grading System for Ovarian Serous Carcinoma is an Independent Prognostic Factor: A Population-based Study of 4,317 Women diagnosed in Denmark 1978–2006

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Abstract

Objective—To evaluate the prognostic significance of histologic grade on survival of ovarian serous cancer in Denmark during nearly 30 years.

Methods—Using the nationwide Danish Pathology Data Bank, we evaluated 4,317 women with ovarian serous carcinoma in 1978–2006. All pathology reports were scrutinized and tumors classified as either low-grade serous carcinomas (LGSC) or high-grade serous carcinomas (HGSC). Tumors in which the original pathology reports were described as well-differentiated were classified as LGSC, and those that were described as moderately or poorly differentiated were classified as HGSC. We obtained histologic slides from the pathology departments for women with a diagnosis of well-differentiated serous carcinoma during 1997–2006, which were then reviewed by expert gynecologic pathologists. Data were analyzed using Kaplan-Meier methods and Cox proportional hazards regression analysis with follow-up through June 2009.

Results—Women with HGSC had a significantly increased risk of dying (HR=1.9; 95% CI: 1.6–2.3) compared with women with LGSC while adjusting for age and stage. Expert review of 171 women originally classified as well-differentiated in 1997–2006 were interpreted as LGSC in 30% of cases, whereas 12% were interpreted as HGSC and 50% as serous borderline ovarian tumors (SBT). Compared with women with confirmed LGSC, women with SBT at review had a significantly lower risk of dying (HR=0.5; 95% CI: 0.22–0.99), and women with HGSC at review had a non-significantly increased risk of dying (HR=1.6; 95% CI: 0.7–3.4).

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Conflict of Interest

The authors declare no conflicts of interest.

Conclusions—A binary grading system is a significant predictor of survival for ovarian serous carcinoma.

Keywords

Ovarian serous carcinoma; binary grading system; overall survival; population-based; registry-based; expert gynecologic pathology slide review

Introduction

Ovarian cancer is the sixth most common malignancy in the Western world and the leading cause of death from gynecologic cancers [1]. 5-year survival rates range from 90% in women with disease confined to the ovaries to less than 10% in women with distant metastases [2]. Two thirds of ovarian cancers are diagnosed after the disease has spread beyond the ovaries because most patients are asymptomatic in low stages [3,4]. Ovarian serous carcinoma is the most common histologic type of ovarian cancer, representing about 50% of cases [5,6], and accounts for the vast majority of deaths [7].

Staging according to the International Federation of Gynecology and Obstetrics (FIGO) is the most important prognostic factor in determining survival of women with cancer of the ovaries [8,9]. Although several studies have shown that histologic grade is of prognostic importance [3,8,10–25], these studies utilized different grading systems, included various stages of disease, generally included only a small number of cases and did not specify the histologic type. Nevertheless, histologic grade is considered important in treatment decisions [7].

Traditionally, ovarian cancer has been graded as well-, moderately, and poorly differentiated but recently, a 2-tier system which divides serous carcinoma into low-grade serous carcinomas (LGSC) and high-grade serous carcinomas (HGSC) has been proposed [26]. The system is based primarily on the assessment of nuclear atypia using the mitotic index as a secondary feature [27]. The 3-tier system is highly subjective and implies that serous carcinoma progresses from well- to moderately and then poorly differentiated carcinoma. In contrast, the 2-tier system has been shown to be highly reproducible and is supported by molecular biologic studies indicating that LGSC and HGSC develop along different pathways [28–30], not as a progression from well- to moderately and poorly differentiated carcinoma. This has important clinical implications as evidenced by the lack of sensitivity of LGSC to the standard cytotoxic chemotherapy that is effective for HGSC. Molecular genetic studies have shown that LGSC are characterized by mutations of the KRAS, BRAF or ERBB2 genes and are relatively genetically stable. In contrast, HGSC are characterized by TP53 mutations and a high level of genetic instability. The majority of ovarian serous carcinomas are HGSC (90%), whereas LGSC comprise about 10% [31].

Only a few studies have examined histologic grade as a prognostic factor for women diagnosed with ovarian serous carcinoma using the 2-tier system [4,7,26,32,33]. Three studies [4,26,32] found that women with LGSC had a significantly better survival compared with women with HGSC, whereas two studies [7,33] did not; however, the latter two studies were based on only few cases of LGSC, and one of the studies [7] approached statistical significance.

The aim of this population-based study was to assess the prognostic significance of histologic grade using the 2-tier system on overall survival of women diagnosed with ovarian serous carcinoma in Denmark over a period of nearly 30 years. In addition, an

expert review was performed on a subset of cases to add information about the binary grading system.

Material and Methods

Identification of women with ovarian serous carcinoma

From the Danish Pathology Data Bank, we identified all women diagnosed with primary ovarian serous cancer from January 1, 1978 through December 31, 2006. The population-based and nationwide Danish Pathology Data Bank was established in 1997 and includes all cytologic and histologic diagnoses performed at pathology departments in Denmark [34]. All pathology departments are mandated to report to the national Pathology Data Bank daily through an online-system. Most pathology departments have to a certain degree also transferred information to the Pathology Data Bank from 1997 and back to 1978. However, data from this period are not complete [35]. The Pathology Data Bank uses the Systematized Nomenclature of Medicine (SNOMED) that is based on codes for topography and morphology. In our study, women were identified by SNOMED topography codes starting with T87 and T86910, T86920, T86921 and T86922 and the SNOMED morphology codes M84413, M84603, M84613 and M90143. Apart from the codes for topography and morphology, the pathology descriptions in text are also included in the Pathology Data Bank. An increasing degree of completeness is also seen for these descriptions over time [35].

Histologic grade and stage

We retrieved the pathology reports for all women diagnosed with ovarian serous carcinoma from the Pathology Data Bank. An expert gynecologic pathologist (J.J) went through all the pathology reports and determined the grade of the tumor as either LGSC if the original diagnosis was well-differentiated carcinoma or HGSC if the original diagnosis was moderately or poorly differentiated carcinoma. If the original pathology report qualified for both LGSC and HGSC, the tumor was classified as HGSC. In several cases, it was not possible to determine whether the tumor was LGSC or HGSC because it was not stated in the pathology report or there was no text pathology description available. If based on the interpretation of the original report the tumor qualified as both LGSC and unknown grade, the tumor was classified as unknown grade since the tumor may have been HGSC. A report, in which the tumor was interpreted as HGSC and unknown grade, was classified as HGSC.

To obtain information about stage at diagnosis, we linked our cohort of women with ovarian serous carcinomas with the Danish National Patient Registry using the personal identification number (PIN) as key identifier. The National Patient Registry is a nationwide registry of virtually all somatic discharges in Danish hospitals since 1977 [36]. The National Patient Registry uses the FIGO classification system to classify stage of disease (stage I–IV). For women where the FIGO stage was not available in the National Patient Registry, we linked our cohort with the Danish Cancer Registry. The nationwide Cancer Registry has collected information on all incident cancer cases in Denmark since 1943 and includes information from hospital departments, general practitioners and specialists [37]. To classify stage of disease, the Cancer Registry uses the FIGO classification system as well as the categories localized disease, regional spread and distant metastases. For women where the FIGO stage was not available in the Cancer Registry, we used localized disease, regional spread and distant metastases to classify stage. To be able to use all information and thereby to gain maximum statistical power in our analyses, we used a combination of the two groupings and categorized stage of disease for all women with ovarian serous carcinoma as localized disease (including FIGO stage I), regional spread (including FIGO stage II and III) or distant metastases (including FIGO stage IV).

Follow-up procedure

All residents in Denmark since April 1, 1968 have been assigned the unique PIN. These numbers are recorded in the nationwide computerized Danish Civil Registration System which contains information about name, sex, addresses, migration and death as well as dates of death if such events occurred [38]. The PIN is included in all health registries in Denmark and can be used as a key identifier to insure accurate linkage of information between registries. All women diagnosed with ovarian serous cancer in our study were followed through linkage with the Civil Registration System and vital status (alive, emigrated or dead) was determined for each woman through June 23, 2009.

Collection of histologic slides

We collected the microscopic slides from the various pathology departments throughout Denmark for all women with a diagnosis of well-differentiated ovarian serous carcinoma diagnosed in 1997–2006. The slides were reviewed by two expert gynecologic pathologists (R.J.K and R.V) who were blinded to the women's vital status at the end of the study and the text description included in the pathology report, and a review diagnosis was obtained classifying each ovarian carcinoma as LGSC, HGSC, using a modification of the criteria reported by Malpica et al. [26], serous borderline ovarian tumors (SBT) or other types of tumor. The Malpica et al. criteria [26] for grading ovarian serous carcinoma use nuclear features as a primary feature with mitotic index as a secondary feature. Thus, the emphasis on this classification is nuclear features. In our application of these criteria, we employed the same morphologic findings to assess nuclear features as specified by Malpica et al. [26]. However, our modification was only minor in that we did not use a specific mitotic index [28]. Instead, we assessed mitotic activity by simply estimating whether mitotic figures were sparse (which is more common in low-grade tumors) or easily identifiable (which is more common in high-grade tumors). In all other respects, our grading per this system (low versus high) was essentially similar to that of Malpica et al. [26].

Statistical analysis

Survival was measured from the date of the ovarian serous carcinoma diagnosis until date of death, emigration or end of follow-up, whichever came first. Survival times were calculated for stage at diagnosis and histologic grade, respectively, and for histologic grade stratified by stage using Kaplan-Meier curves, and the survival curves were compared using the Log-Rank test.

We used Cox proportional hazards regression analysis with follow-up time as timescale to evaluate the prognostic value on survival of age, year and stage at diagnosis and histologic grade. The effect on risk of death was estimated by hazard ratios (HR) and 95% confidence intervals (95% CI). The following clinical and pathologic parameters were evaluated: age at diagnosis (continuous), year of diagnosis (continuous), stage at diagnosis (localized disease, regional spread and distant metastases), and histologic grade (LGSC, HGSC and unknown grade). In addition, survival of women with an original diagnosis of well-differentiated carcinoma in 1997–2006 who after expert pathology review was classified as LGSC, HGSC or SBT was evaluated. Statistical modeling was performed using the SAS/STAT version 8.2 (SAS Institute, Cary, NC, USA). The study was approved by the Danish Protection Agency and the Danish Scientific Ethical Committee.

Results

Baseline characteristics

We identified 4,592 women with ovarian serous carcinoma in the Pathology Data Bank in 1978–2006. Thirty two women with ovarian cancer detected at autopsy only, cases in which

the diagnosis was made prior to the beginning of our study or had an unknown date of the primary diagnosis were excluded, leaving 4,560 women. In the Cancer Registry and National Patient Registry, we identified 243 women with unknown stage at diagnosis whom we excluded from our analyses, leaving 4,317 women consisting of 636 women with localized disease, 2,626 women with regional spread and 1,055 women with distant metastases.

During the process of going through the pathology reports from the 4,317 women, we identified 279 women with LGSC, 2,029 women with HGSC and 2,009 women with unknown grade (Table 1). The mean age at diagnosis was 62.3 years, ranging from 18.7 to 94.7 years. Women with LGSC were slightly younger at diagnosis (mean=56.4 years) compared with women with unknown grade (mean=61.9 years) and HGSC (mean=63.4 years). More women with LGSC were diagnosed with localized disease (37.3%) compared with women with unknown grade (16.1%) and HGSC (10.3%), whereas more women with unknown grade (27.1%) and HGSC (23.9%) were diagnosed with distant metastases compared with women with LGSC (9.3%). Linkage with the Civil Registration System showed that 3,524 women died during follow-up (81.6%). Among these, 25.8% died within the first year. This number was similar for women with LGSC (22.2%), unknown grade (24.8%) and HGSC (27.0%).

Women diagnosed with ovarian serous carcinoma during 1978–2006

The 5- and 10-year survival rates were 69% and 52% in women with localized disease; 31% and 19% in women with regional spread; and 25% and 19% in women with distant metastases. Furthermore, 5- and 10-year survival rates were 69% and 56% for LGSC; 38% and 28% for unknown grade; and 28% and 15% for HGSC. We found similar patterns for women diagnosed in the two time periods 1978–1996 and 1997–2006, respectively (data not shown).

The survival of women with LGSC, unknown grade and HGSC in relation to stage at diagnosis is shown in Figure 1a–c. Women with LGSC had a significantly better overall survival compared with women with unknown grade and HGSC within each stage of disease ($p<0.0001$).

We also analyzed the effect of grade on survival after adjusting for age and stage in a multivariate Cox model (Table 2) and found that women with regional spread (HR=2.5; 95% CI: 2.2–3.8) and distant metastases (HR=5.0; 95% CI: 4.4–5.6), respectively, had a significantly increased risk of dying compared with women with localized disease while adjusting for age and histologic grade. In addition, women with HGSC (HR=1.9; 95% CI: 1.6–2.3) had a significantly increased risk of dying compared with women with LGSC while adjusting for age and stage. We found the same results when classifying stage using localized disease (including FIGO stage I), regional spread (including FIGO stage II) and distant metastases (including FIGO stage III and IV) (data not shown). In addition, similar results were reached when repeating the analyses for women with FIGO stages I, II, III and IV instead of using extent of disease in three groups (localized disease (including FIGO stage I), regional spread (including FIGO stage II and III) and distant metastases (including FIGO stage IV)) (data not shown). Finally, similar findings were seen for women diagnosed in the two time periods 1978–1996 and 1997–2006, respectively, the estimates being slightly stronger for women diagnosed in 1997–2006 (data not shown).

Women with well-differentiated serous carcinoma during 1997–2006

We identified 179 women with a diagnosis of well-differentiated serous carcinoma during 1997–2006 which were reviewed by two expert gynecologic pathologists (R.J.K and R.V).

Eight women were excluded due to missing slides. At the expert review of the remaining 171 women, 51 women had LGSC (29.8%), 21 had HGSC (12.3%), 86 had SBT (50.3%), 12 women had another type of tumor (7.0%) (clear cell carcinoma (n=7), endometrioid carcinoma (n=1), unclassified high-grade adenocarcinoma (n=1), suspected primary peritoneal tumor (n=1), borderline endometrioid tumor (n=1) and endometrioma (n=1)), and 1 woman had insufficient tissue (0.6%).

Among the 158 women with well-differentiated serous carcinoma and an expert review diagnosis of LGSC, HSCG and SBT, 63 women had localized disease (39.9%), 84 had regional spread (53.1%) and 11 women had distant metastases (7.0%). The 5- and 10-year survival rates were 91% and 83% for women with localized disease; 69% and 56% for women with regional spread; and 41% and 41% for women with distant metastases. In addition, 5- and 10-year survival rates were 69% and 48% for women with LGSC; 49% and 16% for HGSC; and 87% and 85% for SBT.

Table 3 shows that women with regional spread (HR=2.8; 95% CI: 1.3–6.0) and distant metastases (HR=3.4; 95% CI: 1.1–10.1), respectively, had a significantly increased risk of dying compared with women with localized disease while adjusting for age and review diagnosis. In addition, women with a review diagnosis of SBT (HR=0.5; 95% CI: 0.22–0.99) had a significantly lower risk of dying, and women with a review diagnosis of HGSC (HR=1.6; 95% CI: 0.74–3.4) had a non-significantly increased risk of dying compared with women with a confirmed review diagnosis of LGSC. Similar results were found while repeating the analyses using localized disease (including FIGO stage I), regional spread (including FIGO stage II) and distant metastases (including FIGO stage III and IV) and the FIGO classification instead of stage in the three groups (data not shown).

Discussion

FIGO staging and the amount of residual tumor following cytoreductive surgery are the most important prognostic factors in ovarian serous carcinoma [8,9]. The importance of histologic grade has, however, been questioned [26]. In the present study, we found that histologic grade routinely made by Danish gynecologic pathologists or expert gynecologic pathologists was a significant prognostic factor in ovarian carcinoma as women with LGSC had a significantly longer survival than women with HGSC even after adjusting for age and stage.

Our 69% 5-year survival rate for LGSC is longer than the 56% reported by Seidman et al. [7] and the 40% reported by Malpica et al. [26] but this may be explained by the fact that 50% of women with an original diagnosis of LGSC in 1997–2006 in our study were judged as SBT after expert review. Accordingly, it is likely that this also occurred in 1978–1996. However, our 10-year survival rate of 56% for women with LGSC is lower as compared with the 71% reported by Motohara et al. [4]. Furthermore, our 5-year survival rate for HGSC of 49% is higher than the 34% reported by Seidman et al. [7] and the 9% rate reported by Malpica et al. [26]. In addition, our 10-year survival rate of 16% for HGSC is similar to the 13% reported by Motohara et al. [4]. Finally, Bodurka et al. [32] found 3-year survival rates of 90.5% and 67.6%, respectively, for LGSC and HGSC.

Eighty eight percent of women in our study had HGSC whereas only 12% had LGSC. This is in line with the other studies [4,7,32,33] examining survival of ovarian serous carcinomas using the 2-tier system [26]. Women with LGSC in our study were younger at diagnosis (mean=56 years) than women with HGSC (mean=63 years). Similar results were found in the studies by Malpica et al. [26], Bodurka et al. [32] and Seidman et al. [7] for women with LGSC (42, 51 and 57 years, respectively) and HGSC (55, 57 and 65 years, respectively). In

addition, Gershenson et al. [31] found a mean age of 45 years for women with LGSC. Thus, LGSC seem to occur in women around 6–13 years earlier than HGSC.

In the present study, we were able to perform histologic slide review by expert gynecologic pathologists for all tumors with an original diagnosis of well-differentiated carcinoma in 1997–2006. Based on this review, a large proportion of these women were judged as having SBT (50%) or HGSC (12%). It was therefore not surprising, that women with well-differentiated carcinoma that on expert review were classified as SBT had a significantly longer survival than women in whom the original diagnosis was well-differentiated carcinoma and confirmed by the expert review as LGSC. It should be mentioned that in the majority (65%) of well-differentiated carcinomas that were reclassified as SBT, the pathology description revealed that the Danish routine pathologists had been in doubt as to whether the tumor was SBT or well-differentiated carcinoma; however, it was not reflected in the final diagnosis. Thus, expert slide review further confirms the utility of the binary grading system.

Our study has several strengths. Data were collected from a population-based, nationwide registry in Denmark covering a period of nearly 30 years. We included 4,317 women of which 2,308 had LGSC or HGSC which is by far the largest study examining survival of serous carcinoma using the 2-tier grading system [26]. Previous studies have all been limited by relatively small number of cases (44–241 cases) [4,7,26,32,33]. In the present study, we took advantage of the existence of the PIN, which insures accurate linkage between health registries and indicates that it is possible to do follow-up studies with virtually no loss to follow-up. In addition, the use of nationwide registries reduces the risk of patient referral bias that may occur in case-control studies. However, our study also has some limitations. Since our nationwide study was based on pathology reports and pathologic slide review, we did not have information on clinical factors such as residual disease which is also an important independent prognostic factor in ovarian serous carcinoma [8,26]. In addition, we were not able to calculate disease-specific survival. However, since ovarian cancer-related deaths are high among women with this disease [39], we may assume that most women who died during follow-up in our study were ovarian cancer-related deaths. Furthermore, we found that the survival for reviewed LGSC and HGSC was not significantly different; however, this analysis might be limited by having too few cases of HGSC. In addition, we had a large number of tumors with unknown grade in the first half of our study period (1978–1996). However, we observed the same trends in survival in the latter study period (1997–2006) where we had fewer cases with unknown grade. Finally, we were unable to perform expert review of well-differentiated serous carcinomas diagnosed in the first half of the study period 1978–1996 because a lot of the histologic material from that period is no longer available. In addition, the Pathology Data Bank is not complete before 1997. Thus, the survival of LGSC in the first half of the study period may be slightly overestimated as they likely contain a number of SBT which was the case for the period 1997–2006. However, we found similar trends in survival of ovarian serous carcinomas regardless of whether the histologic diagnosis was routinely made by the Danish pathologists or an expert gynecologic pathologist review was performed. Thus, the review by our expert gynecologic pathologists further added information to our results found by the routine pathologists, but the findings were similar. In addition, we did not perform expert review of the 1,425 cases with HGSC in 1997–2006, but we do not believe that the extent of misclassification that was found in LGSC exists among HGSC since the differentiation between LGSC and SBT is the most complicated differentiation.

In conclusion, we have examined a binary histologic grading system as a prognostic factor in ovarian serous carcinoma based on a large cohort in Denmark over nearly 30 years, and our findings suggest that histologic grade (low-grade versus high-grade), based on the

diagnosis of either Danish gynecologic pathologists in the everyday clinic or expert gynecologic pathologists, is a significant independent predictor of survival.

Highlights

- The histologic diagnosis based on a binary grading system is an independent predictor of survival following ovarian serous carcinoma.
- Expert gynecologic pathologists' review of the histologic diagnosis further confirms the utility of the binary grading system.

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Figure 1.

a–c. Survival of 4,317 women with ovarian serous carcinoma in Denmark 1978–2006 by histologic grade at the time of diagnosis (low-grade serous carcinomas (LGSC), high-grade serous carcinomas (HGSC) and unknown grade).

Table 1

Baseline characteristics of 4,317 women with ovarian serous carcinoma in Denmark 1978–2006

	Overall (n=4,317)		LGSC (n=279)		HGSC (n=2,029)		Unknown grade (n=2,009)	
	n	(%)	n	(%)	n	(%)	n	(%)
Year of diagnosis								
1978–1982	316	(7.3)	6	(2.2)	15	(0.7)	295	(14.7)
1983–1987	585	(13.5)	15	(5.4)	107	(5.3)	463	(23.0)
1988–1992	742	(17.2)	38	(13.6)	212	(10.4)	492	(24.5)
1993–1997	798	(18.5)	55	(19.7)	369	(18.2)	374	(18.6)
1998–2002	1,070	(24.8)	100	(35.8)	701	(34.6)	269	(13.4)
2003–2006	806	(18.7)	65	(23.3)	625	(30.8)	116	(5.8)
Age at diagnosis (years)								
<50	712	(16.5)	97	(34.8)	257	(12.7)	358	(17.8)
50–59	1,015	(23.5)	60	(21.5)	509	(25.1)	446	(22.2)
60–69	1,241	(28.7)	53	(19.0)	603	(29.7)	585	(29.1)
70+	1,349	(31.3)	69	(24.7)	660	(32.5)	620	(30.9)
Mean age at diagnosis	62.3	years	56.4	years	63.4	years	61.9	years
Stage at diagnosis								
Localized	636	(14.7)	104	(37.3)	208	(10.3)	324	(16.1)
Regional spread	2,626	(60.8)	149	(53.4)	1,336	(65.8)	1,141	(56.8)
Distant metastases	1,055	(24.5)	26	(9.3)	485	(23.9)	544	(27.1)
Vital status (end of follow-up)								
Alive	787	(18.2)	153	(54.8)	372	(18.3)	262	(13.0)
Emigrated	6	(0.2)	0	(0.0)	4	(0.2)	2	(0.1)
Dead	3,524	(81.6)	126	(45.2)	1,653	(81.5)	1,745	(86.9)
Survival time (years)*								
<1	908	(25.8)	28	(22.2)	447	(27.0)	433	(24.8)
1–4	1,657	(47.0)	45	(35.7)	885	(53.5)	727	(41.7)
5–9	540	(15.3)	35	(27.8)	252	(15.3)	253	(14.5)
10+	419	(11.9)	18	(14.3)	69	(4.2)	332	(19.0)

* Based on 3,524 women with ovarian serous carcinoma who died during follow-up

Survival analysis using Cox proportional hazards regression model of 4,317 women diagnosed with ovarian serous carcinoma in Denmark 1978–2006

Table 2

	No. of women (n=4,317)		No. of deaths (n=3,524)		Age-adjusted			Mutually adjusted*		
	n		n		HR	(95% CI)	p-value	HR	(95% CI)	p-value
Age at diagnosis (years)	(continuous - per year)									
					1.04	(1.04–1.04)	<0.0001			
Stage at diagnosis										
Localized	636		364		1.0	-	-	1.0	-	-
Regional spread	2,626		2,178		2.6	(2.3–2.9)	<0.0001	2.5	(2.2–3.8)	<0.0001
Distant metastases	1,055		982		5.3	(4.7–6.0)	<0.0001	5.0	(4.4–5.6)	<0.0001
Histologic grade										
LGSC	279		126		1.0	-	-	1.0	-	-
Unknown	2,009		1,745		2.6	(2.2–3.2)	<0.0001	2.1	(1.8–2.5)	<0.0001
HGSC	2,029		1,653		2.5	(2.1–3.0)	<0.0001	1.9	(1.6–2.3)	<0.0001

* Adjusted for age and stage at diagnosis and histologic grade

Survival analysis using Cox proportional hazards regression model of 158 women with a diagnosis of well-differentiated serous carcinoma in Denmark 1997–2006

Table 3

	No. of women (n=161)	No. of deaths (n=49)		Age-adjusted		Mutually adjusted*		
	n	n	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Age at diagnosis (years)	(continuous - per year)							
Stage at diagnosis								
Localized	63	9	1.0	-	-	1.0	-	-
Regional spread	84	33	3.3	(1.6–6.9)	0.0016	2.8	(1.3–6.0)	0.0075
Distant metastases	11	6	4.0	(1.4–11.4)	0.0096	3.4	(1.1–10.1)	0.0300
Review diagnosis								
SBT	86	13	0.4	(0.19–0.80)	0.0108	0.5	(0.22–0.99)	0.0460
LGSC	51	22	1.0	-	-	1.0	-	-
HGSC	21	13	1.6	(0.79–3.2)	0.1912	1.6	(0.74–3.4)	0.2418

* Adjusted for age and stage at diagnosis and review diagnosis