A Nationwide Study of Ovarian Serous Borderline Tumors in Denmark 1978–2002. Risk of Recurrence, and Development of Ovarian Serous Carcinoma

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Abstract

Objective: Absolute risk and risk factors for recurrence and ovarian serous carcinoma following ovarian serous borderline tumors (SBTs) is not well-established.

Methods: We included all women with SBTs in Denmark, 1978–2002. Diagnoses were confirmed by centralized pathology review and classified as atypical proliferative serous tumor (APST) or noninvasive low-grade serous carcinoma (LGSC). Implants were classified as noninvasive or invasive. Medical records were collected and reviewed, and follow-up was obtained. Subsequent diagnoses were also confirmed by centralized pathology review. We examined absolute risk and risk factors for recurrent APST and serous carcinoma using Cox regression.

Results: The absolute serous carcinoma risk after, respectively, five and 20 years was 5.0% and 13.9% for noninvasive LGSC, and 0.9% and 3.7% for APST. Serous carcinoma risk was significantly higher following noninvasive LGSC compared with APST among stage I patients/patients without implants (HR=5.3; 95% CI: 1.7–16.3), whereas no significant association with tumor type was found in advanced stage patients/patients with implants. Advanced stage – notably invasive implants – bilaterality, surface involvement, and residual disease increased serous carcinoma risk. However, women with stage I APST also had a higher risk than the general population.

Conclusions: This largest population-based cohort of verified SBTs revealed that women with noninvasive LGSC are significantly more likely to develop serous carcinoma than women with APST, which could not entirely be explained by invasive implants. Although invasive implants was a strong risk factor for serous carcinoma, even women with stage I APST were at increased risk compared with the general population.

Abstract word count: 249 words

Key words: Ovarian serous borderline tumor (SBT); atypical proliferative serous tumor (APST); noninvasive low-grade serous carcinoma (LGSC); population-based; centralized pathology review; long-term follow-up; risk of recurrent APST; risk of development of ovarian serous carcinoma

Introduction

An ovarian serous borderline tumor (SBT) generally has a favorable prognosis when tumor is confined to the ovaries but a substantially worse prognosis with advanced stage disease, particularly when invasive implants are present [1]. The importance of other factors is less well established and indeed some, such as a micropapillary pattern, have been controversial [2–11]. We therefore undertook this study to further explore the role of a variety of risk factors in predicting recurrence and development of ovarian serous carcinoma following an SBT.

In several previous studies, recurrence and development of serous carcinoma after an SBT diagnosis have been treated as a combined outcome [7, 9, 12–14]. Therefore, the precise risk of developing serous carcinoma is not clear. In addition, previous studies have a number of limitations, including a relatively small number of cases (≤ 276) [2, 4–13, 15–25], short median follow-up time (< 10 years) [2, 4, 6–14, 17, 18, 20–24], significant loss to follow-up [2, 4, 6, 17], no distinction between histologic subtypes [12–14], and evaluation of advanced stage tumors only [5, 8, 10, 13, 15, 18, 19].

We performed a nationwide cohort study of more than 1000 women in Denmark with an SBT diagnosis during 1978–2002. The aims of the present study were to estimate the absolute risk of and associated risk factors for developing recurrence, and ovarian serous carcinoma in women with an SBT diagnosis, confirmed by central pathology review, with a follow-up period up to 36 years. Among the various clinical and pathologic features associated with these risks, special attention was directed at tumors displaying a micropapillary pattern as well as the presence of invasive and noninvasive implants.

Methods

Study Population

The study design, methodology, and characteristics of the study population have previously been described in detail [1]. The study was approved by the Danish Data Protection Agency and the Danish Scientific Ethical Committee. Briefly, all cases of an SBT were identified in the nationwide Danish Pathology Data Bank and/or the national Danish Cancer Registry during 1978–2002. The Pathology Data Bank contains all histologic diagnoses made in pathology departments in Denmark since 1997. Most pathology departments have also transferred information to the Pathology Data Bank from 1997 back to 1978, but data from this period are not entirely complete. The Cancer Registry has collected information on cancers in Denmark since 1943. Reporting of cancers to this registry became mandatory in 1987, but not for ovarian borderline tumors which are, therefore, probably underreported. However, using both registries makes it likely that our study includes virtually all SBT cases in Denmark in the study period.

All histologic slides from the primary ovarian tumors and extra-ovarian implants were collected as well as any subsequent tissue samples following initial surgery from the Danish pathology departments. The slides were reviewed by expert gynecologic pathologists (RV and RJK) who were blinded to all clinical parameters. Tumors were classified according to the 2014 World Health Organization (WHO) Classification of Tumours of the Female Reproductive Organs [26], which regards a typical SBT as synonymous with an atypical proliferative serous tumor (APST), and an SBT with a micropapillary pattern as synonymous with noninvasive low-grade serous carcinoma (LGSC). We have used the terms “APST” and “noninvasive LGSC” in this paper. Implants were classified as noninvasive (epithelial or desmoplastic) or invasive (LGSC) based on the 2014 WHO Classification which regards invasive implants as synonymous with LGSC [26]. In addition to implants demonstrating unequivocal invasion [27], implants resembling

LGSC without demonstrable evidence of invasion were also classified as LGSC (invasive implants) [28].

We identified 1487 women with an SBT during the study period in the two nationwide registries. At the expert pathology review, the SBT diagnosis was confirmed in 1042 women and categorized as an APST or noninvasive LGSC. Concomitant ovarian serous carcinoma was found in 16 women, who were excluded, leaving 1026 women for analysis in this paper.

We linked our cohort with the Danish National Patient Registry, a nationwide registry of virtually all patient discharges from all Danish hospitals and outpatient clinics since 1977 and 1995, respectively. Medical records were collected from the relevant hospitals in Denmark, and data were abstracted. All women were treated according to the Danish clinical guidelines for ovarian borderline tumors which previously did not include staging and lymph node dissection. Tumor stage was determined using the International Federation of Gynecology and Obstetrics (FIGO) staging system [29], and was based on information collected from the medical records and pathology review of the histologic slides from the ovarian tumors and extra-ovarian implants.

Outcome Information

Since April 1, 1968 all residents in Denmark have been assigned a unique personal identification number. This number is included in all health registries and can be used as a key identifier to insure accurate linkage of information between registries. Information about recurrent APST and development of serous carcinoma for women initially diagnosed with an APST or noninvasive LGSC was obtained by linkage of our cohort with the Pathology Data Bank until August 31, 2013 using the personal identification number as key identifier. All women were followed for

recurrent APST and development of serous carcinoma in the Pathology Data Bank from six months following their primary SBT diagnosis, and all pathology records were abstracted.

Statistical Analysis

The absolute risk of, respectively, recurrent APST following an APST and subsequent serous carcinoma according to initial SBT type (APST or noninvasive LGSC) as a function of time since diagnosis were estimated non-parametrically using the Aalen-Johansen estimator. Death was regarded as a competing risk for both outcomes, and for recurrent APST, the development of serous carcinoma was additionally treated as a competing risk. The expected number of serous carcinoma among all women with an APST as well as in subgroups according to diagnosed stage during the total follow-up period was calculated by applying the age- and period-specific Danish incidence rates derived from the Cancer Registry.

To address associations between potential risk factors and the two outcomes (recurrent APST or subsequent serous carcinoma), while adjusting for age at diagnosis, we used Cox proportional hazard models to estimate hazard ratios (HRs) with 95% confidence intervals (95% CIs). Time since diagnosis was used as the underlying time scale, and women were censored at time of emigration, death, or end of follow-up (August 31, 2013). When looking at recurrent APST as outcome, women were additionally censored at time of subsequent serous carcinoma as it was considered a competing risk.

HRs for the association between the initial SBT type (noninvasive LGSC versus APST) and risk of developing serous carcinoma was estimated for all women, all women excluding women with invasive implants, and among women with stage I (the latter additionally adjusted for, respectively, surface involvement and capsular rupture). In addition, the variables FIGO stage (I,

II+), implants (none, noninvasive, invasive), tumor size (continuous – per cm), laterality (unilateral, bilateral), surface involvement (no, yes), capsular rupture (no, yes), and residual disease after surgery (no, yes) were investigated as risk factors for recurrent APST among women with an APST as well as for subsequent serous carcinoma separately among women with an APST and women with noninvasive LGSC. Analysis for both outcomes were repeated excluding women with invasive implants. Statistical analyses were performed using the SAS/STAT version 8.2 (SAS Institute, Cary, NC, USA).

Results

Study Cohort

Our cohort comprised 1026 women with a confirmed SBT diagnosis during 25 years in Denmark covering 946 women with an APST (92.2%) and 80 women with noninvasive LGSC (7.8%).

Women with an APST were slightly younger at diagnosis (median=50 years; range: 16–97; 25% were ≤ 40 years) compared with noninvasive LGSC (median=54 years; range: 24–91; 25% were ≤ 43 years), but the difference was not statistically significant ($p=0.10$). The median follow-up time for the entire cohort was 15 years (range: <1–36 years), resulting in a total of 16 005 women-years of follow-up.

Risk of Recurrent APST

Among 946 women with an APST, 50 women (5.3%) experienced recurrent APST during follow-up. A little more than half of recurrent cases occurred in the contralateral ovary. Figure 1 shows that the absolute risk of recurrent APST increased at approximately the same pace within the first 10 years after the primary APST diagnosis and then levelled off; the risk estimate within the first five years being 2.9% (95% CI: 1.8–3.9) and 5.5% (95% CI: 3.8–7.1) within 20 years after the first diagnosis.

Factors Associated with Recurrent APST

Table 1 shows that among women with an APST, advanced stage (HR=2.1; 95% CI: 1.1–4.1; stage II+ versus I), applying to both the presence of noninvasive (HR=2.0; 95% CI: 1.0–3.9; yes versus no implants) and invasive implants (HR=8.4; 95% CI: 1.1–62.9; yes versus no implants), capsular rupture (HR=1.9; 95% CI: 1.1–3.6; yes versus no), and residual disease after surgery (HR=3.5; 95% CI: 1.6–7.8; yes versus no) increased the risk of recurrent APST significantly (in age-adjusted analyses). After excluding women with invasive implants, the estimates remained largely unchanged (Table 1).

Risk of Subsequent Serous Carcinoma

During follow-up, a total of 34 women (3.6%) developed serous carcinoma (32 women LGSC and two women HGSC) among 946 women with an APST and nine women (11.3%) (eight women LGSC and one woman HGSC) among 80 women with noninvasive LGSC. Only one woman with an APST had recurrent APST prior to her development of LGSC. The most common anatomic site of subsequent serous carcinoma was the peritoneum (40%).

Figure 2 shows the absolute risk of developing serous carcinoma among women with, respectively, an APST and noninvasive LGSC. In both groups, the absolute risk continued to rise at the same pace until around 20 years after the primary SBT diagnosis. For women with an APST, the absolute risk of subsequent serous carcinoma within five years was 0.9% (95% CI: 0.3–1.4) and 3.7% (95% CI: 2.3–5.1) within 20 years, whereas for women with noninvasive LGSC, the risk of developing serous carcinoma within five years was 5.0% (95% CI: 0.2–9.8) and 13.9% (95% CI: 4.9–22.9) within 20 years. Compared with the general female population of same age in the same calendar period, one would expect only 2.5 cases of serous carcinoma

among women with an APST versus 34 observed in our study ($p<0.0001$). This was present both within stage I and stage II+ as fourteen women (2%) with stage I APST developed serous carcinoma compared with 2.2 expected ($p<0.0001$), and 20 women (17%) with stage II+ APST developed serous carcinoma versus 0.2 expected ($p<0.0001$).

In an additional age-adjusted analysis (data not shown in Tables), where we directly compared women with an ASPT to those with noninvasive LGSG, we found that the hazard of developing serous carcinoma during follow-up was significantly increased in women with noninvasive LGSC compared with women with an APST (HR=4.3; 95% CI: 2.1–9.1). When we stratified this analysis by stage/presence of implants, we found that among women with stage I/without implants, the risk of subsequent serous carcinoma for the association was even stronger (HR=5.3; 95% CI: 1.7–16.3). Further adjustment for, respectively, surface involvement (HR=4.3; 95% CI: 1.4–13.5) and capsular rupture (HR=5.1; 95% CI: 1.7–15.8) did not change the estimates markedly. In contrast, among women with advanced stage/presence of implants, we did not find a significantly increased risk of subsequent serous carcinoma in women with noninvasive LGSC compared with an APST (HR=1.6; 95% CI: 0.5–4.7).

Factors Associated with Subsequent Serous Carcinoma

Factors associated with a significantly increased risk of subsequent serous carcinoma (age-adjusted analyses) in women with an APST were advanced stage (HR=10.9; 95% CI: 5.4–21.8; stage II+ versus I), including presence of noninvasive (HR=9.3; 95% CI: 4.5–19.1; yes versus no implants) and invasive implants (HR=115.9; 95% CI: 29.6–454.7; yes versus no implants), bilaterality (HR=7.7; 95% CI: 3.3–17.7; yes versus no), surface involvement (HR=4.8; 95% CI: 2.2–10.4; yes versus no), and residual disease after surgery (HR=3.8; 95% CI: 1.5–9.9; yes

versus no) (Table 2). After exclusion of women with invasive implants, the estimates were virtually identical (Table 2).

In women with noninvasive LGSC, we found that the following factors increased the risk of developing serous carcinoma, although none achieved statistical significance, being based on only nine women: advanced stage (HR=2.6; 95% CI: 0.6–10.5; stage II+ versus I), presence of invasive implants (HR=4.5; 95% CI: 0.9–22.4; yes versus no implants) (borderline significant), surface involvement (HR=2.2; 95% CI: 0.4–11.4; yes versus no), capsular rupture (HR=1.7; 95% CI: 0.4–7.5; yes versus no), and residual disease after surgery (HR=2.2; 95% CI: 0.4–12.1; yes versus no) (Table 3). In analyses where women with invasive implants were excluded, the estimates were virtually unchanged (Table 3).

Discussion

The superior prognosis of women with an SBT diagnosis compared with serous carcinoma is well recognized [1]. However, the difference in behavior of an SBT with a micropapillary pattern (noninvasive LGSC) compared to those lacking a micropapillary pattern (APST) has been extensively debated [2–11]. We found that for women with an APST, the absolute risk of developing serous carcinoma within five years after the diagnosis was 0.9% and 3.7% within 20 years, whereas among women with noninvasive LGSC the risk was considerably higher, namely 5.0% and 13.9% within five and 20 years, respectively. Thus, compared to women with an APST, women with noninvasive LGSC had a higher risk of developing serous carcinoma up to 20 years following their initial diagnosis. Furthermore, in an age-adjusted analysis directly comparing the risk following APST to that in women with noninvasive LGSC, we found that the rate of developing serous carcinoma was significantly higher in women with noninvasive LGSC,

especially among women with stage I/without implants, and this finding could not be explained by the presence of surface involvement or capsular rupture.

Considering the entire follow-up period, we found 34 women who developed serous carcinoma following an APST. This number is significantly higher than the number of cases expected when compared to the general female population of same age in the same calendar period (2.5 women). Hence, even though women with an APST have a better outcome than women with noninvasive LGSC, women with an APST are still at higher risk of developing serous carcinoma compared with the general population. Furthermore, when divided by stage, we found that the risk of serous carcinoma both for women with stage I APST and stage II+ APST, respectively, was significantly higher than expected when compared with the general population. Thus, it is important to appreciate that even women with stage I APST are at increased risk of developing serous carcinoma. A similar result was found by Longacre et al. [7].

Previous studies of SBTs have reported that 0–34% of women develop serous carcinoma [4, 6, 8–10, 12, 15, 18, 19, 21, 23, 24] and 0–44% of women experience recurrence [2, 4, 6, 8–11, 15–24]. However, a number of issues have obscured our understanding of the behavior of SBTs. One of these relates to the manner by which the disease evolves, specifically whether subsequent disease resembles an APST or whether it has the appearance of LGSC, because many previous studies fail to distinguish recurrent APST from development of serous carcinoma [7, 9, 12–14]. This is important as the clinical management of an APST may differ from that of serous carcinoma. Moreover, it should be noted that three women in our study developed HGSC after an APST (2 cases) or noninvasive LGSC (1 case). The two carcinomas developing after an APST occurred after 21.8 and 24.9 years, and the one case following noninvasive LGSC occurred 16.2 years later. A similar finding was reported by Prat et al. [4]. It is not clear whether

this represents a long latent period of progression of a low-grade tumor or development of a new independent primary neoplasm. We are currently conducting molecular analyses of all subsequent serous carcinomas in our cohort, and these findings will be reported in a separate study.

We found that 50 women with an APST experienced recurrent APST during the study period and of those cases, a little more than half occurred in the contralateral ovary. Among women who had bilateral oophorectomy performed, only 2.9% (22 of 752 women) experienced recurrent APST, whereas this number was higher for women who had, respectively, unilateral oophorectomy and cystectomy performed, namely 12.2% (20 of 164 women) and 26.7% (8 of 30 women). This indicates that having conservative surgery performed may increase the risk of recurrence in women diagnosed with an APST.

Our study confirms previous ones showing that advanced stage, i.e. presence of implants, a micropapillary pattern in the primary tumor (noninvasive LGSC), bilaterality, surface involvement, capsular rupture, and residual disease after surgery are risk factors for recurrent APST and development of serous carcinoma, but the presence of invasive implants is, by far, the factor associated with the highest risk of predicting a poor outcome. As already mentioned, invasive implants are now regarded as LGSC by the WHO [26], and in a recent study, we demonstrated that invasive implants share the same mutational profile as the primary ovarian tumor indicating that they are metastases [30]. The importance of invasive implants in predicting outcome is well established, but our finding that noninvasive implants are also associated with an increased risk of recurrent APST and development of serous carcinoma confirms what was found in a study by Silva et al. [19]. We are currently analyzing noninvasive implants to determine if

there are any morphologic or molecular features that might predict a poor outcome associated with these implants.

In contrast to several previous studies, in which the length of follow-up has been less than ten years [2, 4, 6–14, 17, 18, 20–24], we were able to assess long-term risk of developing recurrent APST and serous carcinoma. Women in our study whose tumors recurred as an APST, most frequently did so within ten years after their initial diagnosis; although up to 29 years for some women; and women who developed serous carcinoma did so evenly distributed within 20 years following their primary diagnosis. The latter finding was the case both for women with an APST and noninvasive LGSC. Thus, the risk of developing serous carcinoma seems to remain up to 20 years following the SBT diagnosis.

Although prior studies have shown some molecular differences between an APST and noninvasive LGSC in a subset of cases, inclusion of any type of current commercially available molecular diagnostic assay for this distinction is not likely practical in the near future (particularly as SBTs are often heterogeneous with mixed areas of an APST and noninvasive LGSC), and the current standard of practice for distinguishing these two subtypes of an SBT is based on H&E slides. However, we are unaware of any interobserver reproducibility studies evaluating subtypes of an SBT. Nonetheless, given the findings in our study, further investigations assessing histologic agreement between pathologists for diagnosing an APST and noninvasive LGSC are warranted.

In conclusion, our study provides strong evidence that especially invasive implants but also noninvasive implants are associated with an increased risk of recurrent APST and, in particular, subsequent development of serous carcinoma. Nevertheless, women with stage I APST are also

at higher risk of developing serous carcinoma compared to the general population. Comparing APST to noninvasive LGSC, significantly more women with noninvasive LGSC developed serous carcinoma, especially among women with stage I/without implants. Thus, the presence of noninvasive LGSC is strongly associated with an increased risk of subsequent serous carcinoma in stage I patients/patients without implants, however, in patients where implants are present, the type of tumor (noninvasive LGSC versus an APST) does not seem to be strongly associated with the risk of subsequent serous carcinoma. The strengths of the study include its large size, the population-based design (includes the entire female population of Denmark), the long follow-up with virtually no loss to follow-up, and the central, blinded expert pathology review.

Conflict of Interest

All authors of the paper declare not conflicts of interest.

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Figure and Table Legends

Figure 1. Absolute risk of developing recurrent APST

Table 1. Age-adjusted risk estimates of recurrence of an atypical proliferative serous tumor (APST) among 946 women diagnosed with an APST in Denmark 1978–2002 who were followed through August 31, 2013

Figure 2. Absolute risk of developing ovarian serous carcinoma

Table 2. Age-adjusted risk estimates of subsequent ovarian serous carcinoma (low-grade serous carcinoma [LGSC] or high-grade serous carcinoma [HGSC]) among 946 women diagnosed with an atypical proliferative serous tumor (APST) in Denmark 1978–2002 who were followed through August 31, 2013

Table 3. Age-adjusted risk estimates of subsequent ovarian serous carcinoma (low-grade serous carcinoma [LGSC] or high-grade serous carcinoma [HGSC]) among 80 women diagnosed with noninvasive LGSC in Denmark 1978–2002 who were followed through August 31, 2013

4. **Table 1**
Table 1 Age-adjusted risk estimates of recurrence of an atypical proliferative serous tumor (APST) among 946 women diagnosed with an APST in Denmark 1978–2002 who were followed through August 31, 2013

	No. of women with APST (<i>n</i> =946) <i>n</i>	No. of women with recurrence (APST) (<i>n</i> =50) <i>n</i>	Risk of recurrence (APST)		Risk of recurrence (APST) (excluding women with invasive implants)	
			HR	(95% CI)	HR	(95% CI)
FIGO stage						
Stage I	821	37	1.0		1.0	
Stages II–III*	118	12	2.1	(1.1–4.1)	2.0	(1.0–4.0)
Noninvasive implants	109	11	2.0	(1.0–3.9)	–	–
Invasive implants	9	1	8.4	(1.1–62.9)	–	–
Undefinable stage	7	1	–	–	–	–
Biggest tumor size (continuous - per cm)						
	922	46	1.00	(0.99–1.01)	1.00	(0.99–1.01)
Unknown	24	4	–	–	–	–
Laterality						
Unilateral	631	29	1.0		1.0	
Bilateral	315	21	1.4	(0.8–2.5)	1.4	(0.8–2.4)
Surface involvement						
No	582	25	1.0		1.0	
Yes	341	21	1.6	(0.9–2.9)	1.5	(0.8–2.8)
Unknown	23	4	–	–	–	–
Capsular rupture						
No	603	21	1.0		1.0	
Yes	231	24	1.9	(1.1–3.6)	2.1	(1.1–3.8)
Unknown	112	5	–	–	–	–
Presence of residual disease after surgery						
No	798	37	1.0		1.0	
Yes	48	7	3.5	(1.6–7.8)	3.0	(1.3–7.2)
Unknown	100	6	–	–	–	–

Abbreviations: number (*n*); hazard ratio (HR); confidence interval (CI); International Federation of Gynecology and Obstetrics (FIGO).

*No women had stage IV disease.

4. Table 2

Table 2 Age-adjusted risk estimates of subsequent ovarian serous carcinoma (low-grade serous carcinoma [LGSC] or high-grade serous carcinoma [HGSC]) among 946 women diagnosed with an atypical proliferative serous tumor (APST) in Denmark 1978–2002 who were followed through August 31, 2013

	No. of women with APST (<i>n</i> =946)	No. of women with subsequent serous carcinoma (LGSC/HGSC) (<i>n</i> =34)§	Risk of subsequent serous carcinoma (LGSC/HGSC)		Risk of subsequent serous carcinoma (LGSC/HGSC) (excluding women with invasive implants)	
	<i>n</i>	<i>n</i>	HR	(95% CI)	HR	(95% CI)
FIGO stage						
Stage I	821	14	1.0		1.0	
Stages II–III*	118	20	10.9	(5.4–21.8)	9.3	(4.5–19.1)
Noninvasive implants	109	17	9.3	(4.5–19.1)	–	–
Invasive implants	9	3	115.9	(29.6–454.7)	–	–
Undefinable stage	7	0	–	–	–	–
Biggest tumor size (continuous - per cm)						
	922	32	1.00	(0.99–1.01)	1.00	(0.99–1.01)
Unknown	24	2	–	–	–	–
Laterality						
Unilateral	631	7	1.0		1.0	
Bilateral	315	27	7.7	(3.3–17.7)	6.9	(2.9–15.9)
Surface involvement						
No	582	9	1.0		1.0	
Yes	341	24	4.8	(2.2–10.4)	5.0	(2.2–11.3)
Unknown	23	1	–	–	–	–
Capsular rupture						
No	603	22	1.0		1.0	
Yes	231	8	0.6	(0.3–1.4)	0.6	(0.3–1.5)
Unknown	112	4	–	–	–	–
Presence of residual disease after surgery						
No	798	25	1.0		1.0	
Yes	48	5	3.8	(1.5–9.9)	4.0	(1.5–10.6)
Unknown	100	4	–	–	–	–

Abbreviations: number (*n*); hazard ratio (HR); confidence interval (CI); International Federation of Gynecology and Obstetrics (FIGO).

*No women had stage IV disease.

§Thirty-two women developed LGSC (94%), and two women developed HGSC (6%).

4. Table 3

Table 3 Age-adjusted risk estimates of subsequent ovarian serous carcinoma (low-grade serous carcinoma [LGSC] or high-grade serous carcinoma [HGSC]) among 80 women diagnosed with noninvasive LGSC in Denmark 1978–2002 who were followed through August 31, 2013

	No. of women with noninvasive LGSC (<i>n</i> =80)	No. of women with subsequent serous carcinoma (LGSC/HGSC) (<i>n</i> =9)§	Risk of subsequent serous carcinoma (LGSC/HGSC)		Risk of subsequent serous carcinoma (LGSC/HGSC) (excluding women with invasive implants)	
	<i>n</i>	<i>n</i>	HR	(95% CI)	HR	(95% CI)
FIGO stage						
Stage I	58	4	1.0		1.0	
Stages II–IV*	20	4	2.6	(0.6–10.5)	1.3	(0.1–11.4)
Noninvasive implants	10	1	1.2	(0.1–11.1)	–	–
Invasive implants	10	3	4.5	(0.9–22.4)	–	–
Undefinable stage	2	1	–	–	–	–
Biggest tumor size (continuous - per cm)						
	77	7	1.01	(1.00–1.03)	1.01	(0.99–1.03)
Unknown	3	2	–	–	–	–
Laterality						
Unilateral	33	4	1.0		1.0	
Bilateral	47	5	0.8	(0.2–2.8)	1.3	(0.2–6.9)
Surface involvement						
No	39	2	1.0		1.0	
Yes	37	5	2.2	(0.4–11.4)	4.2	(0.5–38.2)
Unknown	4	2	–	–	–	–
Capsular rupture						
No	55	5	1.0		1.0	
Yes	14	3	1.7	(0.4–7.5)	1.2	(0.1–10.6)
Unknown	11	1	–	–	–	–
Presence of residual disease after surgery						
No	56	4	1.0		1.0	
Yes	12	3	2.2	(0.4–12.1)	2.0	(0.2–24.5)
Unknown	12	2	–	–	–	–

Abbreviations: number (*n*); hazard ratio (HR); confidence interval (CI); International Federation of Gynecology and Obstetrics (FIGO).

*Only one woman had stage IV disease without subsequent development of ovarian serous carcinoma.

§Eight women developed LGSC (89%), and one woman developed HGSC (11%).

Figure 1. Absolute risk of developing recurrent APST

Figure 2. Absolute risk of developing ovarian serous carcinoma