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Long-term Behavior of Serous Borderline Tumors Subdivided into Atypical Proliferative Tumors and Non-invasive Low-grade Carcinomas: A Population-based Clinicopathologic Study of 942 Cases

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Abstract

Ovarian serous borderline tumors (SBTs) have been the subject of considerable controversy, particularly with regard to terminology and behavior. It has been proposed that they constitute a heterogeneous group of tumors composed, for the most part, of typical SBTs that are benign and designated “atypical proliferative serous tumor (APST)” and a small subset of SBTs with micropapillary architecture that have a poor outcome and are designated “non-invasive low-grade serous carcinoma (niLGSC)”. It also has been argued that the difference in behavior between the two groups is not due to the subtype of the primary tumor but rather the presence of extra-ovarian disease, specifically invasive implants. According to the terminology of the 2014 WHO Classification, typical SBTs are equivalent to APSTs and SBTs displaying micropapillary architecture are synonymous with niLGSC. In addition, “invasive implants” were renamed “low-grade serous carcinoma” (LGSC). The argument as to whether it is the appearance of the primary tumor or the presence of extra-ovarian LGSC that determines outcome remains unsettled.

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The current study was initiated in 2004 and was designed to determine what factors were predictive of outcome, with special attention to the appearance of the primary tumor (APST vs. niLGSC) and that of the extra-ovarian disease (non-invasive vs. invasive implants). Our study is population-based, involving the entire female population of Denmark. None of the women in the study were lost to follow-up, which ranged up to 36 years (median, 15 years). All the microscopic slides from the contributing hospitals were re-reviewed by a panel of two pathologists (RV and RJK) who were blinded to the follow-up. After excluding those that were not SBTs by the pathology panel, as well as cases with a prior or concurrent cancer or undefined stage, 942 women remained, of which 867 were APSTs and 75 were niLGSCs.

The median patient age was 50 years (range, 16–97). Eight hundred nine women (86%) presented with FIGO stage I disease while 133 (14%) had advanced stage disease. Compared to APSTs, niLGSC exhibited a significantly greater frequency of bilaterality, residual gross disease after surgery, microinvasion/microinvasive carcinoma, advanced stage disease, and invasive implants at presentation (p-values <0.003). Because the cause of death is difficult to accurately ascertain from death certificates, we used development of invasive serous carcinoma as the primary endpoint since following development of carcinoma, the mortality is very high. In the entire cohort, subsequent development of carcinoma occurred in 4%, of which 93% were low-grade and 7% high-grade (median time, 10 years; range, up to 25 years). After adjusting for age at and time since diagnosis of APST or niLGSC, occurrence of subsequent carcinoma was significantly higher with niLGSC than APST among all stages combined (hazard ratio [HR] = 3.8; 95% confidence interval [CI]: 1.7–8.2). This difference was still significant for stage I but not advanced stage cases. Moreover, all-cause mortality was not statistically significantly different between APST and niLGSC. Of all women with advanced stage disease, 114 (86%) had non-invasive implants whereas 19 (14%) were invasive. Non-invasive implants were significantly associated with subsequent development of carcinoma (HR = 7.7; 95% CI: 3.9–15.0), but the risk with invasive implants was significantly higher (HR = 42.3; 95% CI: 16.1–111.1).

In conclusion, although invasive implants are the most important feature in predicting an adverse outcome, subclassification into APST and niLGSC is important as it stratifies women with respect to risk for advanced stage disease and invasive implants for all women and development of serous carcinoma for stage I cases.

Keywords

Serous borderline tumor; Serous borderline tumor; micropapillary variant; atypical proliferative serous tumor; non-invasive low-grade serous carcinoma; non-invasive micropapillary serous carcinoma; and serous tumor of low malignant potential

INTRODUCTION

Since the establishment of ovarian serous borderline tumors (SBTs) as a distinct group in the FIGO and WHO ovarian tumor classifications in the early 1970s, there have been significant advances in our understanding of these neoplasms.^{1–8} One was that invasive implants were a very important factor in predicting adverse outcome and another that SBTs with a micropapillary or cribriform pattern were more frequently associated with invasive implants

and aggressive behavior.^{9,10} The latter finding led to the proposal that the typical SBTs were benign and that micropapillary SBTs were a non-invasive low-grade serous carcinoma. Accordingly, it was proposed that the former tumor be designated “atypical proliferative serous tumor (APST)” and the latter “non-invasive low-grade serous carcinoma” (niLGSC), which offered an apparent explanation for the “low malignant potential” behavior of this entire group of tumors. Subsequently, a number of studies comparing the clinicopathologic features of typical SBT and the micropapillary variant were performed yielding different results. This led to considerable debate^{11–21} as it was argued that the poor prognosis associated with the niLGSC was not due to the appearance of the ovarian neoplasm but was due to the associated invasive implants. According to the terminology of the 2014 WHO Classification, typical SBTs are equivalent to APSTs and SBTs displaying micropapillary architecture are synonymous with niLGSC.⁵ In addition, “invasive implants” were renamed “low-grade serous carcinoma (LGSC).” The argument as to whether it is the appearance of the primary tumor or the presence of extra-ovarian LGSC that dictated outcome remains unsettled.

Reviews of the literature^{6,22} drew attention to a variety of limitations in the previously published studies of SBTs that compromised an accurate understanding of their behavior. These usually included relatively small numbers of cases (<200 cases), relatively short follow-up (8 years), a substantial number of patients lost to follow-up, and selection bias as virtually all investigations were from tertiary care institutions. Lastly, the small number of population-based studies either lacked pathology re-review or had relatively small numbers of patients or short follow-up.^{23–29}

In an effort to address these issues, we conducted a large population-based study of non-invasive low-grade serous tumors involving the entire female population of Denmark including pathology re-review and long-term follow-up, with no losses to follow-up. The main aim of the current study was to describe the clinicopathologic features of APSTs and niLGSCs, as well as implants and microinvasion/microinvasive carcinoma, and to assess the behavioral differences between APSTs and niLGSCs and non-invasive and invasive implants, where women with a history of cancer (ovarian or non-ovarian sites except for non-melanoma skin cancers) have been excluded.

MATERIAL and METHODS

Study population

The study was approved by the Danish Data Protection Agency and the Danish Scientific Ethical Committee. The complete epidemiologic characteristics and details of study design of this Danish cohort have been previously reported.³⁰ Briefly, all cases with a file diagnosis of SBT during 1978–2002 were identified in the Danish Pathology Data Bank and/or Danish Cancer Registry, which are nation-wide registries. Of 1,487 such cases, slides were retrieved for 1,259, and after re-review of H&E slides, 265 cases were excluded as not being an SBT. Of these, 237 were serous cystadenoma/adenofibroma with minute/focal epithelial proliferation, 12 were non-serous borderline tumors, and 16 were invasive carcinomas of various types. In order to detect SBTs misclassified as carcinoma, cases with a file diagnosis of well-differentiated serous carcinoma from 1997 to 2002 were identified, and of the 107

such cases, 48 were interpreted as SBT after re-review. In summary, 1,042 cases from all searched registries were considered SBT after re-review. In all analyses, we excluded women with a history of cancer (ovarian or non-ovarian sites except for non-melanoma skin cancers) prior to or concurrent with the diagnosis of SBT, as well as women with undefined stage of SBT, leaving 942 women with a confirmed diagnosis of SBT for analysis in the present study.

Pathology re-review

All H&E slides from the primary ovarian tumor and non-ovarian sites were obtained from the various pathology departments in Denmark. Slides from all cases were reviewed by two of the authors (RV and RJK) who were blinded to all clinical parameters. The SBTs were classified according to the criteria of the National Cancer Institute's Borderline Ovarian Tumor Workshop in 2003⁷ and 2014 WHO.⁵ An SBT was defined as a non-invasive low-grade serous tumor with intracystic or exophytic growth, with papillary architecture and papillae lined by stratified epithelium, and displaying greater architectural proliferation than a cystadenoma/adenofibroma but lacking destructive stromal invasion of invasive carcinoma. A diagnosis required at least 10% epithelial proliferation of the tumor for the distinction from papillary forms of serous cystadenoma/adenofibroma.

Neoplasms were subclassified as APST or niLGSC. Tumors with foci of micropapillary growth measuring ≥ 5 mm in greatest dimension were classified as niLGSC whereas tumors with no micropapillary foci or foci of micropapillary growth measuring <5 mm in greatest dimension were classified as APST. It is important to emphasize that in making the diagnosis of a niLGSC, the cytologic features should be considered. Unlike APSTs that are composed of a heterogeneous population of cuboidal, columnar, ciliated, and rounded cells with abundant eosinophilic cytoplasm containing bland nuclei, the cells in niLGSC are relatively uniform in appearance, with a higher nuclear:cytoplasmic ratio, coarser nuclear chromatin, and frequently small but prominent nucleoli. They closely resemble invasive LGSC. Furthermore, they lack the eosinophilic cells and ciliated cells that are so conspicuous in APSTs.

Implants were classified as non-invasive (epithelial or desmoplastic type) or invasive based on traditional ("tissue invasion")¹ or expanded criteria.³ The latter were used when there were implants showing micropapillary or cribriform/confluent patterns similar to niLGSC, and/or solid nests surrounded by a clear space, but in which there was no obvious infiltration into normal underlying tissue. For purposes of this study, cases meeting either traditional or expanded criteria were classified as invasive implants.

As the threshold for distinguishing the upper size limit of "microinvasion" from the lower limit of invasive low-grade serous carcinoma varies in different studies and since no scientifically validated measurement has been established, no specific size cut-off was used in this study as long as the foci in question did not exhibit destructive stromal invasion as defined elsewhere.³¹ Thus, patterns of stromal invasion not showing destructive stromal invasion were included regardless of the size or number of foci. The greatest linear dimension for the largest single focus in any case was classified as <3 mm, ≥ 3 to <5 mm, or ≥ 5 mm.

The 2014 WHO Classification for Gynecologic Tumors, describes two types of “microinvasion”.⁵ The more common pattern is the conventional type, which frequently contains single cells, small clusters of cells, and small papillae within stroma, which is termed “microinvasion.” The other less common type features a micropapillary pattern, which in addition to micropapillae, often contains small solid nests of cells surrounded by a clear space or cleft within the stroma, as well as inverted macropapillary and cribriform patterns, and is designated “microinvasive carcinoma” since it resembles invasive low-grade serous carcinoma. In this study, cases were classified as having either only the conventional-type of microinvasion or microinvasive carcinoma (regardless of the co-existing presence of the conventional-type of microinvasion).

Surgical procedures and staging

Hospitals in which the study patients were admitted for surgery and subsequent treatment were identified by linkage with the National Patient Registry in Denmark. All medical records were reviewed, and data were extracted. All women were treated according to the Danish clinical guidelines for ovarian borderline tumors/cancer, which previously did not necessarily include complete staging and lymph node dissection. Given the small number of lymph nodes removed in this cohort, meaningful interpretation of the role of lymph node involvement could not be performed; however, lymph node involvement by SBT is generally not regarded as an adverse prognostic factor,^{2,5,6,32,33} and, therefore, lack of lymph node data is not likely to bias our survival analysis.^{34,35} Tumor stage was determined using the pre-2014 FIGO staging system and was based on information collected from the medical records as well as histologic slide re-review of extra-ovarian tissue.

Follow-up

Recurrent tumor in the form of APST was classified as “recurrence,” which was classified separately from subsequent development of serous carcinoma. The cohort was linked with the Danish Pathology Data Bank until August 31, 2013. All women were followed in the Pathology Data Bank from six months following the primary diagnosis of SBT. All pathology records were abstracted, and all H&E slides (recurrence/subsequent serous carcinoma) were obtained for re-review, including additional comparison with slides of the primary tumor and implants from the initial surgery. The subsequent serous carcinomas were classified according to the 2014 WHO criteria.⁵

We did not determine disease-specific survival because non-invasive low-grade serous tumors are often indolent and recur over the course of many years, confounding the exact cause of death. Death certificates often cite the cause of death as “ovarian cancer” even when there is no evidence to indicate that tumor is present at the time of death. Accordingly, in lieu of disease-specific survival, subsequent development of histologically confirmed invasive serous carcinoma was used as a primary endpoint given its known poor outcome.^{36–40} As patients with a diagnosis of a non-invasive low-grade serous tumor may have died from tumor progression or have deaths related to non-malignant complications (such as bowel obstruction due to adhesions from implants, which is not an infrequent complication of non-invasive low-grade serous tumors), death due to any cause is also

provided in order to establish differences in life expectancy for women with a diagnosis of APST versus niLGSC.

Statistical analysis

Chi-square test or Fisher's exact test was used to compare categorical variables, and t-test was used to compare continuous variables. Time to subsequent development of histologically confirmed invasive serous carcinoma and death from all causes, respectively, was calculated from the date of the primary ovarian tumor (APST or niLGSC). Cox proportional hazards regression analysis with time since diagnosis as the underlying time scale was used to estimate associations between type of ovarian tumor and type of implant, respectively, and development of serous carcinoma and all-cause mortality, respectively. Associations were presented as hazard ratios (HRs) and 95% confidence intervals (95% CIs). In all analyses, age was included as a continuous covariate. Statistical modeling was performed using the SAS/STAT version 8.2 (SAS Institute, Cary, NC, USA).

RESULTS

General clinicopathologic features

Nine hundred forty two women with either APST or niLGSC met inclusion criteria and were suitable for follow-up. Of these, 867 women (92%) had only APST while 75 (8%) had niLGSC. Twenty one women with niLGSC (28%) had a contralateral APST. Compared with APST, niLGSC was associated with significantly higher frequencies of bilaterality (45/75 [60%] vs. 294/867 [34%]; $p<0.0001$), microinvasion/microinvasive carcinoma (7/75 [9%] vs. 18/867 [2%]; $p=0.003$) [see *Microinvasion/microinvasive carcinoma section below for further details*], and residual gross disease after surgery (12/75 [16%] vs. 42/867 [5%]; $p<0.0001$). There was no significant difference in age, tumor size, or frequency of ovarian surface involvement or endosalpingiosis between both tumor types (Table 1).

Histologic features of primary ovarian tumors

Atypical proliferative serous tumor (APST)—The level of tissue sampling was 1.1 (mean) blocks per centimeter of tumor (range, 0.1–11.3); information on sampling was missing in 26 cases. Tumors were intracystic and/or exophytic (with or without “autoimplants”) and exhibited features typical of APST with hierarchical papillary branching, in which larger papillae progressively branched into smaller papillae terminating in small and detached papillary clusters (Fig. 1). The papillae were lined by a heterogeneous population consisting of cuboidal, columnar, and rounded cells with abundant eosinophilic cytoplasm. Cilia were frequently present, and nuclei were relatively bland. Psammoma bodies were occasionally present.

Forty women (5%) had a micropapillary component measuring 1 mm but <5 mm in greatest dimension and, therefore, did not satisfy quantitative criteria for a diagnosis of niLGSC.⁵ Eight hundred twenty seven women (95%) had no micropapillary component.

Two hundred thirty-four women (27%) had tumors with architecture that was predominantly cystadenomatous/adenofibromatous, in which the APST component accounted for <50% of

the tumor and that the majority of the tumor contained a serous cystadenoma/adenofibroma component (Fig. 1D). In contrast, 73% of cases either contained no cystadenomatous/adenofibromatous component or had a cystadenoma/adenofibroma component that accounted for <50% of the tumor.

Non-invasive low-grade serous carcinoma (niLGSC)—The level of tissue sampling was 1.5 (mean) blocks per centimeter of tumor (range, 0.3–7.7); information on sampling was missing in three cases. Tumors were intracystic and/or exophytic (with or without “autoimplants”) and exhibited features characteristic of niLGSC (Fig. 2). In general, niLGSC lacked the classic hierarchical papillary branching pattern of APST. Instead, large papillae frequently showed immediate transition to elongated micropapillary structures that were usually five times longer than wide (“Medusa head appearance”). Frequently, sheets of detached micropapillae were present between the larger papillae. Variable amounts of cribriform architecture were also noted (Fig. 3). Psammoma bodies were occasionally present.

Some tumors were pure niLGSC while others contained a background of APST. The proportion of any tumor containing 5 mm of micropapillary growth in greatest dimension, as described above in order to qualify for a diagnosis of niLGSC, varied from case to case (70%, median; 60%, mean; range, 1–100%).

Eleven women (15%) had tumors with architecture that was predominantly cystadenomatous/adenofibromatous, in which the niLGSC component accounted for <50% of the tumor. In contrast, 85% of cases either contained no cystadenomatous/adenofibromatous component or had a cystadenoma/adenofibroma component that accounted for <50% of the tumor.

FIGO stage

The stage distribution for APST was as follows: stage I in 754 women (87%), II in 54 (6%), and III in 59 women (7%). For niLGSC, the corresponding distribution was: stage I in 55 women (73%), II in 11 (15%), III in eight (11%), and IV in one (1%). Presentation with advanced stage was significantly more frequent with niLGSC (Table 2).

Implants

Among women with advanced stage APST, 104 (92%) had non-invasive implants (Fig. 4) while 9 (8%) had invasive implants. For advanced stage niLGSCs, 10 (50%) had non-invasive implants and 10 (50%) women had invasive implants (Fig. 5). niLGSC was associated with a significantly higher frequency of invasive implants (Table 2).

Microinvasion/microinvasive carcinoma

Of 18 women with APST and microinvasion/microinvasive carcinoma, 10 (10/18; 56%) had only the conventional type of microinvasion (Fig. 6), and 8 (8/18; 44%) had microinvasive carcinoma (Table 3). These ranged from one focus per case to multiple; the largest dimension of any individual focus measured <3 mm in 15 women, 3 – <5 mm in one

woman, and 5 mm in two patients. However, neither type exhibited destructive stromal invasion.

Seven women with niLGSC (7/75; 9%) contained microinvasive carcinoma (Fig. 7), and one of these (1/7; 14%) also had microinvasion of the conventional type (Table 4). None of these seven women had only the conventional type of microinvasion. These ranged from one focus per case to multiple; the largest dimension of any individual focus measured <3 mm in two women, 3 – <5 mm in three patients, and 5 mm in two women. Of the seven cases, one focus displayed an “inverted macropapillary” pattern (Fig. 8), and two had a cribriform pattern.

Among women with microinvasion/microinvasive carcinoma, microinvasion of the conventional type-only was more frequent in APST compared with niLGSC (10/18 [56%] vs. 0/7 [0%] in APST and niLGSC, respectively) while microinvasive carcinoma was more frequent in niLGSC as opposed to APST (7/7 [100%] vs. 8/18 [44%] in niLGSC and APST, respectively) [$p=0.02$]. Furthermore, microinvasive carcinoma was associated with advanced stage disease more frequently than microinvasion of the conventional type-only (7/15 [47%] vs. 2/10 [20%], respectively), but this difference was not statistically significant ($p=0.2$). Of APSTs, subsequent serous carcinoma developed during follow-up time in one of 10 (10%) with only microinvasion of the conventional type and two of 8 (25%) with microinvasive carcinoma. In niLGSCs, carcinoma developed in none of the seven (0%) with microinvasive carcinoma. Further statistical analysis of either only microinvasion of the conventional type or microinvasive carcinoma with respect to significance of size was not possible due to small numbers.

Risk of subsequent serous carcinoma and death in relation to APST vs. niLGSC

None of the women in the study were lost to follow-up, which ranged up to 36 years (median, 15 years). Forty-one women (4%) with either APST or niLGSC subsequently developed an invasive serous carcinoma, 38 of which were low-grade and 3 high-grade. The median time from diagnosis of APST/niLGSC to serous carcinoma was 10 years (range, 0.6–25). Serous carcinoma (Fig. 9) developed in 33 women (4%) with APST and 8 (11%) with niLGSC (Table 5). The rate for subsequent serous carcinoma was significantly higher for niLGSC as compared with APST (HR = 3.8; 95% CI: 1.7–8.2) when adjusting for age at and time since diagnosis of APST or niLGSC.

Using all-cause mortality as another endpoint, the risk of death for women with niLGSC was not significantly different from APST after adjusting for age at and time since diagnosis of APST or niLGSC (HR = 1.2; 95% CI: 0.8–1.9) [Table 5].

Risk of subsequent serous carcinoma and death in relation to presence and type of implant

In an analysis of implants regardless of type of ovarian tumor (APST or niLGSC), non-invasive implants as well as invasive implants were associated with statistically significantly higher rates of subsequent development of serous carcinoma compared to no implants (HR = 7.7; 95% CI: 3.9–15.0 for non-invasive versus no implants; HR = 42.3; 95% CI: 16.1–111.1 for invasive versus no implants) [Table 5], but this risk was higher with invasive implants.

When directly comparing non-invasive versus invasive implants, invasive implants were associated with a statistically significantly higher risk for subsequent development of serous carcinoma (HR = 9.0; 95% CI: 2.5–32.7) [Table 6]. Additionally, non-invasive and invasive implants were associated with a statistically significantly increased risk of death of any cause after adjusting for age at and time since diagnosis of APST or niLGSC: non-invasive implants versus stage I disease (HR = 1.8; 95% CI: 1.3–2.6) and invasive implants versus stage I disease (HR = 6.6; 95% CI: 3.7–11.8) [Table 5].

Risk of subsequent serous carcinoma and death in relation to APST vs. niLGSC and presence and type of implant

In women with no implants, subsequent serous carcinoma developed in 13 of 754 APSTs (2%) whereas in niLGSC without implants, carcinoma developed in a higher proportion (4/55 [7%]). In contrast, in women with implants, no statistically significant differences were found between APST and niLGSC as serous carcinoma developed in 17 of 104 (16%) APSTs with non-invasive implants and in one of 10 (10%) niLGSCs with non-invasive implants; in APSTs with invasive implants, carcinoma developed in three of nine (33%) and in three of 10 (30%) niLGSCs with invasive implants.

After adjusting for age at and time since diagnosis of APST or niLGSC among women without implants, those with niLGSC had a significantly increased risk of developing serous carcinoma compared to women with APST (HR = 5.4; 95% CI: 1.8–16.9). Even after adjusting for microinvasive carcinoma (presence vs. absence), this difference was statistically significant (HR = 6.2; 95% CI: 2.0–19.3) [Table 6]. However, no difference in the risk of death from all causes was observed (HR = 1.1; 95% CI: 0.7–1.8) [Table 6]. In contrast, among women with implants, the risk of subsequent serous carcinoma was not significantly related to APST vs. niLGSC when adjusting for age at and time since diagnosis of APST or niLGSC and type of implant (Table 6). This difference also was not statistically significant with further adjustment for microinvasive carcinoma (HR = 0.5; 95% CI: 0.1–2.5) [Table 6]. On the other hand, the type of implant was a significant predictor of serous carcinoma after adjusting for age at and time since diagnosis and type of ovarian tumor (APST vs. niLGSC) [HR = 9.0; 95% CI: 2.5–32.7]. Even after adjusting for microinvasive carcinoma, this difference was statistically significant (HR = 6.9; 95% CI: 1.6–30.5) [Table 6]. A similar pattern was seen for risk of death from all causes although less pronounced (Table 6).

DISCUSSION

We have previously analyzed our total cohort with regard to the risk of subsequent serous carcinoma and identified risk factors for recurrence and progression.⁴¹ In the present long-term population-based study, we show that APSTs/niLGSCs are very indolent and that the risk of developing subsequent serous carcinoma is significantly higher among women with stage I niLGSCs compared with APSTs (Tables 5 and 6). Even when controlling for surface involvement (i.e., stage IC) in this cohort, this higher risk with niLGSC among stage I cases was still statistically significant.⁴¹ However, the overall risk of death (all-cause mortality) is similar for APST and niLGSC among either stage I or >I cases (Table 6) suggesting that

other factors, apart from the development of carcinoma, can result in a fatal outcome (e.g., small bowel obstruction from adhesions due to non-invasive implants, etc.). These findings have not been observed in previous studies.^{3,10,26,42–55} However, interpreting data from other outcome-based studies is complicated by multiple factors. These include variation in surgical treatment (conservative/fertility-sparing surgery vs. variable degrees of completeness of surgical staging), lack of a uniform pathology review, differing criteria for invasive implants, small number of cases, selection bias, insufficient duration of follow-up, losses to follow-up, and that person-years at risk may not have been taken into account when comparing APSTs and niLGSCs.

Another interesting finding in this study was that while stage I niLGSCs had a significantly higher risk for subsequent serous carcinoma compared with stage I APSTs, there was no difference in this risk between advanced stage niLGSCs and advanced stage APSTs. In general, advanced stage non-invasive low-grade serous tumors with non-invasive implants had a significantly higher risk for subsequent serous carcinoma compared with stage I non-invasive low-grade serous tumors although this risk was not as high as with invasive implants. More specifically, in one of our prior epidemiologic studies of this cohort, even APSTs with non-invasive implants had a significantly higher risk for subsequent serous carcinoma compared with stage I APSTs.⁴¹ Thus, in the setting of advanced stage disease, the presence of implants (even non-invasive) is such an important driver of behavior that the histologic type of ovarian tumor loses significance.

In our study, 21% of cases submitted to the pathology panel as SBTs were disqualified, most often because they were serous cystadenomas/adenofibromas with slight epithelial proliferation that represented less than 10% of the neoplasm. A smaller proportion were carcinomas of various types. Although architectural/quantitative features allow for distinction between APST and niLGSC, it is important to acknowledge cytologic differences between both tumors as the diagnosis of niLGSC can be erroneous if attention is not directed to cytologic features but is based solely on the presence of a micropapillary pattern. Specifically, APSTs can exhibit focal micropapillary areas but are otherwise composed of a heterogeneous population of cells consisting of cuboidal, columnar, and rounded cells with abundant eosinophilic cytoplasm. Cilia are frequently present, and nuclei are relatively bland. In contrast, the cells in niLGSC are relatively uniform in appearance and lack eosinophilic cytoplasm and cilia. There is a higher nuclear:cytoplasmic ratio, the nuclear chromatin is coarser, and nuclei frequently contain a small but prominent nucleolus. The cells are virtually identical to those in invasive LGSC. Therefore, examination of areas of micropapillary architecture on high-power magnification can allow for the cytologic features to help further refine the distinction between APST and niLGSC although occasionally there can be some cytologic overlap between these tumors.

Criteria for classification of implants have been controversial.² The traditional criteria for the diagnosis of invasive implants require infiltration of underlying tissue,¹ but in this study we used expanded criteria, which in addition to infiltration of underlying tissue, include exophytic or endophytic micropapillary architecture resembling niLGSC or solid nests surrounded by a clear space.³ Previously, a study by K. Bell *et al* demonstrated that the expanded criteria were associated with poor outcome.³ However, in a recent study by

McKenney *et al*, invasive implants diagnosed by expanded criteria without classic destructive stromal invasion (i.e., micropapillary architecture or solid nests surrounded by cleft-like spaces) were found to be often associated with tissue invasion but did not add significant prognostic value beyond classic invasion alone.⁵⁶ In that study, the median follow-up for the entire cohort of advanced stage serous borderline tumors was 7.8 years, and 26% of women with invasive implants having only classic destructive stromal invasion and 23% of women with invasive implants having only micropapillary architecture or solid nests surrounded by cleft-like spaces were lost to follow-up, respectively.

Nonetheless, since we found that invasive implants, as defined in this study, were associated with higher risks of both subsequent serous carcinoma and all-cause mortality (Table 6), this supports the use of the expanded criteria and that the WHO recommendation that invasive implants be termed “LGSC”⁵ is valid. A detailed analysis of both traditional and expanded criteria for invasive implants in this cohort, including correlation with *KRAS/BRAF* genotype for potential prediction of malignant potential of non-invasive and invasive implants, will be the subject of a forthcoming study.

Previously, it has been suggested that advanced stage niLGSC is not an independent adverse prognostic factor when controlling for implant type,⁴⁷ a finding also observed in our study. Specifically, a few studies have demonstrated that niLGSC compared with APST have a significantly poorer progression-free or disease-specific survival with univariate analysis but that this difference was not statistically significant upon multivariate analysis.^{42,47,50} Adjusting for implant type in niLGSCs in the setting of multivariate analysis is problematic given that invasive implants and niLGSC co-vary with one another and that essentially all studies on advanced stage niLGSC with follow-up are limited by relatively small numbers of such cases.^{10,26,42,43,45–49,52,53,55} Thus, subdividing small numbers of patients with advanced stage niLGSCs into smaller groups with non-invasive and invasive implants, respectively, yields very low numbers. Additionally, such a survival analysis between APST and niLGSC with stratification according to implant type ideally should take into account differences in age and length of follow-up between groups. In order to achieve sufficient statistical power, a large number of advanced stage niLGSCs is required. Even in our large series, only 20 niLGSCs were of advanced stage since the frequency of this tumor in the population is low (8% in our series) and that even advanced stage non-invasive low-grade serous tumors (APST + niLGSC combined) in a population-based setting are uncommon (14% in our series). Our findings, however, in conjunction with a number of prior studies, clearly show that niLGSC is significantly associated with invasive implants, which is a known poor prognostic factor.^{3,10,42,43,45–49,52,53,55}

Another controversial and confusing feature is “microinvasion”.² Much of the literature has shown that microinvasion is not an adverse prognostic factor.^{2,5,6} However, some studies suggest that microinvasion may co-vary with other adverse prognostic factors such as invasive implants, advanced stage, unresectable disease, and micropapillary architecture in the SBT.³¹ Indeed, in the 2014 WHO Classification for Gynecologic Tumors, two types of “microinvasion” are described.⁵ The more common pattern is the conventional type, which is composed of single cells and small clusters of cells with abundant eosinophilic cytoplasm within the stroma of the papillae. The less common type is one with micropapillary-rich

architecture and cells resembling LGSC and is designated “microinvasive carcinoma.” Given that the majority of the literature shows that the conventional type of microinvasion is not an adverse prognostic factor, as well as immunohistochemical studies showing that the constituent cells exhibit features of terminal differentiation and senescence,⁵⁷ it has been proposed that microinvasion does not play a role in the pathogenesis of tumor progression. In contrast, it has been suspected that “microinvasive carcinoma” may represent an early form of invasive low-grade serous carcinoma. In this study, microinvasive carcinoma did not have any prognostic effect (development of subsequent serous carcinoma) after adjusting for type of ovarian tumor (APST vs. niLGSC) and implant type. Nevertheless, the finding that microinvasive carcinoma was much more common in niLGSC while microinvasion of the conventional type occurred more frequently with APST provides support that microinvasive carcinoma may represent an early form of invasive low-grade serous carcinoma.

A potential limitation of the current study is that disease-specific survival is not available for reasons detailed in the *Materials & Methods*. However, when mortality for APST versus niLGSC was compared, there was no significant difference in the risk for death from any cause despite the greater risk of developing carcinoma among women with niLGSC. We were unable to determine the exact cause of death in this study, but it is likely that the cohort of women with niLGSCs experienced a higher fraction of tumor-related deaths while the cohort with APSTs had a greater proportion of non-tumor-related deaths. This is an important finding since the management of benign complications will be very different from those that are cancer related.

However, in our prior epidemiologic studies of this cohort, there are some important observations worth noting with regard to the natural history of non-invasive low-grade serous tumors: stage I APSTs had no difference in overall survival (all-cause mortality) compared with the background general population;³⁰ the risk of subsequent serous carcinoma in women with stage I APSTs was low (2%), stage I APSTs showed a significantly higher risk for subsequent serous carcinoma compared with the background general population, and this risk for APSTs (all stages combined) significantly increased over 20 years.⁴¹ In the current study, serous carcinomas developing after a diagnosis of either APST or niLGSC (all stages) occurred up to 25 years later. In a study of advanced stage serous borderline tumors with non-invasive implants by Silva *et al*, survival of this subset of non-invasive low-grade serous tumors was time-dependent.⁵⁸ Based on the findings from the current study and our prior ones using this same cohort, we, therefore, agree with the recommendations of Silva *et al*⁵⁸ that 20 years of follow-up is necessary to fully assess the behavior of non-invasive low-grade serous tumors, even for stage I APSTs.

In conclusion, this long-term, population-based study of non-invasive low-grade serous tumors involving the entire female population of Denmark showed that the risk of subsequent serous carcinoma was significantly higher with niLGSC compared with APST among patients with stage I disease. Nonetheless, the mortality from all causes is not different between APST and niLGSC among either stage I or >I cases. In addition, although the presence of invasive implants is the single most adverse prognostic factor, subclassification into APST and niLGSC is important as it stratifies women with respect to risk for advanced stage disease and invasive implants among all women and subsequent

development of serous carcinoma among stage I cases. Lastly, it is important to emphasize that even though invasive implants carry the highest risk for subsequent serous carcinoma and all-cause mortality, non-invasive implants are also associated with a statistically significantly increased risk, albeit not nearly as high as with invasive implants.

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Figure 1.

Atypical proliferative serous tumor (APST). (A, B) Large papillae progressively branch into smaller ones in a hierarchical fashion terminating in detached small epithelial clusters (B, C). Others areas showed a predominantly papillary adenofibromatous pattern (D). Figs. 1A–D are all from the same case.

Figure 2.

Non-invasive low-grade serous carcinoma (LGSC). (A) Large rounded papillae show elongated micropapillae emanating directly from the larger papillae without the typical hierarchical branching pattern of atypical proliferative serous tumor (“Medusa appearance”). (B) Closely packed micropapillae between larger papillae. (C) The low-grade cytologic features are similar to those of invasive LGSC. Figs. 2A–C are all from the same case. Contrast cytologic features with those of atypical proliferative serous tumor in Fig. 1.

Figure 3.
Non-invasive low-grade serous carcinoma with cribriform architecture.

Figure 4. Non-invasive implants. (A) Epithelial-type implant with medium-sized papillae within an epithelial-lined space. The appearance is similar to that of ovarian atypical proliferative serous tumor. (B, C) Desmoplastic-type implants with abundant desmoplastic stroma and relatively scant epithelium.

Figure 5. Invasive implants. (A) Infiltration into underlying normal tissue. (B) No invasion into underlying tissue. Exophytic micropapillary pattern resembling ovarian non-invasive low-grade serous carcinoma (expanded criteria for invasive implants). (C) No invasion into underlying tissue. Solid nests of cells and micropapillae within clear lacunar spaces (expanded criteria for invasive implants).

Figure 6. Conventional type of microinvasion. Individual cells and small clusters of cells with abundant eosinophilic cytoplasm are present within stroma. The nuclei are bland.

Figure 7. Microinvasive carcinoma. Micropapillae in clear lacunar spaces within stroma. Note the relative uniform population of cells with rounded nuclei, many of which contain a small prominent nucleolus, and the higher nuclear:cytoplasmic ratio compared to the conventional type of microinvasion as shown in Fig. 6.

Figure 8.

Microinvasive carcinoma with inverted macropapillae. Papillae larger than those shown in Fig. 7 are present in clear lacunar spaces within stroma. They have abundant fibrous stromal cores, and the qualitative features of the papillae are essentially identical to those of the so-called inverted macropapillary pattern of invasive low-grade serous carcinoma. This pattern is included within the spectrum of microinvasive carcinoma.

Figure 9. Subsequent development of low-grade serous carcinoma. (A) Original ovarian tumor (non-invasive low-grade serous carcinoma). (B) Invasive low-grade serous carcinoma 8 years later. Note morphologic similarity between the non-invasive and invasive neoplasms.

Table 1

Comparison of general clinicopathologic features

	Atypical proliferative serous tumor (n=867)	Non-invasive low-grade serous carcinoma (n=75)	p-value
<i>Median age (range)</i>	49 years (16–91)	54 years (24–91)	0.1
<i>Median size (range)</i>	9 cm (1.0–30.0) [*]	8 cm (2.7–26.0) [†]	0.2
<i>Bilaterality</i>	294 (34%)	45 (60%)	<0.0001
<i>Ovarian surface involvement</i>	312 (36%) [§]	35 (47%) [¶]	0.1
<i>Endosalpingiosis</i>	81 (9%)	9 (12%)	0.5
<i>Microinvasion/microinvasive carcinoma</i>	18 (2%)	7 (9%)	0.003
<i>Residual gross disease after surgery</i>	42 (5%) [‡]	12 (16%) ^{**}	<0.0001

^{*}, Data missing in 22 cases;

[†], data missing in 2 cases;

[§], data missing in 20 cases;

[¶], data missing in 3 cases;

[‡], data missing in 71 cases; and

^{**}, data missing in 9 cases.

Table 2

Comparison of stage and implants

	Atypical proliferative serous tumor (n=867)	Non-invasive low-grade serous carcinoma (n=75)	p-value
<i>Stage I</i>	754 (87%)	55 (73%)	<0.0011
<i>Stage >I</i>	113 (13%)	20 (27%)	
<i>Non-invasive implants</i> *	104 (92%)	10 (50%)	<0.0001
<i>Invasive implants</i> *	9 (8%)	10 (50%)	

*, Among women with stage >I.

Table 3

Microinvasion/microinvasive carcinoma in atypical proliferative serous tumor

Case	Age (years)	Pattern of stromal invasion	Greatest size of largest individual focus	Stage	Invasive implants	Subsequent serous carcinoma	Follow-up*
<i>1</i>	51	Microinvasion	<3 mm	I	N/A	No	Alive
<i>2</i>	60	Microinvasion	<3 mm	I	N/A	No	Alive
<i>3</i>	62	Microinvasion	<3 mm	I	N/A	No	Alive
<i>4</i>	44	Microinvasion	<3 mm	I	N/A	No	Dead at 12.7 yr
<i>5</i>	54	Microinvasion	<3 mm	I	N/A	No	Dead at 4.3 yr
<i>6</i>	50	Microinvasion	<3 mm	I	N/A	No	Alive
<i>7</i>	48	Microinvasion	<3 mm	I	N/A	No	Dead at 8.3 yr
<i>8</i>	70	Microinvasion	<3 mm	I	N/A	No	Dead at 18.0 yr
<i>9</i>	55	Microinvasion	<3 mm	II	No	No	Dead at 0.6 yr
<i>10</i>	50	Microinvasion	<3 mm	II	No	Yes	Dead at 1.1 yr
<i>11</i>	71	Microinvasive carcinoma	<3 mm	I	N/A	No	Dead at 11.6 yr
<i>12</i>	27	Microinvasive carcinoma	<3 mm	I	N/A	No	Alive
<i>13</i>	50	Microinvasive carcinoma	<3 mm	II	Yes	Yes	Dead at 5.6 yr
<i>14</i>	67	Microinvasive carcinoma	<3 mm	III	No	No	Alive
<i>15</i>	61	Microinvasive carcinoma	<3 mm	III	Yes	No	Dead at 3.1 yr
<i>16</i>	52	Microinvasive carcinoma	3 – <5 mm	III	Yes	Yes	Dead at 10.9 yr
<i>17</i>	45	Microinvasive carcinoma	5 mm	II	No	No	Alive
<i>18</i>	67	Microinvasive carcinoma	5 mm	II	Yes	No	Dead at 1.8 yr

N/A, not applicable because stage I, yr, years;

*, death refers to all-cause mortality.

Table 4

Microinvasive carcinoma in non-invasive low-grade serous carcinoma

Case	Age (years)	Greatest size of largest individual focus	Stage	Invasive implants	Subsequent serous carcinoma	Follow-up *
1	54	<3 mm	I	N/A	No	Alive
2	45	<3 mm	III	Yes	No	Dead at 1.6 yr
3	65	3 – <5 mm	I	N/A	No	Alive
4	62	3 – <5 mm	I	N/A	No	Alive
5	59	3 – <5 mm	I	N/A	No	Dead at 24.3 yr
6	71	5 mm	I	N/A	No	Alive
7	43	5 mm	I	N/A	No	Alive

N/A, not applicable because stage I; yr, years;

*, death refers to all-cause mortality.

Table 5

Subsequent development of serous carcinoma and all-cause mortality according to APST vs. nLGGC and presence and type of implant

	Subsequent serous carcinoma					All-cause mortality				
	n	Number of events	%	HR*	95% CI	Number of events	%	HR*	95% CI	
Type of ovarian tumor										
•APST	867	33	3.8	1.0 (ref)		248	28.6	1.0 (ref)		
•nILGSC	75	8	10.7	3.8	1.7–8.2	24	32.0	1.2	0.8–1.9	
Type of implant										
•None	809	17	2.1	1.0 (ref)		224	27.3	1.0 (ref)		
•Non-invasive	114	18	15.8	7.7	3.9–15.0	35	30.7	1.8	1.3–2.6	
•Invasive	19	6	31.6	42.3	16.1–111.1	13	68.4	6.6	3.7–11.8	

APST, atypical proliferative serous tumor; CI, confidence interval; HR, hazard ratio; n, number of cases; nLGGC, non-invasive low-grade serous carcinoma; ref, reference; %, percentage of cases; and
 * , adjusted for age at and time since diagnosis of APST or nLGGC.

Table 6

Subsequent development of serous carcinoma and all-cause mortality among women with or without implants and according to APST vs. niLGSC and type of implant

	n	Subsequent serous carcinoma				All-cause mortality			
		Number of events	%	HR	95% CI	Number of events	%	HR	95% CI
Women without implants (n=809)									
•APST	754	13	1.7	1.0 (ref)		208	27.6	1.0 (ref)	
•niLGSC	55	4	7.3	5.4 [*]	1.8–16.9	16	29.1	1.1 [*]	0.7–1.8
Women with implants (n=133)									
Type of ovarian tumor									
•APST	113	20	17.7	1.0 (ref)		40	35.4	1.0 (ref)	
•niLGSC	20	4	20.0	0.4 [†]	0.1–1.7	8	40.0	0.6 [‡]	0.2–1.4
Type of implant									
•Non-invasive	114	18	15.8	1.0 (ref)		35	30.7	1.0 (ref)	
•Invasive	19	6	31.6	9.0 [§]	2.5–32.7	13	68.4	5.3 [§]	2.5–11.5

APST, atypical proliferative serous tumor; CI, confidence interval; HR, hazard ratio; n, number of cases; niLGSC, non-invasive low-grade serous carcinoma; ref, reference; %, percentage of cases;

* , adjusted for age at and time since diagnosis of APST or niLGSC;

† , adjusted for age at and time since diagnosis of APST or niLGSC and type of implant (non-invasive vs. invasive); and

§ , adjusted for age at and time since diagnosis of APST or niLGSC and type of ovarian tumor (APST vs. niLGSC).