Original Article

Risk of Recurrence, Prognosis, and Follow-Up for Danish Women With Cervical Cancer in 2005-2013: A National Cohort Study

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BACKGROUND: In developed countries, women attend follow-up after treatment for cervical cancer to detect recurrence. The aim of this study was to describe the Danish population of women with early-stage cervical cancer at risk for recurrence and death due to recurrence. **METHODS:** Data were extracted from 3 nationwide databases to find women diagnosed with stage 1A1 to 1B1 cervical cancer in 2005-2013. Recurrences were determined from data on oncological or surgical treatment more than 3 months after the initial diagnosis and were cross-checked with patient journals. **RESULTS:** In all, 1523 patients were diagnosed with stage 1A1 to 1B1 cervical cancer. Eighty women experienced recurrences: 8 at International Federation of Gynecology and Obstetrics (FIGO) stage 1A1, 0 at FIGO stage 1A2, and 72 at FIGO stage 1B1. The 5-year recurrence rate was 6.4%; 67.5% of the women had symptomatic recurrences, and 28.8% had asymptomatic recurrences. At significantly greater risk for recurrence were women at stage 1B1, regardless of their lymph node (LN) status at diagnosis (hazard ratio with a positive LN, 5.10; 95% confidence interval [CI], 1.65-15.76; $P = .0047$; hazard ratio with a negative LN, 3.14; 95% CI, 1.25-7.93; $P = .0153$; hazard ratio with LN data missing, 6.33; 95% CI, 1.80-22.26; $P = .004$), women older than 50 years (hazard ratio, 1.81; 95% CI, 1.12-2.94; $P = .0158$), and women with lymphatic and lymphovascular space invasion (LVSI; hazard ratio, 1.92; 95% CI, 1.11-3.30; $P = .0188$). In a multivariate analysis, significantly inferior survival was found after recurrence for patients with lymphatic LVSI (hazard ratio, 2.23; 95% CI, 1.04-4.80; $P = .0401$), a symptomatic diagnosis of recurrence (hazard ratio, 2.52; 95% CI, 1.08-5.90; $P = .0332$), and multiple sites of recurrence (hazard ratio, 2.72; 95% CI, 1.32-5.61; $P = .0066$). **CONCLUSIONS:** This study has identified a group of women at FIGO stage 1A1 in no need of specialized, hospital-based follow-up. Many of the recurrences at FIGO stage 1B1 are asymptomatic, and this may show a need for follow-up in this group. Further prospective investigation is needed. ***Cancer*** **2018;124:943-51.** © *2017 American Cancer Society.*

KEYWORDS: cervical cancer, early stage, follow-up, mortality, risk of recurrence.

INTRODUCTION

Cervical cancer is accountable for approximately 528,000 new cases per year worldwide and approximately 266,000 deaths per year.[1,2] Screening, diagnosis, and treatment have all improved the outcomes for women with cervical cancer over the past decades, and this has resulted in an increased prevalence in industrialized countries.[3] This puts strain on health care systems worldwide and has an impact on current practice, notably with respect to follow-up because the majority of these patients are without disease and yet are taking up an abundance of resources within hospitals.[4,5]

Patients diagnosed with cervical cancer are treated according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines and are allocated to follow-up regardless of their initial FIGO classification.[6] Patients are clinically staged before treatment and are not upstaged if there are unexpected perioperative or postoperative findings such as metastatic lymph nodes (LNs). Danish patients at FIGO stages 1A1 to 2A with tumor sizes ≤ 4 cm are considered low-risk patients with respect to the risk of recurrence and death and undergo primary surgical treatment. In Denmark, patients at FIGO stages 1B1 to 2A are offered adjuvant oncological treatment with radiotherapy and concomitant chemotherapy if any of the following risk factors are present: positive LNs; parametrial invasion; tumor size > 3 cm and depth of stromal invasion (DSI) $> 2/3$; tumor size > 2 cm and DSI $> 1/3$ and lymphovascular space invasion (LVSI); and nonradical resection.[7] Patients with a higher FIGO stage at the initial diagnosis undergo radiotherapy and concomitant chemotherapy and are categorized as high-risk patients. However, this division into low and high risk seems irrelevant to patients in the low-risk group who experience recurrence and a subsequent risk of cancer death. To the study group's knowledge,

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there are no other methods (eg, clinical, demographic, or biological) with which to classify patients according to the risk of recurrence and hence to handle patients in the follow-up period.

An important aim of follow-up is to diagnose early recurrence under the assumption that an early pelvic recurrence results in prolonged survival because of the possibility of salvage treatment, either by surgery or by radiotherapy.[8] For this reason, a smear has been a part of routine follow-up visits for patients treated with hysterectomy at the initial diagnosis. Systematic evidence-based literature to support this assumption is lacking, and this has resulted in large variations in the management of follow-up regimens across Europe.[3,9-11] Previous studies inform us that 10% to 20% of patients with low-risk disease will experience relapse, 4% to 5% of whom will have a pelvic recurrence and approximately 1% to 2% of whom can be salvaged.[1,8,12] Hence, it is of grave importance to describe and classify the patients at risk to optimize the follow-up program. One study even suggested that routine follow-up delays the detection of recurrences because symptomatic women postpone seeking medical advice until the next planned visit.[13]

To accommodate known recurrence patterns, the Danish health authorities and experts agreed in 2015 on more individualized follow-up and aimed to augment the focus on rehabilitation after treatment.[14] However, we do not know the impact on survival of either the prior or current follow-up regimen. A systematic review of the literature on the effects of follow-up with respect to the recurrence rate and survival was conducted in 2009; it included 17 retrospective studies from 1980 to 2007. The review could not present any overall benefit for survival from the detection of asymptomatic recurrences and encouraged further subgrouping of women treated for cervical cancer to identify individuals who may benefit particularly from surveillance.[1] To date, there are no randomized controlled trials for evaluating the follow-up of patients with treated cervical cancer. Here we present the first nationwide study aiming to investigate the recurrence rate, recurrence presentation, and mortality among women diagnosed with low-risk, early-stage cervical cancer. We intend to further stratify patients treated for early-stage cervical cancer in need of routine follow-up (traditional or intensified) as well as patients for whom follow-up may be of greater harm than benefit.

MATERIALS AND METHODS

During the study period, the posttreatment follow-up for cervical cancer in Denmark was planned for every 3, 6, or 12 months for 5 years, with a decrease in visits later during the follow-up period. The decrease in visits correlated well with the timing of recurrences of cervical cancer because the majority of all recurrences (62%-89%) are detected within the first 2 years after the initial treatment.[1,15,16]

Data were extracted from 3 nationwide databases:

1. The Danish Gynecological Cancer Database (DGCD), established in 2005, covers all gynecologic cancers and includes information on the diagnosis, treatment, and patient characteristics. The completeness is required by Danish law to be greater than 90%, and in 2013-2014, the database was estimated to be 95% to 97% complete.[17]
2. The National Patient Registry (NPR) was established in 1977. All Danish residents have a unique personal identification number used universally in Danish society. Information comprising hospital admissions, discharge diagnoses according to the *International Classification of Diseases, Tenth Revision*, emigration, and death is registered in the NPR. The proportion of missing data has been estimated to be low (<5%).[18]
3. The Danish National Pathology Registry, established in 1999, contains the results of all cytology and histopathology specimens obtained in Denmark. The proportion of missing data is considered extremely low.[19]

From the DGCD, we extracted data on all patients diagnosed with cervical cancer in Denmark from January 2005 to September 2013 (*International Classification of Diseases, Tenth Revision* code C53.9). We excluded patients with an FIGO stage > IB1. From the DGCD, we collected the following clinical data on the patients: preliminary examinations, pathological information (DSI and LVSI), information on surgical treatment, and follow-up registration. To subgroup the women with DSI, we placed them into 1 of 3 groups according to the depth of invasion with respect to the total diameter of the cervix: < 1/3, > 1/3 and <2/3, or > 2/3.

We merged the DGCD findings with the NPR data to find patients registered with a new oncological treatment more than 3 months after the primary surgical treatment that was likely to be related to a recurrence: a new surgical intervention (conization or hysterectomy) or recurrent disease during palliative follow-up (according to coding). The identified patients were listed according to the FIGO stage, age, pathology, histology, LN status, DSI, and LVSI. All patients who had a recurrence or new treatment or were listed as dead in the NPR were cross-checked with their hospital charts and the Danish National Pathology Registry to ensure the correct

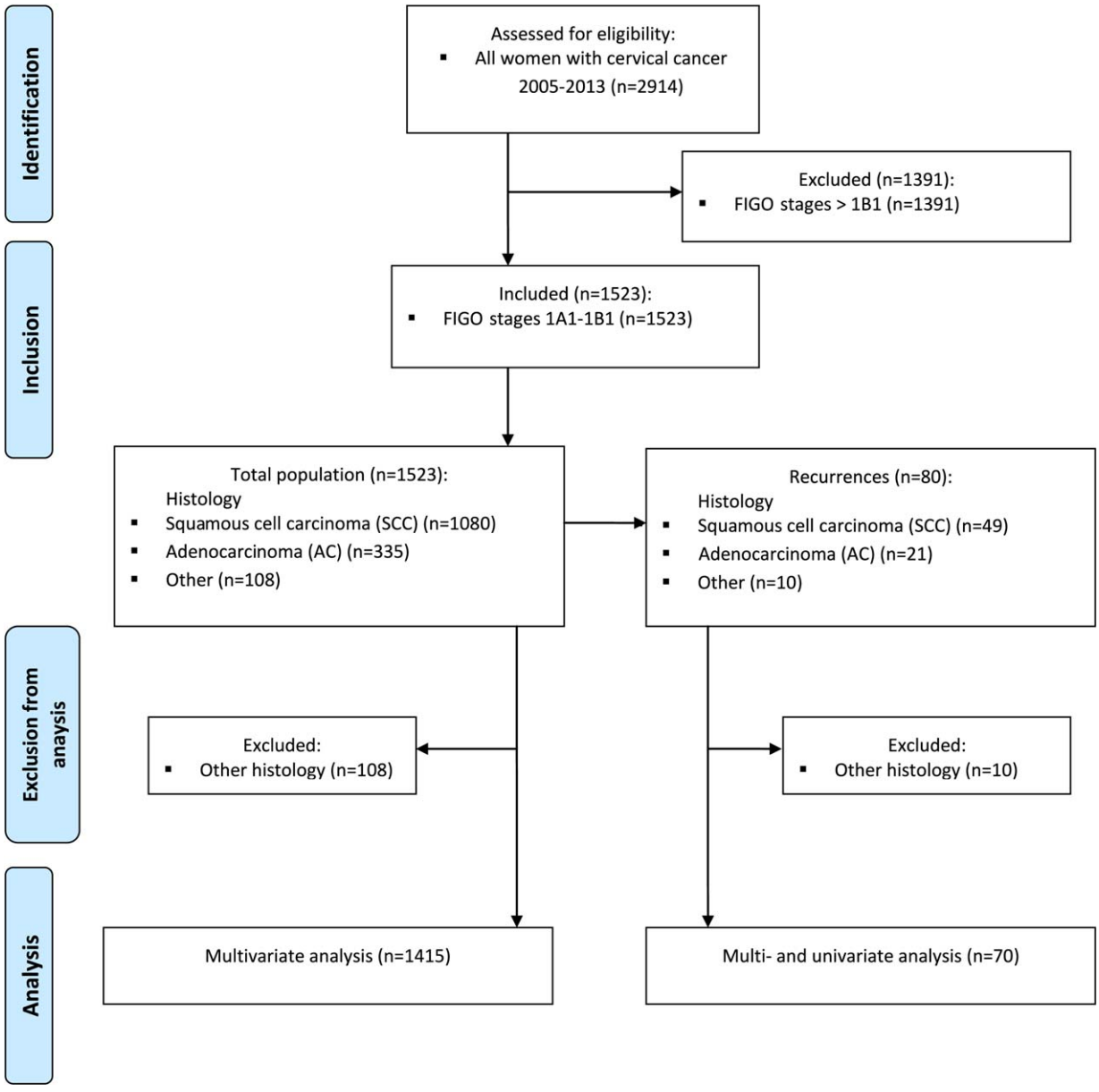

Figure 1. Consolidated Standards of Reporting Trials diagram of the study population. FIGO indicates International Federation of Gynecology and Obstetrics.

classification. The hospital charts were also searched for information on the characteristics of the recurrence (symptomatic vs asymptomatic, location, and date). If any symptom mentioned by the patient led to further examination and henceforth the finding of a recurrence, the recurrence was classified as symptomatic, whereas asymptomatic recurrences were found clinically by a physician or, for example, radiologically as part of follow-up or as part of other workup. The recurrence rate and the mortality rate were calculated on the basis of all patients diagnosed with cervical cancer at FIGO stage IB1 or lower in Denmark in 2005-2013. The risk of recurrence was analyzed in patients with squamous cell carcinoma (SCC) or adenocarcinoma (AC). A Consolidated Standards of Reporting Trials diagram of the patients is displayed in Figure 1.

Ethics

The required approvals for the database and chart review were granted by the Danish Data Protection Agency (journal number 2013-41-2418), the Regional Clinical Quality Development Program (journal number 2013-331-0580),

and the Danish Health and Medicines Authority (journal number 3-3013-449/1).

Statistics

Univariate and multivariate analyses were performed for patients with either SCC or AC. The time to recurrence and the time to death for patients with recurrence were analyzed with a Cox proportional hazards model. The time to death for patients with recurrence was calculated from the date of recurrence to death from all causes. The included explanatory variables were the tumor stage with the nodal status, histology, and age dichotomized at 50 years. For patients with recurrence, the method of diagnosis of recurrence, the site of recurrence, and pathological information were included as explanatory variables. Results are presented as hazard ratios with 95% confidence intervals (CIs), and the level of significance was $P < .05$. The assessment of model assumptions was performed with martingale residuals. Survival curves are based on Kaplan-Meier methods. Statistical calculations were performed with SAS (version 9.3; SAS Institute, Cary, North Carolina).

RESULTS

From the database, we identified 2914 patients with cervical cancer from January 2005 to September 2013. Of these, 1523 patients had cervical cancer at stage IB1 or lower. The distribution between the FIGO stages was as follows: 510 patients (33.5%) had stage 1A1 cervical cancer, 33 patients (2.2%) had stage 1A2 cervical cancer, and 980 patients (64.3%) had stage 1B1 cervical cancer. Table 1 shows descriptive data for the early-stage population. Among the 1523 patients, 80 recurrences and 97 deaths (6.4%) were detected. The 5-year recurrence rate was 6.4% (95% CI, 4.9%-7.9%) when we censored those women for whom we did not have 5 years of follow-up in our database at the time of data extraction (n = 791) and 5.3% for the gathered population. The recurrences were dispersed according to the clinical data listed in Table 2. We were unable to find data for recurrence diagnoses for 3 patients. Fifty-one of the 97 deaths were not related to cervical cancer. The remaining 46 deaths (3% of the entire population and 57.5% of the 80 recurrences) were distributed according to FIGO stages: 1 at stage 1A1 (the only patient with a positive LN at the initial diagnosis at stage 1A1) and 45 at stage 1B1.

The median time from recurrence to death was 27.3 months (95% CI, 16.5-49.1 months), and 64% (n = 47) had their relapse within the first 2 years after the initial diagnosis.

TABLE 1. Descriptive Table of the Population of Patients With Early-Stage Cervical Cancer, 2005-2013 (n = 1523)

Variable	No.	%
Age		
20-29 y	171	11.2
30-39 y	530	34.8
40-49 y	418	27.4
50-59 y	190	12.5
60-69 y	119	7.8
70-79 y	70	4.6
≥80 y	25	1.6
FIGO stage		
1A1	510	33.5
1A2	33	2.2
1B1	980	64.3
Histology		
Squamous cell carcinoma	1080	70.9
Adenocarcinoma	335	22.0
Other	108	7.1
LN metastasis		
Yes	89	5.8
No	786	51.6
No LN removed	435	28.6
Missing	213	14.0
DSI		
<1/3	678	44.5
1/3 < DSI < 2/3	296	19.4
>2/3	533	35.0
Missing	16	1.1
LVSI		
Vascular	85	5.6
Lymphatic plus lymphovascular	320	21.0
None	1118	73.4

Abbreviations: DSI, depth of stromal invasion; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lymphovascular space invasion.

Thirteen of the 23 patients with an asymptomatic recurrence had central pelvic recurrences, which were potentially detectable by a smear. However, only 4 of these patients' recurrences were found by a routine smear as part of the follow-up; the remaining 9 were determined by the biopsying of a suspicious lesion.

Among the patients at risk for recurrence in the population of 1415 women with either SCC or AC in the multivariate analysis, we found women at FIGO stage 1B1 to be at greater risk for recurrence, regardless of their LN status at diagnosis. We also found women who were older than 50 years or had lymphovascular LVSI at the initial diagnosis to have a significantly greater risk of recurrence, whereas histology (AC vs SCC), vascular LVSI, and DSI did not predict recurrence (Table 3).

Figure 2A,B shows the overall survival of the entire population and the patients with recurrence. The effects of the clinical presentation at the initial diagnosis on survival after recurrence according to a univariate analysis are presented in Figure 3A-D. There was significantly inferior

TABLE 2. Descriptive Table of Patients With Recurrence (n = 80)

Variable	No.	%
Age		
20-29 y	10	12.5
30-39 y	21	26.3
40-49 y	18	22.5
50-59 y	12	15.0
60-69 y	10	12.5
70-79 y	7	8.7
>80 y	2	2.5
FIGO stage		
1A1	8	10.0
1A2	0	0.0
1B1	72	90.0
Histology		
Squamous cell carcinoma	49	61.3
Adenocarcinoma	21	26.2
Other	10	12.5
LN metastasis		
Yes	20	25.0
No	54	67.5
No LN removed	6	7.5
DSI		
<1/3	18	22.5
1/3 < DSI < 2/3	23	28.8
>2/3	39	48.7
LVSI		
Vascular	8	10.0
Lymphatic plus lymphovascular	35	43.8
None	37	46.2
Site of recurrence		
Central pelvis	29	36.3
Sidewall pelvis	8	10.0
Subdiaphragmatic LN	9	11.2
Multiorgan involvement	33	41.3
Missing	1	1.2
Diagnosis of recurrence		
Symptomatic	54	67.5
Asymptomatic	23	28.7
Missing	3	3.8

Abbreviations: DSI, depth of stromal invasion; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lymphovascular space invasion.

TABLE 3. Risk of Recurrence: Multivariate Analysis (n = 1415)

Variable	Hazard Ratio	95% CI	*P*
FIGO stage			
1A1, any LN	1		
1B1, LN not sent	3.11	0.90-10.75	.0729
1B1, LN negative	3.14	1.25-7.93	.0153
1B1, LN positive	5.10	1.65-15.76	.0047
1B1, LN missing	6.33	1.80-22.26	.0040
Histology			
Squamous cell carcinoma	1		
Adenocarcinoma	1.40	0.84-2.34	.1979
Age			
≤50 y	1		
>50 y	1.81	1.12-2.94	.0158
DSI			
>2/3	1		
<1/3	0.68	0.35-1.35	.2737
1/3 < DSI < 2/3	1.12	0.64-1.97	.6865
LVSI			
None	1		
Vascular	1.91	0.83-4.38	.1265
Lymphatic plus lymphovascular	1.92	1.11-3.30	.0188

Abbreviations: CI, confidence interval; DSI, depth of stromal invasion; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lymphovascular space invasion.

survival for patients with positive LNs, multiple sites of recurrence, and a symptomatic diagnosis of recurrence, whereas there was no significant difference in survival after recurrence when we looked at an age > 50 years or histology (AC vs SCC). For patients with a DSI < 1/3, the analysis showed statistically better survival in comparison with patients with a DSI > 2/3 (Fig. 3A-D). In a multivariate analysis, we found multiple sites of recurrence, a symptomatic diagnosis of recurrence, and LVSI to be significant parameters for death, whereas histology, LN status, age, and DSI were not (Table 4).

DISCUSSION

In this study, we have presented the characteristics of women diagnosed with low-risk cervical cancer in Denmark between 2005 and 2013. Of the 1523 women with low-risk cervical cancer, 6.4% developed a recurrence, and 57.5% of these women died of their recurrence. We found that 67.5% of the recurrences were diagnosed symptomatically, and 28.8% had asymptomatic recurrences. The multivariate analysis showed that women older than 50 years, women with LVSI in their pathology report, and women diagnosed with stage 1B1 cervical cancer had a significantly greater risk of experiencing a recurrence. Furthermore, we found significantly inferior survival for women with a symptomatic recurrence or with recurrence at multiple sites in both univariate and multivariate analyses.

Our study portrays a recurrence rate markedly lower than the rates reported in the majority of previous publications, which showed recurrence rates ranging from 8% to 26%.[1,4,16,20] However, our findings are similar to the findings of Srisomboon et al,[21] who in a population of women with stage 1B1 cervical cancer found a recurrence rate of 5.8%. The incongruence in the published recurrence rates may be due to improvements in treatment over the past decades. The difference may also be explained by differences in the classification of early-stage cervical cancer. Some studies define *early stage* by surgical treatment, whereas others set their cutoff at FIGO stage 1B1 or 2A, regardless of high-risk factors, which could alter treatment from surgery to radiotherapy and chemotherapy; this makes comparisons between studies challenging.[1] Another reason for a lower recurrence rate in our population could

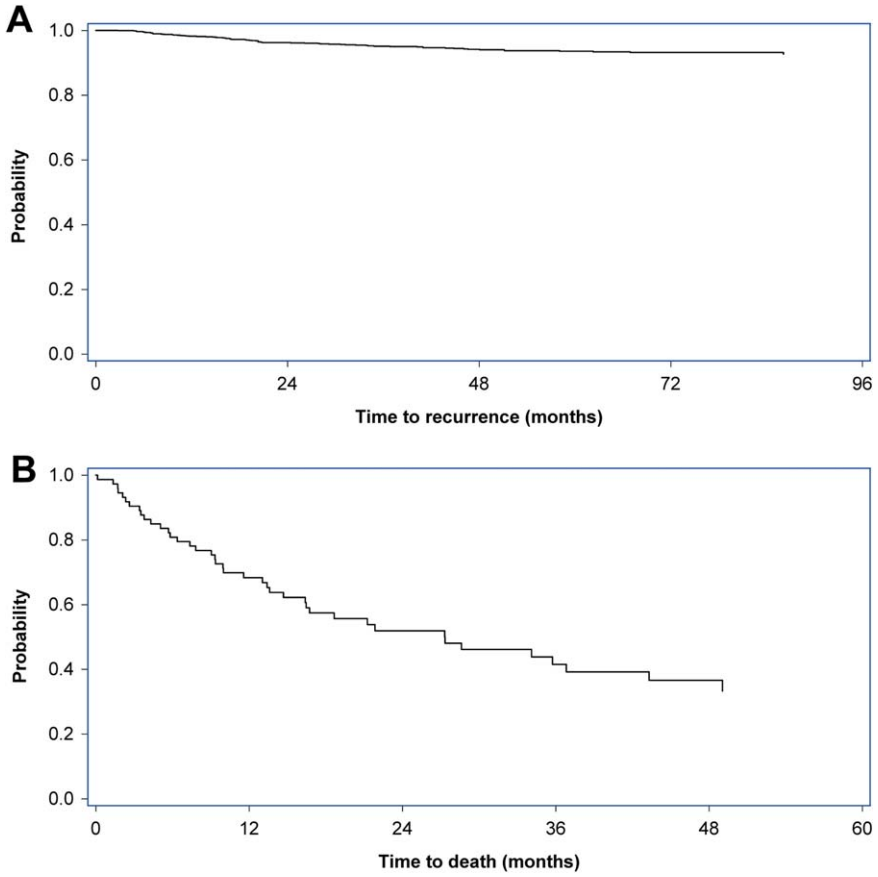

Figure 2. Overall survival (A) of the early-stage population (n = 1415) and (B) patients with recurrence (n = 70).

be the insufficient registration of patients who are not undergoing treatment for their recurrence and patients with undiscovered recurrences. However, we estimate this group of women to be very small because women with untreated recurrences are assumed to die within a short time frame and would, therefore, be included in the NPR and hence in our examination of hospital charts.

Our findings are supported by the 2009 systematic review by Elit et al[1] and strengthen the assumption that a majority of patients have a symptomatic recurrence. However, unlike Elit et al, we did find a difference in survival when we looked at symptomatic diagnoses of recurrence versus asymptomatic diagnoses in our multivariate model; this finding was perhaps enabled by our large cohort. In addition, the mean time from recurrence to death was longer among the asymptomatic patients than the symptomatic patients in our univariate analysis. These findings are supported by Mabuchi et al[12] and indicate the importance of a routine follow-up program for detecting asymptomatic recurrences and perhaps finding remaining recurrences before they become symptomatic. Conversely, the findings also suggest that the follow-up attended by the women during the study period did not have the desired effect because the majority of cases are found by the women themselves, and this appears to have a negative impact on survival. However, the role of possible lead-time and length-time biases with respect to the detection of recurrences cannot be disregarded. A lead-time bias is introduced when the early detection of recurrence falsely makes us believe that survival is longer, but the reality is that the patient lives with the knowledge of the recurrence for a longer period of time and can, in fact, die at the same time as another patient who has only recently been diagnosed with a recurrence. Likewise, a length-time bias occurs when fast-growing tumors, which are typically more aggressive and have a poorer prognosis, give rise to symptoms earlier than slow-growing tumors. By screening or follow-up, a disproportionate number of recurrences will be found in favor of asymptomatic recurrences, which in turn represent better survival because of tumor biology and not because of the early detection of the recurrence. A length-time bias tends to overestimate the value of screening/follow-up.[22,23]

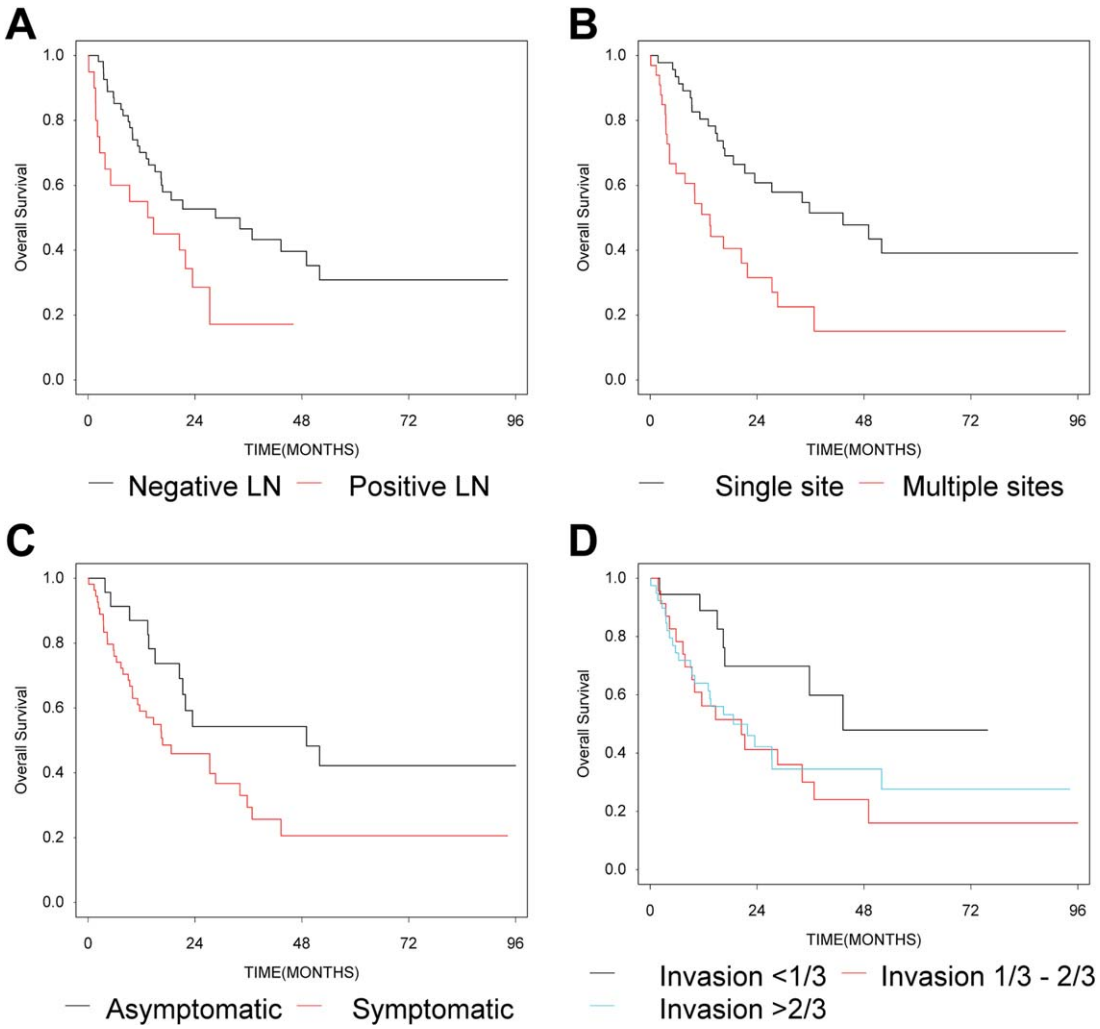

Figure 3. Survival after recurrence (n = 70). (A) Positive LN, N = 18, Negative LN, N = 47, HR = 2.08(1.12-3.86), *P* = .02. (B) Single site, N = 41, Multiple sites, N = 29, HR = 2.6(1.44-4.66), *P* = .001. (C) Asymptomatic diagnosis, N = 19, Symptomatic diagnosis, N = 49, HR = 2.09(1.06-4.11), *P* = .03. (D) DSI < 1/3, N = 18, 1/3< DSI <2/3, N = 23, DSI >2/3, N = 39, with DSI>2/3 as reference: HR(DSI 1/3-2/3) = 1.06(0.54-2.09), *P* = .8661, HR(DSI <1/3) = 0.338(0.13-0.9), *P* = .0299. DSI indicates depth of stromal invasion; LN, lymph node.

Our findings on LVSI as a prognostic factor for recurrence are supported by the existing literature and could enhance a practice in which these factors are taken into consideration when follow-up is being planned.[21,24-28] The pathological subgrouping of LVSI into vascular, lymphovascular, or lymphatic space invasion that takes place in Denmark may serve as guidance to the clinician but should not determine guidelines because the majority of the studies do no subgrouping of LVSI. We also found significantly inferior survival among patients diagnosed with multiple sites of recurrence, and this corresponded to the findings by Sartori et al.[29] Finally, we demonstrated inferior survival for patients with positive LNs at the initial diagnosis, albeit only in our univariate model. However, this is consistent with the findings of Srisomboon et al.[21]

Interestingly, only 4 recurrences were found by a regular smear over the 9-year period in which a smear was performed regularly as part of the follow-up. As is the case for corpus cancer, regular smears do not seem to have a place in the follow-up for detecting recurrences, nor do they seem to make sense from a cost-benefit point of view, with approximately 13,707 smears performed during our study period (9 smears per patient per follow-up × 1523 patients).[30,31]

The method of retracting recurrence data from the NPR through an examination of new surgical or oncological treatments is supported by the hospital charts, but the study group acknowledges that an inverse method in which all charts from 2005 to 2013 were read might have been superior in terms of detecting more recurrences. Unfortunately, that was not within the scope or possibility

TABLE 4. Risk of Death After Recurrence: Multivariate Analysis (n = 70)

Variable	Hazard Ratio	95% CI	*P*
FIGO stage			
1A1, any LN	1		
1B1, LN not sent	2.88	0.29-28.72	.3677
1B1, LN negative	1.78	0.22-14.58	.5890
1B1, LN positive	2.29	0.24-21.53	.4695
Histology			
Squamous cell carcinoma	1		
Adenocarcinoma	0.77	0.36-1.65	.4989
Age			
≤50 y	1		
>50 y	1.67	0.84-3.33	.1449
DSI			
>2/3	1		
<1/3	0.64	0.21-1.97	.4394
1/3 < DSI < 2/3	1.40	0.60-3.27	.4333
LVSI			
None	1		
Vascular	2.09	0.75-5.81	.1596
Lymphatic plus lymphovascular	2.23	1.04-4.80	.0401
Diagnosis of recurrence			
Asymptomatic	1		
Symptomatic	2.52	1.08-5.90	.0332
Site of recurrence			
Single site	1		
Multiple sites	2.72	1.32-5.61	.0066

Abbreviations: CI, confidence interval; DSI, depth of stromal invasion; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lymphovascular space invasion.

of our resources. However, the unique NPR that we have in Denmark enabled us to find all deaths, all of which were cross-checked with hospital charts; this minimized the chance of a recurrence going unnoticed in our data.

With respect to the median time of 22 months from the initial diagnosis to recurrence, our study is limited by the short follow-up for women diagnosed in 2012-2013. A longer follow-up period for the women diagnosed in the latter period would have allowed more accurate listings of recurrence and death. A longer follow-up would also presumably result in a greater number of recurrences and thereby strengthen our conclusions.

To our knowledge, this is the first nationwide collection of data from women with early-stage cervical cancer. The data have been collected from 3 nationwide databases, and the results have been validated by chart review. The study presents the largest cohort of patients with early-stage cervical cancer to date. We found a low rate of recurrence in Denmark; however, we have with statistical significance managed to further characterize women with cervical cancer at a greater risk for recurrence and death, and this is what we initially set out to do.

In conclusion, our results identify a group of women at FIGO stage 1A1 in no need of specialized, hospital-based follow-up after treatment for cervical cancer because there were only 8 recurrences and 1 death among 510 patients in this group over the past 9 years. Since our collection of data, these patients have, on account of a revision of the Danish follow-up program in 2015, no longer been seen routinely after treatment. Women with stage 1B1 cervical cancer have, on account of this revision, all been offered individualized follow-up, predominantly to cope with possible morbidity after treatment; the detection of recurrence is not the main focus because of the insufficient evidence to date for the effect of the early detection of recurrence on survival.[14] Likewise, no smear is performed regularly during this follow-up, which is highly patient-initiated.[7] However, our results point out that women with stage 1B1 cervical cancer would likely profit from regular clinical visits to detect asymptomatic recurrences because our results identify subgroups of women who are at greater risk for death and for whom intensified follow-up could potentially prolong life, although this latter conclusion remains uncertain. There are, therefore, strong implications for establishing evidence-based guidelines in this area, perhaps by further characterization of the group of women who could benefit from follow-up, and we, therefore, urge further prospective investigations in the future, possibly based on molecular risk markers.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Gry Assam Taarnhøj: Conceptualization, study design, collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of the manuscript. **Ib Jarle Christensen**: Conceptualization, study design, collection and assembly of data, data analysis and interpretation, and manuscript writing. **Henrik Lajer**: Conceptualization, study design, collection and assembly of data, data analysis and interpretation, and manuscript writing. **Katrine Fuglsang**: Collection and assembly of data, data analysis and interpretation, and manuscript writing. **Mette Moustgaard Jeppesen**: Collection and assembly of data, data analysis and interpretation, and manuscript writing. **Henriette Strøm Kahr**: Collection and assembly of data, data analysis and interpretation, and manuscript writing. **Claus Høgdall**: Conceptualization, study design, collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of the manuscript.

REFERENCES

1. Elit L, Fyles AW, Devries MC, Oliver TK, Fung-Kee-Fung M. Follow-up for women after treatment for cervical cancer: a systematic review. *Gynecol Oncol.* 2009;114:528-535.
2. International Agency for Research on Cancer. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Default.aspx. Accessed November 2017.
3. Vistad I, Cvancarova M, Salvesen HB. Follow-up of gynecological cancer patients after treatment—the views of European experts in gynecologic oncology. *Acta Obstet Gynecol Scand.* 2012;91:1286-1292.
4. Kew FM, Roberts AP, Cruickshank DJ. The role of routine follow-up after gynecological malignancy. *Int J Gynecol Cancer.* 2005;15:413-419.
5. Oonk MH, de Hullu JA, Hollema H, et al. The value of routine follow-up in patients treated for carcinoma of the vulva. *Cancer.* 2003;98:2624-2629.
6. Marth C, Landoni F, Mahner S, et al. Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017;28:iv72-iv83.
7. Dansk Gynaekologisk Cancer Gruppe. http://www.dgcg.dk/. Accessed November 2017.
8. Friedlander M, Grogan M. Guidelines for the treatment of recurrent and metastatic cervical cancer. *Oncologist.* 2002;7:342-347.
9. Kew FM, Cruickshank DJ. Routine follow-up after treatment for a gynecological cancer: a survey of practice. *Int J Gynecol Cancer.* 2006;16:380-384.
10. Vistad I, Moy BW, Salvesen HB, Liavaag AH. Follow-up routines in gynecological cancer—time for a change? *Acta Obstet Gynecol Scand.* 2011;90:707-718.
11. Leeson S, Stuart N, Sylvestre Y, Hall L, Whitaker R. Gynaecological cancer follow-up: national survey of current practice in the UK. *BMJ Open.* 2013;3:e002859.
12. Mabuchi S, Isohashi F, Yoshioka Y, et al. Prognostic factors for survival in patients with recurrent cervical cancer previously treated with radiotherapy. *Int J Gynecol Cancer.* 2010;20:834-840.
13. Olaitan A, Murdoch J, Anderson R, James J, Graham J, Barley V. A critical evaluation of current protocols for the follow-up of women treated for gynecological malignancies: a pilot study. *Int J Gynecol Cancer.* 2001;11:349-353.
14. Danish Health Authority. Follow-up programme for gynaecological cancers. 2015. https://www.sst.dk/da/udgivelser/2015/-/media/7A5551B622F74EF79392E20495AFF608.ashx
15. Larson DM, Copeland LJ, Stringer CA, Gershenson DM, Malone JM Jr, Edwards CL. Recurrent cervical carcinoma after radical hysterectomy. *Gynecol Oncol.* 1988;30:381-387.
16. Zanagnolo V, Minig LA, Gadducci A, et al. Surveillance procedures for patients for cervical carcinoma: a review of the literature. *Int J Gynecol Cancer.* 2009;19:306-313.
17. Danish Gynaecologic Cancer Database. Annual report 2013/2014. http://www.dgcg.dk/images/rsrapport_DGCD_2013-14_endelig%20-version.pdf. Accessed November 2017.
18. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health.* 2011;39:30-33.
19. Erichsen R, Lash TL, Hamilton-Dutoit SJ, Bjerregaard B, Vyberg M, Pedersen L. Existing data sources for clinical epidemiology: the Danish National Pathology Registry and Data Bank. *Clin Epidemiol.* 2010;2:51-56.
20. Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. *Am J Obstet Gynecol.* 2011;204:466-478.
21. Srisomboon J, Kietpeerakool C, Suprasert P, et al. Survival and prognostic factors comparing stage IB 1 versus stage IB 2 cervical cancer treated with primary radical hysterectomy. *Asian Pac J Cancer Prev.* 2011;12:1753-1756.
22. Jeppesen MM, Mogensen O, Hansen DG, Iachina M, Korsholm M, Jensen PT. Detection of recurrence in early stage endometrial cancer—the role of symptoms and routine follow-up. *Acta Oncol.* 2017;56:262-269.
23. Duffy SW, Nagtegaal ID, Wallis M, et al. Correcting for lead time and length bias in estimating the effect of screen detection on cancer survival. *Am J Epidemiol.* 2008;168:98-104.
24. Twu NF, Ou YC, Liao CI, et al. Prognostic factors and adjuvant therapy on survival in early-stage cervical adenocarcinoma/adenosquamous carcinoma after primary radical surgery: a Taiwanese Gynecologic Oncology Group (TGOG) study. *Surg Oncol.* 2016;25:229-235.
25. Hertel H, Kohler C, Michels W, Possover M, Tozzi R, Schneider A. Laparoscopic-assisted radical vaginal hysterectomy (LARVH): prospective evaluation of 200 patients with cervical cancer. *Gynecol Oncol.* 2003;90:505-511.
26. Marchiole P, Buenerd A, Benchaib M, Nezhat K, Dargent D, Mathevet P. Clinical significance of lymphovascular space involvement and lymph node micrometastases in early-stage cervical cancer: a retrospective case-control surgico-pathological study. *Gynecol Oncol.* 2005;97:727-732.
27. De La Mota J, Thomas B, Fengwei W, Micaily B, Yajue H, Hernandez E. Surgical and immunohistochemical (IC) risk factors for metastatic disease in stage IB1 cervical cancer (CC). *J Clin Oncol.* 2009;27:e16578.
28. Liu Y, Zhao LJ, Li MZ, Li MX, Wang JL, Wei LH. The number of positive pelvic lymph nodes and multiple groups of pelvic lymph node metastasis influence prognosis in stage IA-IIB cervical squamous cell carcinoma. *Chin Med J (Engl).* 2015;128:2084-2089.
29. Sartori E, Pasinetti B, Carrara L, Gambino A, Odicino F, Pecorelli S. Pattern of failure and value of follow-up procedures in endometrial and cervical cancer patients. *Gynecol Oncol.* 2007;107:S241-S247.
30. Lajer H, Jensen MB, Kilsmark J, et al. The value of gynecologic cancer follow-up: evidence-based ignorance? *Int J Gynecol Cancer.* 2010;20:1307-1320.
31. Agboola OO, Grunfeld E, Coyle D, Perry GA. Costs and benefits of routine follow-up after curative treatment for endometrial cancer. *CMAJ.* 1997;157:879-886.