Optimising follow-up strategy based on cytology and human papillomavirus after fertility-sparing surgery for early stage cervical cancer: a nationwide, population-based, retrospective cohort study

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Summary

Background The optimal follow-up strategy to detect recurrence after fertility-sparing surgery for early stage cervical cancer is unknown. Tailored surveillance based on individual risks could contribute to improved efficiency and, subsequently, reduce costs in health care. The aim of this study was to establish the predictive value of cervical cytology and high-risk human papillomavirus (HPV) testing to detect recurrent cervical intraepithelial neoplasia grade 2 or worse (CIN2+; including recurrent cervical cancer) after fertility-sparing surgery.

Methods In this nationwide, population-based, retrospective cohort study, we used data from the Netherlands Cancer Registry and the Dutch Nationwide Pathology Databank. All patients aged 18–40 years with cervical cancer of any histology who received fertility-sparing surgery (ie, large loop excision of the transformation zone, conisation, or trachelectomy) between Jan 1, 2000, and Dec 31, 2020, were included. Pathology data from diagnosis, treatment, and during follow-up were analysed. The primary and secondary outcomes were the cumulative incidence of recurrent CIN2+ and recurrence-free survival, overall and stratified by results for cytology and high-risk HPV.

Findings 1548 patients were identified, of whom 1462 met the inclusion criteria. Of these included patients, 19 568 pathology reports were available. The median age at diagnosis was 31 years (IQR 30–35). After a median follow-up of 6·1 years (IQR 3·3–10·8), recurrent CIN2+ was diagnosed in 128 patients (cumulative incidence 15·0%, 95% CI 11·5–18·2), including 52 patients (cumulative incidence 5·4%, 95% CI 3·7–7·0) with recurrent cervical cancer. The overall 10-year recurrence-free survival for CIN2+ was 89·3% (95% CI 87·4–91·3). By cytology at first follow-up visit within 12 months after fertility-sparing surgery, 10-year recurrence-free survival for CIN2+ was 92·1% (90·2–94·1) in patients with normal cytology, 84·6% (77·4–92·3) in those with low-grade cytology, and 43·1% (26·4–70·2) in those with high-grade cytology. By high-risk HPV status at first follow-up visit within 12 months after surgery, 10-year recurrence-free survival for CIN2+ was 91·1% (85·3–97·3) in patients who were negative for high-risk HPV and 73·6% (58·4–92·8) in those who were positive for high-risk HPV. Cumulative incidence of recurrent CIN2+ within 6 months after any follow-up visit (6–24 months) in patients negative for high-risk HPV with normal or low-grade cytology was 0·0–0·7% and with high-grade cytology was 0·0–33·3%. Cumulative incidence of recurrence in patients positive for high-risk HPV with normal or low-grade cytology were 0·0–15·4% and with high-grade cytology were 50·0–100·0%. None of the patients who were negative for high-risk HPV without high-grade cytology, at 6 months and 12 months, developed recurrence.

Interpretation Patients who are negative for high-risk HPV with normal or low-grade cytology at 6–24 months after fertility-sparing surgery, could be offered a prolonged follow-up interval of 6 months. This group comprises 80% of all patients receiving fertility-sparing surgery. An interval of 12 months seems to be safe after two consecutive negative tests for high-risk HPV with an absence of high-grade cytology, which accounts for nearly 75% of all patients who receive fertility-sparing surgery.

Funding KWF Dutch Cancer Society.

Introduction

Fertility-sparing surgery can be offered to patients with early stage cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] 2018 stages IA1 to IB2) and wanting to conceive.[1–3] Oncological outcomes seem similar to (radical) hysterectomy, especially in tumours up to 2 cm, with recurrence rates of 2·4–5·2%.[4–6] Moreover, most recurrences after fertility-sparing surgery are local (ie, located in the remaining cervix or isthmus) allowing for curative treatment options.[7] An adequate follow-up strategy to detect local cancer recurrence is crucial for favourable prognosis. However, data are scarce

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See Online for appendix

Research in context

Evidence before this study

We performed a systematic review according to the PRISMA guidelines (PROSPERO CRD42020192417) on the role of cervical cytology and high-risk human papillomavirus (HPV) testing to detect recurrence (cervical intraepithelial neoplasia grade 2 or worse [CIN2+] or cervical cancer) after fertility-sparing surgery for early stage cervical cancer (appendix pp 2–5). We searched MEDLINE, Embase, and Scopus using terms for uterine cervical neoplasms combined with terms for fertility-sparing surgery, cervical cytology, and high-risk HPV from database inception to June 18, 2020, and updated on May 12, 2022 (appendix p 2). No restrictions were applied for publication date or study design. We limited the results to articles in English, Dutch, French, or German. Case reports, opinions, and editorials were excluded. Reference lists of included studies and retrieved review articles were searched to identify additional studies. We identified six eligible studies (study populations range n=43–104), of which five reported on recurrent CIN2+ (48 [15%] of 327 patients; appendix p 5). All six studies reported on recurrent cervical cancer (20 [5%] of 421 patients). The role of cervical cytology for the detection of recurrence was evaluated by four studies and the role of high-risk HPV testing was evaluated by five studies.

Added value of this study

To our knowledge, this nationwide cohort study is the largest study on this topic to date, including 1462 patients, which exceeds all previous studies combined. We show that the recurrence-free survival for CIN2+ and cervical cancer is strongly associated with the results of cervical cytology and high-risk HPV testing during follow-up. These follow-up tests distinguish a group of patients in whom less frequent follow-up seems safe. Interval and total duration of follow-up can be stratified on the basis of the results of co-testing (ie, cervical cytology and high-risk HPV combined).

Implications of all the available evidence

The development of a tailored surveillance strategy after fertility-sparing surgery could contribute to improved efficiency of follow-up in patients with cervical cancer and subsequently reduce costs in health care. Our findings indicate that a prolonged follow-up interval of 12 months seems safe after two consecutive negative high-risk HPV tests with absence of high-grade cytology, representing nearly 75% of all patients who receive fertility-sparing surgery. An extended follow-up of 6 months could be offered to patients who tested negative for high-risk HPV without high-grade cytology 6–24 months after fertility-sparing surgery. Prospective trials are required to formulate strong recommendations for an optimal and cost-effective follow-up strategy that can be used in clinical practice.

on the most effective follow-up strategy regarding interval, duration, and method.

In the Dutch national guidelines on cervical cancer, the advised follow-up schedule for all patients with cervical cancer is every 3–4 months in the first 2 years, every 4–6 months in the third year, and every 6–12 months in the fourth and fifth year.[1] No recommendations are made for follow-up after fertility-sparing surgery specifically. In European and US guidelines, an interval of 6–12 months between follow-up visits after the first 2 years following fertility-sparing surgery is recommended, with a total follow-up of 5 years.[2,3] This duration might be extended depending on recurrence risk or treatment-related side-effects.

Methods used for surveillance include physical examination, cervical cytology, high-risk human papillomavirus (HPV) DNA testing, and colposcopy, with additional biopsy if indicated. According to the European Society of Gynaecological Oncology guidelines, high-risk HPV testing, with or without cytology, is mandatory.[2] Incorporation of high-risk HPV testing at months 6, 12, and 24 is advocated and, if negative, every 3–5 years provided follow-up is indicated.[2]

Clinical surveillance after fertility-sparing surgery can be challenging because total or partial removal of the cervix might have resulted in fibrosis and changed anatomy. Moreover, intensive follow-up schemes might negatively affect patients' concerns about cancer recurrence.[8,9] Additionally, intensive follow-up visits considerably add to increasing costs in health care and clinician's increasing workload.[10] Ideally, the surveillance strategy after fertility-sparing surgery should be tailored and based on patients' risk of recurrence. However, clinical practice guidelines recommend a uniform follow-up schedule regardless of individual risks and follow-up test results. These recommendations are consensus-based and not supported by strong evidence.[2,3]

In 2021, an article was published on a new tool for tailored surveillance for five prognostically different subgroups of patients with early stage cervical cancer that was based on tumour characteristics at diagnosis.[11] Of all included patients in the study, 7% underwent fertility-sparing surgery. Several prognostic models for the risk of recurrence in cervical cancer have also been developed.[12–15] However, patients who had fertility-sparing surgery were not or were minimally represented in these models, and more importantly, none included outcomes of follow-up tests.

The aim of this study was to evaluate the predictive value of cytology and high-risk HPV testing in detecting recurrence during follow-up after fertility-sparing surgery for early stage cervical cancer. We also aimed to provide a recommendation for optimising clinical surveillance in these patients.

Methods

Study design and patients

We did a nationwide, retrospective cohort study using data from the population-based Netherlands Cancer Registry (NCR) and the Dutch Nationwide Pathology Databank (Palga). The NCR is maintained by the Netherlands Comprehensive Cancer Organisation (IKNL) and includes data on all patients newly diagnosed with cancer, including information on patient characteristics, diagnosis, tumour staging, and treatment. For cervical cancer, the NCR used the FIGO 2009 staging system until 2021 and then converted to the revised FIGO 2018 classification. In the databank of Palga, the excerpts of all histopathology and cytopathology reports are registered.[16]

From the NCR, we identified all patients aged 18–40 years with early stage cervical cancer (FIGO 2009 stages IA1 to IB1) who had fertility-sparing surgery (large loop excision of the transformation zone [LLETZ], conisation, or vaginal or abdominal radical trachelectomy) between Jan 1, 2000, and Dec 31, 2020. Eligible patients were linked with the Palga database to obtain additional information on pathology results at diagnosis, treatment, and during follow-up. These pathology data were also used to retrospectively determine the FIGO 2018 stage at diagnosis. Patients were excluded if fertility-sparing surgery was followed by hysterectomy (simple or radical), radiotherapy, or chemoradiotherapy within 3 months (ie, final treatment was not fertility-sparing), or if no follow up information was reported in the Palga database. Follow-up data of eligible patients were retrieved up to Sept 15, 2022.

Revised pathology reports by tertiary oncology centres were merged with the original reports to avoid duplication, as well as addendum reports on only high-risk HPV test results, which were incorporated in the original, corresponding reports.

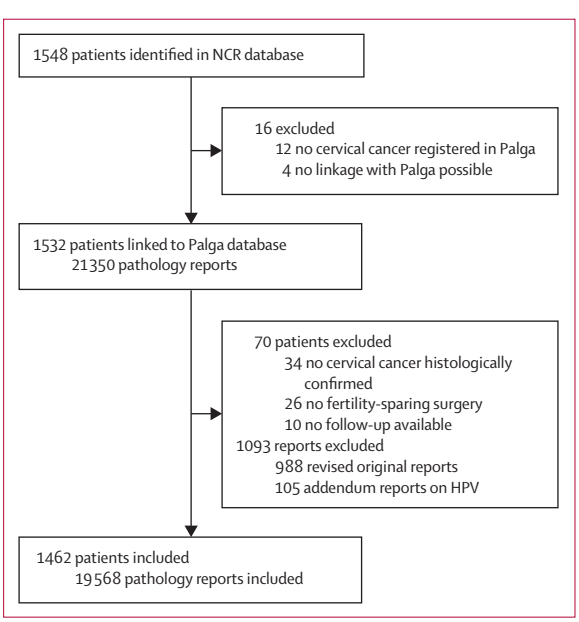


Figure 1: **Study profile**
NCR=Netherlands Cancer Registry. HPV=human papillomavirus.

	Total (n=1462)	Recurrent CIN2+	
		Total recurrent CIN2+ (n=128)	Recurrent cervical cancer (n=52)
Age at diagnosis, years	31 (30–35)	33 (30–35)	33 (30–35)
Year of diagnosis			
2000–04	256 (18%)	22 (17%)	10 (19%)
2005–09	278 (19%)	39 (30%)	19 (37%)
2010–14	371 (25%)	34 (27%)	10 (19%)
2015–20	557 (38%)	33 (26%)	13 (25%)
Pathology-based FIGO 2018 stage*			
IA	129 (9%)	15 (12%)	5 (10%)
IA1	907 (62%)	66 (52%)	19 (37%)
IA2	217 (15%)	22 (17%)	9 (17%)
IB	13 (1%)	3 (2%)	2 (4%)
IB1	112 (8%)	12 (9%)	10 (19%)
IB2	29 (2%)	6 (5%)	6 (12%)
IB3	2 (<1%)	1 (1%)	0
Not available	53 (4%)	3 (2%)	1 (2%)
Histology			
Squamous cell carcinoma	1169 (80%)	107 (84%)	41 (79%)
Adenocarcinoma	238 (16%)	16 (13%)	9 (17%)
Adenosquamous carcinoma	21 (1%)	3 (2%)	2 (4%)
Adenocarcinoma and squamous cell carcinoma	14 (1%)	1 (1%)	0
Carcinoma not otherwise specified	20 (1%)	1 (1%)	0
Lymph–vascular space invasion			
No	674 (46%)	47 (37%)	23 (44%)
Yes	192 (13%)	24 (19%)	13 (25%)
Not available	596 (41%)	57 (45%)	16 (31%)
Type of fertility-sparing surgery			
LLETZ	364 (25%)	26 (20%)	8 (15%)
Conisation, portio amputation, or simple trachelectomy	789 (54%)	73 (57%)	26 (50%)
Vaginal radical trachelectomy	54 (4%)	6 (5%)	5 (10%)
Abdominal radical trachelectomy	13 (1%)	0	0
Radical trachelectomy not otherwise specified	242 (17%)	23 (18%)	13 (25%)
Lymph node assessment			
Sentinel lymph node procedure	15 (1%)	1 (1%)	1 (2%)
Sentinel lymph node procedure and pelvic lymph node dissection	68 (5%)	6 (5%)	2 (4%)
Single lymph node removal	3 (<1%)	0	0
Pelvic lymph node dissection	261 (18%)	31 (24%)	19 (37%)
Not performed	1115 (76%)	90 (70%)	30 (58%)
Surgical margins			
Positive	151 (10%)	31 (24%)	11 (21%)
CIN or adenocarcinoma in situ	139 (10%)	27 (21%)	8 (15%)
Carcinoma	12 (1%)	4 (3%)	3 (6%)
Negative	1128 (77%)	82 (64%)	38 (73%)
Not available	183 (13%)	15 (12%)	3 (6%)
Follow-up, years	6·1 (3·3–10·8)	5·1 (2·4–9·5)	3·3 (1·8–6·9)

(Table continues on next page)

	Total (n=1462)	Recurrent CIN2+	
		Total recurrent CIN2+ (n=128)	Recurrent cervical cancer (n=52)
(Continued from previous page)			
Time to recurrence, years	NA	1·9 (1·9–4·7)	2·0 (1·1–4·1)
Location of recurrence			
Local	NA	99 (77%)	23 (44%)
CIN2–3 or adenocarcinoma in situ	NA	76 (59%)	NA
Carcinoma	NA	23 (18%)	23 (44%)
Local and regional or distant	NA	11 (9%)	11 (21%)
Regional	NA	10 (8%)	10 (19%)
Regional and distant	NA	4 (3%)	4 (8%)
Distant	NA	4 (3%)	4 (8%)

Data are n (%) or median (IQR). CIN2+=cervical intraepithelial neoplasia grade 2 or worse (including CIN2–3, adenocarcinoma in situ, and carcinoma). LLETZ=large-loop excision of the transformation zone. NA=not applicable. *Patients were included according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system used by the Netherlands Cancer Registry, after which the stage was converted to FIGO 2018 on the basis of pathology data provided by Palga.

Table: **Patients' characteristics**

Ethical approval was provided by the Institutional Review Board of the Netherlands Cancer Institute (IRBd20–331). Written informed consent was not compulsory since we analysed anonymous patient data.

Outcomes

The primary outcomes were the cumulative incidence of histologically confirmed recurrence after fertility-sparing surgery and recurrence-free survival. Two types of recurrence were analysed: (1) recurrent cervical intraepithelial neoplasia (CIN) of grade 2 or worse (CIN2+), defined as CIN of grade 2 or 3, adenocarcinoma in situ or carcinoma, and (2) recurrent cervical cancer, as a subgroup of recurrent CIN2+. Recurrence of cervical cancer was subdivided into local when situated in the (residual) cervix, regional when confined to the pelvis, and distant when occurring outside the pelvis. CIN2+ lesions and cervical cancer diagnosed within 6 months after primary cancer treatment were considered residual lesions and not recurrences.

Secondary outcomes were the cumulative incidence and recurrence-free survival after fertility-sparing surgery stratified by results of cervical cytology, high-risk HPV testing, and co-testing (cytology and high-risk HPV combined). Cytology results were divided into normal (Bethesda 2014 negative for intraepithelial lesion or malignancy), low grade (atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion, and atypical glandular cells not otherwise specified [NOS]), and high grade (high-grade squamous intraepithelial lesion, atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion, atypical glandular cells favour neoplastic, adenocarcinoma in situ, and invasive cervical carcinoma).[17] The tertiary outcomes were risk factors for recurrence after fertility-sparing surgery.

Statistical analysis

The general characteristics were described using standard descriptive statistics (percentages, proportions, or median). The cumulative incidence of recurrence and recurrence-free survival were calculated using Kaplan-Meier analyses. The time origin was the end of treatment, which was defined as the date of last primary treatment or, if applicable, treatment of a residual lesion. Time-to-event was defined as the time between the end of treatment and diagnosis of recurrence. Patients were censored if they had a hysterectomy during follow-up or after their last available pathology report.

For analyses by cytology and HPV status, only patients who had cytology and HPV data were included. To calculate the predictive value of cervical cytology and high-risk HPV testing for the detection of recurrences over time, two analyses were done. First, the cumulative incidences of recurrence were compared on the basis of cytology and high-risk HPV results at the first follow-up visit anytime within 12 months after primary treatment. p values were calculated using the log-rank test. Second, the cumulative incidences of recurrence were compared after a cytology or high-risk HPV test result in four prespecified time intervals (months 6, 12, 18, and 24, each ±3 months). If multiple tests were performed during these intervals, the cytology result was based on the highest Bethesda classification. Additionally, high-risk HPV status was considered positive if at least one high-risk HPV test during the corresponding interval was positive. Furthermore, recurrences that occurred within 6 months after the interval (months 6, 12, 18, and 24, each ±3 months) were included. A subgroup analysis of local recurrences was performed in which patients were censored if a regional or distant recurrence (without concomitant local recurrence) was diagnosed.

Cox regression analyses were done to calculate risk factors for recurrence within 5 years of follow-up by calculating hazard ratios (HRs) and 95% CIs. A 5-year interval was chosen post hoc to provide reliable, clinically relevant results due to the large number of patients at risk. We analysed the following predefined potential risk factors: FIGO 2018 stage (IA *vs* IB), primary treatment (large loop excision of the transformation zone or conisation *vs* trachelectomy), histology (squamous cell carcinoma *vs* adenocarcinoma or other), lymph–vascular space invasion (absence *vs* presence), surgical margins (negative *vs* positive), and cytology (normal or low grade *vs* high grade) or high-risk HPV test results (negative *vs* positive) at the first follow-up visit within 12 months. Positive surgical margins were defined as CIN 1–3, adenocarcinoma in situ, or carcinoma present in the resection margin of the pathology specimen of the final treatment. In the multivariable Cox regression analysis, variables were included when available at baseline and considered relevant on the basis of expert opinion. The proportional hazard assumption was tested for all Cox regression analyses using Schoenfeld residuals. If the

proportional hazard assumption was not met, the HR for risk factors for recurrence was calculated using a time-dependent Cox model (indicated in the univariable analysis of recurrent CIN2+ for the risk factors of surgical margins and cytology at the first follow-up visit within 12 months; appendix p 8).

All analyses were performed using R (version 4.2.0). p values of less than 0·05 were considered to be significant.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

1548 patients were identified from the NCR database, of whom 1462 were included in the study (figure 1). 19 568 pathology reports (median 12 [IQR 9–16] per patient) were analysed, including 10 533 on cervical cytology, 3806 on cervical cytology with HPV testing, 674 on HPV testing only, and 4555 on histology. Patient characteristics are summarised in the table; race and ethnicity data were unavailable.

During a median follow-up of 6·1 years (IQR 3·3–10·8), a median of seven cervical smears (IQR 4–10) were performed per patient. During the first 2 years after primary treatment, cervical smears were done in 1415 patients. Of these 1415 patients, 413 (29·2%) had one or two smears, 842 (59·5%) had three to five smears, and 160 (11·3%) had six or more smears. 614 (42·3%) of 1451 patients had at least one abnormal cervical smear during follow-up (493 [80·3%] of 614 had low-grade cytology and 121 [19·7%] had high-grade cytology) with a median time to abnormal smear of 14·4 months (IQR 5·6–39·2). The remaining 837 (57·7%) of 1451 patients had normal cytology during follow-up. In total, 3654 high-risk HPV tests were performed on cervical smears and cervicovaginal self-samples during follow-up with a median of two per patient (IQR 1–4). Of 1191 patients who were tested for high-risk HPV, 335 patients (28·1%) had at least one positive test result during follow-up.

128 (8·8%) of 1462 patients had CIN2+ recurrence during follow-up (cumulative incidence 15·0%, 95% CI 11·5–18·2), and 52 (3·6%) had recurrent cervical cancer (cumulative incidence 5·4%, 95% CI 3·7–7·0; table). Median time to recurrence was 1·9 years (IQR 0·9–4·7) for CIN2+ and 2·0 years (IQR 1·1–4·1) for cervical cancer. Of 52 cancer recurrences, 23 (44·2%) were local and 11 (21·2%) were local and regional or distant (table).

16 (1·1%) of 1462 patients had residual disease (six [38%] of 16 had CIN2, six [38%] had CIN3, one [6%] had adenocarcinoma in situ, and three [19%] had carcinoma) within 6 months after primary cancer treatment; three of six patients with CIN2 received no subsequent treatment. 79 (5·4%) of 1462 patients had a hysterectomy during follow-up (median 42·9 months [IQR 17·0–61·3] after primary treatment). Of these 79 patients, 25 (32%) had a diagnosis of recurrent CIN2+ before the hysterectomy and 12 (15%) had recurrent CIN2+ in the hysterectomy specimen. No patients developed a recurrence after hysterectomy was performed.

The overall 5-year and 10-year recurrence free survival was 92·5% (95% CI 91·1–94·0) and 89·3% (95% CI 87·4–91·3), respectively, for CIN2+ and 96·7% (95% CI 95·7–97·7) and 95·5% (95% CI 94·2–96·8), respectively, for cervical cancer (appendix p 6). By cytology as measured at first follow-up visit within 12 months after

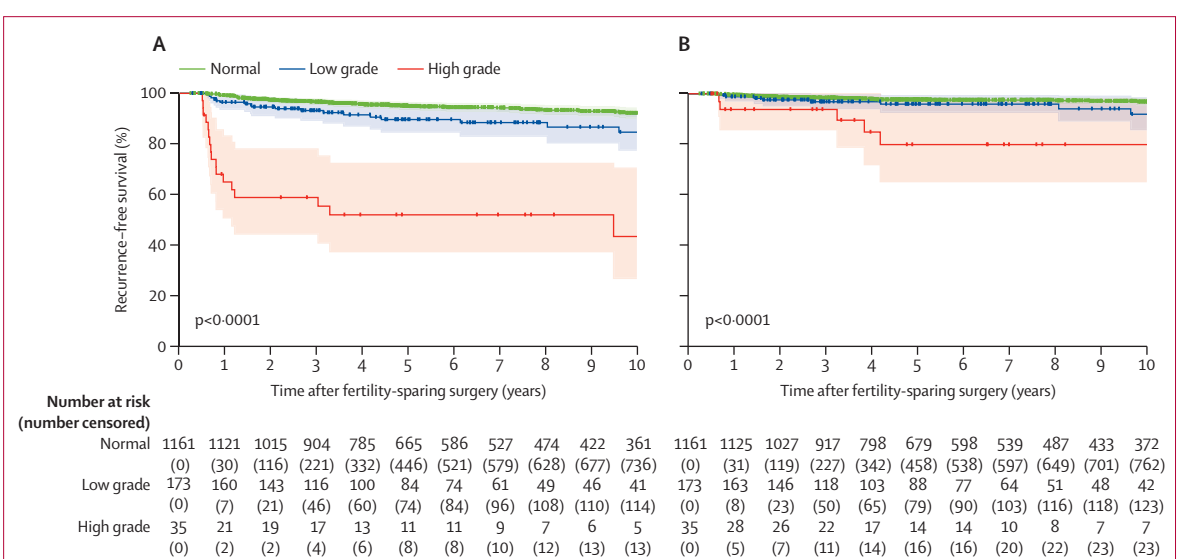


Figure 2: **10-year recurrence-free survival, based on cytology**
(A) CIN2+. (B) Cervical cancer. Data are based on cytology results at first follow-up visit within 12 months after primary treatment. CIN2+=cervical intraepithelial neoplasia grade 2 or worse.

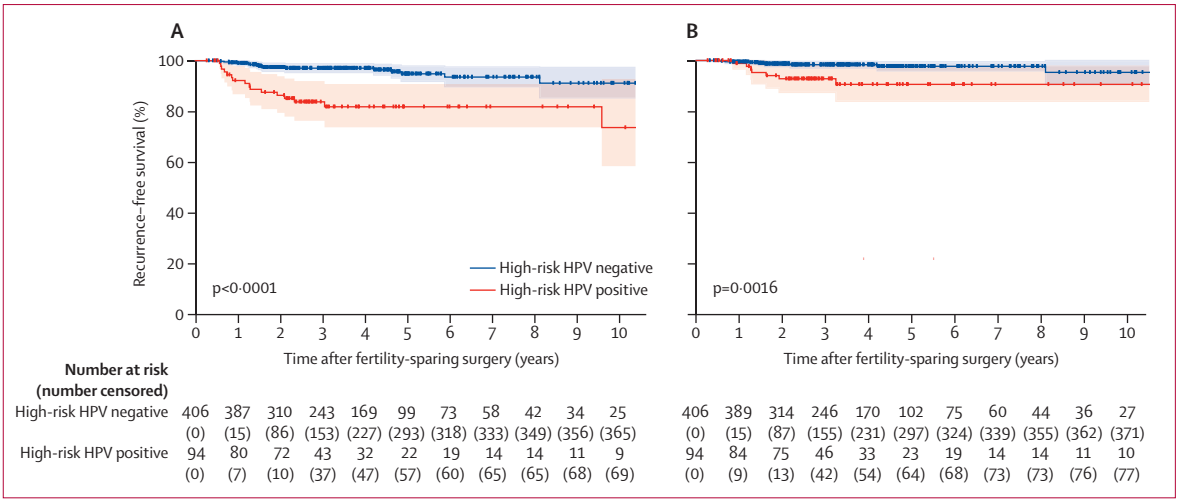


Figure 3: **10-year recurrence-free survival, based on high-risk HPV status**
(A) CIN2+. (B) Cervical cancer. Data are based on high-risk HPV test results at first follow-up visit within 12 months after primary treatment. CIN2+=cervical intraepithelial neoplasia grade 2 or worse. HPV=human papillomavirus.

primary treatment, the 10-year recurrence-free survival for recurrent CIN2+ was 92·1% (90·2–94·1) for normal cytology, 84·6% (77·4–92·3) for low-grade cytology, and 43·1% (26·4–70·2) for high-grade cytology (figure 2A; appendix p 6). For recurrent cervical cancer, 10-year recurrence-free survival was 96·8% (95·6–98·1) for normal cytology, 91·9% (85·8–98·4) for low-grade cytology, and 79·8% (65·1–97·9) for high-grade cytology (figure 2B; appendix p 6).

For recurrent CIN2+, 10-year recurrence-free survival was 91·1% (95% CI 85·3–97·3) when high-risk HPV status was negative and 73·6% (58·4–92·8) when it was positive at first testing within 12 months after primary treatment (figure 3A; appendix p 6). For recurrent cervical cancer, 10-year recurrence-free survival was 95·3% (90·5–100) when high-risk HPV status was negative and 90·6% (84·2–97·8) when it was positive (figure 3B; appendix p 6). The 5-year and 10-year recurrence-free survival and cumulative incidence of recurrent CIN2+ and cervical cancer, based on co-testing are presented in the appendix (p 7).

Among patients who were high-risk HPV negative with normal or low-grade cytology at any of the prespecified time intervals, cumulative incidence of recurrent CIN2+ within 6 months was 0·0–0·7% (figure 4). These co-test results were present in 337 (81·4%) of 414 patients tested at 6 months follow-up, 219 (77·7%) of 282 patients tested at 12 months, 207 (80·2%) of 258 patients tested at 18 months and 211 (82·1%) of 257 patients tested at 24 months (figure 4). Among those who were high-risk HPV negative with high-grade cytology, cumulative incidence of recurrent CIN2+ was 0·0–33·3%. Among those who were high-risk HPV positive with normal or low-grade cytology, cumulative incidence of recurrent CIN2+ was 0·0–15·4%, and among those who were high-risk HPV positive with high-grade cytology, cumulative incidence was 50·0–100%.

337 (81%) of 414 patients tested negative for high-risk HPV with normal or low-grade cytology at 6 months follow-up. 143 (42%) of these 337 patients were also tested for cytology and high-risk HPV at 12 months follow-up. 128 (90%) of 143 patients tested negative again at 12 months, none of whom developed recurrence (median follow-up 3·2 years [IQR 2·0–4·5]). The expected percentage of patients with negative co-testing results at 6 months and 12 months follow-up is 73% (81%×90%). 15 (10%) of 143 patients who tested high-risk HPV negative without high-grade cytology at 6 months follow-up tested high-risk HPV positive or had high-grade cytology at 12 months (median follow-up 3·7 years [IQR 3·0–4·2]). One of these 15 patients developed recurrent CIN2+ (cumulative incidence 20·0%, 95% CI 0·0–48·4).

Results of our subgroup analysis by local recurrence and results of the univariable and multivariable Cox regression analyses are presented in the appendix (pp 8–12).

Discussion

In this nationwide, retrospective cohort study, we found that recurrence-free survival for CIN2+ and cervical cancer was strongly associated with cytology and high-risk HPV test results at first follow-up visit within 12 months after fertility-sparing surgery. Within 6 months after a follow-up visit, recurrence rates of CIN2+ were 0·0–0·7% in patients who tested negative for high-risk HPV without high-grade cytology, whereas they were 0·0–15·4% in patients positive for high-risk HPV with normal or low-grade cytology and 50·0–100·0% in those with high-grade cytology. No patients developed recurrence who tested negative for high-risk HPV with absence of high-grade cytology at both 6 months and 12 months follow-up. These findings show

that clinical surveillance should be stratified on the basis of co-testing results.

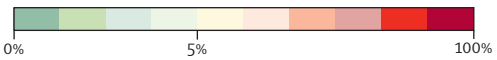
The follow-up schedule for all patients with cervical cancer indicates 9–15 visits over the course of 5 years.[1–3] Reducing the number of follow-up visits, and subsequently the number of follow-up tests, in patients with low risk of recurrence on the basis of co-testing, has the potential to substantially reduce health-care costs. In cervical cancer care, outpatient visits account for almost 20% of total medical expenses.[10] The current emphasis on saving costs and improving efficiency in health care supports the need for tailored surveillance.

Our results suggest that co-testing seems to be the best follow-up strategy, but even separate test results are highly predictive. If we accept a threshold of 1% recurrence risk for an individualised follow-up scheme, patients who are high-risk HPV negative with normal or low-grade cytology at months 6, 12, 18, or 24 after fertility-sparing surgery could be offered a prolonged interval of 6 months between follow-up visits. This adjustment would affect 77·7–81·4% of all patients. Additionally, none of the patients who tested negative for high-risk HPV with normal or low-grade cytology at both 6-months and 12-months follow-up developed recurrence. Therefore, these patients could be advised to prolong the follow-up interval to 12 months.

Using co-testing to individualise follow-up has previously been suggested for patients with CIN lesions treated by LLETZ.[18] Double-negative cytology and high-risk HPV testing identifies patients as low risk and allows screening intervals of at least 3 years.[18]

	6 months							12 months						
	N	Recurrent CIN2+			Recurrent cervical cancer			N	Recurrent CIN2+			Recurrent cervical cancer		
		Events	Cumulative incidence	Cumulative number of censored patients	Events	Cumulative incidence	Cumulative number of censored patients		Events	Cumulative incidence	Cumulative number of censored patients	Events	Cumulative incidence	Cumulative number of censored patients
High-risk HPV														
Negative	340	3	0·9%	11	2	0·6%	11	223	0	0·0%	22	0	0·0%	22
Positive	74	7	9·9%	5	1	1·5%	7	61	3	5·0%	3	1	1·7%	3
Total	**414**	**10**	**2·5%**	**16**	**3**	**0·7%**	**18**	**284**	**3**	**1·1%**	**25**	**1**	**0·4%**	**25**
Cytology														
Normal	1063	4	0·4%	25	2	0·2%	26	974	3	0·3%	40	1	0·1%	41
Low grade	176	5	2·9%	7	3	1·7%	7	98	4	4·2%	9	1	1·1%	10
High grade	31	14	45·2%	0	2	6·9%	4	23	11	50·0%	1	3	13·0%	1
Total	**1270**	**23**	**1·8%**	**32**	**7**	**0·6%**	**37**	**1095**	**18**	**1·7%**	**50**	**5**	**0·5%**	**52**
Co-testing (high-risk HPV and cytology)														
Negative and normal	281	2	0·7%	9	1	0·4%	9	199	0	0·0%	19	0	0·0%	19
Negative and low grade	56	0	0·0%	2	0	0·0%	2	20	0	0·0%	2	0	0·0%	2
Negative and high grade	3	1	33·3%	0	1	33·3%	0	2	0	0·0%	0	0	0·0%	0
Positive and normal	39	1	2·6%	1	1	2·6%	1	35	0	0·0%	0	0	0·0%	0
Positive and low grade	27	1	4·2%	4	0	0·0%	4	22	0	0·0%	3	0	0·0%	3
Positive and high grade	8	5	62·5%	0	0	0·0%	2	4	3	75·0%	0	1	25·0%	0
Total	**414**	**10**	**2·5%**	**16**	**3**	**0·7%**	**18**	**282**	**3**	**1·1%**	**24**	**1**	**0·4%**	**24**

(Figure 4 continues on next page)



	18 months							24 months						
	N	Recurrent CIN2+			Recurrent cervical cancer			N	Recurrent CIN2+			Recurrent cervical cancer		
		Events	Cumulative incidence	Cumulative number of censored patients	Events	Cumulative incidence	Cumulative number of censored patients		Events	Cumulative incidence	Cumulative number of censored patients	Events	Cumulative incidence	Cumulative number of censored patients
High-risk HPV														
Negative	210	1	0·5%	36	0	0·0%	37	215	0	0·0%	56	0	0·0%	56
Positive	48	5	11·3%	6	4	9·0%	7	43	3	7·3%	7	1	2·5%	7
Total	**258**	**6**	**2·5%**	**42**	**4**	**1·7%**	**44**	**258**	**3**	**1·4%**	**63**	**1**	**0·5%**	**63**
Cytology														
Normal	769	4	0·5%	61	4	0·5%	61	776	1	0·1%	82	1	0·1%	81
Low grade	78	2	2·7%	9	2	2·7%	8	68	2	3·1%	5	0	0·0%	5
High grade	15	8	53·3%	0	1	7·1%	3	9	4	44·4%	1	3	33·3%	2
Total	**862**	**14**	**1·7%**	**70**	**7**	**0·8%**	**72**	**853**	**7**	**0·9%**	**88**	**4**	**0·5%**	**88**
Co-testing (high-risk HPV and cytology)														
Negative and normal	194	0	0·0%	35	0	0·0%	35	196	0	0·0%	50	0	0·0%	50
Negative and low grade	13	0	0·0%	1	0	0·0%	1	15	0	0·0%	5	0	0·0%	5
Negative and high grade	3	1	33·3%	0	0	0·0%	1	3	0	0·0%	1	0	0·0%	1
Positive and normal	22	1	5·3%	3	1	5·3%	3	29	0	0·0%	7	0	0·0%	7
Positive and low grade	22	2	9·8%	3	2	10·1%	3	13	2	15·4%	0	0	0·0%	0
Positive and high grade	4	2	50·0%	0	1	25·0%	1	1	1	100·0%	0	1	100·0%	0
Total	**258**	**6**	**2·5%**	**42**	**4**	**1·7%**	**44**	**257**	**3**	**1·4%**	**63**	**1**	**0·5%**	**63**

Figure 4: **Cumulative incidence of recurrent CIN2+ and recurrent cervical cancer within 6 months after each prespecified follow-up interval, stratified by cytology or high-risk HPV test result**
Only cytology and high-risk HPV tests performed before diagnosis of recurrence were included. Patients were censored if they underwent a hysterectomy or after their last pathology report. The number of patients tested (N) represents the patients of whom a cytology or high-risk HPV test result was available at that follow-up visit. Patients with recurrent CIN2+ or cervical cancer who were not tested for cytology or high-risk HPV within each of the four time intervals are not included in this table. HPV=human papillomavirus. CIN2+=cervical intraepithelial neoplasia grade 2 or worse.

By contrast to the studies included in our systematic review, which reported a negative predictive value of 100% for high-risk HPV testing during follow-up (appendix p 5),[7,12,19–21] we found some recurrences after a negative high-risk HPV test. To our knowledge, our study has a larger population than other studies to date, allowing for detection of rare events. Other explanations for recurrences after a negative high-risk HPV test could be false-negative sampling due to concentrations of high-risk HPV DNA being below the detection limit in first post-treatment tests or patients becoming re-infected with (other oncogenic types of) HPV.[12,22] Reinfection could possibly be prevented by HPV vaccination at time of treatment; however, the effectiveness of HPV vaccination at preventing recurrence in patients treated for CIN lesions remains inconclusive.[23] Data on HPV vaccination were not available in our cohort, but we expect most patients were not vaccinated because vaccination after treatment for cervical cancer or CIN is not standard of care, reimbursed, nor incorporated into the Dutch guidelines.

Of 1451 patients, 614 (42·3%) had at least one abnormal cervical smear during follow-up, most of which were classified as low-grade cytology (80·3%). In our

systematic review, the finding of abnormal cervical smear during follow-up ranged from 19·2% to 74·5% of patients (appendix p 5).[19–21,24] There are a few known pitfalls in interpreting cytology after fertility-sparing surgery. Regular misinterpretation comes from the presence of glandular cells of the lower uterine segment, endometrial stromal cells, or tubal metaplasia, all of which could be falsely interpreted as atypical.[19,20,25] False-positive results are most frequent after trachelectomy.[7,19] An endometrial component is identified in nearly 60% of cervical smears after fertility-sparing surgery.[19,25] These findings could lead to unnecessary diagnostic investigation and anxiety in patients. Another limitation of cervical cytology after fertility-sparing surgery is the absence of endocervical cells due to post-treatment fibrosis and the inability to sufficiently reach the (newly formed) squamocolumnar junction. This inadequate sampling is reported in 32–57% of cervical smears and should be an indication for repeated sampling, and if necessary, preceded by cervical dilatation.[19,21,25]

Although cervical cytology and high-risk HPV testing are used to detect local recurrence, we report primarily on overall recurrences and did not exclude patients with regional or distant (or both) recurrences. As such, we report more comprehensive recurrence risks that can be used in clinical practice. Inclusion of such patients is also in line with studies retrieved from our literature search (appendix p 5). Moreover, several studies report on circulating HPV DNA as a biomarker to predict overall cervical cancer recurrence, irrespective of the site of recurrence.[26,27] High-risk HPV status on cervical smear, as representative of general HPV status, might also be associated with overall risk of recurrence. We report on CIN2+ as a primary outcome, which is consistent with existing literature. Although recurrent cervical cancer is most important from an oncological perspective, CIN2–3 or adenocarcinoma in situ will most often be treated, which will negatively affect future fertility. Considering oncological and fertility outcomes, we chose primarily to report on the combined outcome, with recurrent cervical cancer as a subgroup.

To the best of our knowledge, this is the largest study on follow-up methods after fertility-sparing surgery for early stage cervical cancer. The strengths of this study are the comprehensive population obtained from the Netherlands Cancer Registry, the large number of pathology reports retrieved from Palga, and a long median follow-up of 6·1 years. Less than 1% of patients were excluded because of missing or insufficient data. However, the retrospective design has some limitations. First, data on patients' symptoms, physical examination, or colposcopic findings were unavailable. This absence of data might contribute to confounding, despite the shortage of available literature indicating that most local recurrences appear asymptomatic after fertility-sparing surgery.[7,28] Additionally, due to the absence of clinical data, it is unknown why patients with positive surgical margins (which is associated with recurrence) were not re-treated. For CIN lesions, clinicians might refrain from re-intervention because extensive coagulation was performed, and follow-up was preferred for fertility reasons. Omitting re-intervention for a positive margin for cervical cancer might have been done because patients declined treatment or were re-treated outside of the Netherlands. Second, biopsies, which are considered the gold standard for diagnosing recurrence are not routinely taken during follow-up, but only when indicated. Therefore, the diagnostic value of the follow-up methods could only be evaluated indirectly (ie, based on the absence or presence of recurrence detected shortly afterwards), possibly masking false-negative results. Third, the types of high-risk HPV tests used in our cohort were not registered and might vary between medical centres. However, all high-risk HPV tests used in the Netherlands must meet strict criteria according to a national guideline;[29] therefore, our data on high-risk HPV are assumed to be reliable and representative of clinical practice. Finally, built-in selection bias might affect the interpretation of HRs in our regression analyses. Patients most susceptible to developing recurrence will develop a recurrence at an early stage, whereas less susceptible patients remain in the cohort, consequently reducing the period-specific HR of predictive factors at a later stage. To minimise this effect, only HRs for the first 5-year follow-up were presented.

Our dataset can aid the development of a predictive risk model on recurrence after fertility-sparing surgery, which is primarily based on cytology and high-risk HPV testing during follow-up. This model will help to provide recommendations for tailored surveillance strategies based on a patient's risk of recurrence and allow calculation of the cost-effectiveness of different follow-up schemes. Patients can be identified in whom a follow-up of more than 5 years is indicated and in whom cervical cytology during follow-up can be completely omitted.

In this study, 10% of recurrent CIN2+ and recurrent cervical cancer were diagnosed more than 9·6 years and 8·7 years after fertility-sparing surgery, respectively (data not shown). A long-term increased risk of recurrence was also seen in a study showing HPV-related malignancies and premalignancies up to 20 years in patients previously diagnosed with CIN3.[30] These findings indicate the need for a prolonged follow-up of at least 10 years for a selection of patients, depending on individual risk factors, local costs, and benefit considerations. Risk stratification tools should be prospectively validated for future implications.

Other future research directions might focus on the added value of using biomarkers to further individualise follow-up strategies. DNA methylation markers to triage high-risk HPV positive cervical smears and vaginal self-tests to detect cervical cancer show favourable results.[31] These methods might help to identify patients at increased risk for recurrence during follow-up.

Contributors
NEvT, CHM, TNS, and MS conceptualised the study, interpreted data, and wrote the original draft. AGS, HHBW, MS, and KHT curated the data. MS and KHT accessed and verified the study data. MS, TNS, and KS did the formal analysis. NEvT acquired funding. All authors contributed to the data collection and had permission to access the data. MS, TNS, NEvT, CHM, and KS contributed to the methodology. NEvT, CHM, and MCGB were responsible for project supervision. MS and TNS visualised the data. TNS, VMJV, and NEvT searched the literature and analysed the data of the systematic review. All authors reviewed and approved the final manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests
We declare no competing interests.

Data sharing
De-identified data that underlie the results can be shared with other researchers on request by contacting the corresponding author after publication.

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