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GYNECOLOGIC ONCOLOGY

The impact of a cervical dysplasia diagnosis on individual cancer prevention habits over time: a bicentric case–control study

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Abstract

Purpose Annual cervical cancer screening is recommended in Germany as a part of the statutory preventive care. Abnormal results can provoke psychological distress and anxiety, compromising women's adherence. Little is known about how a cervical dysplasia impacts adherence follow-up visits and prevention habits over time. To optimize care strategies, this study aims to identify women at risk for nonadherence to follow-up visits after a screening event.

Methods Between November 2015 and May 2017, participants with an abnormal Pap smear at the Heidelberg and Leipzig University Hospitals received a four-part questionnaire (sociodemographic data, PHQ-D, self-designed fear and prevention habit questions) at the first consultation (T1) and subsequently after 3 (T2) and 6 (T3) months; healthy controls completed the questionnaire at T1.

Results 132 women with an abnormal Pap smear [with conization: S1 ($n=68$, 51.5%), without intervention: S2 ($n=64$, 48.5%)] and healthy controls (K, $n=101$) generally adhered to gynecological checkups, except S1 6 months after the first diagnosis (S1/T3 −0.47, signed rank $p<0.0005$). Knowledge of primary prevention information, i.e., HPV vaccination, was significantly higher among K (K 58%, S1 29%, S2 44%, Chi-squared $p=0.01$) as was vaccine uptake (K 39% versus S1/S2 7% and 17%, respectively, Chi-squared $p=0.0004$). Fear of upcoming Pap smears rose significantly over time (S1/T1–S1/T2–S1/T3, Wilcoxon signed-rank test $p<0.001$) and was higher among those with conization at T2 (Chi-square test, $p=0.01$) and partially accompanied by panic disorders at T1 (Chi-square test $p=0.035$). Realization of general preventive habits rose significantly among women without an operative procedure (S2) over the study.

Conclusion This study advances the understanding of non-participation in follow-up visits after a dysplasia diagnosis, identifying post-conization women as a special risk group for decreased adherence.

Keywords Cervical dysplasia · Conization · Cancer prevention habits · Adherence · PHQ-D

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Introduction

Cervical cancer screening has been established worldwide and aims to reduce invasive cervical carcinoma (CC). In Germany, an annual Pap smear is currently recommended beginning at the age of 20 as part of statutory preventive care and is covered by public health insurance [1]. Since the introduction of this Germany-wide CC screening program in 1971, the mortality rate for CC has decreased by approximately 50%, and its incidence has remained stable ever since [1–3]. However, due to screening implementation, the detection rate of precancerous lesions known as cervical dysplasia has risen, as has the required treatment, a conization of the cervix uteri [4, 5]. High-grade cervical dysplasia (CIN III) transforms into CC in approximately 12–30% of the cases

within a 5–10-year period and is mostly caused by human papillomavirus (HPV) infection [6–10].

To date, the German screening program is still organized at an individual level and depends on patients' adherence and their own proactive initiative. Data from German insurance companies show that participation rates only reach 25–55% yearly, whereby 20–40% of women aged under 65 did not attend CC screening at all within a 3-year period [2, 3, 9, 11, 12]. 60% of women with a newly diagnosed invasive CC have a history of not participating in yearly screening, underlining the importance of screening to reduce CC incidence [13]. It has been reported that an abnormal Pap smear result, which occurs in approximately 1–10% of screened women, can provoke psychological distress and increased anxiety and fear, compromising women´s adherence for screening habits [14–17]. However, little is known about how a cervical dysplasia diagnosis impacts adherence to gynecological follow-up visits and general prevention habits over time.

This bicentric case–control study evaluated the psychological consequences of an abnormal Pap smear and its related treatment strategies over time. Furthermore, the long-term impact on individual gynecological prevention habits was evaluated. The aim of this study was to identify women at risk for nonadherence to optimize post-intervention strategies to increase the outreach of gynecological follow-up modalities.

Methods

Study population and study protocol

All women with an abnormal Pap smear (at least Pap III) aged 18–75 years, who attended the special dysplasia outpatient consultation at the University Hospitals in Heidelberg and Leipzig between November 2015 and May 2017 were eligible to participate in this explorative case–control study. Treatment was recommended in accordance with the current guidelines, regardless of patients' study participation. After enrollment with written consent, each participant received a questionnaire at the first consultation (T1) as described elsewhere [18]. In brief, all women who returned the T1 questionnaire formed the study population; they subsequently received a follow-up questionnaire by mail 3 (T2) and 6 (T3) months after T1. If no response was received after 2 weeks, the study participants were contacted via phone. Potential candidates actively refusing or withdrawing participation after T1 represented active decliners. Secondary loss of contact, for example due to invalid contact information, defined passive decliners.

The study population was divided into two groups: S1—patients on whom a subsequent conization was performed— and S2—patients requiring no operative procedure. The operational technique was a large loop excision of the transformation zone (LLETZ) performed under general anesthesia with additional cervical block.

The control group (*K*) without cervical dysplasia was randomly assigned via social interaction and received only the T1 questionnaire. The study protocol was approved by the local ethical authorities in Heidelberg and Leipzig (S-399/2015and 091/17-lk).

Study instruments

The four-part questionnaire consisted of 208 items at T1 and 165 items at T2 and T3. At inclusion, a medical history was obtained for the study group via System IS-H/i.s.h. med_UC EhP8 (SAP_Basis 7.50 SP005/SAP_IS-H6.18 SP007) as described previously [18, 19]. Data on prevention habits, fear and anxiety, sociodemographic data, risk factors for cervical dysplasia, the realization of an HPV vaccination as well as the Patient Health Questionnaire-D (PHQ-D) [20, 21] are analyzed in this publication; further analyses are published elsewhere [18, 19]. Individual prevention habits and participation rates were evaluated by three questions designed by the authors (Table 1). HPV vaccination and the

Table 1 Prevention habits of the study population S1 and S2, and the control group *K* at first visit T1

n	S1 68 (%)	S2 64 (%)	K 101 (%)
Usage of gynecological preventive checkup			
> Once per year	29 (43)	45 (70)	35 (35)
Once per year	31 (45)	19 (30)	51 (50)
< Once per year	4 (6)	–	12 (12)
< every 3 years	2 (3)	–	3 (3)
Not attended at all	2 (3)	–	–
Do you know how often you are entitled to attend a gynecological preventive checkup?			
> 3 checkups per year	3 (4)	5 (8)	–
3 checkups per year	–	3 (5)	3 (3)
2 checkups per year	21 (31)	19 (30)	33 (33)
1 checkup per year	40 (59)	35 (54)	63 (62)
< once per year	2 (3)	–	–
Not indicated	2 (3)	2 (3)	2 (2)
How often do you undertake other preventive checkups (e.g., family doctor/ophthalmologist, early detection colonoscopy)?			
> once per year	3 (4)	4 (6)	5 (5)
Once per year	15 (22)	24 (38)	28 (28)
< once per year	20 (30)	8 (12)	23 (23)
< every 3 years	11 (16)	20 (16)	17 (17)
Not attended at all	19 (28)	18 (28)	28 (27)

S1 subgroup with subsequent conization, *S2* subgroup without conization, *K* healthy controls, % is indicated in ()

patient-related fear and anxiety about CC screening over time after a cervical dysplasia diagnosis were addressed by three questions designed by the authors in addition to the PHQ-D (Figs. 1, 2, 3).

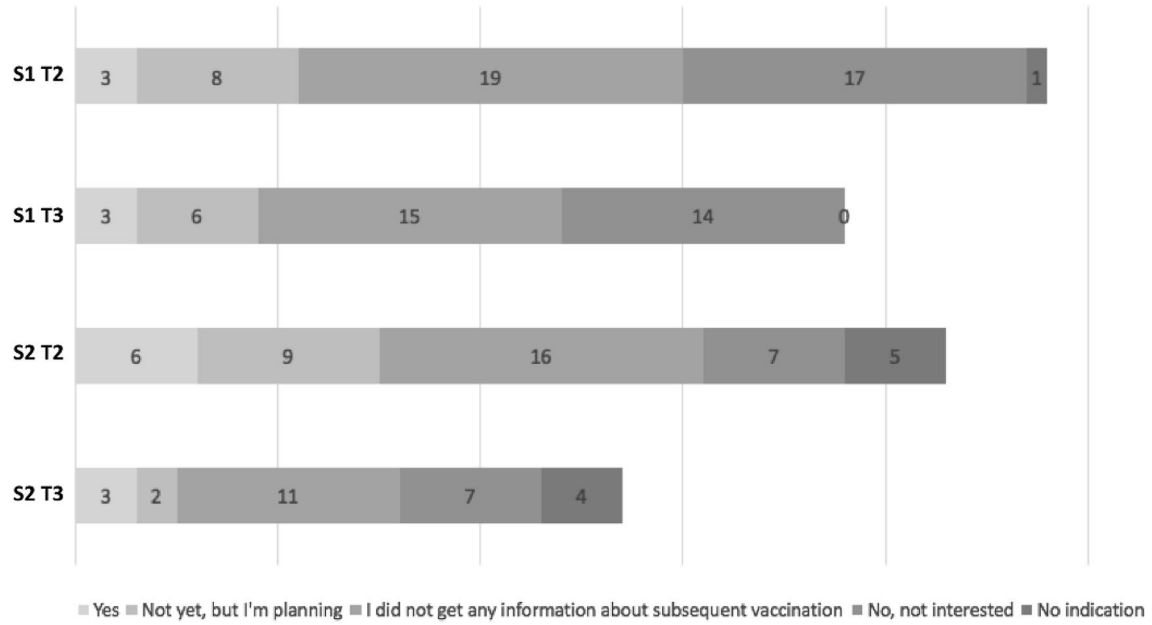

Fig. 1 After the diagnosis of a cervical dysplasia or a conization were you subsequently vaccinated for HPV *S1* subgroup with subsequent conization, *S2* subgroup without conization, *T2* 3 months after study onset, *T3* 6 months after study onset, *X-axis* absolute numbers (*n*) are indicated within the bars, *Y*-axis subgroups S1 and S2 at the different times T2 and T3

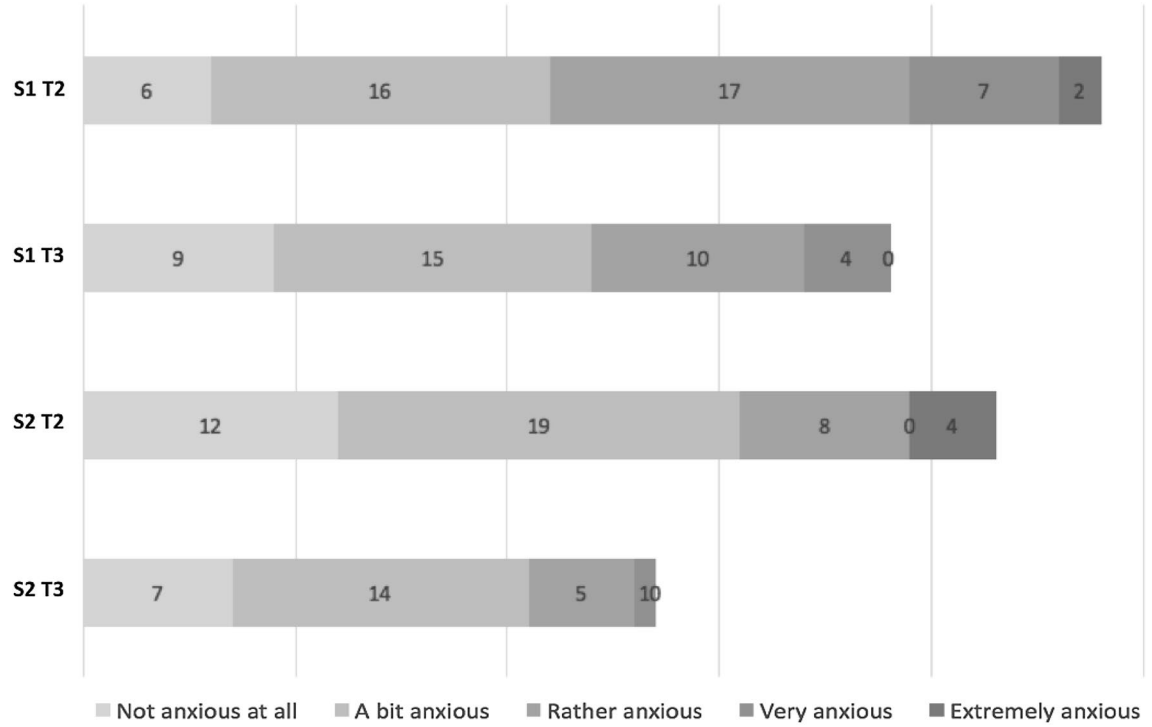

Fig. 2 How anxious do you feel about your next Pap smear check? *S1* subgroup with subsequent conization, *S2* subgroup without conization, *T2* 3 months after study onset, *T3* 6 months after study onset, *X-axis* absolute numbers (*n*) are indicated within the bars, *Y*-axis subgroups S1 and S2 at the different times T2 and T3

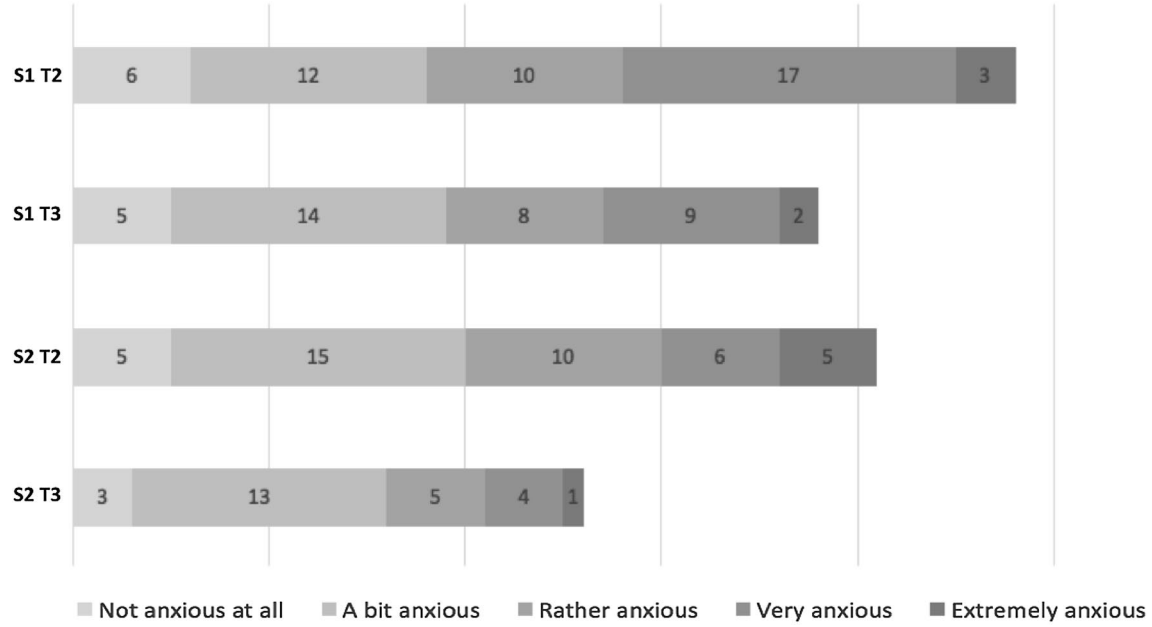

Fig. 3 How anxious do you feel about the re-occurrence of a cervical dysplasia or even about a possible (re-)operation? *S1* subgroup with subsequent conization, *S2* subgroup without conization, *T2* 3 months after study onset, *T3* 6 months after study onset, *X*-axis absolute numbers (*n*) are indicated within the bars, *Y*-axis subgroups S1 and S2 at the different times T2 and T3

Statistical analysis

The statistical analyses were performed in accordance with Heinzler et al. [18]. In brief, statistical tests were performed using SAS 9.1 Documentation (SAS, Cary, NC). Continuous data were presented using standard deviation, median, mean value, minimum, maximum values, *n*, and percent. Differences between groups were evaluated with the Wilcoxon–Mann–Whitney test and Chi-squared test. All tests were two sided. Spearman's rank correlation coefficient was used for correlation. Results were considered statistically significant if the *p* value was < 0.05.

Results

Study populations S1 and S2 and control group *K*

Of 209 eligible participants, 132 women (63.1%) with an abnormal Pap smear formed the study population at T1 after the exclusion of passive ($n = 39$, 18.7%) and active ($n = 38$, 18.1%) decliners [18]. A detailed flow chart is published in our previous work [18]. In brief, the study population was grouped into S1 ($n = 68$, 51.5%), those with a subsequent conization, and S2 ($n = 64$, 48.5%) if no operation was required [18].

After 3 months (T2), a total participation rate of 68.9% was obtained ($n = 91$ participants: S1/T2 = 48; S2/T2 = 43; total decliners/T2 = 41) [18]. After 6 months (T3), 65 of the 91 T2 participants (49.2%; S1/T3: $n = 38$; S2/T3: $n = 43$) returned the questionnaire; 26 (19.7%) were lost to follow-up [18]. The control group (*K*) comprised 101 healthy women [18].

Patients' characteristics of S1, S2, and *K* at T1

All patient characteristics at T1 are shown in Table 2 [18]. In brief, there were no significant differences between S1 and S2 in respect to age, marital and educational status, living situation, number of pregnancies, and smoking. The average participant in S1 was married (S1 46%, S2 26%), a mother (S1 50%, S2 44%, average number pregnancies of S1 1.25, range 0–5; S2 1.16, range 0–7), aged 35.9 years [range 19–56 versus S2 34.1 years (range 22–52)], mostly with a secondary school degree (S1 43% secondary and 25% with college degree; S2 44% secondary and 25% college degree), and living with their partner and children (S1 39% versus S2 25%). 26% of S1 and 10% of S2 participants stated having had a former conization. Almost one-third of the study population were smokers [S1 32%, S2 39% with a respective average of 12 (range 2–25) and 8.7 (range 1–20) cigarettes per day].

The average woman from the control group (*K*) was significantly younger (30.9 years, range 19–72, Chi-square test S1: $p = 0.002$; S2: $p = 0.05$), similar to S2 in terms of marital status (21%), mostly childless (mothers *K* 18%), had had significantly fewer pregnancies (average number of pregnancies 0.44, range 0–6, Chi-square test S1:

Table 2 Patients' characteristics at first visit T1

n at T1	S1 (68, T1) *n* (%)	S2 (64, T1) *n* (%)	*K* (101) *n* (%)
Ø age in years, range	35.9 I19–56I	34.1 I22–52I	30.9 I19–72I
Children, yes	34 (50)	28 (44)	19 (18)
Number of pregnancies, range	I0–5I	I0–7I	I0–6I
Marital status			
Single	9 (13)	12 (19)	38 (37)
Married	31 (46)	17 (26)	21 (21)
In a relationship	21 (31)	30 (47)	37 (37)
Divorced	7 (10)	5 (8)	4 (4)
Widowed	–	–	1 (1)
Living situation			
Alone	9 (13)	11 (17)	25 (25)
With partner (*p*)	22 (32)	22 (34)	27 (27)
With children (*c*)	7 (10)	7 (11)	1 (1)
With *p* and *c*	27 (39)	16 (25)	8 (8)
Shared apartment	1 (2)	3 (5)	33 (32)
Others	2 (3)	5 (8)	7 (7)
Education			
None	1 (1)	1 (2)	–
Primary school	7 (11)	6 (9)	1 (1)
Secondary or junior high school	29 (43)	29 (44)	14 (14)
Technical diploma/secondary diploma	12 (18)	10 (16)	54 (54)
College	17 (25)	16 (25)	31 (31)
Others	1 (1)	–	–
Not indicated	1 (1)	2 (3)	1 (0.99)
History of gynecological operations			
Previous conization	18 (26)	6 (10)	–
Laser vaporization of vulva/vagina	3 (4)	6 (10)	–
Biopsy vulva/vagina	6 (9)	16 (25)	8 (8)
Curettage	15 (22)	13 (21)	8 (8)
Smoking history			
Yes	22 (32)	25 (39)	20 (20)
No, never	25 (37)	27 (42)	72 (71)
Not anymore	21 (31)	11 (17)	9 (9)
HPV vaccination			
Yes	5 (7)	11 (17)	39 (39)
No	49 (73)	44 (70)	50 (49)
Never heard	3 (4)	1 (1)	3 (3)
I do not know	10 (15)	7 (11)	3 (3)
Not indicated	1 (1)	1 (1)	–

S1 subgroup with subsequent conization, *S2* subgroup without conization, *K* healthy controls, *T1* point of study onset/first visit, *Ø* average, % is indicated in (), range is indicated in I I, *p* partner, *c* children (adapted according to Heinzler et al. [18])

$p < 0.001$; S2: $p = 0.0005$), and very few were living with their partner and children (8%). Generally, fewer *K* women had a secondary school degree (14%), yet more had gone to college (31%). 20% reported being a smoker (9.8 cigarettes per day range 1–25), significantly less than in the study group (Chi-squared test $p < 0.0001$).

Prevention habits

HPV vaccination uptake at inclusion, T1

The HPV vaccination rate was highest in the control group (*K* 39% versus S1 and S2 7% and 17%, respectively,

Chi-squared test $p = 0.0004$). The study population was significantly less informed about HPV vaccination, some even having never spoken about this possibility with their specialist before (S1 56%, S2 46%; *K* 29%, Chi-squared test $p = 0.01$).

HPV vaccination uptake by subgroups S1 and S2 over time (T2, T3)

Almost 40% of both subgroups were never vaccinated for HPV at any time throughout this study. A maximum of one-third (S1, S2) were subsequently vaccinated against HPV after the diagnosis of a cervical dysplasia (highest value S2/T2 34.8%); Fig. 1 indicates the HPV vaccination status during study participation. During the course of the study, a large number of women remained uninformed about the possibility of a subsequent HPV vaccination (S1/T2 35.4%, S1/T3 16.3%; S2/T2 16.3%, S2/T3 31.8%, Wilcoxon signed-rank test $p > 0.05$).

Secondary prevention habits of subgroups S1, S2, and *K* at inclusion, T1

General knowledge about gynecological checkup modalities was reported by almost half of all participants (Table 1) and did not differ significantly between the three groups. However, a yearly Pap smear was undergone significantly more often by the women in S2 with a suspicious lesion (S2 100%, S1 88%, *K* 85%, Chi-square test $p = 0.0002$). General preventive habits such as ophthalmologist visits, general practitioner visits, and early detection colonoscopy were present equivalently in all groups at inclusion (T1).

Secondary prevention habits of subgroups S1 and S2 over time (T1, T2, T3)

The entire study population (S1 and S2 combined) at T1, T2, and T3 went to the gynecologist significantly more often than the control group *K* at T1 (Wilcoxon signed-rank test $p < 0.0004$). Subgroup S1 changed their gynecological prevention habits over time (Table 3). S1 went significantly less often to the gynecologist after 3 months (T2/T1, Wilcoxon signed-rank test $p < 0.01$) as well as 6 months later (T3/T1 − 0.47, Wilcoxon signed-rank test $p < 0.0005$).

The participation rate for general preventive habits among S2 was significantly higher 3 months after the event but not 6 (Wilcoxon signed-rank test $p < 0.04$). No impact was noticed in the S1 group with conization (Wilcoxon signed-rank test $p > 0.05$).

Psychological distress and patients' general anxiety related to an abnormal Pap smear

Women who underwent a conization (S1) were generally "rather anxious" to "extremely anxious" (Figs. 2, 3) about their upcoming smear test. Their fear about the next smear test even rose significantly during the course of the study (S1/T1–S1/T2–S1/T3, Wilcoxon signed-rank test $p < 0.001$). Additionally, these women were significantly more anxious 3 months after the intervention than those women who were only recommended to have regular checks (S1–S2/T2 Chi-square test $p = 0.01$). In S2, we could not see any change in dysplasia-related anxiety during the course of the study.

PHQ-D analyses for panic and anxiety disorders (T1, T2, T3) revealed that group S1 suffered significantly more from panic disorders than S2 at inclusion (Chi-square test $p = 0.035$), while there were no significant differences regarding the general anxiety at this time point.

Discussion

Knowledge of prevention programs is a prerequisite for taking advantage of their benefits. This study evaluated the impact of a cervical dysplasia on gynecological and general prevention habits over time. In our cohort, women with a suspicious Pap smear visited their gynecologist for checkups significantly more often than controls at inclusion. However,

Table 3 Prevention habits of subgroup S1 and S2 over time

Prevention checkup	S1				S2			
	T1 → T2		T2 → T3		T1 → T2		T2 → T3	
	x	*p*	*x*	*p*	*x*	*p*	*x*	*p*
Gynecological	−0.27	< 0.01*	−0.24	> 0.05	−0.02	> 0.05	−0.07	> 0.05
Others (family doctor/ophthalmologist/early detection colonoscopy)	−0.12	> 0.05	+ 0.06	> 0.05	−0.02	> 0.05	−0.26	< 0.04*

x absolute participation differences in gynecological visits between the time points, *p* value in terms of the different time points, *T2* 3 months after study onset, *T3* 6 months after study onset, *S1* subgroup with conization, *S2* subgroup without conization

*Statistically significant result $p < 0.05$

6 months after a conization, women were significantly less adherent to the German S3 guidelines, not realizing the recommended Pap smear 6 months after intervention. This is in accordance with Soutter et al., who observed decreasing compliance for gynecological follow-up visits after CIN treatment over time in a retrospective study, causing an increased risk for CC after the treatment for CIN [22, 23]. Although our data are of a prospective nature, our results on prevention habits should be interpreted with caution as further long-term follow-up is required to support Soutter´s analysis.

Fear and anxiety might be the major factors for nonadherence. Fear of dysplasia re-occurrence in the upcoming Pap smear or a possible re-operation was rather high among all study participants. This is supported by the previous studies showing that an abnormal Pap smear result was found to provoke psychological distress and an increased level of anxiety leading to decreased screening compliance [14–17, 24]. Anxiety was impacted by a conization at first but had a declining impact over 6 months. However, avoidance behavior might trigger a selection bias due to the anxiety issue, and particularly anxious women might not respond. This might explain the low response rate of 49.2% after 6 months, with passive decliners evading all further confrontation with the disease including follow-up Pap smear checks.

Surprisingly, aside from the gynecological screening, at their first visit nearly a quarter of the study population reported regularly missing other general prevention habits. Nevertheless, we observed that the participation rate for general preventive habits among women without an operative procedure (S2) rose significantly after study onset. One can argue that a positive screening result, i.e., a dysplasia diagnosis, triggers short-term adherence to prevention modalities in general in this subgroup. The long-term impact needs to be evaluated in future projects.

Non-participation in cervical cancer programs has been found to correlate with missing knowledge, as a recent UK survey described. They found that one-third of non-participants (28%) missed out on CC screening due to low knowledge rather than active denial [25, 26]. In our cohort, the general knowledge about gynecological screening recommendations was found to be up to 59%. In Germany, other cancer surveillance programs such as mammography screening show a realization rate of only 47–64%, while breast cancer surveillance for women with a familial high-risk situation merely meets 59% [27, 28]. Low socioeconomic status, women with a low or a really high education level, older age, high body mass index, single women, lack of familial history of breast cancer, and women living in cities tend to participate in mammography screening less often [29–31]. Patient-focused educational interventions might be the potential strategies to reduce nonadherence to cancer screening [32]. This includes taking into account that screening participation is known to positively correlate with middle age and high social and educational status; this was also seen in our study population in respect to age [29, 33].

Furthermore, individual aspects should be addressed during doctors' consultations. Risk factors and prevention strategies for cervical dysplasia and cancer remain major issues. Significant differences in HPV vaccination rates and smoking habits were still seen in our study population, as was previously described in a larger epidemiological study by Klug et al. Their results indicated that only 3.2% knew about HPV as a risk factor for CC, correlating with social class. 70% stated being poorly informed about the pathogenesis of CC and related risk factors, outlining the necessity for clear information to improve the outreach of gynecological care and increase adherence [29].

Besides the risk factors, primary prevention strategies such as the HPV vaccination also need improvement, as only 7–17% of the study subjects were vaccinated compared to 39% of the controls. This is in accordance with other studies showing vaccination rates from 24 to 62% [34, 35]. Higher vaccination rates are known to depend on a high educational level, interest in health-related issues, and belief in vaccination, as previously shown by two German surveys [36, 37]. The fact that up to 56% of our study subjects had never spoken about an HPV vaccination with their specialist compared to 29% of the controls is appalling and needs urgent improvement. Specialists and other health care providers have neglected to give strong and consistent recommendations on HPV vaccines as stated in Rosen's review [26]. Other studies have found a varying lack of awareness and information among clinicians that also needs improvement to implement current guidelines as the standard of care [34, 35]. The low vaccination rate among our study participants might be due to an age bias as the German national immunization program was adjusted in 2007; therefore, some of our women might not have been addressed regarding vaccination, but this would not fully explain our findings. Additionally, our control group seemed better informed about the vaccine, possibly impacted by a selection bias in terms of convenience controls, 42% of whom were medical students or hospital employees in contrast to almost 25% in the study group. Therefore, one can assume that medical employees in general might be more adherent and better informed about the prevention modalities than the general population.

New concepts are urgently needed not only in terms of prevention strategies but also for completing follow-up visits. One can also argue that increasing patient involvement through new technologies is one example of such a concept. Sultana et al. found that HPV self-sampling kits not only increase CC screening participation but also found that women who tested positive subsequently follow the recommended appropriate clinical intervention, such as colposcopy (62.2%) and cytology (20%) [38]. Other studies

found an improvement in adherence and compliance through home-based self-sampling kits, partly in combination with reminder letters [39, 40]. Pap smear-specific reminders in the form of invitation letters or an SMS with fixed scheduled appointments for women overdue for CC screening significantly increased participation rates [41–43]. These aspects might also be useful and desirable for follow-up visits to impact long-term benefits. Our data have shown that gynecological outreach must be adjusted according to individual distress risk factors and further factors of nonadherence to sustainably improve the screening modalities. The new age of e- and m-health with high-end technology including wearable devices and health apps open different options to align patient motivation and to impact adherence, but studies are needed to implement validated instruments. Furthermore, subgroups at risk for psychological distress need to be identified to adjust care strategies and offer psychological support if needed.

Conclusion

This study advances the understanding of nonparticipation in recommended dysplasia follow-up visits and identifies women having undergone conization as a special risk group for decreased adherence to preventive measures and for high levels of anxiety and fear. Educational interventions with invitation letters for follow-up exams, reminder apps on smartphones, or psychological support for this subgroup at risk might be possible options for further follow-up strategies and should be discussed to ensure gynecological care and to improve the sustainable outreach of screening modalities.

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Author contributions NR: manuscript writing/editing and data analysis. JH: data collection and management, data analysis, and manuscript editing. TB: data analysis and manuscript editing. JB: data collection. CD: data collection. JH: data collection. ND: data collection. SS: data collection. JR: manuscript editing. CS: manuscript editing. TCS: protocol/project development and manuscript editing. SS: protocol/project development, manuscript writing/editing, and project supervision.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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