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The Unintended Consequences of Cervical Screening: Distress in Women Undergoing Cytologic Surveillance

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■ **Abstract**

Objective. It is well known that receipt of an initial abnormal cervical cytology test can trigger considerable anxiety among women. Less is known about the impact of follow-up by repeat cytology tests. We quantified prevalence, and identified predictors, of distress after repeat cytologic testing in women with a single low-grade test.

Methods. Within the framework of the TOMBOLA randomized controlled trial of alternative managements, 844 women aged 20 to 59 years with a single routine cytology test showing borderline nuclear abnormalities (BNA; broadly equivalent to atypical squamous cells of undetermined significance) were assigned to follow-up by repeat cytology in primary care (the first test was due 6 months after the initial BNA result). Women completed sociodemographic and psychosocial questionnaires at recruitment and the Impact of Event Scale (IES) 6 weeks after their first follow-up cytology test. Factors associated with significant psychologic distress (IES $\geq$ 9) were identified using logistic regression.

Results. The response rate was 74% (n = 621/844). Of all the respondents, 39% scored in the range for significant distress. Distress varied by follow-up cytology result: negative, 36%; BNA or mild dyskaryosis, 42%; other (including high grade and inadequate), 55%. After adjusting for the cytology result, risk of distress was significantly raised in women who had significant anxiety at recruitment, reported experiencing pain after the follow-up cytology, had children, or were dissatisfied with support they had received after their initial BNA test.

Conclusions. Substantial proportions of women experience surveillance-related psychologic distress after a follow-up cytology test, even when the result is negative. This is an important, albeit unintended, consequence of cervical screening. Strategies to alleviate this distress merit attention. ■

Key Words: atypical squamous cells of undetermined significance, cervical screening, follow-up, distress

In countries with population-based screening programs between 4% and 12% of all adequate cytology tests show low-grade abnormalities [1–3], most of which are classified as atypical squamous cells of uncertain significance

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(ASC-US) or equivalent. Guidelines in many jurisdictions state that repeat cytologic testing is an acceptable management option for women with a single ASC-US test result [4–7].

It is well established that a routine cervical cytology test that shows abnormalities often causes women considerable anxiety [8, 9]. However, relatively little is known about the psychologic impact of follow-up by repeat cytologic tests. A small number of studies have investigated psychologic consequences of repeat cytology testing, mainly in the context of comparing different management approaches. Two of these studies did not include women with ASC-US (or equivalent) routine cytology tests [10, 11] and two others included mixed groups of women with cytology showing ASC-US and low-grade squamous intraepithelial lesions (LSILs), or borderline nuclear abnormalities (BNAs) and mild dyskaryosis [12, 13]. One study from Australia was limited to women who had had a routine BNA cytology test; in that study, the mean distress score estimated from 3 measurements taken for 12 months among 71 women who were managed by repeat cytology was double that for women with a negative routine cytology test [14]. Although these findings indicate that women with a BNA result who require repeat cytology tests are at an increased risk of distress, they do not distinguish between the effects of the initial (routine) test and the follow-up test.

The aims of this study were to quantify the prevalence of distress after repeat cytologic testing in women with a single BNA routine cytology test, to determine how this varies according to the result of the repeat test, and to identify other predictors of distress.

METHODS

Participants

This study was nested within the cytologic surveillance arm of the TOMBOLA randomized controlled trial, full details of which are described elsewhere [15, 16]. Briefly, women were eligible if they were aged 20 to 59 years and were residents of the Grampian, Tayside, and Nottingham areas of the United Kingdom and had had a recent routine low-grade cervical cytology result (mild dyskaryosis or BNA; broadly equivalent to LSIL and ASC-US) [17] taken within the NHS Cervical Screening Programmes (CSPs). Women who agreed to take part in TOMBOLA were randomized to either repeat cytology tests (cytologic surveillance) or a colposcopy examination.

Women who were randomized to cytologic surveillance were recommended to have 6-monthly cytology tests in primary care (i.e., at their general practitioner or family planning clinic), with the first surveillance test due 6 months after the cytology test that made them eligible for TOMBOLA. About 1 month before the first surveillance test being due, a "trigger" letter was sent to both the woman and her GP reminding them that the test was due. Women who attended for that test, and for whom the test result was negative or low-grade, remained on 6-monthly surveillance cytology testing; those who had an inadequate result were recommended to have another test within 3 months; and those with a high-grade result were referred to colposcopy in the local NHS clinic.

Women included in the current study had a BNA recruitment test result, no abnormal cytology in the previous 3 years, and attended for their first surveillance cytology test after the date on which the administration of psychologic questionnaires began (December 2001).

Ethical approval was obtained from the joint Research Ethics Research Committee of NHS Grampian and the University of Aberdeen, the Tayside Committee on Medical Research Ethics and the Nottingham Research Ethics Committee.

Assessment of Outcome

The primary outcome was cytologic surveillance-related distress, assessed by the Impact of Event Scale (IES), a validated and reliable 15-item measure of subjective psychologic distress associated with a specific stressful or traumatic event [18, 19]. Respondents assess how often they have experienced each of the 15 phenomena in the past 7 days (e.g., "I thought about it [the event] when I didn't mean to"). The event, in this instance, was defined as the first surveillance cytology test.

Women were sent the IES approximately 6 weeks after their surveillance cytology test. Six weeks was chosen to ensure that, by the time women received the questionnaire, they would have received their cytology result. Those who did not respond to the questionnaire were sent a maximum of 2 reminders, 2 weeks apart.

Assessment of Potential Explanatory Variables

Information on potential explanatory variables was obtained from sociodemographic, lifestyle, and psychologic questionnaires administered at trial recruitment (on average, 8 weeks after they received the result of their routine cytology test) and from a physical after-effects questionnaire completed at the same time as the IES. The psychologic questionnaires included the Hospital Anxiety and Depression Scale (HADS) [20], the Multidimensional

Health Locus of Control Scale (MHLCS), which measures three dimensions of health locus of control (internal, chance, and powerful others) [21], and the process outcome specific measure (POSM), which asks about specific issues that are of concern to women undergoing follow-up for abnormal cytology results [22]. The physical after-effects questionnaire asked about pain, bleeding, and discharge experienced after the surveillance cytology test [23]. For analysis purposes, women were also classified by the time between the BNA cytology that made them eligible for the trial and their first surveillance cytology test (≤6, 7–9, 10–12, and ≥13 mo).

Statistical Analysis

Women who completed all 15 IES items were included in the analysis. IES scores were not normally distributed, therefore women were classified dichotomously as "cases" or "noncases," using a total IES score of 9 or higher to define cytologic surveillance-related psychologic distress [24, 25]. Using recognized cutoffs, "cases" were also classified as having mild (score = 9–25), moderate (score = 26–43), or severe (score ≥44) distress. Logistic regression models were used to identify factors associated with distress of any severity. There were 2 stages of model fitting. In the first stage, we built a multivariate model from among the sociodemographic, lifestyle, HADS, MHLCS, physical after-effects, and time-to-surveillance test variables. Because we were specifically interested in associations between the result of the follow-up test and distress, cytology result was forced into the model (with the result classified as negative, low-grade [BNA/mild dyskaryosis], or other [moderate or severe dyskaryosis/inadequate/?glandular]). We then assessed variables relating to anxiety or depression at recruitment; then physical after-effects, sociodemographic, and lifestyle variables; the MHLCS dimensions; and finally, time to the surveillance cytology test. In these analyses, women were classified into 3 groups for anxiety and depression using standard cutoffs (noncase, subscale score <8; possible case, score = 8–10; probably case, score ≥11); scores for the 3 MHLCS dimensions were treated as continuous and responses to the questions about the 3 physical after-effects were coded dichotomously according to whether a reported having experienced each after-effect. Variables were included in the final models only if they were significant on a likelihood ratio test (LRT, $p \leq .05$) comparing the (adjusted) model with, and the model without, the relevant variable. The multivariate model from this stage of the analysis had adequate fit as assessed by the Hosmer and Lemeshow test [26]. In the second stage of model fitting, we investigated whether the variables from the POSM were associated with distress, after adjusting for other important predictors (i.e., the variables from the first stage of model fitting). For this analysis, women's responses to the POSM questions were classified into 2 groups (yes/no). This final model was used to produce adjusted percentages of women who were distressed.

To investigate the possibility that time since last procedure influenced distress, a sensitivity analysis was conducted in which prevalence of distress was computed according to whether women had responded to the initial questionnaire mailing, the first reminder, or the second reminder.

RESULTS

Response Rate

The study included 844 women, of whom 621 completed all 15 items on the IES (response rate = 74%).

Characteristics of Participants

Of the 621 respondents, 36% (n = 224) were aged 20 to 29 years, 27% (n = 167) were 30 to 39 years, 25% (n = 157) were 40 to 49 years, and 12% (n = 73) were 50 to 59 years. Of the 611 who reported their marital status, 60% (n = 366) were married or cohabiting. Of the 618 who reported their ethnic group, 96% (n = 596) classed themselves as white. One quarter (156/618) had a degree from college or university. Just under one third (195/620) currently used the oral contraceptive pill. Approximately two-thirds (416/621) had ever been pregnant, and 58% (354/621) had children.

Of all the women, 66% (n = 409) had a negative result in the surveillance cytology test, 24% had a low-grade result (mild dyskaryosis, 37; BNA, 115), and 10% had an "other" result (moderate dyskaryosis, 20; severe dyskaryosis, 6; ?glandular, 1; inadequate, 33).

Prevalence of Cytologic Surveillance-Related Distress

Six weeks after the surveillance cytology test, 39% (244/621) of respondents scored in the range for cytologic surveillance-related distress. Of all the women, 24% had mild distress (IES score = 9–25; n = 151), 13% had moderate distress (IES score = 26–43; n = 79), and 2% had severe distress (IES score ≥44; n = 14). The mean IES score was 10.3 (SD = 12.81), but the distribution of scores across all women was highly skewed; the median was 5 (interquartile range = 0–17).

There was no significant difference in the prevalence of distress according to the time between the initial and follow-up cytology tests (≤6 mo, 40%; 7–9 mo, 39%; 10–12 mo, 46%; ≥13 mo, 33%). In addition, the prevalence of distress did not vary significantly according to whether women had responded to the initial questionnaire mailing or the first or second reminder.

Predictors of Cytologic Surveillance-Related Distress

In multivariate models, compared to women with a negative surveillance cytology test result, those with a low-grade result had a modest, nonsignificant, increased risk of distress of any severity, and those with an "other" result had a more than 2-fold increased risk (see Table 1). These odds ratios translated into adjusted prevalence of distress of 36.4% (95% confidence interval [CI] = 31.1%–41.7%), 42.0% (95% CI = 33.7%–50.8%), and 55.1% (95% CI = 40.3%–69.0%) for those with negative, low-grade, and "other" results, respectively (see Figure 1). Among the group with "other" surveillance cytology results, there was little difference in the prevalence of distress among those with an inadequate result (58%) and those with a high-grade result (52%). Women with moderate or severe surveillance-related distress were distributed across all 3 surveillance test result groups, although the prevalence was lower among those with negative cytology (13%) compared to those with low-grade (18%) and "other" cytology (22%).

In addition to the surveillance test result, the following variables were significantly associated with surveillance-related distress in the multivariate analyses: HADS anxiety score at recruitment, reported pain after the surveillance test, and reproductive history (see Table 1). There was an almost 3-fold increased risk of distress among women who scored 11 or higher on the HADS anxiety subscale (probable cases) compared to those who scored less than 8 (noncases). Women who reported pain had a 2-fold increased risk of distress compared to those who did not. Women who had never been pregnant had a 40% lower risk of surveillance-related distress compared to women who had children. None of the other variables tested in the first stage of model fitting was significantly associated with risk of distress.

When the individual components of the POSM were considered, risk of distress was significantly increased among those who had reported, after their recruitment

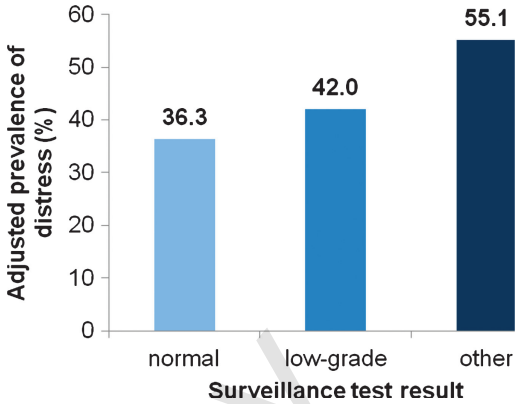

Figure 1. Adjusted prevalence of distress,[a] by surveillance cytology test result.[b] [a] Adjusted for anxiety after BNA recruitment cytology test, pain after the surveillance cytology test, and reproductive history. [b] Low-grade result includes BNA and mild dyskaryosis; "other result" includes inadequate, moderate or severe dyskaryosis, and ?glandular.

Table 1. Characteristics Significantly Associated[a] With Cytologic Surveillance-Related Distress—Multivariate Odds Ratios (OR), Adjusted Prevalence, and 95% Confidence Intervals (CI)

Characteristic		Multivariate[b] OR (95% CI)	Adjusted prevalence[b] (95% CI)
Surveillance cytology test result[c]	Normal	1 (reference)	36.3% (31.4%–41.7%)
	Low-grade	1.27 (0.83–1.92)	42.0% (33.7%–50.8%)
	Other	2.15 (1.13–4.06)	55.1% (40.3%–69.0%)
Anxiety after recruitment BNA cytology test[d]	Noncase	1 (reference)	33.2% (28.2%–38.7%)
	Possible case	1.29 (0.82–2.03)	39.1% (30.4%–48.6%)
	Probable case	2.72 (1.73–4.26)	57.5% (48.1%–66.4%)
Pain after the surveillance cytology test	No	1 (reference)	36.9% (32.5%–41.6%)
	Yes	1.98 (1.22–3.21)	53.6% (42.6%–64.3%)
Reproductive history	Pregnant with children	1 (reference)	43.6% (38.0%–49.4%)
	Pregnant – no children	0.88 (0.49–1.58)	40.4% (28.3%–53.8%)
	Never pregnant	0.61 (0.40–0.91)	31.9% (25.2%–39.4%)

[a] In the multivariate model.
[b] Mutually adjusted for surveillance cytology test result, anxiety after recruitment BNA cytology test, pain after the surveillance cytology test and reproductive history.
[c] Low-grade includes BNA and mild dyskaryosis; other includes moderate and severe dyskaryosis, inadequate, and ?glandular.
[d] Assessed using the HADS at recruitment; on average, 8 weeks after receipt of BNA cytology test result.
BNA, borderline nuclear abnormality; HADS, Hospital Anxiety and Depression Scale.

cytology test, that they were worried about their general health, their next cytology test being abnormal, having cervical cancer, and having sex (see Table 2). Women who were not satisfied with the support they had received from other people were also at a significantly increased risk of distress.

DISCUSSION

Prevalence of Cytologic Surveillance-Related Distress

An important finding of this study was the high prevalence of cytologic surveillance-related distress among women with a single BNA (broadly equivalent to ASC-US) cytology result managed by a repeat cytology test at 6 months (39% overall). Although we did not assess distress in these women after the initial abnormal cytology test, which was performed within routine call and recall, we have previously shown that the prevalence of significant anxiety after that initial cytology test was high [27]. The current study suggests that that the adverse psychologic effects provoked by the initial test persist over 6 months (and perhaps longer) for many women. Although in most women the level of distress would have been considered mild, 2% overall scored in the range of severe distress and 13% in the range of moderate distress. Considering the number of women who have an ASC-US (or equivalent) routine cytology test each year, our results suggest that follow-up by cytologic surveillance imposes a significant psychologic burden on women. However, this burden is not limited to follow-up by repeat cytologic testing. One of the main management alternatives—colposcopy—is also associated with a significant psychologic impact [28–30]. Interestingly, the prevalence of distress in the current study was higher than that found among women who had a low-grade cytology test followed by a normal colposcopy examination (21%) and was almost as high as among women who had a low-grade cytology test followed by a colposcopy in which an abnormal transformation zone was found (42%) [31].

A lack of data makes it difficult to assess how the level of distress associated with the management of a low-grade cytology test compares to other medical procedures. The average IES score among women in this study (mean = 10.3) was higher than means reported from (i) an assessment made 2 months after lung cancer screening by computed tomography (CT) among smokers (overall mean = 3.6; normal CT result, mean = 2.4; indeterminate CT result, mean = 8.3) [32] and (ii) an assessment conducted 1 week after endoscopy among people with Barrett's esophagus (mean = 3.5) [33]. It was lower than mean scores among women at high breast cancer risk, some of whom had *BRCA1/2* mutations, about to undergo MRI surveillance (mean = 14.5) [34]; and a high-risk group about to undergo genetic testing for hereditary nonpolyposis colorectal cancer (mean = 14.7) [35].

The prevalence of distress was highest among the group of women whose surveillance test result fell into the "other" category (high-grade [equivalent to high-grade squamous intraepithelial lesion], inadequate [called unsatisfactory in some jurisdictions], or glandular). Women with a high-grade result were informed that they would be referred for colposcopy and it seems entirely plausible that the result and/or the referral into hospital services might well lead to higher distress. Those with inadequate tests were recommended to have another test in three months and this more rapid recall than woman may have expected might have served to increase distress. In addition, women may be uncertain about what the label "inadequate" means and distress and anxiety are common reactions to uncertainty [36]. Consistent with our findings, another UK study also reported increased anxiety and concerns at 4 weeks after receipt of results among 180 women whose cytology test result was classified as inadequate [37]. In that study, the authors noted that the levels of anxiety and concerns in women with an inadequate test result were similar to those among women with a low-grade result, whereas in our study, the prevalence of surveillance-related distress among women with an inadequate result was as high as for women with a high-grade result. This may because of a difference in

Table 2. Other Psychosocial Factors[a] Significantly Associated[b] With Cytologic Surveillance-Related Distress—Multivariate Odds Ratios (OR), Adjusted Prevalence, and 95% Confidence Intervals (CI)

		Multivariate OR[c] (95% CI)	Adjusted prevalence[c]
Worried about general health	No	1 (reference)	27.6%
	Yes	1.67 (0.94–2.97)	39.0%
Worried my next smear will show changes to the cells	No	1 (reference)	7.7%
	Yes	7.80 (1.78–35.95)	40.1%
Worried I may have cervical cancer	No	1 (reference)	25.3%
	Yes	2.04 (1.20–3.46)	40.8%
Worried about having sex	No	1 (reference)	32.0%
	Yes	1.76 (1.13–2.76)	45.4%
Satisfied with support from other people	No	1 (reference)	59.4%
	Yes	0.35 (0.16–9.75)	33.9%

[a] From questions included in the POSM.
[b] In a model containing surveillance-cytology test result, anxiety after BNA recruitment cytology test, pain after the surveillance cytology test, and reproductive history.
[c] Adjusted for surveillance cytology test result, anxiety following BNA recruitment cytology, pain after the surveillance cytology test, and reproductive history.
BNA, borderline nuclear abnormality.

study settings: in the study by French et al. [37], women had attended for routine screening, whereas in our study, they were already on surveillance because of an abnormal routine test. However, our finding should be interpreted with a degree of caution because the number of women who had an inadequate result was small.

It might have been expected a priori that women whose surveillance test result was negative would be less often distressed than other women. However, we observed that the prevalence of distress was similar among women with negative and low-grade surveillance test results. This finding is broadly similar to that of Maissi et al. [13] who, in a study of women with BNA and mildly dyskaryotic routine cytology results, reported that the result of the 6-month repeat test was not a predictor of concern at that time, although in that study, many women had not received their surveillance test result by the time the psychologic assessment was conducted. A possible explanation for our finding is that women with negative and low-grade first surveillance test results are subsequently managed in the same way (i.e., by a second surveillance test in another 6 months). By the time women in our study completed the psychologic questionnaire, they would have been informed of their test result and future follow-up. This, in effect, means that women with a negative test result received a mixed message – that their cytology result was "normal," but management would not be returning to "normal" (i.e., routine recall). As well as being associated with a relatively high prevalence of distress, this mixed message may have other consequences. For example, we have previously shown that women are more likely to default from subsequent surveillance cytology tests if their first surveillance test result is negative [38]. This means that it is possible that a single intervention (e.g., additional information, provided when the first surveillance test is reported, including emphasis on the importance of subsequent tests) could help alleviate distress, provide reassurance, and decrease default from follow-up.

The results of this study highlight the unintended consequences of screening for participants. The sensitivity of cytology means that a significant proportion of women who attend for a routine screening test are labeled as "non-negative" and therefore need follow-up, although their risk of developing cancer is low. We have shown that follow-up, irrespective of whether it is by surveillance or colposcopy [31], can have psychologic consequences for a significant proportion of women. Triage by HPV testing is now recommended in some jurisdictions for women with low-grade cytology [39, 40]. Although this strategy avoids the need for women to be managed by repeat cytology tests, it is unlikely to eliminate the adverse psychologic consequences associated with low-grade cytology results. This is because women with low-grade cytology who also test positive for HPV have increased anxiety, distress, and concerns, whereas those who test negative are not reassured [41] and, after 6 months, women remain concerned about their cytology result irrespective of their HPV result [13]. These issues point to the importance, in designing screening protocols, of taking into account sensitivity and specificity of both the primary screening and triage tests: only by doing this can an acceptable balance between the costs and the benefits of screening be achieved.

Predictors of Cytologic Surveillance-Related Distress

It seems unsurprising that women who were anxious after their recruitment cytology test were at increased risk of distress after the repeat test. The association between having experienced pain after the repeat cytology test and distress was also observed in our study of distress after colposcopy [31]. Because pain and distress were assessed contemporaneously, it remains uncertain whether pain is a predictor of distress or vice versa. However, the finding does raise the possibility that providing women with information that quantifies the likelihood of experiencing pain or discomfort after a cytology test, and clarifies that this is not unusual, could ameliorate subsequent distress.

The observed lower risk of distress in women who have never been pregnant compared to those who have children is intriguing. Although women who have never been pregnant are younger, it seems unlikely that the relationship would be due to age because age is not usually an important predictor of IES scores [42]. One possible explanation is that there may be differences between women with and without children in what they consider to be the potential implications of undergoing cytologic surveillance. For example, women who have had abnormal cytology tests and follow-up may worry about cervical cancer [43, 44]; such concerns may be more common or pronounced in women with children, translating into raised levels of distress.

Identification of associations between specific worries or concerns and distress might provide clues as to the issues that underlie surveillance-related distress and help inform the development of interventions to alleviate this. Maissi et al. [13] found that, among women with low-grade cytology managed by repeat cytology tests, those

who had a high perceived risk of developing cervical cancer reported higher concerns at a 6-month follow-up assessment. In our study, although perceived risk was not associated with distress, women who reported after the recruitment cytology test that they were worried that they may have cervical cancer were 3 times more likely to be distressed after the repeat test, than those who were not worried. We support the suggestion of Maissi et al. [13] that providing women on cytologic surveillance with information about their relatively low absolute chance of developing cervical cancer might be effective in reducing the psychologic burden.

The observed association between a lack of satisfaction with support and distress has been reported also among women managed by colposcopy [29, 31]. This suggests another route by which service providers might try to alleviate the adverse psychologic sequelae of follow-up—by providing additional sources of support for women. In the United Kingdom, where TOMBOLA took place, there have been a range of developments since we conducted the study, including the provision of screening program and charity telephone help lines, and standardized information available through the CSPs, and these may have gone some way to providing this support. However, providing support that effectively meets the needs of all women is likely to be challenging because women probably differ widely in their preferences for type, amount, and timing of delivery of support, especially in jurisdictions in which there is substantial ethnic and cultural diversity.

Strengths and Limitations

The major strengths of our study include the prospective design and the fact that it was set within a pragmatic, population-based trial that mimicked routine clinical practice in the NHS CSPs. Although the questionnaire response rate was high (74%), we cannot exclude the possibility that nonresponders differed from responders in their patterns of distress. Nonresponders differed from responders in some (e.g., age, ethnic group) but not other (e.g., employment status, educational level, reproductive history) variables but, with the exception of reproductive history, none of these variables were a significant predictor of distress. A higher proportion of nonresponders, than responders, scored as probable cases on the HADS anxiety subscale at recruitment. Because anxiety was positively related to subsequent distress, it is possible that our study underestimates the prevalence of distress in the population of women with a single BNA (or equivalent) cytology result.

CONCLUSIONS

This study suggests that a substantial proportion of women with a single BNA cytology test experience surveillance-related psychologic distress after a follow-up cytology test, even when the test result is negative. Because many women require follow-up for abnormal cervical cytology, this deserves recognition as an important—albeit unintended—consequence of cervical screening. Strategies to alleviate this distress merit further attention.

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