Interval cancers
of the national screening programme for cervical cancer

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Introduction

Cervical cancer is caused by an infection with a high-risk type of the Human Papillomavirus (HPV). This infection can lead to precancerous changes in the cells of the cervix (known as CIN 1, CIN 2, and CIN 3). Only after these stages does cervical cancer develop. This process usually takes more than 10 years. The aim of the cervical screening programme is to detect and treat these precancerous changes early, in order to prevent cervical cancer from developing.

Sometimes, a screening test gives a normal or reassuring result, even though precancerous changes or cancer are already present. If cancer is later found after a normal screening result but before the next screening round, this is called an interval cancer[1] (Figure 1).

1 In the National Monitor, an interval cancer is defined as a cancer diagnosed after a normal screening result but before the invitation to the next screening round.

It can also happen that a woman already has cancer after a normal screening result, but it causes no symptoms yet and is only detected at the next screening round. Given the slow development of cervical cancer, this may also indicate that the earlier screening result was falsely reassuring. Cancers found after a normal screening result, either before or during the next screening round, are referred to as post-screen detected cancers (Figure 1). A large number of interval or post-screen detected cancers suggests that the test or screening programme is not sensitive enough. In other words, that it misses some cases that should have been detected earlier.

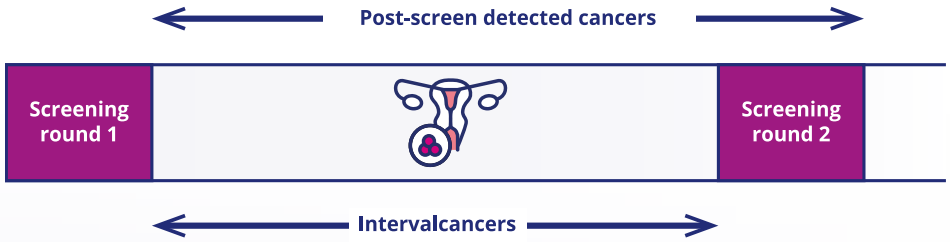

Figure 1 *Schematic overview of the difference between interval and post-screen detected cancers.*

Until 2017, the national cervical cancer screening programme consisted of a five-yearly cytology screening (a test in which cervical cells are examined under a microscope for abnormalities, commonly known as a smear test) for women aged 30 to 60 years. If the result of this primary test was abnormal, the woman was referred to a gynaecologist or invited for a follow-up test.

Since 2017, the programme has started with an HPV test as the primary screening method. If this HPV test result is abnormal, a cytology test is carried out. If that result is also abnormal, the woman is referred to a gynaecologist, or invited for a (cytology) follow-up test. This analysis examines the difference in the risk of cervical cancer after a normal screening result between the previous cytology-based programme and the newer HPV-based programme.

Research question

What is the risk of interval cancers and post-screen detected cancers in the national cervical screening programme after the introduction of primary HPV screening (2017), and how does this compare with the previous cytology-based programme (2014)?

Methods

All analyses were conducted using data from the Dutch Pathology National Automated Archive (Palga). For the cytology-based programme (before 2017), the analysis included all complete screening episodes in the national programme with a normal screening result (that is, a negative primary cytology test or a negative follow-up test) between 1 January 2014 and 31 December 2014. For the HPV-based programme, the same approach was used but for the period 1 January 2017 to 31 December 2017. In both analyses, person-years were counted from the date of the normal screening result until the next screening round five years later (or until the end of the study period for women aged 40 or 50 with a negative HPV test in 2017[2]), or until a new smear was taken outside the programme because of symptoms. Results are presented per 100,000 person-years, adjusted for age and length of follow-up.

2 After a HPV-negative test result at age 40 and 50, the woman is invited again after 10 years, but this will be in 2027 and data on this is not yet available.

Results

Differences between the programmes:

Table 1 shows the number of cancers detected after a normal screening result, broken down by type of result: normal screening outcome, primary test result, and follow-up test. The number of interval cancers detected among women in the cytology-based programme was 3.3 per 100,000 person-years, compared with 2.9 in the HPV-based programme. Among women with a normal primary test result, the rates were 3.2 and 1.7, respectively. Among women with an abnormal primary test result followed by a normal follow-up test, the rates were 5.3 and 28.8, respectively.

The relative risk of an interval cancer after a negative primary HPV test was 1.7 times lower than after a negative primary cytology test, whereas the relative risk after a negative follow-up test was 3.5 times higher in 2017 than in 2014. This difference in relative risk after follow-up testing is partly influenced by the change in the primary test method, and does not mean that the quality of the follow-up test itself has worsened over time.

The number of post-screen detected cancers was 10.0 per 100,000 person-years in the cytology-based programme, compared with 6.7 in the HPV-based programme (Table 1). After a normal primary test result, these rates were 9.8 and 3.6, and after an abnormal primary test followed by a normal follow-up test, 16.4 and 121.5, respectively.

Table 1 *Number of normal screening results, number of cancers, and cancers per 100,000 person-years adjusted for age and duration of follow-up.*

	Number of normal screening results	Number of cancers after a normal screening result	Cancers after a normal screening result per 100,000 person-years (95% CI)
Interval cancer			
Cytology programme	469.116	74	3.3 (2.6 – 4.1)
Primary cytology	460.306	71	3.2 (2.5 – 4.0)
Follow-up test	7.610	3	5.3 (0.4 – 21.8)
HPV programme	362.128	57	2.9 (2.1 – 3.7)
Primary HPV-test	344.779	37	1.7 (1.2 – 2.4)[3]
Follow-up test	17.349	20	28.8 (17.6 – 44.6)[3]
Post-screen detected cancer			
Cytology programme	469.116	195	10.0 (8.8 – 11.4)
Primary cytology	460.306	188	9.8 (8.5 – 11.2)
Follow-up test	7.610	7	16.4 (5.4 – 38.5)
HPV programme	362.128	103	6.7 (5.6 – 8.0)[3]
Primary HPV-test	344.779	50	3.6 (2.8 – 4.6)[3]
Follow-up test	17.349	53	121.5 (96.9 – 150.4)[3]

Abbreviations: *CI, Confidence Interval.*

3 Significant difference compared with 2014 ($p < 0.05$).

Differences within the HPV-based programme:

Within the HPV programme, the relative risk of an interval cancer after an abnormal HPV test followed by a normal follow-up test was 20.8 times higher than after a normal HPV test. There was no significant difference in the relative risk of interval cancer between women with a negative HPV result who had a five-year screening interval (ages 30, 35, 45, 55) and those with a ten-year interval (ages 40 and 50). No significant difference was found either between negative HPV tests conducted via a smear taken by a GP and negative HPV self-sampling tests, in terms of the incidence of interval or post-screen detected cancers.

Conclusion

The number of cervical cancers detected shortly after a normal screening result within the Dutch national cervical screening programme is low. The risk of cervical cancer after a normal screening result has decreased since the introduction of HPV testing as the primary screening method, compared with cytology. However, the relative risk of cervical cancer after an abnormal HPV test followed by a normal follow-up test is much higher than after a normal HPV test. Although this relative risk is higher, the absolute risk remains low. In the future, it may be useful to explore whether alternative types of follow-up testing could further improve outcomes.

Glossary

- **Adjusted**: figures that have been corrected to allow fair comparisons between groups or over time. They take into account differences in the composition of the population.
- **Complete screening episode**: women with a fully completed primary test and, if applicable, a fully completed follow-up test. Women who were invited for a follow-up test but did not attend are therefore not considered to have a complete screening episode.
- **Cytology**: pathological examination in which cervical cells are studied to determine whether they show abnormalities, using a smear test. The assessment follows the Pap classification.
- **Follow-up test**: cytology follow-up test for which participants were invited, if necessary, six months after the primary test.
- **(hr)HPV**: (high-risk) human papillomavirus; HPV types that carry a high risk of developing cervical cancer.
- **Interval cancer**: a cervical cancer found in participants with a complete screening episode without referral advice, before the next screening round.
- **Normal screening result**: a screening test within the national programme without referral advice (i.e. in the cytology-based programme, a primary cytology result of Pap 1 or Pap 2/3a1 without referral; and in the HPV-based programme, a negative HPV result or a positive HPV result without referral).
- **Pap classification**: Papanicolaou classification; a grading system for the smear test. Pap 1: no abnormalities; Pap 2 and 3a1: mild abnormalities; Pap 3a2, 3b, 4 and 5: moderate/severe abnormalities.
- **Post-screen detected cancer**: a cervical cancer found in participants with a complete screening episode without referral advice, before or during the next screening round.
- **Screening round**: a round in which a person has participated in the national cervical screening programme.