EVIDENCE REPORT

Decision Analysis for the Evaluation of Benefits, Harms and Cost-effectiveness of Different Cervical Cancer Screening Strategies to Inform the S3 Clinical Guideline "Prevention of Cervical Cancer" in the Context of the German Health Care System

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3 Introduction

This document describes the methods and results of the decision-analytic study for cervical cancer screening to evaluate the benefits, harms and cost-effectiveness of different screening strategies in order to inform the development of the German evidence-based S3 clinical guideline “Prevention of Cervical Cancer” (AWMF registration number 015 - 027OL).

4 Methods

4.1 Overview

We performed an evidence-based benefit-harm analysis and cost-effectiveness analysis comparing several cervical cancer screening strategies. In order to synthesize all best available evidence, we performed a decision analysis incorporating current evidence on epidemiologic parameters, benefits, harms and costs (1).

The decision-analytic model is designed to be applied in the context of comparative effectiveness analysis and economic evaluation analysis in order to inform evidence-based clinical guideline development. The design of the model follows international standards of decision-analytic modeling, such as the ISPOR-SMDM Joint Task Force Modeling Good Research Practices (2-5) and international key principles for health technology assessment (HTA) (6, 7).

4.2 Model Design and Framework

4.2.1 Model Type and Simulation Technique

We developed a decision-analytic Markov state-transition model for the long-term natural history of cervical cancer development including human papillomavirus (HPV) infection, pre-invasive cancer, invasive cancer, and death. Different screening strategies and follow-up management and treatment algorithms based on the algorithms discussed in the S3 clinical guideline process have been implemented in the model structure.

The model was based on prior health technology assessments (HTA) and previously published and validated models for the German health care context (8-11) and was adapted, updated and extended

to the research questions of this project. The application of the model allows for estimating the long-term clinical and economic consequences (i.e., benefits, harms and costs) of different screening strategies in the context of the German health care system. As the number of health states in this model is manageable, the model is designed for a Markov cohort simulation (4, 5).

4.2.2 Time Horizon and Cycle Length

In order to capture all relevant clinical and economic events, a life-long time horizon was applied for all analyses. The Markov model has a cycle length of one year.

4.2.3 Perspective

The perspective of the German health care system was adopted to assess the consequences of the evaluated screening strategies.

4.2.4 Discounting

For the cost-effectiveness-analysis, all outcomes are discounted. According to the recommendations for health economic evaluations in the general methods guidelines of the Institute for Quality and Efficiency in Health Care (IQWiG), the discount rate for the base-case analysis is set to 3% for the health effects and for costs (12).

4.2.5 Outcomes

For each examined strategy, the following outcomes are projected: (1) reduction in cervical cancer incidence, (2) reduction in cervical cancer mortality, (3) remaining life expectancy, (4) total number of screen-positive test results (with scheduled re-visit within one year or immediate colposcopy), (5) total number of colposcopies, (6) total number of conizations, (7) unnecessary conizations (defined as conizations of low or moderate grade cervical cell lesions), (8) lifetime costs, (9) incremental harm-benefit ratios (IHBR) expressed in units of additional harm per additional benefit, (9) discounted incremental cost-effectiveness ratios (ICER) expressed as Euros per life-year gained (Euro/LYG).

4.2.6 Natural History Model Structure

The model reflects the natural history of cervical cancer development. A cohort of 15 year-old healthy women not vaccinated against HPV 16/18 enters the model and may move over their lifetime through different health states based on the natural history of cervical cancer development. In the Markov model, time is divided in annual cycles.

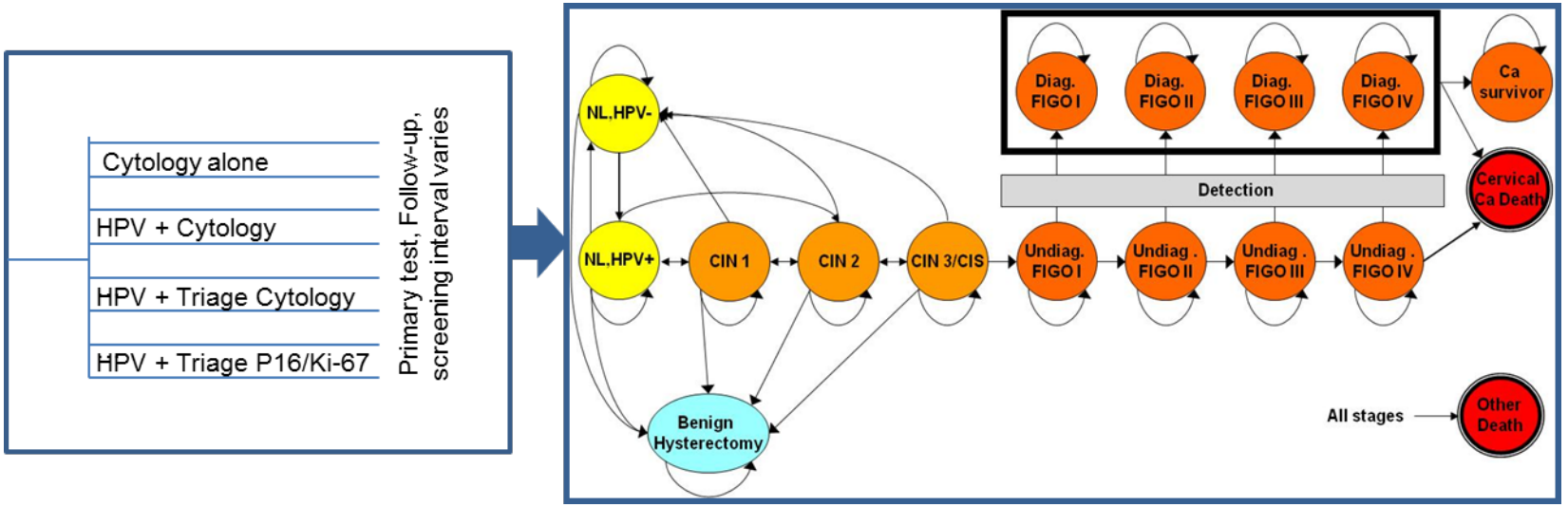
Women can be infected with a high-risk HPV that may be cleared or not. We did not consider heterogeneity of the population with respect to infection with different high-risk HPV-types. We neither considered an infection with a low-risk HPV, as these HPV types are considered not to represent a significant risk for cervical cancer. Persistent HPV infection is associated with a high risk for developing precancerous lesions of the cervix, so called cervical intraepithelial neoplasia (CIN). Precancerous lesions could regress, persist or may progress to a more severe stage and finally into invasive cervical cancer. Invasive cervical cancer is categorized in stages I to IV according to the staging system of the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO). Regression of invasive cervical cancer to precancerous lesions was not considered. As precancerous lesions usually do not cause any symptoms, it was assumed that they could be detected by screening only, whereas invasive cancer cases could be detected by the onset of symptoms and/or screening. Detected precancerous lesions and invasive cancer were assumed to be treated according to the German treatment guidelines. Women treated for precancerous lesions were assumed to return to the healthy state (no HPV-infection and no lesion) and be at a normal risk for future high-risk HPV infection and disease. Women treated for invasive cervical cancer were assumed to have higher risk to die than women without cervical cancer based on FIGO-specific survival rates. However, we assumed equal mortality rates for women with cervical cancer who were tumor-free six years after treatment (cancer survivors) compared with women without cervical cancer. Women of all ages may die from other causes than cervical cancer due to age- and gender-specific mortality. We assumed that women who undergo a hysterectomy because of other reasons than cervical cancer or CIN are no longer at risk for cervical cancer and leave the screening population.

Over time and for each screening strategy, the model assesses outcomes such as cervical cancer cases and deaths, clinical events, remaining life expectancy, and costs.

Figure 1 shows a simplified state-transition diagram of the natural history Markov model structure. Screening strategies are implemented as specific decision strategies. All screening strategies have the same basic structure concerning the natural history. Screening-specific pathways are implemented as Markov cycle trees. Screening-specific differences are indicated by locally assigned values for

variables (e.g., screening test sensitivity and specificity, screening interval, costs) at each screening strategy branch.

Figure 1. State-transition diagram of the natural history Markov model structure of the German cervical cancer screening model



CIN: cervical intraepithelial neoplasia, CIS: carcinoma in situ, Diag.: diagnosed cervical cancer, FIGO: cervical cancer stage classification Fédération Internationale de Gynécologie et d'Obstétrique, HPV: human papillomavirus, NL: no lesion, Undiag.: undiagnosed cervical cancer.

4.3 Screening and Follow-up Strategies

4.3.1 Primary Screening Strategies

The evidence-based decision-analytic model compares several different screening strategies that differ by screening interval, primary screening test(-combinations), and follow-up management algorithms.

In accordance with the S3 clinical guidelines, in the base-case analysis of our model, cervical cancer screening should start at age 25 years, with no upper age limit for the end of screening.

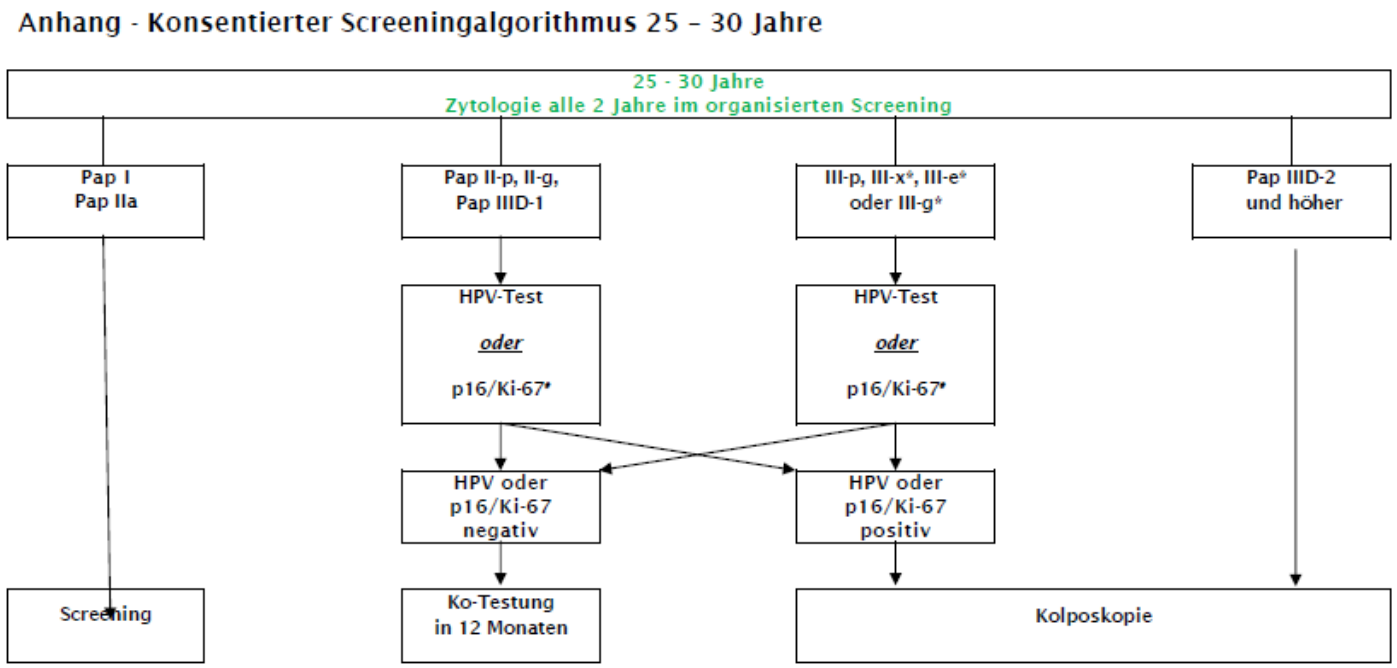
The model compares 33 different primary screening strategies (including no screening) that differ by initial screening test or test combinations, by follow-up algorithms, screening interval and age at which a primary screening test is applied.

In the model, the following screening strategies are assessed: (1.) no screening; (2.) annual Pap cytology in women aged 20 years and older with current recommended follow-up algorithm (for comparison purposes); (3.-6.) Pap cytology alone in women aged 25 years and older in intervals of one, two, three or five years with p16/Ki-67 dual stain triage; (7.-10.) Pap cytology alone in women aged 25 years and older in intervals of one, two, three or five years with HPV triage; (11.-14.) liquid based cytology (LBC) alone in women aged 25 years and older in intervals of one, two, three or five years with p16/Ki-67 dual stain triage; (15.-18.) LBC cytology alone in women aged 25 years and older in intervals of one, two, three or five years with HPV triage; (19.-21.) cotesting with HPV and Pap cytology in women older than 30 years in intervals of two, three or five years, and biennial Pap testing in women aged 25 to 30 years; (22.-24.) cotesting with HPV and LBC cytology in women older than 30 years in intervals of two, three or five years, and biennial Pap testing in women aged 25 to 30 years; (25.-27.) HPV testing with Pap-cytology triage for HPV-positive women in women older than 30 years and older, in intervals of two, three or five years and biennial Pap testing in women aged 25 to 30 years; (28.-30.) HPV testing with LBC-cytology triage for HPV-positive women in women older than 30 years and older, in intervals of two, three or five years and biennial Pap testing in women aged 25 to 30 years; (31.-33.) HPV testing with p16/Ki-67 dual-stain triage for HPV-positive women in women older than 30 years, in intervals of two, three or five years and biennial Pap testing in women aged 25 to 30 years.

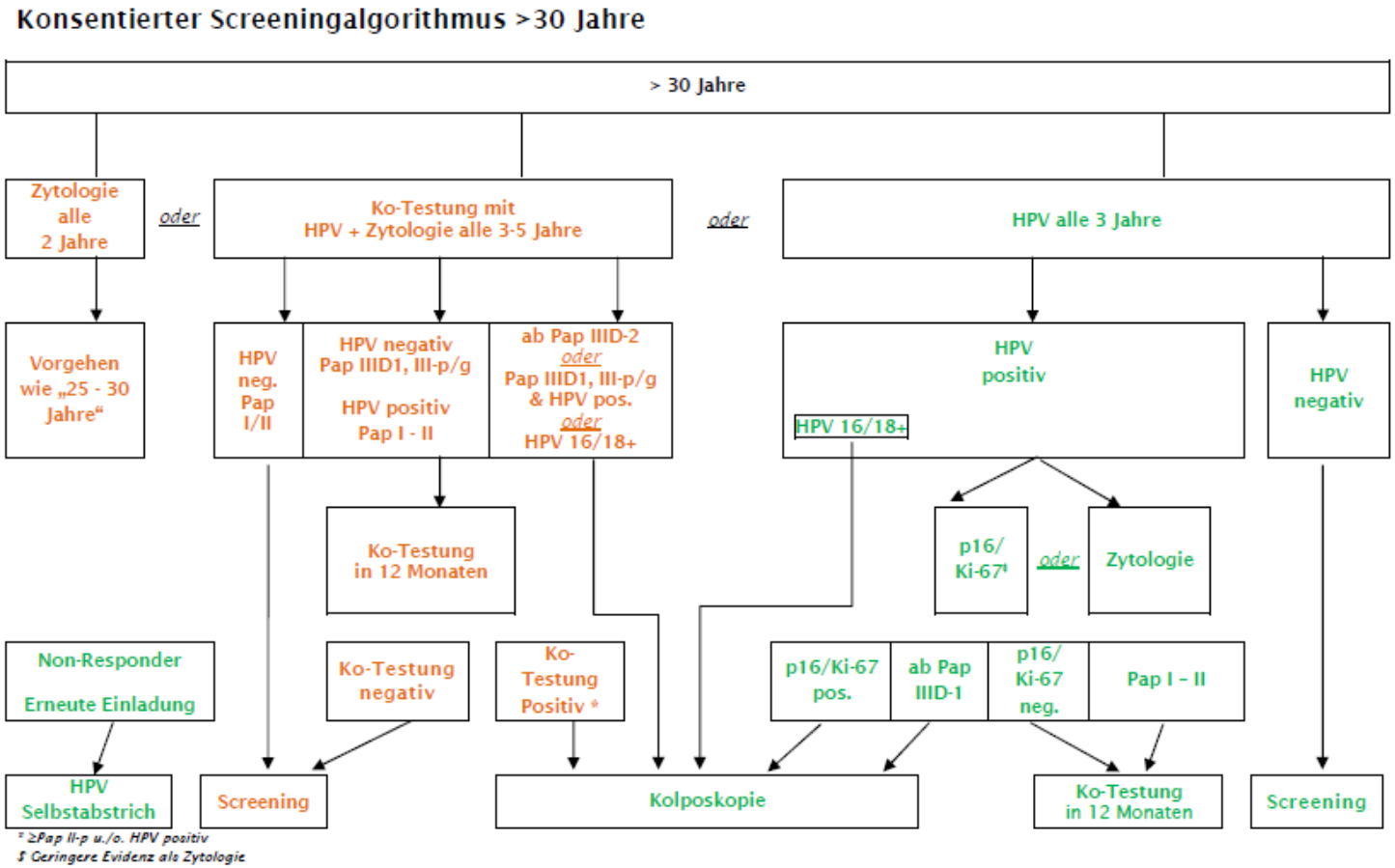
Figure 2 shows a flow-chart diagram of the screening strategies with the respective follow-up algorithms.

Clinical practice data were derived from current guidelines for cervical cancer diagnosis, management and treatment of pre-invasive lesions and invasive cancer in Germany. In the model, diagnostic work-up and treatment procedures for histologically diagnosed preinvasive cervical lesions and invasive cancer are the same for all screening strategies being evaluated.

Figure 2. Screening- and follow-up algorithms (in German)



* Bei Befunden der Gruppe III-x*, III-e* und III-g sollte eine endometriumsspezifische Abklärung zum Ausschluss einer endometrialen Neoplasie erfolgen (Vaginalsonografie, Hysteroskopie, fraktionierte Abrasio etc.).
# Geringere Evidenz als HPV Test



Ko-Testung in 12 Monaten: Kontrolle mit HPV + Zytologie in 12 Monaten

4.4 Model Input Parameters

Model parameters are presented as means. Uncertainty is expressed in 95% confidence intervals (95% CI) or ranges.

4.4.1 Disease Progression

The natural history of cervical cancer development was defined by annual transition probabilities for the progression or regression from a specific health state to another health state of the disease. All natural history parameter values are evidence-based and were derived from the published literature (13-25)) and calibrated (10, 11, 26) to fit specific epidemiologic data observed in an unscreened population in Germany (see Table 1).

Age-specific rates for benign hysterectomy were 0.884% for age 35-39 years, 1.125% for 40-44 years, 1.074% for 45-49 years, and 0.597% for age 50 years and older (25). Stage-specific annual cervical cancer mortality rates were based on original data from the Munich Cancer Registry (MCR) for the years 1988-2006. Based on these data, five-year survival rates for FIGO I, II, III, and IV were 94.2%, 73.5%, 42.0%, and 27.7%, respectively. Women could die from causes other than cervical cancer according to German age-specific all-cause mortality rates for females using German life tables from 2009/2011 from the German Federal Statistical Office (27). These age-specific mortality rates were reduced by the age-specific cervical cancer mortality derived from the German Federal Statistical Office in order to adjust for double counting mortality.

Table 1. Natural history model parameters

Transition				
From	**To**	**Age (years)**	**Annual probability**	**Reference**
Start prevalence HPV	------	15	0.1	(18)
Start prevalence CIN1	------	15	0.01	(18)
No Lesion, HPV-negative	No Lesion, HPV-positive	15 - 19 20 - 23 24 - 29 30 - 49 50 and older	0.1000 - 0.1700 0.1000 - 0.2025 0.0550 0.0120 - 0.0140 0.0045 - 0.0050	(15-17, 28) [a]
No Lesion, HPV-positive	CIN1 (90 %)		0.1075	(15, 17, 18, 20, 28) [a]
No Lesion, HPV-positive	CIN2 (10 %)		0.1075	(15, 17, 18, 20, 28)
CIN1	CIN2	15 - 34 35 and older	0.0176 0.0718	(16, 18, 21, 23, 24, 28) [a]
CIN2	CIN3	16 - 34 35 - 44 45 and older	0.0389 0.0797 0.1062	(14)
CIN3 or CIS	Cancer FIGO I	15 - 24 25 - 34 35 - 38 39 - 49 50 - 64 65 and older	0.0011 0.0013 0.0300 0.0650 0.0820 0.0831	(29) [a]
Cancer FIGO I	Cancer FIGO II		0.2933	(13) [a]
Cancer FIGO II	Cancer FIGO III		0.2793	(13)
Cancer FIGO III	Cancer FIGO IV		0.3461	(13) [a]
				(16, 18, 21, 23, 24, 28) [a]
No Lesion, HPV-positive	No Lesion, HPV-negative	15 - 24 25 - 29 30 and older	0.8026 0.4621 0.1083	
CIN1	No Lesion, HPV-negative (90 %)	15 - 34 35 and older	0.1750 0.0851	(16, 18, 21, 23, 24, 28)
CIN1	No Lesion, HPV-positive (10 %)	15 - 34 35 and older	0.1750 0.0851	(16, 18, 21, 23, 24, 28)
CIN2	No Lesion, HPV-negative (50 %)		0.0693	(16, 18, 21, 23, 24, 28)
CIN2	CIN1 (50 %)		0.0693	(16, 18, 21, 23, 24, 28)
CIN3	No Lesion, HPV-negative (50 %)		0.0693	(16, 18, 21, 23, 24, 28)
CIN3	CIN2 (50 %)		0.0693	(16, 18, 21, 23, 24, 28)
Non-symptomatic	symptomatic			
Cancer FIGO I	Cancer FIGO I		0.150	(13)
Cancer FIGO II	Cancer FIGO II		0.225	(13)
Cancer FIGO III	Cancer FIGO III		0.600	(13)
Cancer FIGO IV	Cancer FIGO IV		0.900	(13)

CIN: cervical intraepithelial neoplasia, CIS: carcinoma in situ, FIGO: invasive cancer stage classification Fédération Internationale de Gynécologie et d'Obstétrique, HPV: human papillomavirus.
[a] calibrated model parameter.

4.4.2 Population Characteristics

The model follows a cohort of 15 year old women not vaccinated against high-risk human papilloma virus 16 and 18. For the starting cohort, HPV prevalence was assumed to be 10%, and CIN 1 prevalence 1% (18).

4.4.3 Screening Adherence

We used aggregated data reported for screening adherence in Germany. In the absence of individual data, screening adherence was modeled to be independent from screening history. Using published German data on age-specific screening adherence (overall mean in the base-case analysis: on average 70-80% for the age younger than 55 yrs), the same screening adherence rates were applied simultaneously to all screening strategies including all screening intervals (Table 2) (30). Due to lack of individual screening pattern data, no systematic screening adherence patterns could have been considered. Compliance with follow-up of abnormal screening results, diagnosis and treatment was considered to be 100%.

Table 2. Age-specific screening adherence

Age (years)	Screening adherence	Source
20 - 29	0.79-0.81	
30 - 39	0.80-0.78	
40 - 49	0.74-0.72	
50 - 59	0.69-0.66	Kerek-Bodden 2008 (31)
60 - 69	0.62-0.55	
70 - 79	0.43-0.32	
80 +	0.17	

4.4.4 Screening Test Characteristics

Primary screening test sensitivity and specificity data for cytology alone, HPV alone and co-testing with HPV plus cytology were derived from international meta-analyses (31-34) and

are displayed in Table 3. The meta-analysis of Arbyn et al. (31) reported similar test performance data for HPV tests other than hybrid capture 2 (HC2). Therefore, in our model all HPV screening strategies include an HPV test with high performance and we used the test performance data for HC2 as a proxy for all HPV tests. As there is no scientific evidence for higher sensitivity or specificity with liquid-based cytology screening, we assumed the same test characteristics in all strategies using LBC as a screening test.

Test accuracy data for secondary testing (e.g., triage after positive primary HPV test) were derived from the published international literature (35-37) (Table 4). For the triage with cytology or LBC, we assumed the same sensitivity and specificity data as used in primary testing. For colposcopy/biopsy, we used 96% sensitivity and 48% specificity (38). For simplicity, the model assumes that a positive biopsy will always diagnose the true underlying health state and that a colposcopy-directed biopsy will always diagnose the true underlying health state.

Table 3. Model parameters: screening test characteristics

Screening test	Threshold	Sensitivity (%)	95% CI (range)	Specificity (%)	95% CI	Reference
Cytology	(ASCUS+) / CIN1 +	47.1	44.8-49.4	94.2	93.3-95.2	Arbyn et al. 2012, Cuzick et al. 2006, Nanda et al. 2000 (31, 32, 34)
	(ASCUS+) / CIN2 +	70.3*	62.5-78.9*			
	(ASCUS+) / CIN3 +	68.5*	55.4-85.2*			
HPV	(1 pg/ml) / CIN1 +	80.6	76.3-84.3	91.4	89.8-92.9	Arbyn et al. 2012, Cuzick et al. 2006 (31, 32)
	(1 pg/ml) / CIN2 +	96.3	94.5-98.1			
	(1 pg/ml) / CIN3 +	98.0	97.0-99.0			
HPV + Cytology	(1 pg/ml / ASCUS+) / CIN1 +	81.5	76.8-84.8	88.8	85.5-92.1	Arbyn et al. 2012, Cuzick et al. 2006 (31, 32)
	(1 pg/ml / ASCUS+) / CIN2 +	99.8	99.0-100.0			
	(1 pg/ml / ASCUS+) / CIN3 +	99.8	99.0-100.0			

ASC-US: Atypical squamous cells of undetermined significance, CIN: cervical intraepithelial neoplasia, HCII: Hybrid Capture II, HPV: Human papillomavirus, CI: confidence interval, LSIL: low-grade squamous intraepithelial lesion, Pap: Papanicolaou test. *calculated based on relative sensitivity HC2 vs. cytology (basecase: 1.37 for (ASCUS+)/ CIN2+ and 1.43 for (ASCUS+)/ CIN3+) in European and North-American studies

Table 4. Test accuracy data of secondary tests (triage)

Screening test	Threshold	Sensitivity (%)	95% CI (range)	Specificity (%)	95% CI	Reference
	Triage of Pap ASCUS					
HPV	(1 pg/ml) / CIN1 +	90.9§	82.2-96.3	36.3	30.7-42.2	Schmidt et al. 2011 (36)
	(1 pg/ml) / CIN2 +	90.9	82.2-96.3			
	(1 pg/ml) / CIN3 +	90.2	78.6-96.7			
P16/Ki-67	(≥ 1 cell) /CIN1+	92.2§	83.8-97.1§	80.6	75.6-85.1	Schmidt et al. 2011 (36)
	(≥ 1 cell) /CIN2+	92.2	83.8-97.1			
	(≥ 1 cell) /CIN3+	92.2	81.1-97.8			
	Triage of Pap LSIL					
HPV	(1 pg/ml) / CIN1 +	96.4§	91.7-98.8	19.1	14.6-24.2	Schmidt et al. 2011 (36)
	(1 pg/ml) / CIN2 +	96.4	91.7-98.8			
	(1 pg/ml) / CIN3 +	95.8	88.3-99.1			
P16/Ki-67	(≥ 1 cell) /CIN1+	94.2§	88.8-97.4§	68.0	62.2-73.4	Schmidt et al. 2011 (36)
	(≥ 1 cell) /CIN2+	94.2	88.8-97.4			
	(≥ 1 cell) /CIN3+	95.8	88.3-99.1			
	Triage of HPV-positive					
Cytology	(ASCUS+) / CIN1 +	47.1	44.8-49.4	94.2	93.3-95.2	Arbyn et al. 2012, Cuzick et al. 2006, Nanda et al. 2000 (31, 32, 34)
	(ASCUS+) / CIN2 +	70.3*	62.5-78.9*			
	(ASCUS+) / CIN3 +	68.5*	55.4-85.2*			
P16/Ki-67	(≥ 1 cell) /CIN1+	91.9§	78.1-98.3§	82.1	72.9-89.2	Petry et al. 2011 (35)
	(≥ 1 cell) /CIN2+	91.9	78.1-98.3			
	(≥ 1 cell) /CIN3+	96.4	81.7-99.9			

§ not reported in the literature, and therefore assumed to be the same as for CIN2+

In the base-case analysis, we used conservative model parameters and model assumptions, that is, in favor of cytology tests and against HPV tests. Therefore, it is expected that in reality the benefit-harm balance and the cost effectiveness for the HPV-based screening strategies is better than reported in our results when compared with the cytology-based screening strategies. We performed comprehensive sensitivity analyses and varied the model parameters for test sensitivity and specificity in order to assess robustness of results and identify need for further research.

4.4.5 Resource Utilization and Cost Data

All health state costs were derived from the previously validated and published cost-effectiveness model for the German health care context and inflated to the index year 2014

by using the German Consumer Price Index (CPI) (www.destatis.de). For screening tests, current prices were applied.

Direct annual costs were calculated based on actual reimbursement costs, including frequencies of diagnostic and laboratory testing, medication, and treatment procedures related to the specific cervical cancer stages. Health resource utilization frequencies were derived from diagnostic and treatment guidelines, HTA experts (10, 11, 26) and experts from the current guideline group. Reimbursement costs were derived from healthcare databases and applicable pharmaceutical prices. We adjusted reimbursement prices for ambulatory care costs using a weighted average for East and West Germany and social and private health insurance from published data (39, 40). Inpatient costs for cervical cancer treatment procedures were based on Diagnosis Related Groups (DRG).

Table 5 shows the direct medical costs for cervical cancer screening, diagnostic work-up, and therapy, medications, follow-up and palliative procedures.

Table 5. Aggregated costs (per unit) for screening, diagnostic work-up, therapy, and follow-up procedures (Index year 2014).

Procedure	Costs (Euro)
Screening office visit 59 years [a]	32.82
Screening office visit until 60+ years [a]	33.82
Control office visit (cytology) 59 years [a]	16.58
Control office visit (cytology) until 60+ years [a]	17.58
Control office visit (HPV or p16/Ki-67) 59 years [a]	23.17
Control office visit (HPV or p16/Ki-67) until 60+ years [a]	24.17
Pap cytology	7.40
LBC cytology	25.00
P16/Ki-67 dual stain	59.70
HPV test [‡]	30.40
Colposcopy	23.98
Biopsy	21.12
Conization until 39 years	462.10
Conization 40 to 59 years	469.88
Conization 60+ years	472.91
Follow-up after conization until 59 years [a]	158.97
Follow-up after conization 60+ years [a]	114.68
Therapy FIGO IA1 until 39 years	3,265.57
Therapy FIGO IA1 40 to 59 years	3,269.59
Therapy FIGO IA1 60+ years	3,271.16
Therapy FIGO IA2 until 39 years	4,518.36
Therapy FIGO IA2 40 to 59 years	4,520.96
Therapy FIGO IA2 60+ years	4,521.98
Therapy FIGO IB1 until 18 years	4,588.19
Therapy FIGO IB1 19 to 39 years	4,092.81
Therapy FIGO IB1 40 to 59 years	4,083.19
Therapy FIGO IB1 60+ years	4,085.36
Therapy FIGO IB2 until 18 years	5,707.10
Therapy FIGO IB2 19+ years	5,095.76
Therapy FIGO IIA until 18 years	6,081.91
Therapy FIGO IIA 19+ years	5,412.10
Therapy FIGO IIB until 18 years	5,494.12
Therapy FIGO IIB 19+ years	4,295.39
Therapy FIGO III until 18 years	6,512.94
Therapy FIGO III 19+ years	4,862.68
Therapy FIGO IV until 18 years	7,346.86
Therapy FIGO IV 19+ years	5,573.06
Follow-up after cancer therapy until 59 years, year 1 and 2 after therapy [a]	635.88
Follow-up after cancer therapy 60+ years, year 1 and 2 after therapy [a]	639.88
Follow-up after cancer therapy until 59 years, year 3, 4 and 5 after therapy [a]	317.95
Follow-up after cancer therapy 60+ years, year 3, 4 and 5 after therapy [a]	319.94
Follow-up after cancer therapy until 59 years, year 6 after therapy [a]	158.97
Follow-up after cancer therapy 60+ years, year 6 after therapy [a]	159.97
Palliative costs until 18 years	6,007.00
Palliative costs 19+ years	6,794.82

FIGO: cervical cancer stage classification Fédération Internationale de Gynécologie et d'Obstétrique, HPV: Human papillomavirus, Pap: Pap cytology test. Screening costs: including reimbursement for gynecological work-up and laboratory costs for cytology. Control costs: reimbursement for follow-up testing and work-up is considered.
[a] Aggregated costs per year.

4.5 Model Application and Analyses

The decision-analytic model was calibrated, validated and applied to perform benefit-harm analyses and cost-effectiveness analyses. Analyses are based on deterministic cohort simulations using mean values for all model parameters in the base-case analysis.

All decision analyses were performed using the decision-analytic software package TreeAge Pro 2014 (TreeAge Software Inc., Williamstown, MA, USA). All further statistical analyses were performed with SAS 9 (SAS Institute Inc., Cary, North Carolina) and Excel (Microsoft). For epidemiological calculations of aggregated measures, the Software EpiCalc 2000 Version 1.02 ref(41) was applied.

4.5.1 Calibration

As described previously (10, 11, 26), the model was calibrated in a systematic and hierarchical manner to fit specific epidemiologic data observed in an unscreened population in Germany. Epidemiologic data from the German Common Cancer Registry (CCR) from the years 1964-1966 were used to calibrate the model to fit cervical cancer incidence and FIGO-stage distribution. Age-specific HPV-incidence was calibrated such that the model predicted age-specific HPV prevalence as observed in a German population (42). For more information on calibration methods and calibration results see prior publications (10, 11, 26).

4.5.2 Validation

The model was validated internally and externally on several levels (43). First, plausibility and face validity checks have been performed. Second, a technical verification / debugging of the model programming code has been conducted. Third, using cross-model validation, the model structure and results have been compared with other published models. Forth, an internal validation for multiple criteria has been performed using independent epidemiological data from German cancer registries that have not been used to inform the model. Fifth, an external validation has been conducted comparing the model predictions with (a) epidemiological data from German cancer registries that have not been used to inform the model and its parameters and with (b) German published literature data. The

following target parameters have been used for the validation: (1) age peak (in years) for the development of cervical carcinoma and cervical intraepithelial neoplasia (CIN 1 to CIN 3/CIS), (2) der incidence peak (per 100,000 women), (3) the total incidence (per 100,000 women), (4) the distribution of FIGO cancer stages I to IV (in percent), (5) the lifetime risk for a benign hysterectomy (in percent), (6) the lifetime risk for cervical cancer (in percent), and (7) the lifetime risk for death due to cervical cancer (in percent). The validation showed that model predictions for an unscreened population were consistent with independent data observed in Germany before introduction of screening.

4.5.3 Benefit-Harm Analysis

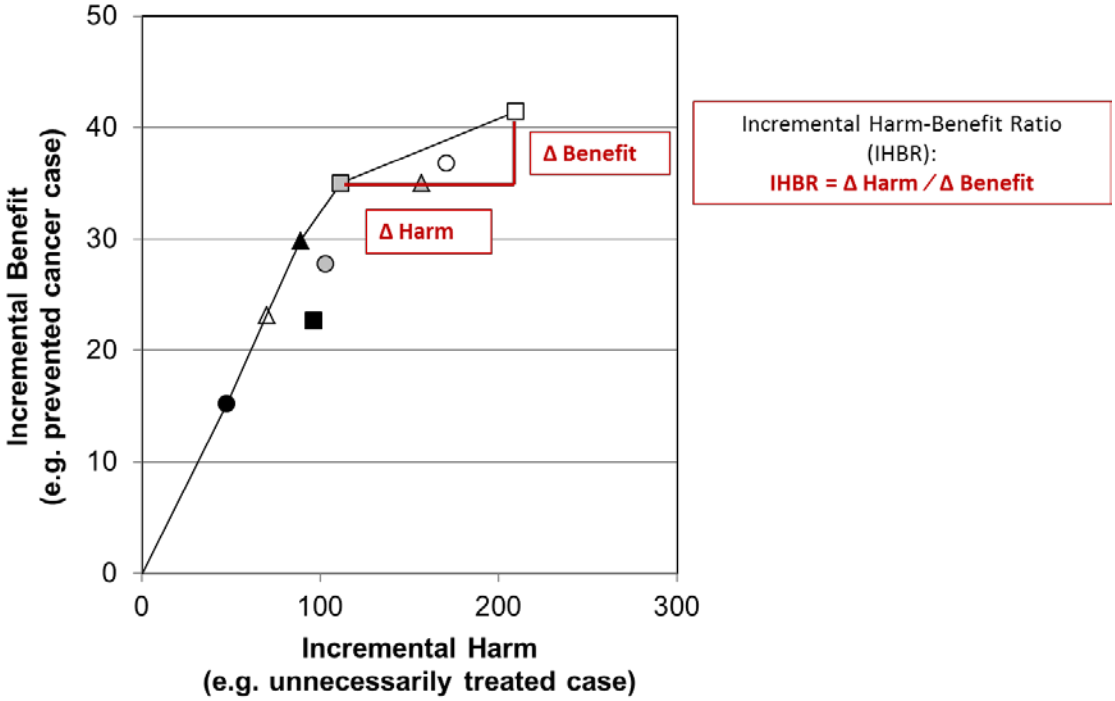
We used a benefit-harm frontier approach to analyze and visualize the trade-off between benefits and harms. The incremental harm-benefit ratios are calculated for the lifelong time horizon. The IHBR is defined by the difference in harms (in harm units), divided by the difference in benefits (in benefit units) between two interventions:

$IHBR = (H_A - H_B) / (B_A - B_B)$,

with H_A and H_B equaling the total lifetime harms for intervention A and B, and B_A and B_B equaling the total lifetime benefits for intervention A and B.

The incremental harm-benefit concept and the IHBR is illustrated in Figure 3. We visualize the incremental harm-benefit ratio using the benefit-harm frontier, where non-dominated strategies lie on the benefit-harm frontier line. All strategies lying below this line are more harmful and equally or less effective compared to other strategies or combinations of other strategies, and are therefore dominated by the strategies on the benefit-harm frontier. From this graph (Figure 3), we can directly derive the incremental harm-benefit ratio representing the units of harms we have to accept for one additional unit of benefit gained, if we consider a specific intervention compared to the next non-dominated intervention.

Figure 3. Illustration of the benefit-harm frontier concept



The black line represents the benefit-harm frontier. All strategies lying below this line are more harmful and provide equal or less benefit compared to other strategies or combinations of other strategies, and are therefore dominated by the strategies on the benefit-harm frontier. From this graph, we can directly derive the incremental harm-benefit ratio representing the additional units of harms we have to accept for one additional unit of benefit gained, if we consider a specific intervention compared to the next non-dominated intervention.

4.5.4 Cost-Effectiveness Analysis

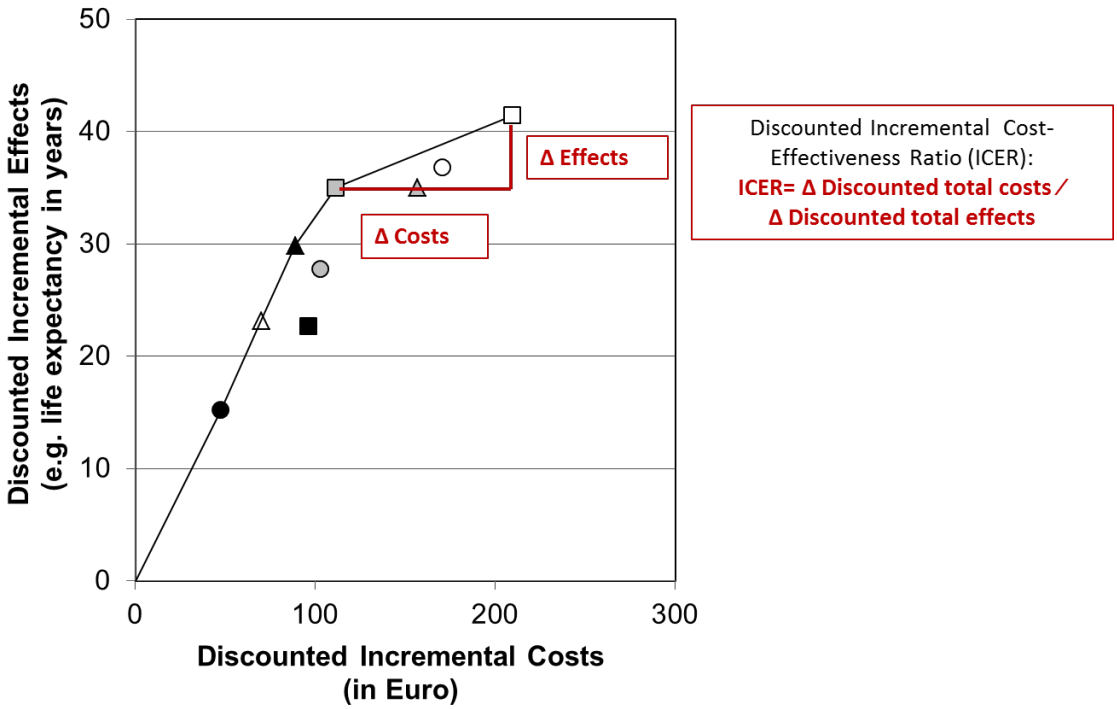
The discounted ICERs are calculated for the lifelong time horizon. The discounted ICER is defined by the difference in discounted costs, divided by the difference in discounted effects between two interventions (Figure 4):

$ICER = (C_A - C_B) / (E_A - E_B)$

With C_A and C_B equaling the total lifetime costs for intervention A and B, and E_A and E_B equaling the total lifetime effects for intervention A and B. We visualize the incremental cost-effectiveness ratio using the cost-effectiveness frontier, where non-dominated strategies lie on the cost-effectiveness frontier line. All strategies lying below this line are more costly and equally or less effective compared to other strategies or combinations of other strategies, and are therefore dominated by these strategies. From the incremental

cost-effectiveness frontier, we can directly derive the ICER representing the additional costs (in Euro) we have to accept for one additional unit of benefit gained, if we consider a specific strategy compared to the next non-dominated strategy.

Figure 4. Cost-Effectiveness Frontier



The black line represents the cost-effectiveness frontier. All strategies lying below this line are more costly and equally or less effective compared to other strategies or combinations of other strategies, and are therefore dominated by the strategies on the cost-effectiveness frontier. From this graph, we can directly derive the incremental cost-effectiveness ratio representing the additional costs we have to accept for one additional unit of effectiveness (e.g., life years) gained, if we consider a specific intervention compared to the next non-dominated intervention.

4.5.5 Sensitivity Analyses

We performed one-way and multi-way sensitivity analyses to evaluate the robustness of the results. In the sensitivity analyses, we used lower and upper 95% CI limits or ranges derived from the published literature to vary model parameters. In multi-way sensitivity analyses, Pap cytology sensitivity values were varied using the lower 95% CI limits for primary and secondary (triage) test values, and for the accuracy of colposcopy a specificity of 0.566 and a sensitivity of 0.760 for CIN1/CIN2 and 0.983 for CIN3+ was used as reported in Cantor et al.

2008 (44). Variation of test performances was particularly important as the assumption of independence of test performance conditional on disease status for repeated tests may be overestimated for lesions with specific morphologic conditions. The screening adherence was increased to 100% in the sensitivity analysis to provide results for “intended strategies”. In the sensitivity analyses, the cancer treatment costs were increased to 4-fold of the base-case values.

5 Results

5.1 Screening-Related Benefits

5.1.1 Reduction in Cervical Cancer Incidence

Compared to no screening with a cervical cancer incidence of 46.2 per 100,000 women, screening with cytology or HPV-based strategies achieves a relative reduction in cervical cancer incidences by 72 – 97% depending on screening interval and screening algorithm. Within the same screening interval, HPV-based screening strategies are more effective (with relative reduction of 83.5%-96.2% for screening intervals 5, 3 or 2 years) compared with cytology screening strategies (relative reduction of 72.4%-91.3% for 5, 3, 2, and 97.3% for 1 year).

Switching from 5-yearly cytology screening to 5-yearly HPV-based screening achieves further 11% relative reduction in cervical cancer incidence. Switching from biennial cytology screening to biennial HPV-based screening achieves further 3% relative reduction in cervical cancer incidence. Annual HPV-based screening was not considered in our analyses. Comparing HPV-based screening strategies, all strategies were very similar regarding effectiveness.

Table 6. Reduction in cervical cancer incidence

	Annual cancer incidence	Reduction in cancer incidence vs. no screening	
		Absolute reduction	Relative reduction
Strategy	per 100,000 women	per 100,000 women	%
15. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	1.27	44.97	97.3
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	1.27	44.97	97.3
11. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	1.27	44.96	97.3
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	1.27	44.96	97.3
2. Conv. Pap: Alter 20J, Intervall 1J	1.61	44.62	96.5
22. HPV + LBC Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	1.75	44.49	96.2
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	1.75	44.49	96.2
31. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	1.79	44.44	96.1
28. HPV / LBC Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	1.84	44.39	96.0
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	1.84	44.39	96.0
23. HPV + LBC Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	3.41	42.82	92.6
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	3.41	42.82	92.6
32. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	3.51	42.72	92.4
29. HPV / LBC Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	3.60	42.64	92.2
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	3.60	42.64	92.2
16. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	4.04	42.20	91.3
8. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	4.04	42.20	91.3
12. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	4.04	42.19	91.3
4. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	4.04	42.19	91.3
17. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	7.11	39.12	84.6
9. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	7.11	39.12	84.6
13. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	7.12	39.11	84.6
5. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	7.12	39.11	84.6
24. HPV + LBC Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	7.31	38.92	84.2
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	7.31	38.92	84.2
33. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	7.50	38.73	83.8
30. HPV / LBC Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	7.63	38.61	83.5
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	7.63	38.61	83.5
18. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	12.75	33.49	72.4
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	12.75	33.49	72.4
14. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	12.75	33.48	72.4
6. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	12.75	33.48	72.4
1. Kein Screening	46.23	0.00	0.0

5.1.2 Reduction in Cervical Cancer Mortality

Compared to no screening with a cervical cancer mortality of 17.6 per 100,000 women, screening with cytology or HPV-based strategies achieves a relative reduction in cervical cancer mortality by 79 – 99% depending on screening interval and screening algorithm. Within the same screening interval, HPV-based screening strategies are more effective (with

relative reduction of 88.7%-98.1% for screening intervals 5, 3 or 2 years) compared with cytology screening strategies (relative reduction of 78.5%-94.8% for 5, 3, 2, and 98.7% for 1 year).

Switching from 5-yearly cytology screening to 5-yearly HPV-based screening achieves further 11% relative reduction in cervical cancer mortality. Switching from biennial cytology screening to biennial HPV-based screening achieves further relative 3% reduction in cervical cancer mortality.

Table 7. Reduction in cervical cancer mortality

	Annual mortality from cancer	Reduction in mortality from cancer vs. no screening	
		Absolute reduction	Relative reduction
Strategy	per 100,000 women	per 100,000 women	%
15. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	0.23	17.32	98.7
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	0.23	17.32	98.7
11. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	0.23	17.32	98.7
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	0.23	17.32	98.7
2. Conv. Pap: Alter 20J, Intervall 1J	0.29	17.26	98.3
22. HPV + LBC Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	0.33	17.22	98.1
19. HPV + Conv.17,32/ Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	0.33	17.22	98.1
31. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	0.34	17.21	98.0
28. HPV / LBC Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	0.35	17.19	98.0
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	0.35	17.19	98.0
23. HPV + LBC Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	0.74	16.80	95.8
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	0.74	16.80	95.8
32. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	0.77	16.78	95.6
29. HPV / LBC Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	0.79	16.76	95.5
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	0.79	16.76	95.5
16. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	0.92	16.63	94.8
8. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	0.92	16.63	94.8
12. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	0.92	16.63	94.8
4. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	0.92	16.63	94.8
17. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	1.85	15.70	89.5
9. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	1.85	15.70	89.5
13. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	1.85	15.70	89.5
5. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	1.85	15.70	89.5
24. HPV + LBC Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	1.88	15.66	89.3
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	1.88	15.66	89.3
33. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	1.95	15.60	88.9
30. HPV / LBC Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	1.98	15.57	88.7
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	1.98	15.57	88.7
18. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	3.78	13.77	78.5
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	3.78	13.77	78.5
14. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	3.78	13.77	78.5
6. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	3.78	13.77	78.5
1. Kein Screening	17.55	0.00	0.0

5.1.3 Gains in Remaining Life Expectancy

Compared to no screening with a remaining life expectancy of 67.9 years (for a 15-year old woman), screening with cytology or HPV-based strategies achieves on average 0.21-0.26 life-years gained (75.1 - 93.4 life days gained), depending on screening interval and screening algorithm.

Within the same screening interval, HPV-based screening strategies are more effective, yielding an expected gain in life years compared to no screening of 0.23 to 0.26 life-year gained for 5- to 2-yearly screening), compared with cytology screening strategies yielding an expected gain in life years compared to no screening of 0.21 to 0.25 life-year gained for 5- to 2-yearly screening.

Switching from 5-yearly cytology screening to 5-yearly HPV-based screening achieves on average 0.027 life-year gained (i.e., 9.7 life-days gained). Switching from biennial cytology screening to biennial HPV-based screening achieves on average 0.008 life year gained (i.e., 3.1 life-days gained).

Table 8. Remaining life expectancy

	Life years	Life-years gained vs. no screening
1. Kein Screening	67.90656	
6. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	68.11225	0.205692
14. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	68.11225	0.205692
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	68.11229	0.205732
18. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	68.11229	0.205732
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	68.13879	0.232237
30. HPV / LBC Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	68.13879	0.232237
33. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	68.13927	0.232713
5. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	68.13959	0.233033
13. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	68.13959	0.233033
9. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	68.13962	0.23306
17. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	68.13962	0.23306
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	68.14024	0.233686
24. HPV + LBC Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	68.14024	0.233686
4. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	68.15295	0.246391
12. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	68.15295	0.246391
8. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	68.15296	0.246408
16. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	68.15296	0.246408
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	68.15525	0.248694
29. HPV / LBC Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	68.15525	0.248694
32. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	68.15551	0.248953
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	68.15595	0.24939
23. HPV + LBC Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	68.15595	0.24939
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	68.16115	0.254593
28. HPV / LBC Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	68.16115	0.254593
31. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	68.16129	0.254733
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	68.16145	0.254891
22. HPV + LBC Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	68.16145	0.254891
2. Conv. Pap: Alter 20J, Intervall 1J	68.16189	0.255334
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	68.1625	0.255944
11. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	68.1625	0.255944
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	68.1625	0.255949
15. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	68.1625	0.255949

5.2 Screening-Related Harms

5.2.1 Total Number of Positive Screening Test Results

Depending on screening strategy and interval test, the total number of positive screening results varies by a factor of 4. Cytology-based screening results in 70 (5-year interval) to 281 (annual screening) screen-positive test results per 100 screened women. HPV-based

screening results in 92 (5-year interval) to 206 (2-year interval) screen-positive test results per 100 screened women.

Within the same screening interval, HPV-based screening results in more positive screening tests compared to cytology. Cotesting with HPV and cytology results in a relative increase of 12-15% (depending on screening interval) in positive test results.

Table 9. Total number of positive screening test results

Strategy	Total number of positive screening test results per 100 screened women
1. Kein Screening	0.00
18. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	69.78
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	69.78
14. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	69.79
6. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	69.79
33. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	91.48
30. HPV / LBC Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	91.54
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	91.54
17. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	96.69
9. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	96.69
13. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	96.70
5. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	96.70
24. HPV + LBC Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	102.73
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	102.73
16. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	128.63
8. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	128.63
12. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	128.65
4. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	128.65
32. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	131.06
29. HPV / LBC Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	131.18
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	131.18
23. HPV + LBC Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	149.61
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	149.61
31. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	178.46
28. HPV / LBC Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	178.67
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	178.67
22. HPV + LBC Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	205.95
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	205.95
15. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	222.66
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	222.66
11. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	222.68
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	222.68
2. Conv. Pap: Alter 20J, Intervall 1J	281.03

5.2.2 Total Number of Colposcopies

Depending on screening strategy and interval, the total number of colposcopies varies by a factor of 4. Cytology-based screening results in 52 (5-year interval) to 224 (annual screening) colposcopies per 100 screened women compared to 60 (5-year interval) to 121 (2-year interval) colposcopies per 100 screened women with HPV-based screening.

Within the same screening interval, HPV-based screening results in more colposcopies compared to cytology. With screening in 5 year intervals, cotesting with HPV plus cytology results in 15% (relative) more colposcopies and HPV screening with a triage in 16% (relative) more colposcopies compared to cytology screening. With a 2-year screening interval, cytology with dual stain triage results in 44% (relative) less colposcopies than cytology with HPV triage. Compared to biennial cytology with dual stain triage, screening with HPV-based strategies results in 6% (cotesting HPV + cytology) to 34% (HPV + dual stain triage) more colposcopies, but colposcopy rates of HPV-based screening strategies are lower than for biennial cytology with HPV triage.

Table 10. Total number of colposcopies

Strategy	Total number of colposcopies per 100 screened women
1. Kein Screening	0.00
14. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	52.44
6. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	52.44
24. HPV + LBC Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	60.21
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	60.21
30. HPV / LBC Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	60.79
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	60.79
13. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	70.36
5. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	70.36
33. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	70.47
18. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	72.58
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	72.58
23. HPV + LBC Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	77.30
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	77.30
29. HPV / LBC Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	78.30
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	78.30
12. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	90.97
4. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	90.97
32. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	94.12
22. HPV + LBC Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	96.82
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	96.82
28. HPV / LBC Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	98.32
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	98.32
17. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	99.59
9. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	99.59
2. Conv. Pap: Alter 20J, Intervall 1J	106.00
31. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	121.63
16. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	131.33
8. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	131.33
11. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	150.39
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	150.39
15. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	224.09
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	224.09

5.2.3 Total Number of Conizations

Depending on screening strategy and interval, the total number of conizations varies by a factor of 1.5. Cytology-based screening results in 7.3 (5-year interval) to 11.1 (annual screening) conizations per 100 screened women compared to 8.5 (5-year interval) to 10.5 (2 year interval) conizations per 100 screened women with HPV-based screening. The total number of conizations below CIN3 is similar in all cytology strategies (with HPV or dual stain triage) within the same screening interval.

Within the same screening interval, HPV-based screening results in more conizations compared to cytology. With screening in 5 year intervals, cotesting with HPV plus cytology results in 17% (relative) more conizations and HPV screening with a triage in 16% (relative) more conizations compared to cytology screening. Compared to biennial cytology, screening with biennial HPV-based strategies results in 8% (HPV + cytology triage) to 9% (HPV + dual stain triage or cotesting HPV + cytology) more total numbers of conizations per 100 screened women.

Table 11. Total number of conizations

Strategy	Total number of conizations per 100 screened women
1. Kein Screening	0
14. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	7.332211
6. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	7.332211
18. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	7.336495
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	7.336495
30. HPV / LBC Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	8.508229
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	8.508229
33. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	8.556666
24. HPV + LBC Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	8.586437
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	8.586437
13. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	8.706213
5. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	8.706213
17. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	8.710712
9. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	8.710712
12. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	9.616706
4. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	9.616706
16. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	9.621273
8. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	9.621273
29. HPV / LBC Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	9.700893
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	9.700893
32. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	9.750206
23. HPV + LBC Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	9.757853
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	9.757853
28. HPV / LBC Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	10.42027
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	10.42027
22. HPV + LBC Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	10.45538
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	10.45538
31. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	10.47316
11. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	10.74401
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	10.74401
15. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	10.74875
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	10.74875
2. Conv. Pap: Alter 20J, Intervall 1J	11.05292

5.2.4 Total Number of Conizations < CIN3

Depending on screening strategy and interval the total number of conizations below CIN3 varies 1.8–fold. Cytology-based screening results in 5.4 (5 year interval) to 9.5 (annual screening) conizations per 100 screened women compared to 6.4 (5 year interval) to 8.8 (2 year interval) conizations below CIN3 per 100 screened women with HPV-based screening. The total number of conizations below CIN3 is similar in all cytology strategies (with HPV or dual stain triage) within the same screening interval.

With screening in 5 year intervals, cotesting with HPV plus cytology or HPV with dual stain triage results in 21% (relative) and HPV screening with cytology triage in 20% (relative) more conization below CIN3 compared to cytology screening. Compared to biennial cytology, screening with biennial HPV-based strategies results in 13% (HPV + cytology triage), 14% (HPV + cytology cotesting), and 15% (HPV + dual stain triage) more conizations below CIN3 per 100 screened women.

Table 12. Total number of conizations < CIN 3

Strategy	Total number of conizations < CIN 3 per 100 screened women
1. Kein Screening	0.00000
14. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	5.36781
6. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	5.36781
18. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	5.37349
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	5.37349
30. HPV / LBC Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	6.41906
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	6.41906
33. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	6.48938
24. HPV + LBC Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	6.49686
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	6.49686
13. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	6.67483
5. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	6.67483
17. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	6.68136
9. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	6.68136
12. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	7.70511
4. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	7.70511
16. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	7.71222
8. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	7.71222
29. HPV / LBC Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	7.76798
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	7.76798
23. HPV + LBC Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	7.83389
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	7.83389
32. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	7.85103
28. HPV / LBC Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	8.74462
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	8.74462
22. HPV + LBC Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	8.78594
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	8.78594
31. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	8.84313
11. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	9.22593
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	9.22593
15. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	9.23405
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	9.23405
2. Conv. Pap: Alter 20J, Intervall 1J	9.47039

5.3 Benefit-Harm Balance

5.3.1 Benefit-Harm Analyses Using Screening Test Positive Results as Harm Outcome

Figure 5 shows the relation between total number of screening test-positive results and the reduction in cervical cancer cases per 100 screened women. Strategies positioned below the benefit-harm frontier are dominated, that is, compared to (combinations of) other

strategies, they yield less benefit (i.e., reduction of cervical cancer risk) while generating more harm (i.e., test-positive results).

For example, in order to prevent 1 additional cervical cancer case in 100 screened women with 5-yearly cytology screening, there are 31 additional positive screening test results. The corresponding numbers for the IHBR are 61 additional positive screening test results per prevented cervical cancer case for 5-yearly HPV with dual triage. and 146 additional positive screening test results for 3-yearly HPV with dual triage For shorter screening intervals, the efficiency curve becomes less steep, for instance, showing more than 400 additional positive screening test results for 2-yearly HPV-based strategies.

5-yearly or 3-yearly HPV screening with dual triage seems to result in a good balance between benefits (reduction in cancer) and harms associated with positive test results.

Figure 5. Benefit-harm frontier: Reduction in cervical cancer cases versus total number primary screening test-positive results

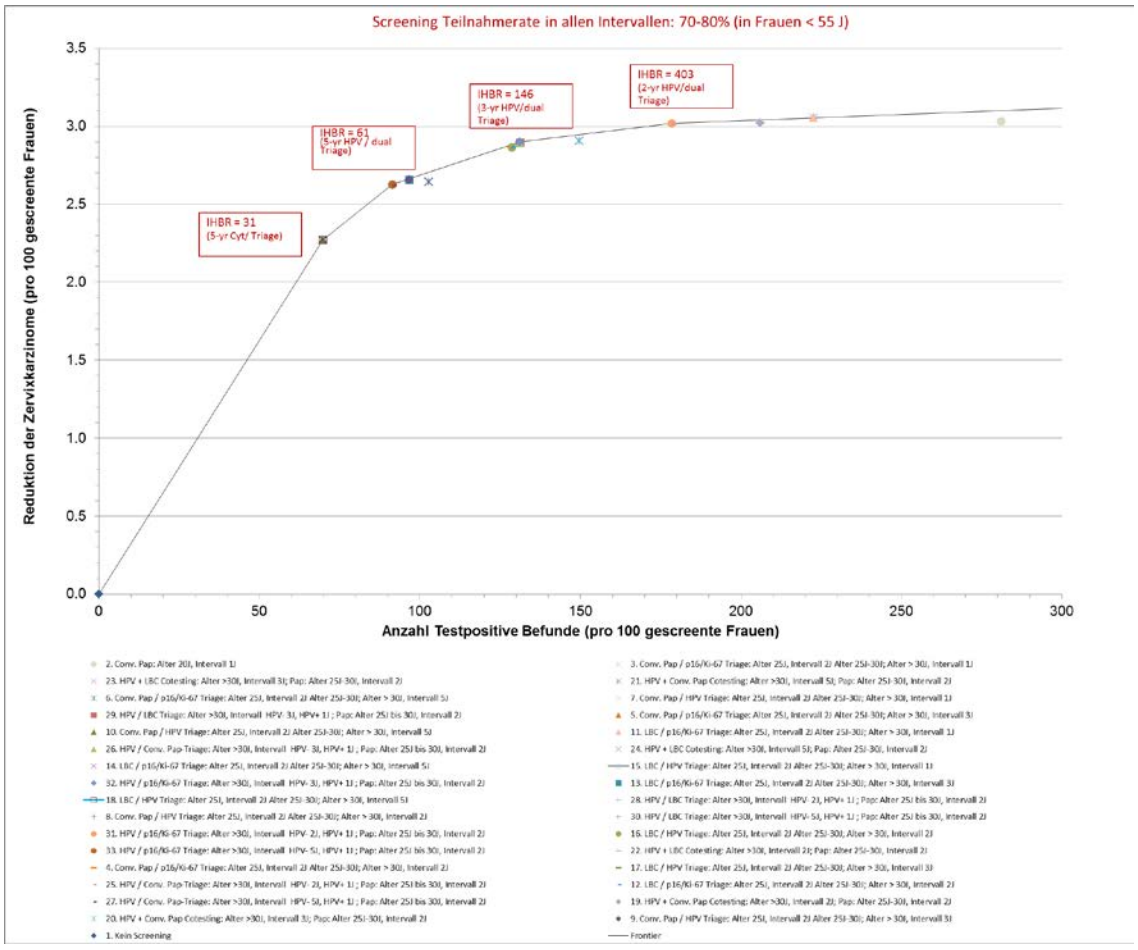


Figure 6 shows the relation between total number of screening test-positive results and the reduction in cervical cancer mortality per 100 screened women. In order to save 1 woman from dying due to cervical cancer in 100 screened women, there are additional 75 positive screening test results with 5-yearly cytology, 174 with 5-yearly HPV with dual triage, 494 with 3-yearly HPV with dual triage, 1,620 with biennial HPV with dual stain triage, and 5,594 with annual cytology. All other screening strategies are dominated.

5-yearly or 3-yearly HPV with dual triage seems to result in a good balance between benefits (reduction in cancer death) and harms associated with positive test results.

Figure 6. Benefit-harm frontier: Reduction in cervical cancer mortality versus total number primary screening test-positive results

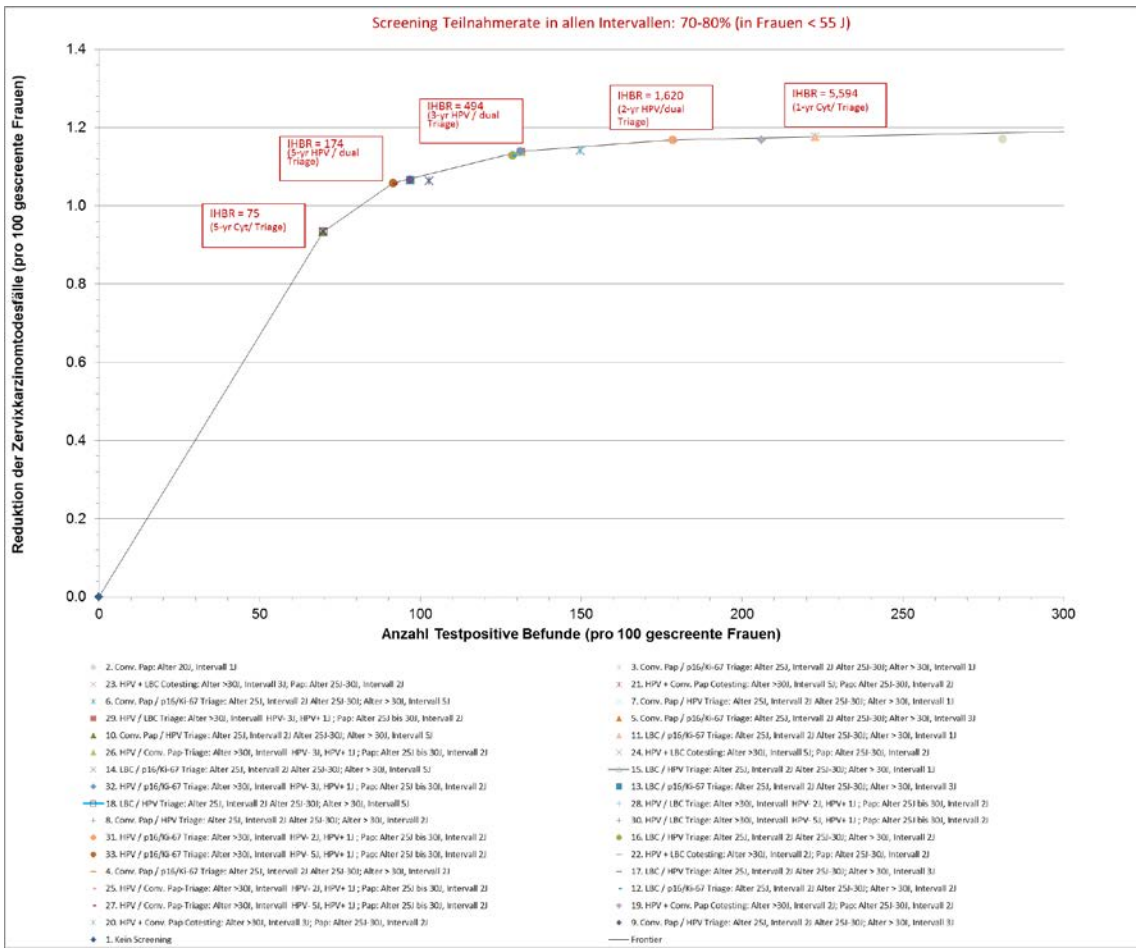
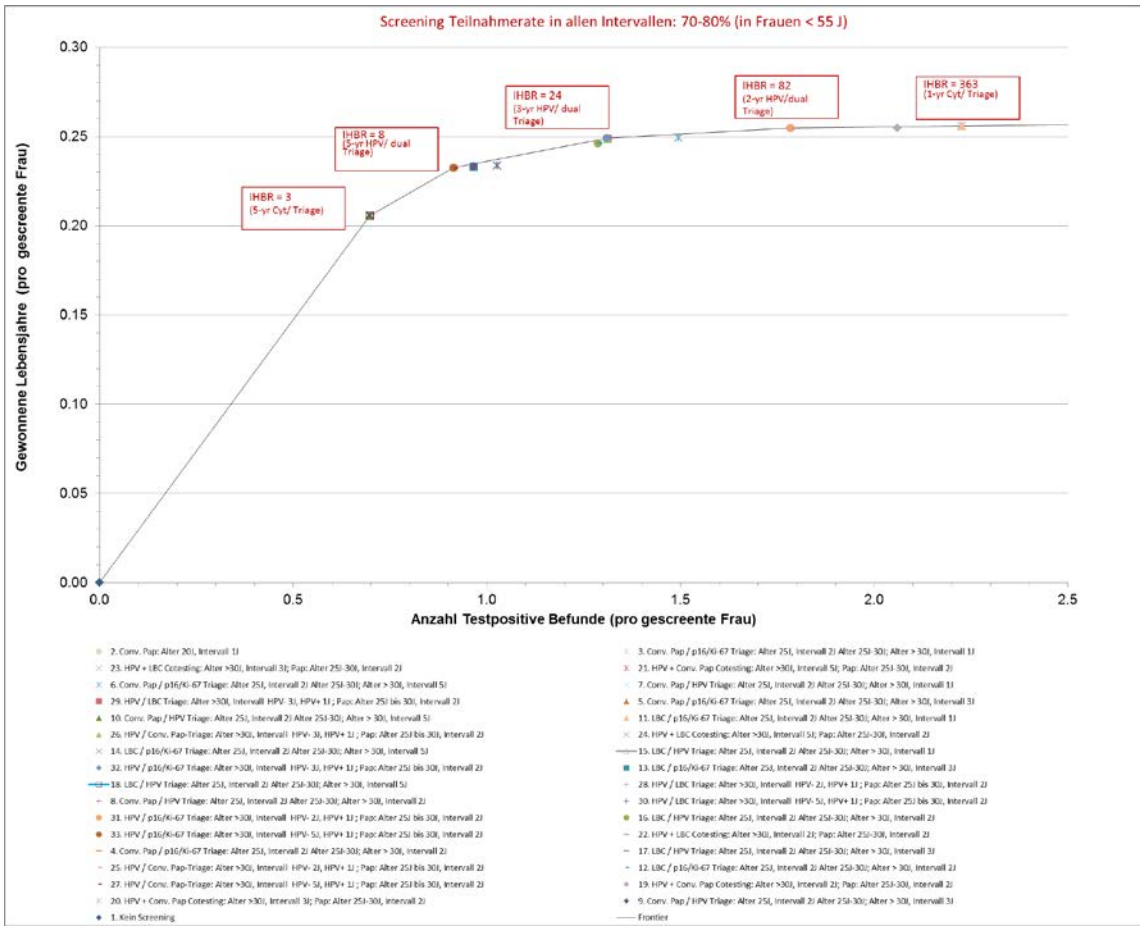


Figure 7 shows the relation between total number of screening test-positive results and the gain in remaining life expectancy per screened woman. In order to gain 1 life year due to screening, there are on average 3 additional positive screening test results with 5-yearly cytology, 8 with 5-yearly HPV with dual triage, 24 with 3-yearly HPV with dual triage, 82 with biennial HPV with dual triage, and 363 with annual cytology during women's lifetime. All other screening strategies are dominated.

5-yearly or 3-yearly HPV with dual triage or triennial HPV with dual stain triage seem to result in a good balance between benefits (gain in life expectancy) and harms associated with positive test results.

Figure 7. Benefit-harm frontier: Life-years gained versus total number primary screening test-positive results



5.3.2 Benefit-Harm Analyses Using Colposcopies as Harm Outcome

Figure 8 shows the relation between total number of colposcopies and the reduction in cervical cancer cases per 100 screened women. In order to prevent 1 additional cervical cancer case, there are additional 23 colposcopies with 5-yearly HPV plus cytology cotesting, 64 colposcopies with 3-yearly HPV plus cytology cotesting, 172 colposcopies with biennial HPV plus cytology cotesting, 972 colposcopies with current annual cytology, 1,919 colposcopies with annual cytology with dual stain triage, and 469,783 colposcopies with annual cytology with HPV triage. All other strategies are dominated.

HPV plus cytology cotesting every 5 or 3 years (depending on the willingness to accept colposcopies) seem to result in a good balance between benefits (reduction in cancer) and harms associated with numbers of colposcopies.

Figure 8. Benefit-harm frontier: Reduction in cervical cancer cases versus total number colposcopies

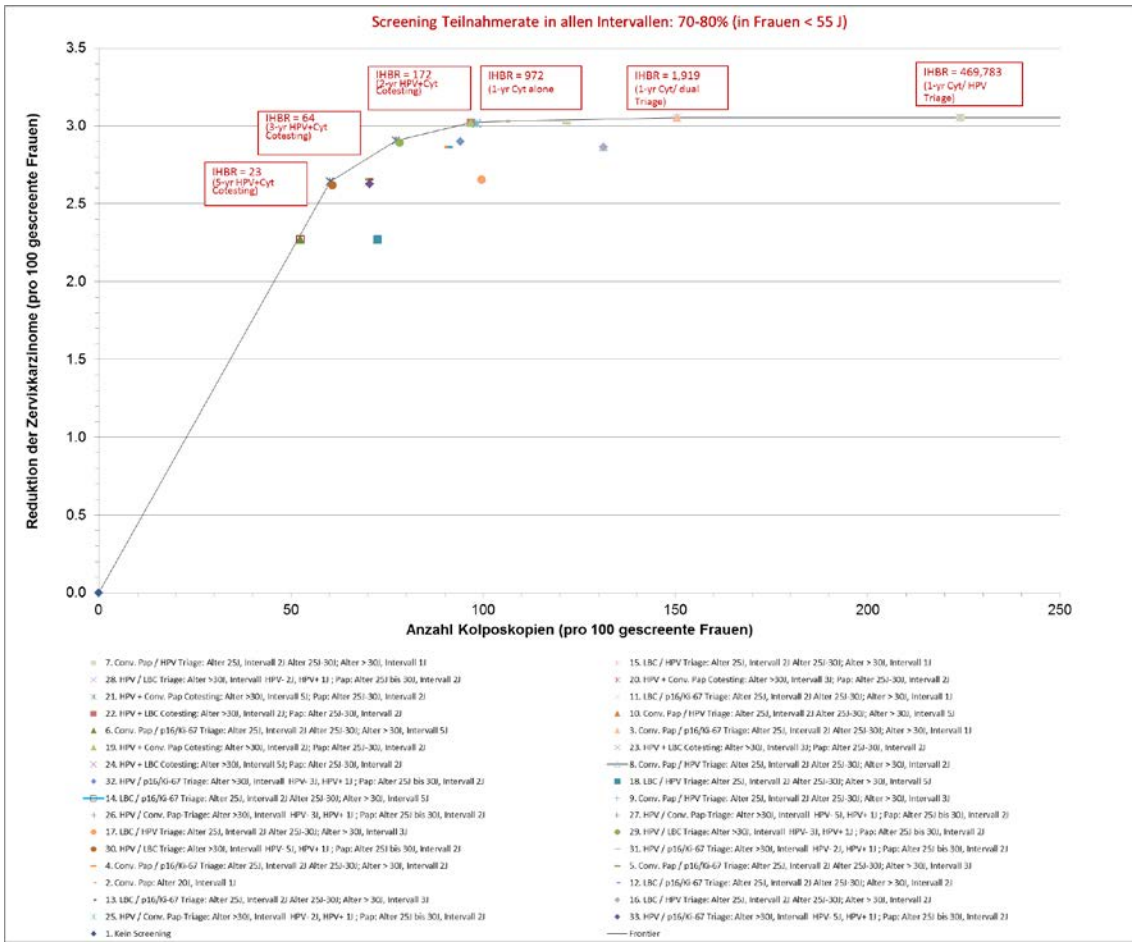


Figure 9 shows the relation between total number of colposcopies and the reduction in cervical cancer death per 100 screened women. In order to prevent 1 death from cervical cancer, there are additional 56 colposcopies with 5-yearly cytology with dual stain triage, 60 colposcopies with 5-yearly HPV plus cytology cotesting, 220 colposcopies with 3-yearly HPV plus cytology cotesting, 696 colposcopies with biennial HPV plus cytology cotesting, 3,233 colposcopies with current annual cytology, 10,323 colposcopies with annual cytology with dual stain triage, and 2,656,152 colposcopies with annual cytology with HPV triage. All other strategies are dominated.

HPV plus cytology cotesting every 5 or 3 years (depending on the willingness to accept colposcopies) seem to result in a good balance between benefits (reduction in cancer death) and harms associated with numbers of colposcopies.

Figure 9. Benefit-harm frontier: Reduction in cervical cancer mortality versus total number colposcopies

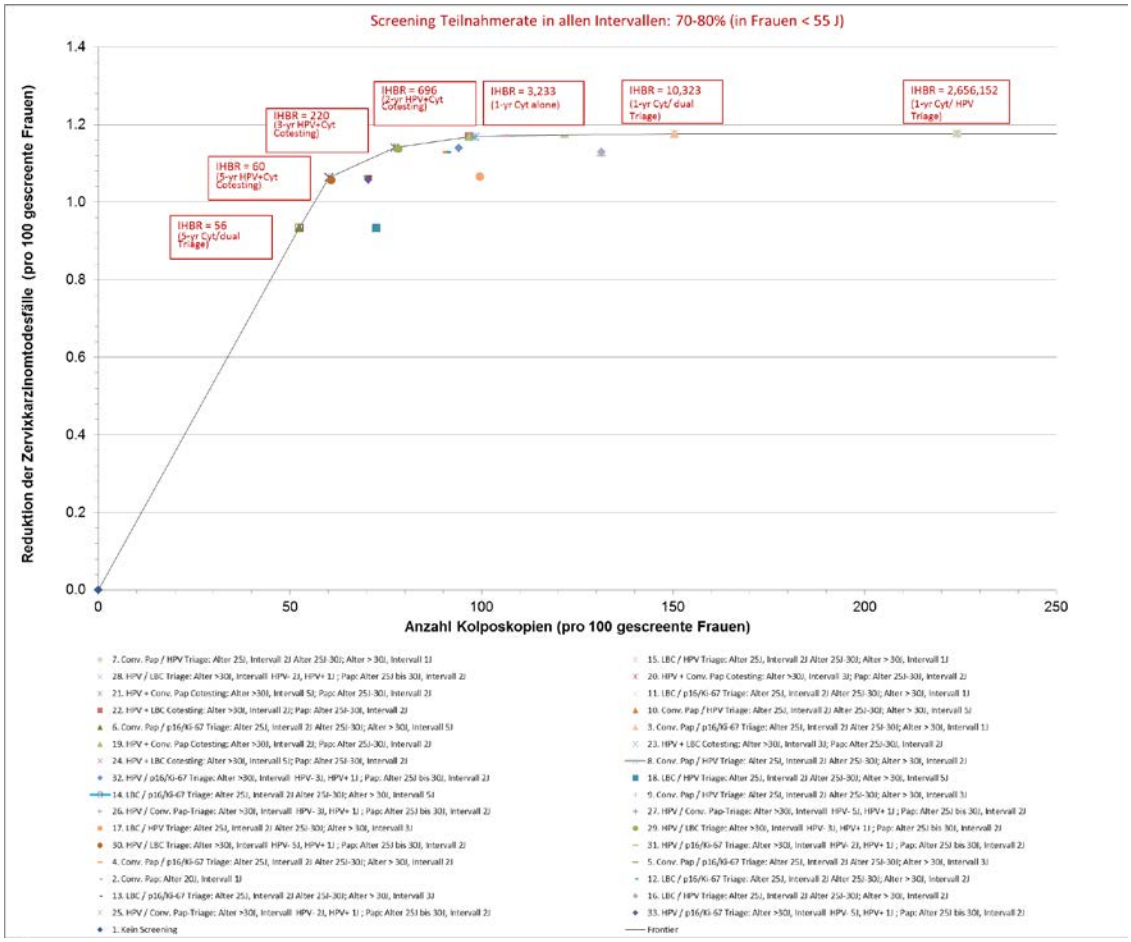
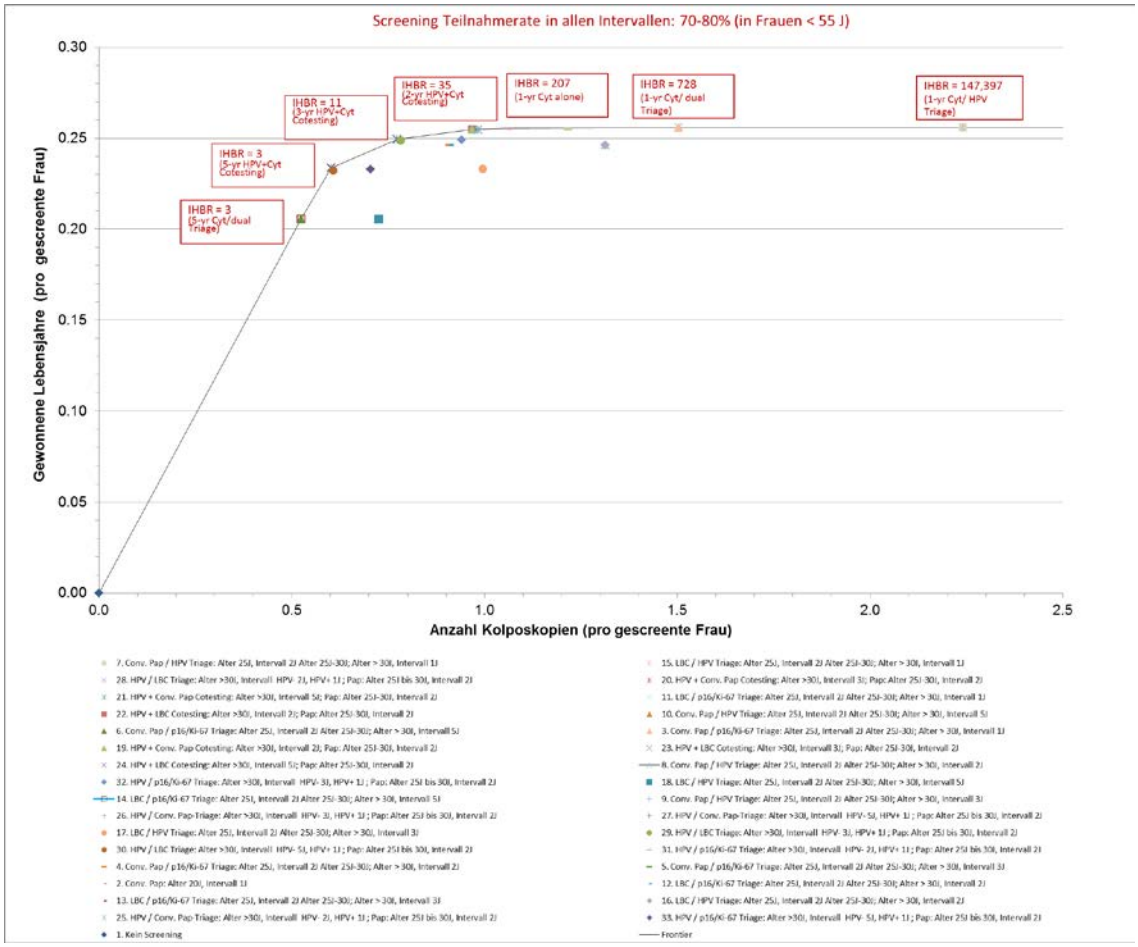


Figure 10 shows the relation between total number of colposcopies and the gain in life expectancy per screened woman. In order to gain 1 life year due to screening, there are additional 3 colposcopies with 5-yearly cytology with dual stain triage, 3 colposcopies with 5-yearly HPV plus cytology cotesting, 11 colposcopies with 3-yearly HPV plus cytology cotesting, 35 colposcopies with biennial HPV plus cytology cotesting, 207 colposcopies with current annual cytology, 728 colposcopies with annual cytology with dual stain triage, and 147,397 colposcopies with annual cytology and HPV triage over the lifetime of screened women. All other strategies are dominated.

HPV plus cytology cotesting every 5 or 3 years (depending on the willingness to accept colposcopies) seem to result in a good balance between benefits (increase in life-years gained) and harms associated with numbers of colposcopies.

Figure 10. Benefit-harm frontier: Life-years gained versus total number colposcopies



5.3.3 Benefit-Harm Analyses Using Conization < CIN3 as Harm Outcome

Figure 11 shows the relation between total number of conizations below CIN3 and the reduction in cervical cancer cases per 100 screened women. In order to prevent 1 additional cervical cancer case, there are additional 2 conizations below CIN3 with 5-yearly cytology with triage, 3 conizations below CIN3 with 5-yearly HPV with cytology triage, 4 conizations below CIN3 with 5-yearly HPV plus cytology cotesting, 5 conizations below CIN3 with 3-yearly HPV with cytology triage, 5 conizations below CIN3 with 3-yearly HPV plus cytology cotesting, 8 conizations below CIN3 with 2-yearly HPV plus cytology cotesting, 14 conizations below CIN3 with annual cytology with dual triage, and 52 conizations below CIN3 with annual cytology with HPV triage. All other strategies are dominated.

HPV plus cytology cotesting or HPV with cytology triage every 5 or 3 years seem to result in a good balance between benefits (reduction in cancer) and harms associated with numbers of conizations below CIN3. It should be mentioned that several other strategies are positioned closely to the latter.

Figure 11. Benefit-harm frontier: Reduction in cervical cancer cases versus total number conizations < CIN 3

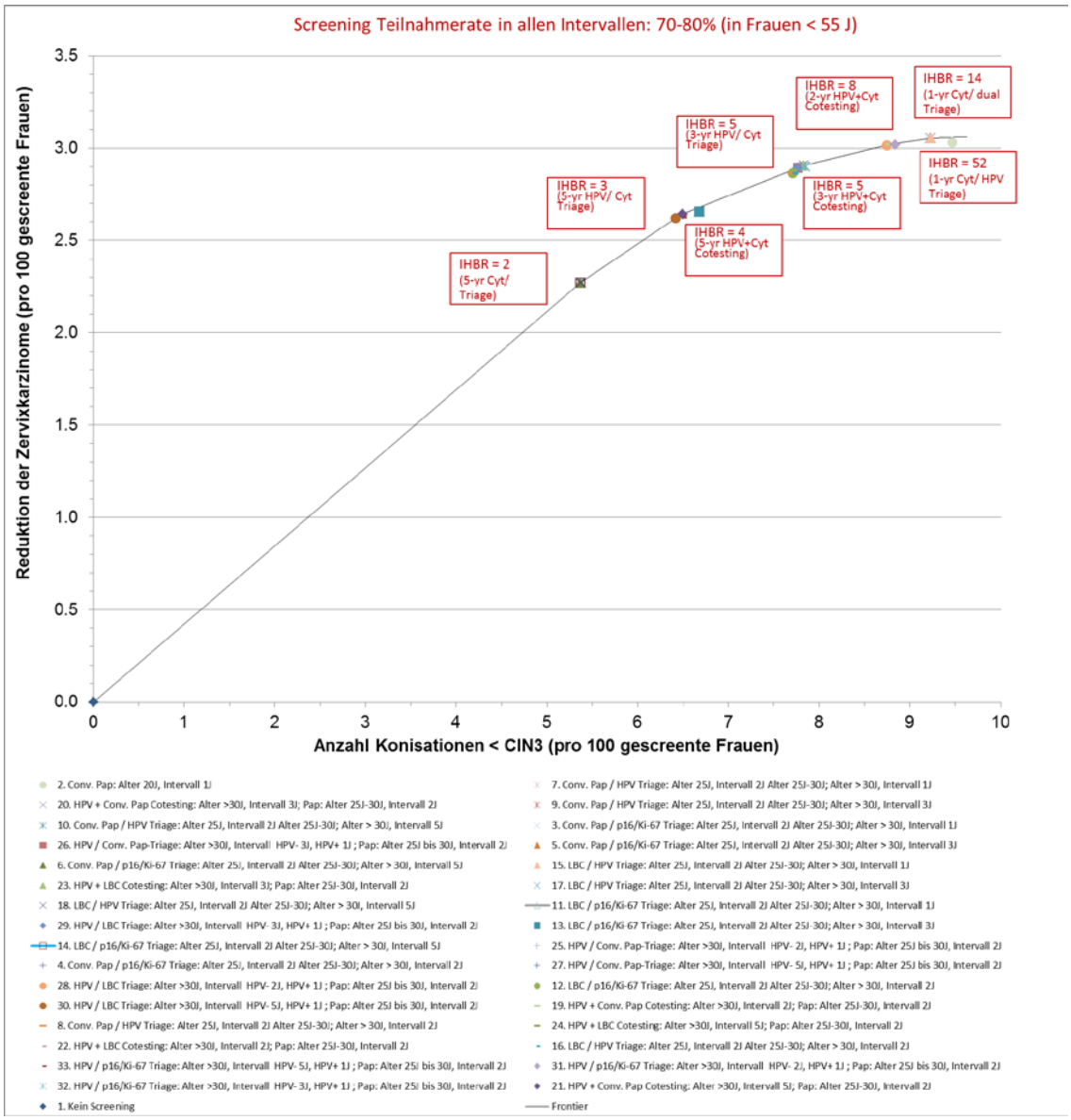


Figure 12 shows the relation between total number of conizations below CIN3 and the reduction in cervical cancer mortality per 100 screened women. In order to prevent 1

additional cervical cancer death, there are additional 6 conizations below CIN3 with 5-yearly cytology with triage, 9 conizations below CIN3 with 5-yearly HPV with cytology triage, 17 conizations below CIN3 with 3-yearly HPV plus cytology cotesting, 34 conizations below CIN3 with biennial HPV plus cytology cotesting, 62 conizations below CIN3 with annual cytology with dual triage, and 293 conizations below CIN3 with annual cytology with HPV triage. All other strategies are dominated.

HPV with a triage every 5 or 3 years seems to result in a good balance between benefits (reduction in cancer deaths) and harms associated with numbers of conizations below CIN3.

Figure 12. Benefit-harm frontier: Reduction in cervical cancer mortality versus total number conizations < CIN 3

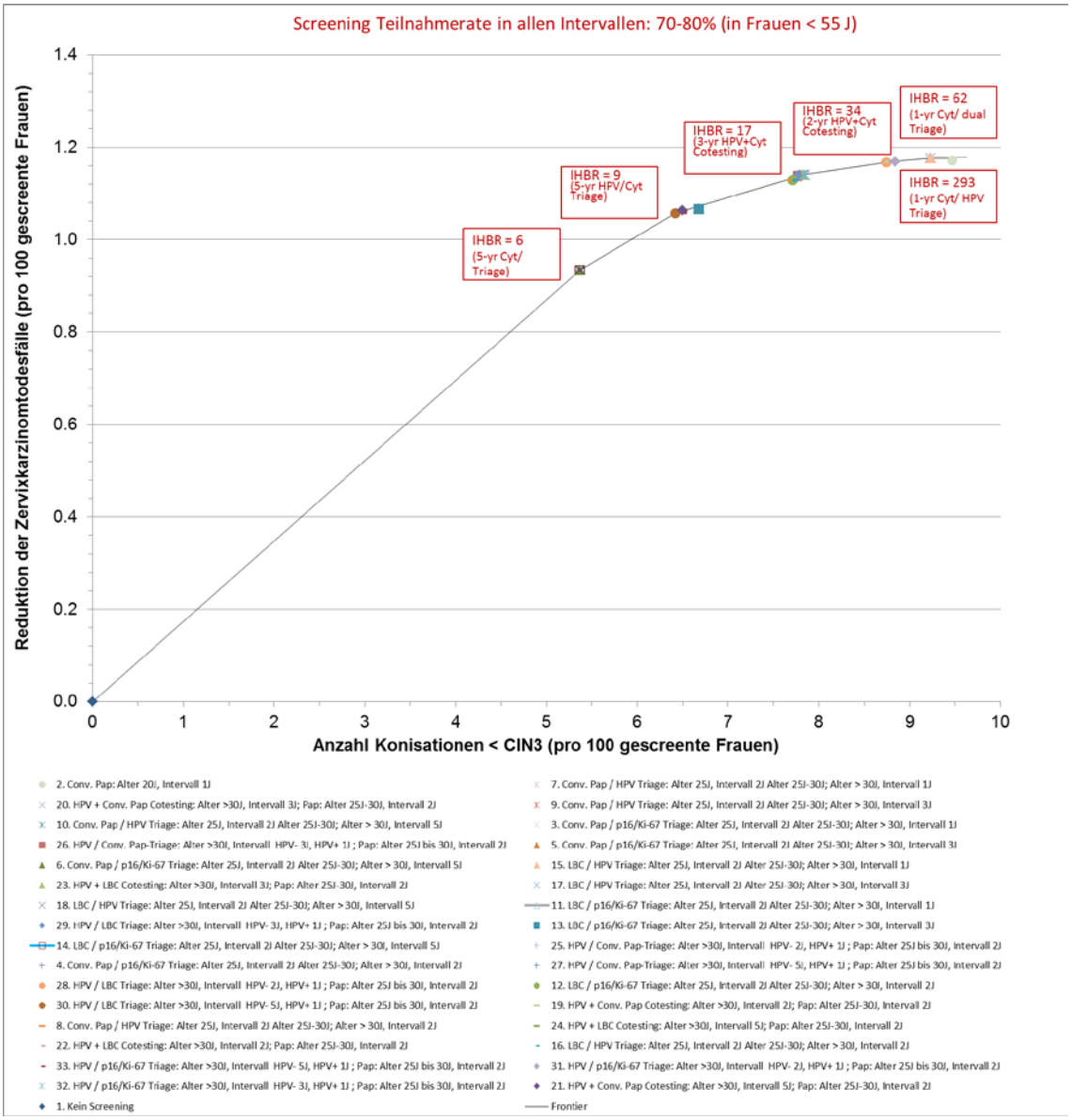
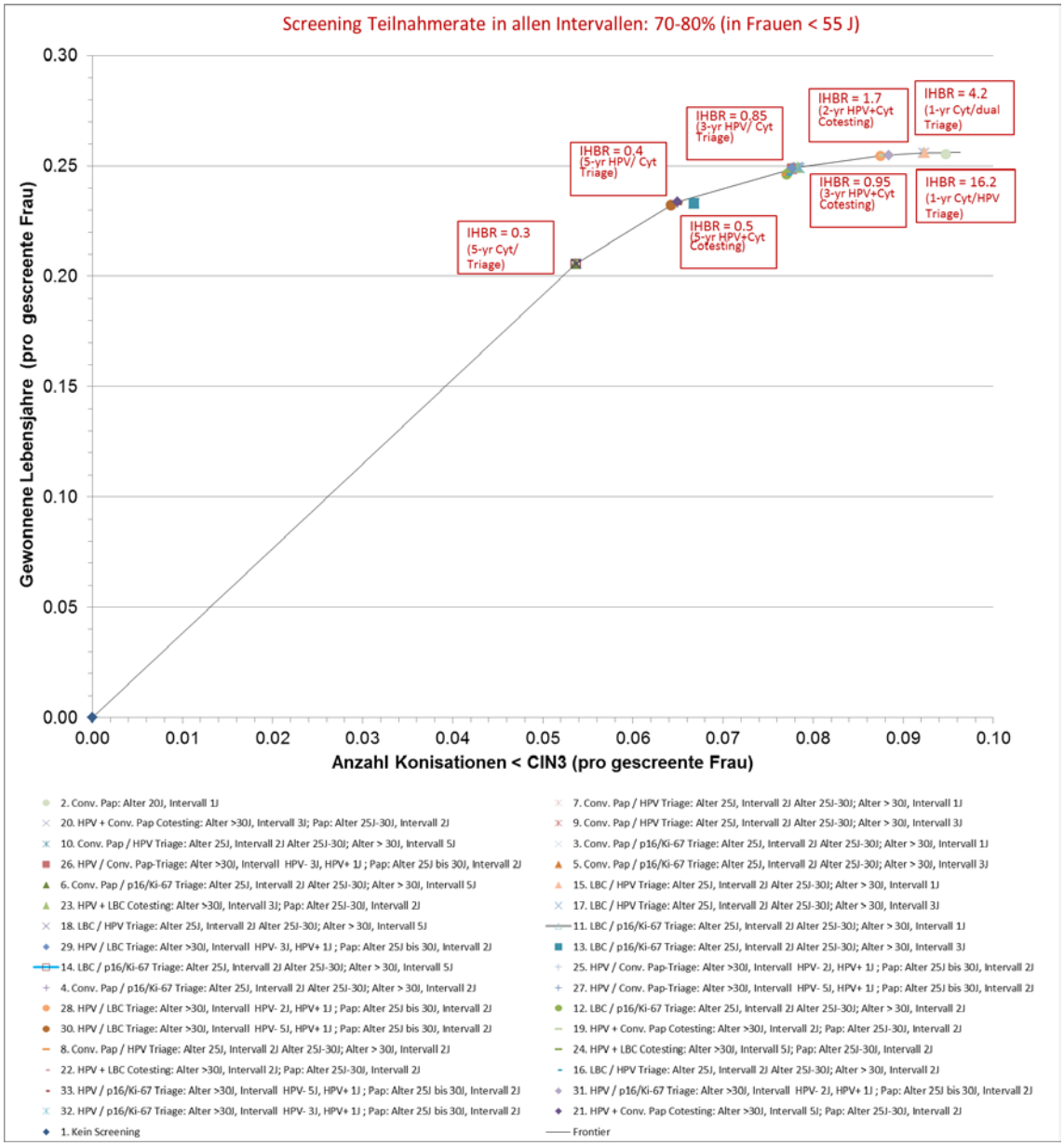


Figure 13 shows the relation between total number of conizations below CIN3 and the gain in life expectancy per screened woman. In order to gain 1 life year due to screening, there are additional 0.3 conizations below CIN3 with 5-yearly cytology with triage, 0.4 conizations below CIN3 with 5-yearly HPV with cytology triage, 0.5 conizations below CIN3 with 5-yearly cotesting with HPV and cytology, 0.8 conizations below CIN3 with 3-yearly HPV with cytology triage, 0.9 conizations below CIN3 with 3-yearly cotesting with HPV and cytology, 1.7 with 2-yearly cotesting with HPV and cytology, 4.2 with annual cytology with dual triage, and 16.2 with annual cytology with HPV triage over the lifetime of screened women. All other strategies are dominated.

HPV plus cytology cotesting or HPV with cytology triage every 5 or 3 years (depending on the willingness to accept conizations) seem to result in a good balance between benefits (increase in life-years gained) and harms associated with numbers of colposcopies.

Figure 13. Benefit-harm frontier: Life-years gained versus total number conizations < CIN 3



5.4 Incremental Cost-Effectiveness

Table 13 shows the discounted total lifetime costs, discounted life expectancy, and the discounted ICER.

Figure 14 shows the cost-effectiveness frontier with 5-yearly screening with cytology and HPV triage or HPV screening and cytology triage, 3-yearly HPV and cytology triage, biennial HPV and cytology triage, and annual cytology with HPV triage on the cost-effectiveness frontier line. All other strategies are dominated by absolute or extended dominance.

The corresponding ICERs are 4,212 Euro/LYG for 5-yearly screening with cytology and HPV triage, 9,210 Euro/LYG for 5-yearly screening with HPV and cytology triage, 30,599 Euro/LYG for 3-yearly HPV with cytology triage, 107,715 Euro/LYG for biennial HPV with cytology triage, and 531,379 Euro/LYG for annual cytology with HPV triage.

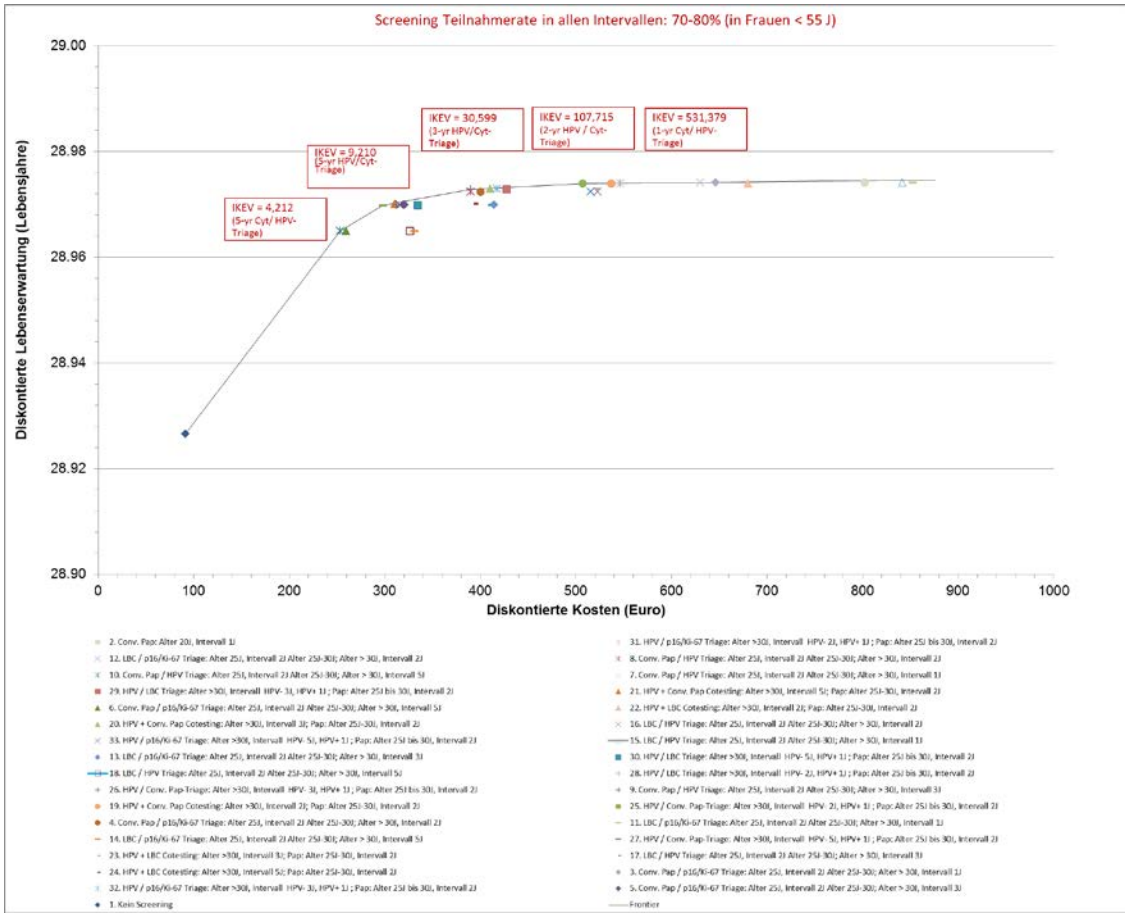
5-yearly screening with HPV and cytology triage is superior to 5-yearly screening with cytology and HPV with cytology triage and is very cost effective. 5-yearly cotesting is only slightly more effective but more costly. 3-yearly HPV with cytology triage is estimated to achieve even higher life expectancy and still seems to be cost effective when compared with other well-accepted interventions in health and medicine (45), that is, 3-yearly HPV with cytology triage seems to provide a good balance between benefits (life-years gained) and costs.

Table 13. Base-case results: discounted total costs, effects, and incremental cost-effectiveness ratios

	Total costs (Euro)	Total life expectancy (Life years)	ICER (Euro/LYG)
1. Kein Screening	91.4	28.92655	0
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	253.2	28.96497	4,212
6. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	259.5	28.96496	Dom.
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	298.1	28.96985	9,210
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	310.5	28.97012	Ext dom.
9. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	312.3	28.96993	Dom.
33. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	315.6	28.96994	Dom.
5. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	320.4	28.96993	Dom.
18. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	326	28.96497	Dom.
14. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	330.6	28.96496	Dom.
30. HPV / LBC Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	334.1	28.96985	Dom.
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	390.0	28.97285	30,599
8. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	390.1	28.9724	Dom.
24. HPV + LBC Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	393.5	28.97012	Dom.
4. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	400.2	28.9724	Dom.
17. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	408.6	28.96993	Dom.
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	410.3	28.97298	Ext. dom.
13. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	414.4	28.96993	Dom.
32. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	417.5	28.9729	Dom.
29. HPV / LBC Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	427.5	28.97285	Dom.
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	506.9	28.97394	107,715
16. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	515.3	28.9724	Dom.
23. HPV + LBC Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	520.4	28.97298	Dom.
12. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	522.4	28.9724	Dom.
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	536.6	28.97399	Ext. dom.
28. HPV / LBC Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	546.0	28.97394	Dom.
31. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	546.4	28.97396	Dom.
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	630.0	28.97417	531,379
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	646.2	28.97417	Dom.
22. HPV + LBC Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	680.0	28.97399	Dom.
2. Conv. Pap: Alter 20J, Intervall 1J	802.2	28.9741	Dom.
15. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	841.4	28.97417	Dom.
11. LBC / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	852.4	28.97417	Dom.

ICER: incremental cost-effectiveness ratio, LYG: life-years gained

Figure 14. Base-case results: cost-effectiveness frontier



6 Results: Sensitivity Analyses

6.1 Benefit-Harm Balance

In general, the model results for the benefit-harm analyses were very robust when selected parameters were varied across plausible ranges in sensitivity analyses. Triennial HPV screening with cytology triage or cotesting may be considered as having a good balance between benefits and potential harms even when the accuracy of cytology or colposcopy is reduced. In women attending the screening program regularly (100% adherence), one may consider extending the screening interval to 5 years in order to balance benefits and harms, if no other factors prohibit such a large screening interval.

6.1.1 Screening Test-Positive Results

Sensitivity of Cytology

In multi-way sensitivity analyses Pap cytology sensitivity values were varied using the lower [44.8% (CIN1), 62.5% (CIN2), 55.4% (CIN3+)] 95% CI limits. All strategies that have Pap cytology as a primary screening test or as a follow-up test are influenced simultaneously in this analysis.

Table 14 shows the incremental harm-benefit ratios (in positive tests / LYG) for the non-dominated strategies, if the test sensitivity values for the Pap cytology test are varied according to the lower 95% CIs.

Figure 15 shows the relation between total number of screen-positives and the gain in remaining life expectancy per screened woman.

In order to gain 1 life year, on average a woman receives 4 positive screening test result with 5-yearly cytology, 6 with 3-yearly cytology, 22 with 3-yearly HPV with dual triage, 90 with biennial HPV with dual triage, and 616 with annual cytology with triage. All other screening strategies are dominated.

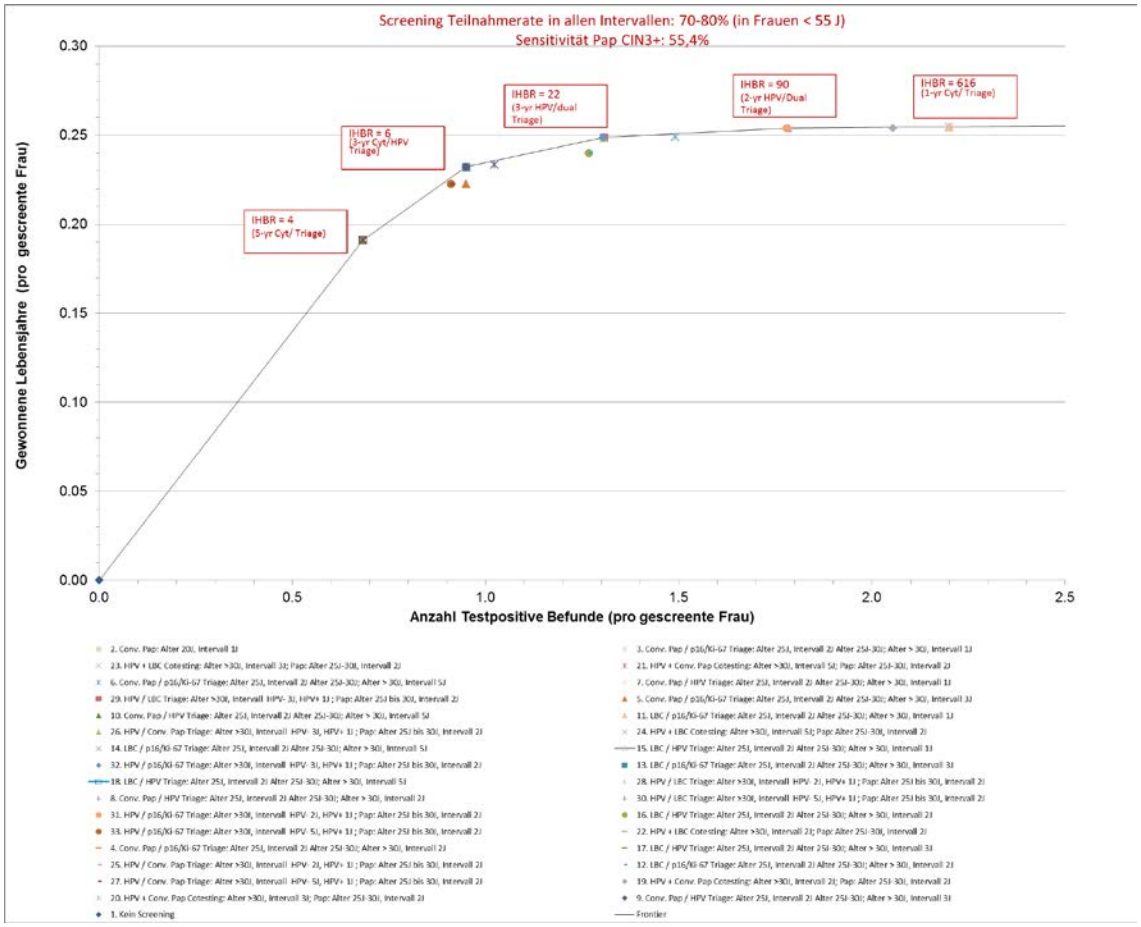
5-yearly or 3-yearly HPV with dual triage seems to result in a good balance between benefits (gain in life expectancy) and harms associated with positive test results.

Table 14. Sensitivity analysis IHBR (positive tests/LYG): decreased cytology sensitivity.

Cytology sensitivity	**55.4% for CIN3+**	**68.5% for CIN3+**
Strategy	**IHBR (Positive tests/LYG)**	**Base case**
1. Kein Screening		
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	4	3
17. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	6	Dom
33. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	Dom	8
32. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	22	24
31. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	90	82
15. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	616	363

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated.

Figure 15. Sensitivity analysis IHBR (positive tests/LYG): decreased sensitivity values for cytology



Sensitivity and Specificity of Colposcopy

In multi-way sensitivity analyses colposcopy accuracy data were varied [specificity of 0.566, and sensitivity of 0.760 for CIN1/CIN2 and 0.983 for CIN3+].

Table 15 shows the incremental harm-benefit ratios (in positive tests / LYG) for the non-dominated strategies, when alternative colposcopy accuracy data are used. Figure 16 shows the benefit-harm frontier for the scenario with alternative sensitivity and specificity values for colposcopy.

In order to gain 1 life year, on average a woman receives 3 positive screening test results with 5-yearly cytology, 8 with 5-yearly HPV with dual triage, 21 with 3-yearly HPV with dual triage, 68 with biennial HPV with dual triage, and 275 with annual cytology with triage. All other screening strategies are dominated.

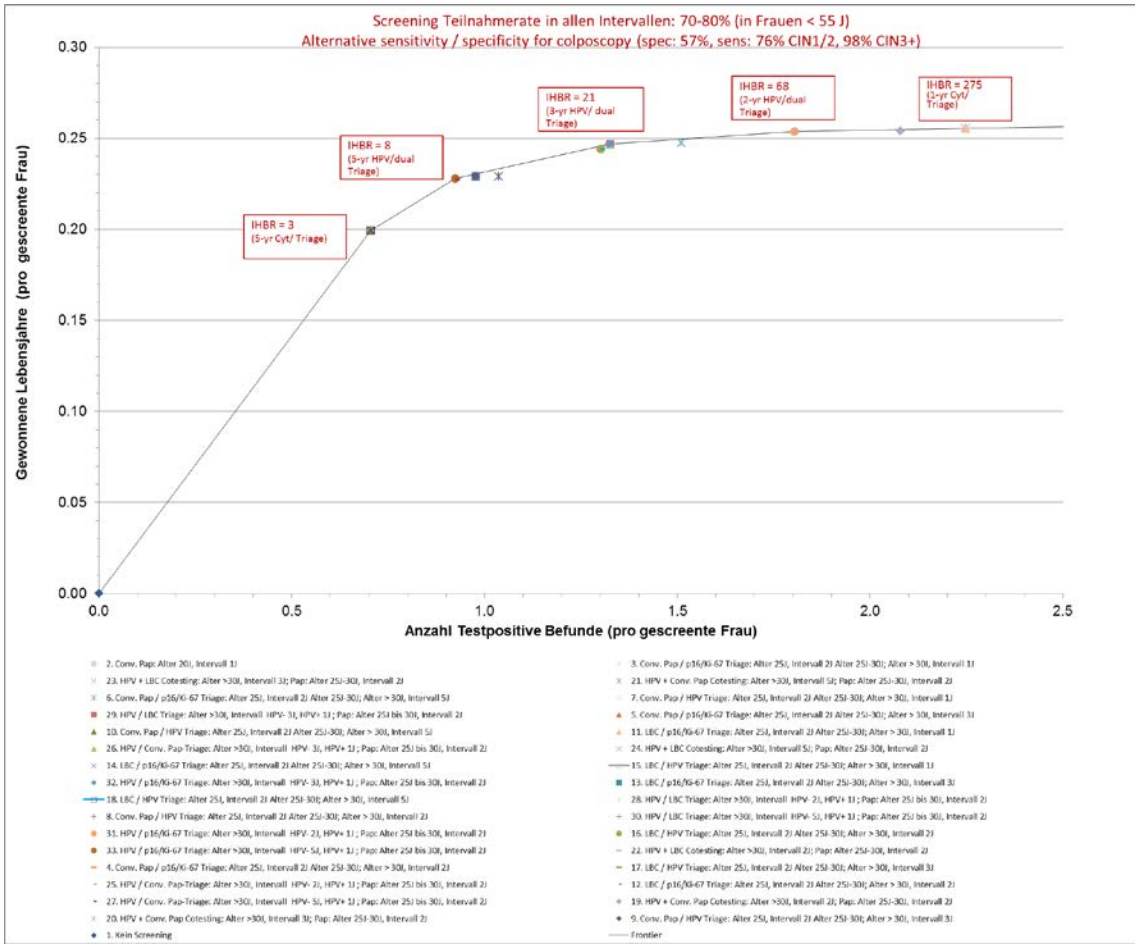
5-yearly or 3-yearly HPV with dual triage seems to result in a good balance between benefits (gain in life expectancy) and harms associated with positive test results.

Table 15. Sensitivity analysis IHBR (positive tests/LYG): alternative sensitivity and specificity values for colposcopy.

Cytology sensitivity	**Cantor 2008**	**Mitchell 1998**
Strategy	**IHBR (Positive tests/LYG)**	**Base case**
1. Kein Screening		
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	3	3
33. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	8	8
32. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	21	24
31. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	68	82
15. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	275	363

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated.

Figure 16. Sensitivity analysis IHBR (positive tests/LYG): alternative sensitivity and specificity values for colposcopy



Screening Adherence

Table 16 shows the incremental harm-benefit ratios (in positive tests / LYG) for the non-dominated strategies, if the screening adherence rate is increased to 100%.

Figure 17 shows the relation between total number of screen-positives and the gain in remaining life expectancy per screened woman.

In order to gain 1 life year, on average a woman receives 4 positive screening test result with 5-yearly cytology, 18 with 5-yearly HPV with dual stain, 182 with triennial HPV with dual stain, 1,393with biennial HPV with dual stain, and 7,467 with biennial HPV and cytology cotesting. All other screening strategies are dominated.

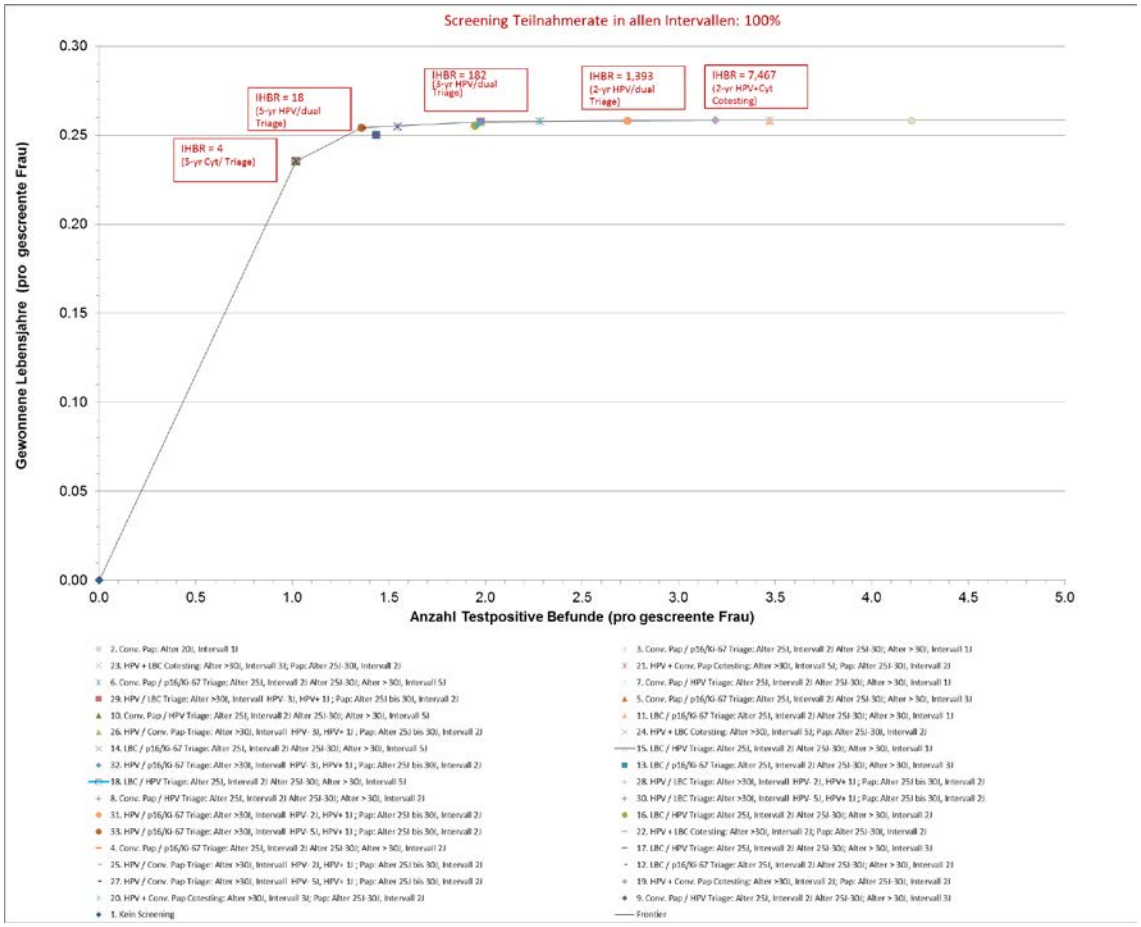
For women with full screening adherence, 5-yearly HPV with dual stain triage seem to result in a good balance between benefits (gain in life expectancy) and harms associated with positive test results.

Table 16. Sensitivity analysis IHBR (positive tests/LYG): 100% screening adherence.

Screening adherence rate	**100%**	**70-80%**
Strategy	**IHBR (Positive tests/LYG)**	**Base case**
1. Kein Screening		
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	4	3
33. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	18	8
32. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	182	24
31. HPV / p16/Ki-67 Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	1393	82
15. LBC / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	Dom	363
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	7467	Dom

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated.

Figure 17. Sensitivity analysis IHBR (positive tests/LYG): 100% screening adherence.



6.1.2 Colposcopies

Sensitivity of Cytology

Table 17 shows the incremental harm-benefit ratios (in colposcopies / LYG) for the non-dominated strategies, if the test sensitivity values for the Pap cytology test are varied according to the lower 95% CIs.

Figure 18 shows the relation between total number of colposcopies and the gain in remaining life expectancy per screened woman.

In order to gain 1 life year, on average a woman receives 3 colposcopies with 5-yearly HPV +cytology cotesting, 11 with 3-yearly HPV +cytology cotesting, 40 with 2-yearly HPV +cytology cotesting, 120 with current annual Pap screening, 3,136 with annual cytology with

dual triage, and 4,603 with annual cytology with HPV triage. All other screening strategies are dominated.

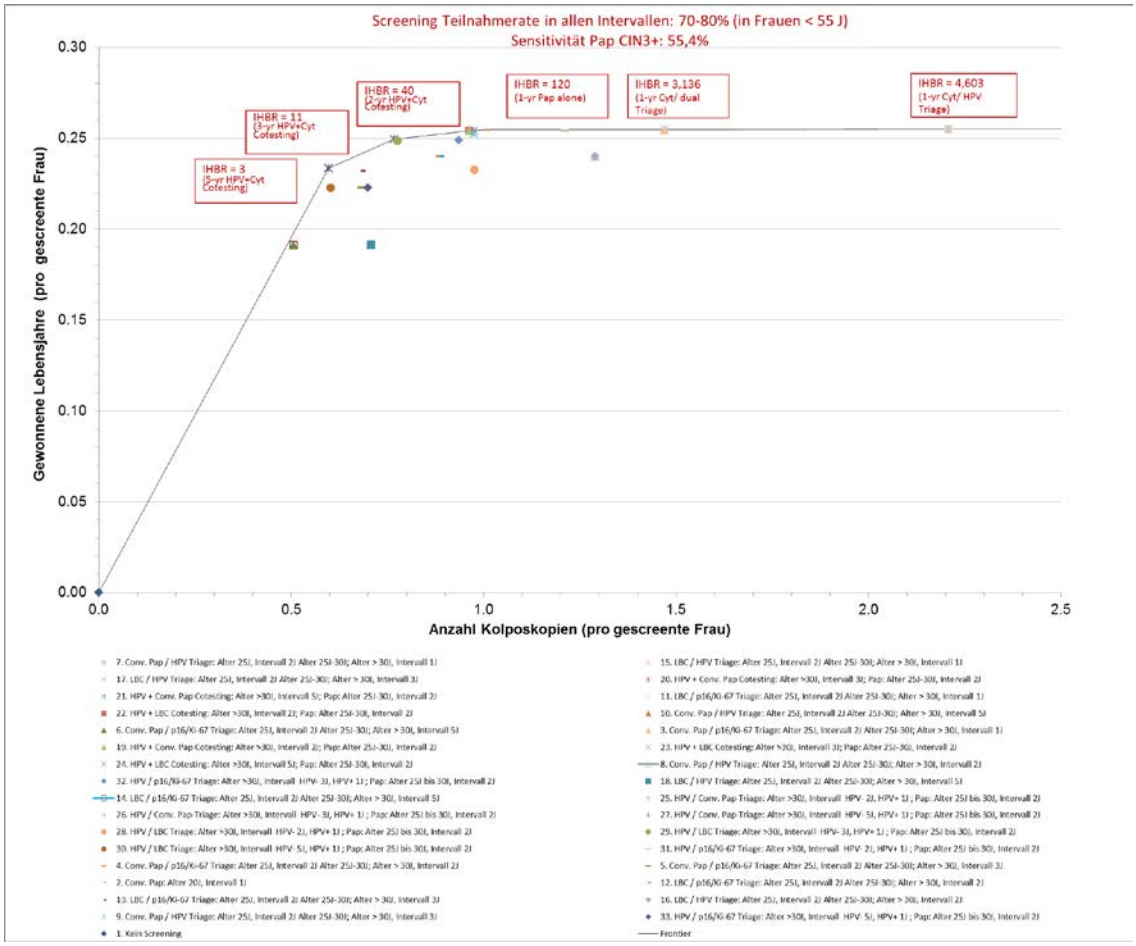
Triennial or biennial HPV plus cytology cotesting seem to result in a good balance between benefits (gain in life expectancy) and harms associated with colposcopies.

Table 17. Sensitivity analysis IHBR (colposcopies/LYG): decreased cytology sensitivity.

Cytology sensitivity	**55.4% for CIN3+**	**68.5% for CIN3+**
Strategy	**IHBR (Colposcopies/LYG)**	**Base case**
1. Kein Screening		
6. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	Dom	3
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	3	3
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	11	11
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	40	35
2. Conv. Pap: Alter 20J, Intervall 1J	120	207
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	3,136	728
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	4,603	147,397

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated.

Figure 18. Sensitivity analysis IHBR (colposcopies/LYG): decreased sensitivity values for cytology



Sensitivity and Specificity of Colposcopy

Table 18 shows the incremental harm-benefit ratios (in colposcopies / LYG) for the non-dominated strategies, if alternative test accuracy data for colposcopy are applied.

Figure 19 shows the relation between total number of colposcopies and the gain in remaining life expectancy per screened woman.

In order to gain 1 life year, on average a woman receives 3 colposcopies with 5-yearly HPV +cytology cotesting, 10 with 3-yearly HPV +cytology cotesting, 30 with 2-yearly HPV +cytology cotesting, 140 with current annual Pap screening, 652 with annual cytology with dual triage, and 147,193 with annual cytology with HPV triage. All other screening strategies are dominated.

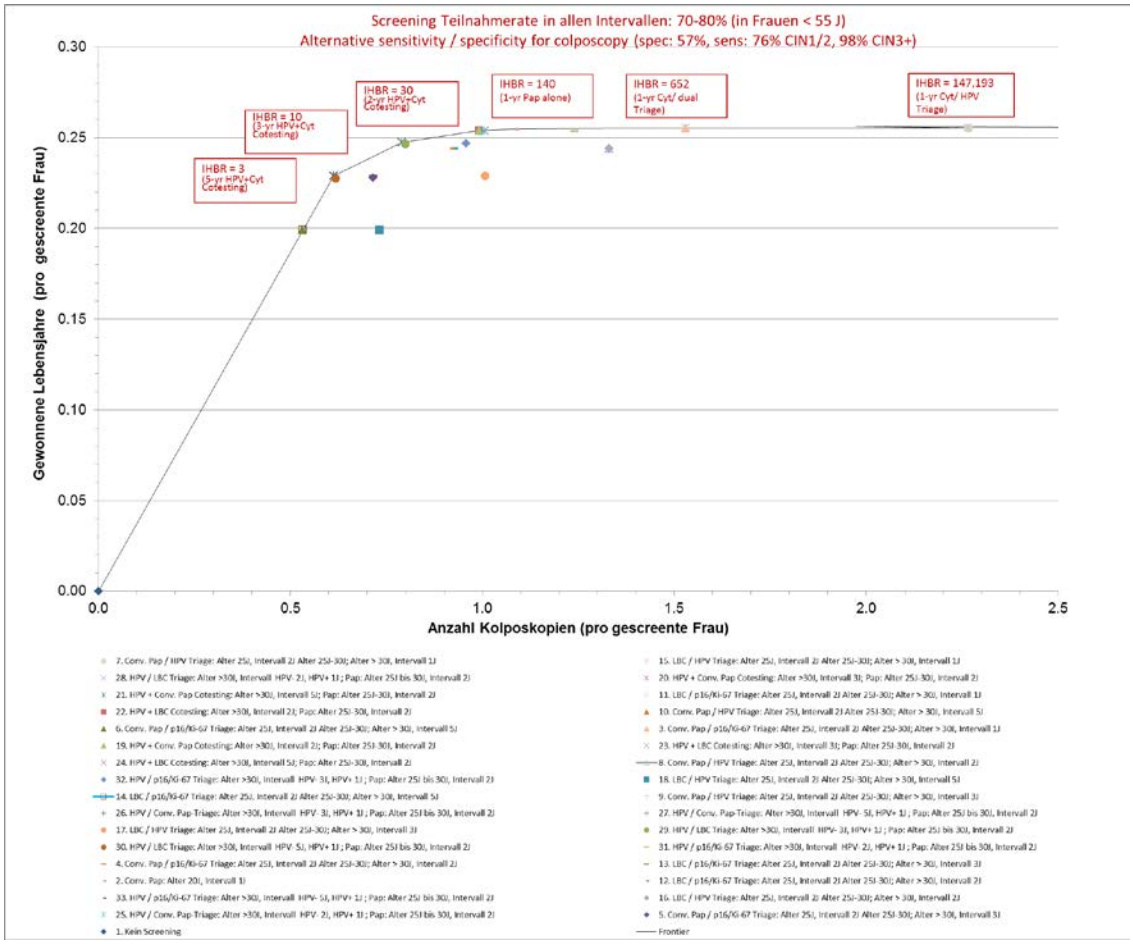
Triennial or biennial HPV plus cytology cotesting seem to result in a good balance between benefits (gain in life expectancy) and harms associated with colposcopies.

Table 18. Sensitivity analysis IHBR (colposcopies/LYG): alternative sensitivity and specificity values for colposcopy.

Colposcopy accuracy	**Cantor 2008**	**Mitchell 1998**
Strategy	**IHBR (Colposcopies/LYG)**	**Base case**
1. Kein Screening		
6. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	Dom	3
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	3	3
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	10	11
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	30	35
2. Conv. Pap: Alter 20J, Intervall 1J	140	207
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	652	728
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	147,193	147,397

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated.

Figure 19. Sensitivity analysis IHBR (colposcopies/LYG): alternative sensitivity and specificity values for colposcopy.



Screening Adherence

Table 19 shows the incremental harm-benefit ratios (in colposcopies / LYG) for the non-dominated strategies, if the screening adherence is increased to 100%.

Figure 20 shows the relation between total number of colposcopies and the gain in remaining life expectancy per screened woman.

In order to gain 1 life year, on average a woman receives 3 colposcopies with 5-yearly cytology with dual stain triage, 5 with 5-yearly HPV with cytology triage, 138 colposcopies with biennial HPV and cytology triage, 312 with 3-yearly cytology with HPV triage, 434 colposcopies with current annual Pap screening. All other screening strategies are dominated.

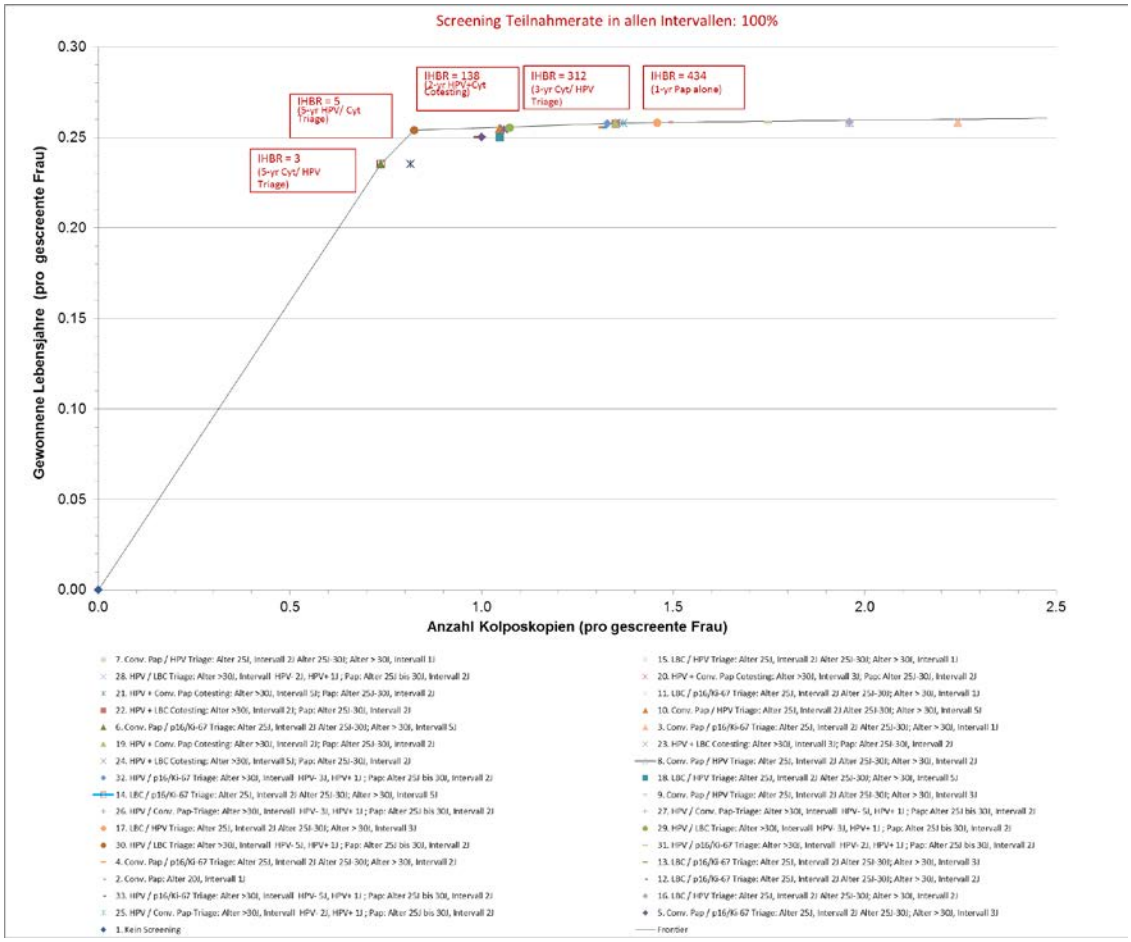
For women with full screening adherence, 5-yearly HPV plus cytology cotesting seem to result in a good balance between benefits (gain in life expectancy) and harms associated with colposcopies.

Table 19. Sensitivity analysis IHBR (colposcopies/LYG): decreased cytology sensitivity.

Cytology sensitivity	**100%**	**70-80%**
Strategy	**IHBR (Colposcopies/LYG)**	**Base case**
1. Kein Screening		
6. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	3	3
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	5	Dom
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	Dom	3
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	138	Dom
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	Dom	11
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	Dom	35
9. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	312	Dom
2. Conv. Pap: Alter 20J, Intervall 1J	434	207
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	Dom	728
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	Dom	147,397

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated.

Figure 20. Sensitivity analysis IHBR (colposcopies/LYG): 100% screening adherence



6.1.3 Conization < CIN3

Sensitivity of Cytology

Table 20 shows the incremental harm-benefit ratios (in conizations < CIN3 / LYG) for the non-dominated strategies, when test sensitivity values for the Pap cytology test are varied according to the lower 95% CIs.

Figure 21 shows the relation between total number of conizations < CIN3 and the gain in remaining life expectancy per screened woman.

In order to gain 1 life year, on average a woman receives 0.3 conizations < CIN3 with 5-yearly or 3-yearly cytology, 0.9 conizations < CIN3 with 3-yearly HPV with cytology triage, 1.0 conizations < CIN3 with 3-yearly HPV - cytology cotesting, 1.9 with biennial HPV with

cytology triage, and 3.8 conizations < CIN3 with annual cytology in her lifetime. All other screening strategies are dominated.

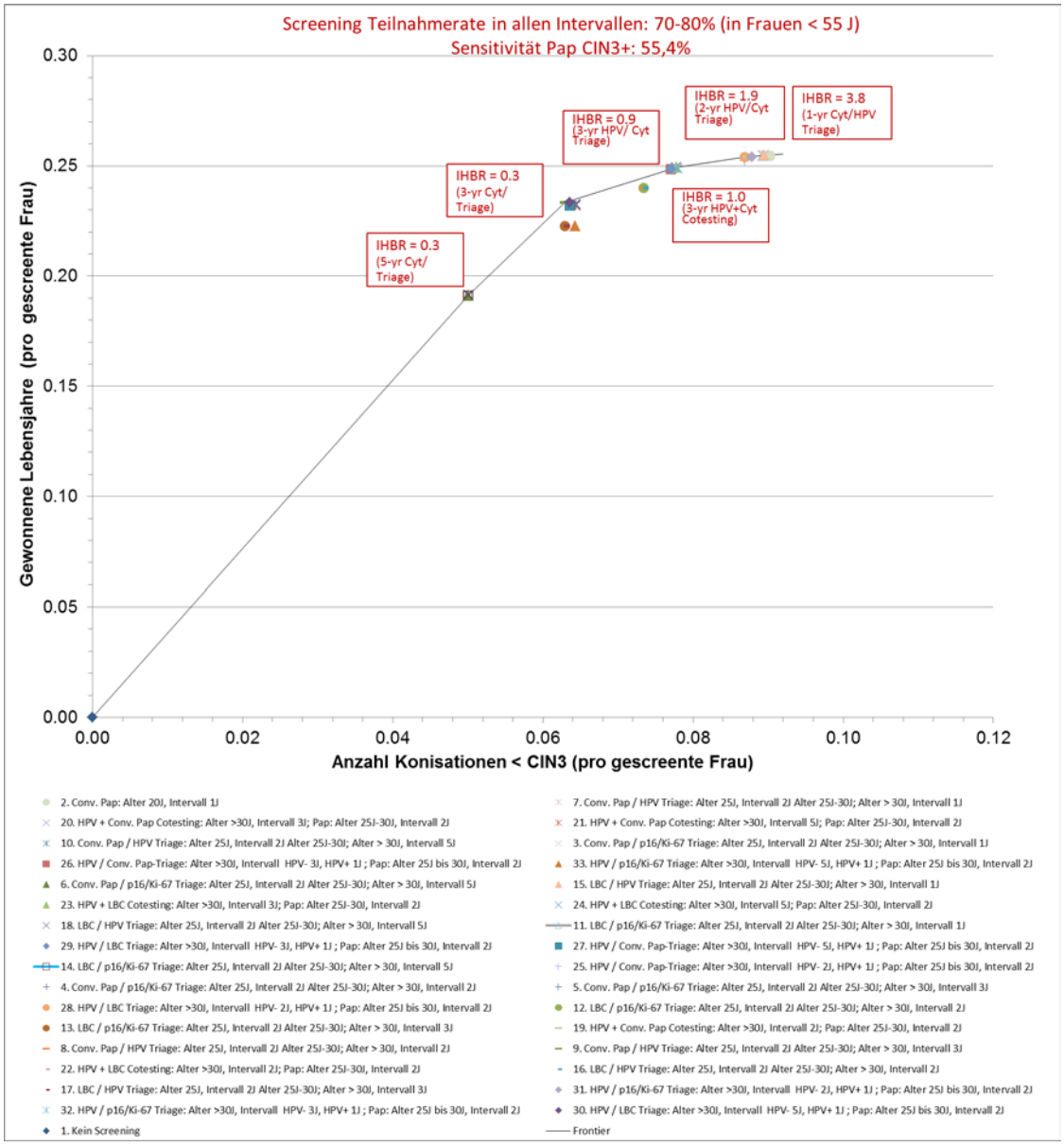
HPV plus cytology cotesting or HPV with cytology triage every 5 or 3 years seem to result in a good balance between benefits (gain in life expectancy) and harms associated with positive test results.

Table 20. Sensitivity analysis IHBR (conizations < CIN3/LYG): decreased cytology sensitivity.

Cytology sensitivity	**55.4% for CIN3+**	**68.5% for CIN3+**
Strategy	**IHBR (conization < CIN3 / LYG)**	**Base case**
1. Kein Screening		
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	0.3	0.3
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	Dom	0.4
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	Dom	0.5
9. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 3J	0.3	Dom
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2Jbis 30J, Intervall 2J	0.9	0.9
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	1.0	1.0
22. HPV + LBC Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	Dom	1.7
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	Dom	4.2
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	1.9	Dom
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	3.8	Dom

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated.

Figure 21. Sensitivity analysis IHBR (conizations < CIN3/LYG): decreased sensitivity values for cytology.



Sensitivity and Specificity of Colposcopy

In multi-way sensitivity analyses colposcopy accuracy data were varied [specificity of 0.566, and sensitivity of 0.760 for CIN1/CIN2 and 0.983 for CIN3+].

Table 21 shows the incremental harm-benefit ratios (in conizations < CIN3 / LYG) for the non-dominated strategies, when alternative data for the accuracy of colposcopy are applied.

Figure 22 shows the relation between total number of conizations < CIN3 and the gain in remaining life expectancy per screened woman.

In order to gain 1 life year, on average a woman receives 0.2 conizations < CIN3 with 5-yearly cytology, 0.3 conizations < CIN3 with 5-yearly HPV with cytology triage, 0.5 conizations < CIN3 with 5-yearly HPV - cytology cotesting, 0.7 with triennial cytology with HPV triage, 0.8 conizations < CIN3 with 3-yearly HPV - cytology cotesting, 1.5 with biennial HPV - cytology cotesting, 4.1 conizations < CIN3 with annual cytology + dual triage and 14.9 with annual cytology with HPV triage. All other screening strategies are dominated.

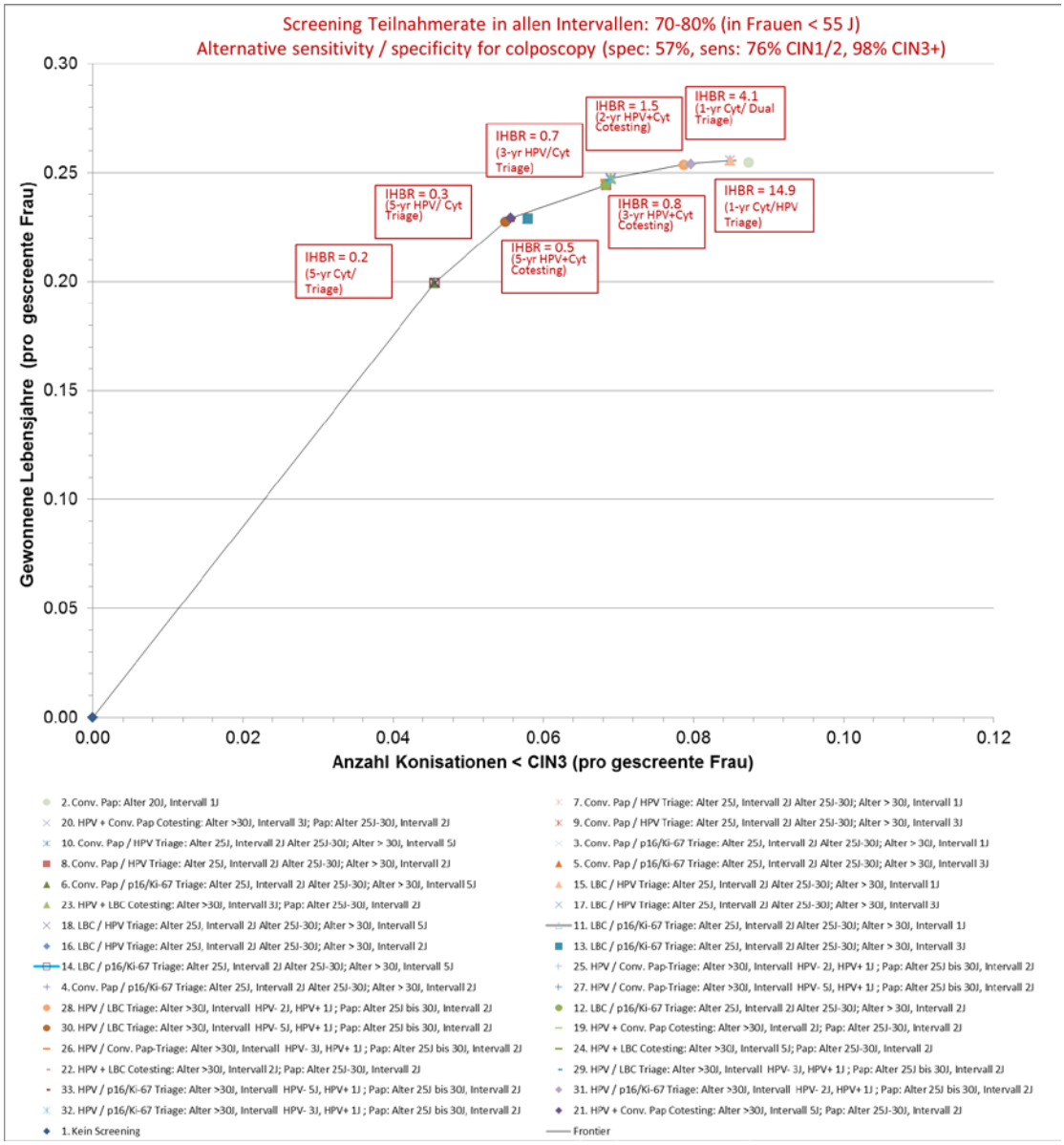
HPV plus cytology cotesting or HPV with cytology triage every 5 or 3 years seem to result in a good balance between benefits (gain in life expectancy) and harms associated with positive test results.

Table 21. Sensitivity analysis IHBR (conizations < CIN3/LYG): alternative sensitivity and specificity values for colposcopy.

Colposcopy accuracy	**Cantor 2008**	**Mitchell 1998**
Strategy	**IHBR (conization < CIN3 / LYG)**	**Base case**
1. Kein Screening		
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	0.2	0.3
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	0.3	0.4
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	0.5	0.5
8. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 2J	0.7	Dom
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2Jbis 30J, Intervall 2J	Dom	0.9
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	0.8	1.0
22. HPV + LBC Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	1.5	1.7
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	4.1	4.2
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	14.9	Dom

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated.

Figure 22. Sensitivity analysis: alternative sensitivity and specificity values for colposcopy



Screening Adherence

Table 22 shows the incremental harm-benefit ratios (in conizations < CIN3 / LYG) for the non-dominated strategies, if the screening adherence is increased to 100%.

Figure 23 shows the relation between total number of conizations < CIN3 and the gain in remaining life expectancy per screened woman.

In order to gain 1 life year, on average a woman receives 0.3 conizations < CIN3 with 5-yearly cytology, 0.7 conizations < CIN3 with 5-yearly HPV with cytology triage, 1.0 conizations <

CIN3 with 5-yearly HPV - cytology cotesting, 4.0 with 3-yearly HPV - cytology cotesting, and 18.1 with 2-yearly HPV - cytology cotesting. All other screening strategies are dominated.

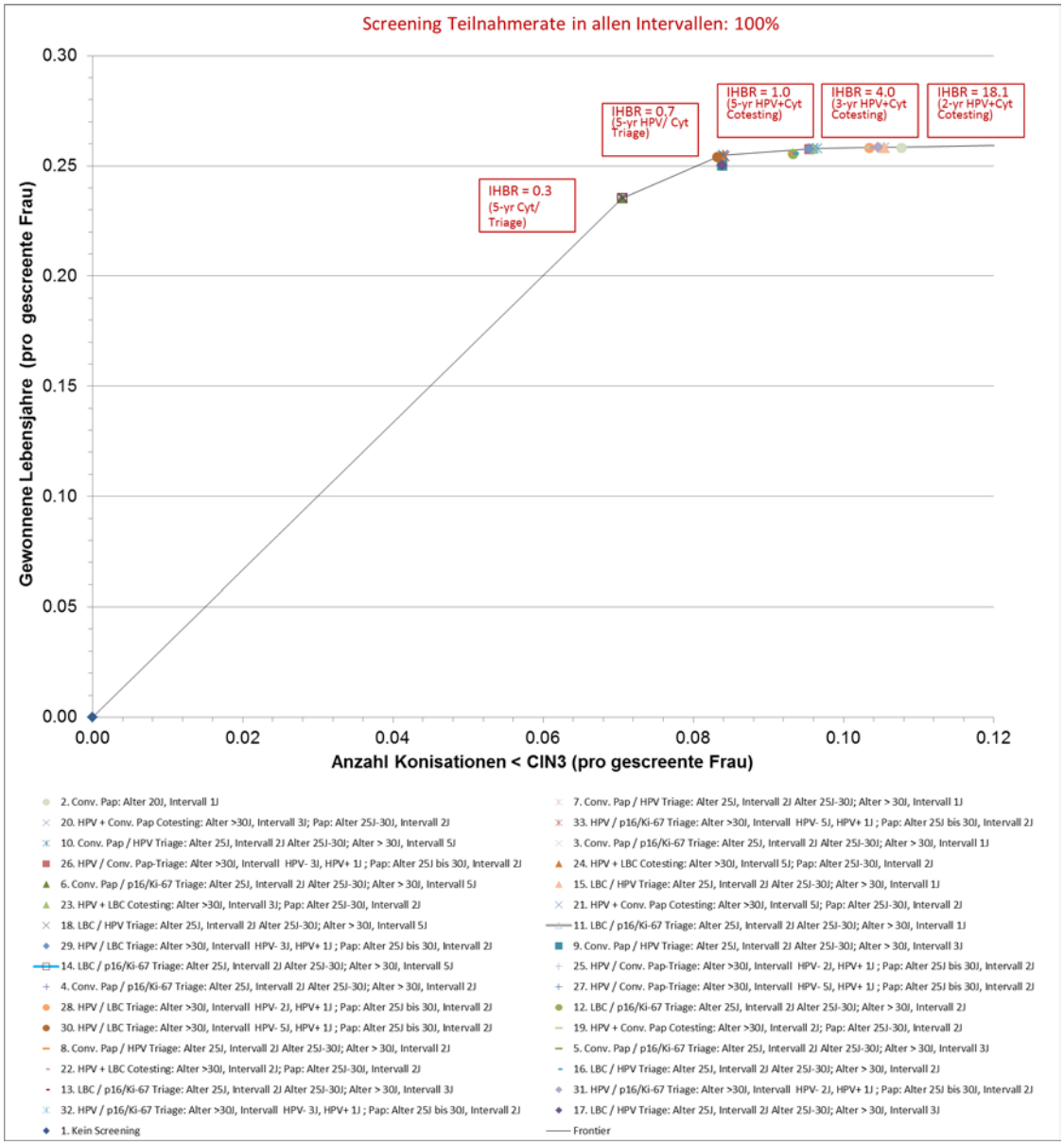
In women with full screening adherence, 5-yearly HPV with cytology triage or cotesting seem to result in a good balance between benefits (gain in life expectancy) and harms associated with positive test results.

Table 22. Sensitivity analysis IHBR (conizations < CIN3/LYG): 100% screening adherence.

Screening adherence	**100%**	**70-80%**
Strategy	**IHBR (conization < CIN3 / LYG)**	**Base case**
1. Kein Screening		
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	0.3	0.3
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	0.7	0.4
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	1.0	0.5
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2Jbis 30J, Intervall 2J	Dom	0.9
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	4.0	1.0
22. HPV + LBC Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	18.1	1.7
3. Conv. Pap / p16/Ki-67 Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	Dom	4.2

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated.

Figure 23. Sensitivity analysis IHBR (conizations < CIN3/LYG): 100% screening adherence



6.2 Incremental Cost-Effectiveness

In general, the model results for the cost-effectiveness analyses were very robust when selected parameters were varied across plausible ranges in sensitivity analyses. Triennial HPV screening with cytology triage may be considered as cost-effective even when the accuracy of cytology or colposcopy is reduced or the cancer treatment costs are increased. In women attending the screening program regularly (100% adherence), triennial HPV screening with cytology triage remained cost-effective.

Cytology Sensitivity

In multi-way sensitivity analyses, Pap cytology sensitivity values were varied using the lower [44.8% (CIN1), 62.5% (CIN2), 55.4% (CIN3+)] 95% confidence interval limits. All strategies that have Pap cytology as a primary screening test or as a follow-up test are influenced simultaneously in this analysis.

Table 23 shows the incremental cost-effectiveness ratios (in Euro / LYG) for the non-dominated strategies, if the test sensitivity values for the Pap cytology test are varied according to the lower 95% CIs. Figure 24 shows the cost-effectiveness frontiers for the scenario with reduced (lower limit) test sensitivity values for cytology.

If the sensitivity of cytology is as low as the lower 95% CI values, the strategy "2-yearly HPV + Pap cotesting" is not dominated anymore and is positioned on the cost-effectiveness frontier, whereas, the strategy "annual cytology with HPV triage" is dominated.

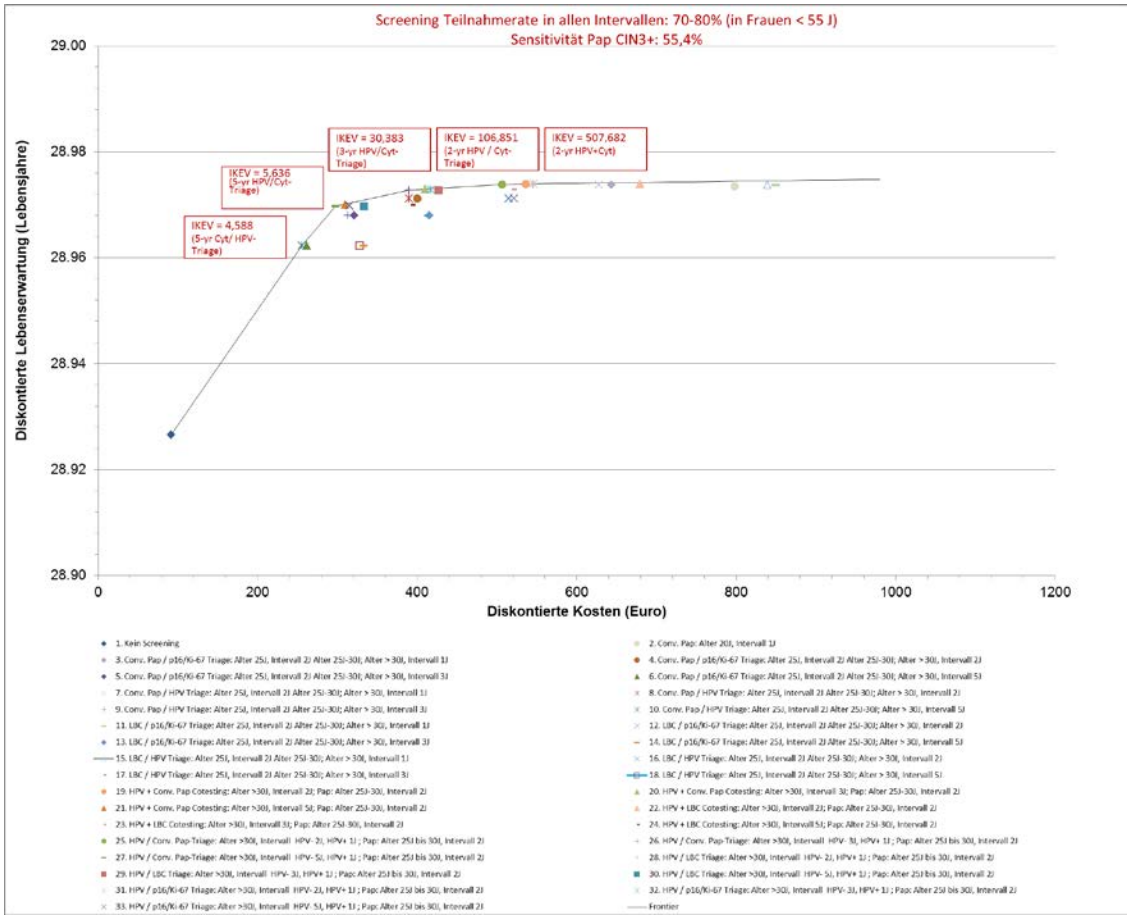
In the scenario with lower test sensitivity values for cytology, triennial HPV / Pap triage remains a cost-effective screening option.

Table 23. Sensitivity analysis: decreased cytology sensitivity.

Cytology sensitivity	**55.4% for CIN3+**	**68.5% for CIN3+**
Strategy	**ICER (Euro/LYG)**	**Base case**
1. Kein Screening		
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	4,588	4,212
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	5,636	9,210
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	30,383	30,599
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	106,851	107,715
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	507,682	Dom
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	Dom	531,379

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated.

Figure 24. Sensitivity analysis: decreased sensitivity values for cytology



Colposcopy Sensitivity and Specificity

In multi-way sensitivity analyses colposcopy accuracy data were varied [specificity of 0.566, and sensitivity of 0.760 for CIN1/CIN2 and 0.983 for CIN3+].

Table 24 shows the incremental cost-effectiveness ratios (in Euro / LYG) for the non-dominated strategies, when alternative colposcopy accuracy data are used. Figure 25 shows the cost-effectiveness frontier for the scenario with alternative sensitivity and specificity values for colposcopy.

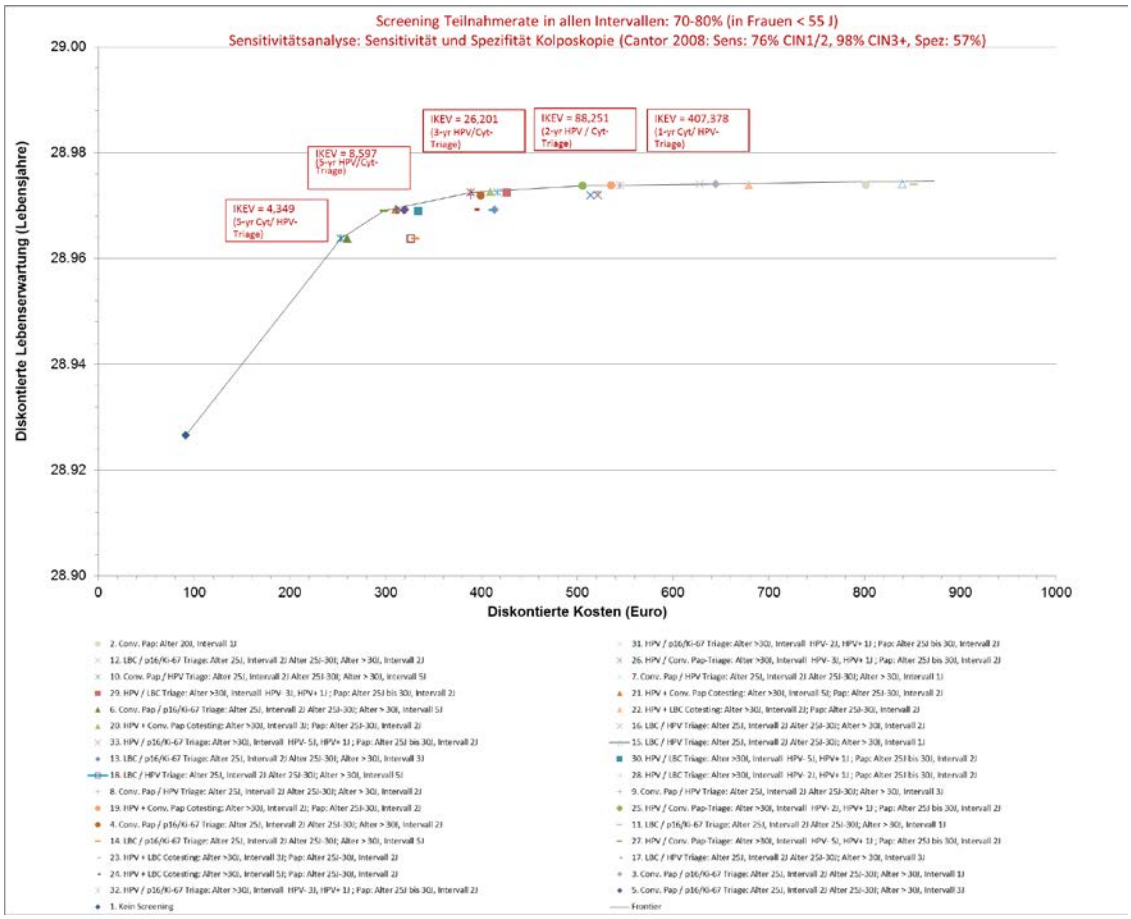
The ranking remained the same with the variation of colposcopy accuracy values. The ICERs of the different strategies changed only slightly. In the scenario with alternative sensitivity and specificity values for colposcopy, triennial HPV / Pap triage remains a cost-effective screening option.

Table 24. Sensitivity analysis: alternative colposcopy accuracy data.

Colposcopy accuracy	Cantor 2008	Mitchell 1998
Strategy	**ICER (Euro/LYG)**	**Base case**
1. Kein Screening		
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	4,349	4,212
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	8,597	9,210
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	26,201	30,599
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	88,251	107,715
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	407,378	531,379

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated.

Figure 25. Sensitivity analysis: alternative sensitivity and specificity values for colposcopy



Screening Adherence

Table 25 shows the incremental cost-effectiveness ratios (in Euro / LYG) for the non-dominated strategies, if the screening adherence is increased to 100%. In general, the screening adherence rate was applied to all strategies and all screening intervals simultaneously. Figure 26 shows the cost-effectiveness frontier for the analysis with 100% screening adherence rate.

Predicted model outcomes are sensitive to screening adherence variation. With increasing adherence rate, ICERs increased for all screening strategies.

The corresponding ICERs are 5,232 Euro/LYG for 5-yearly screening with cytology and HPV triage, 19,593 Euro/LYG for 5-yearly screening with HPV plus cytology triage, 112,594 Euro/LYG for 5-yearly screening with HPV+Pap cotesting, 220,227 Euro/LYG for 3-yearly HPV with cytology triage, 598,886 Euro/LYG for 3-yearly HPV+Pap cotesting, 2,028,149 Euro/LYG for biennial HPV with cytology triage, and 3,016,040 Euro/LYG for biennial HPV+Pap cotesting.

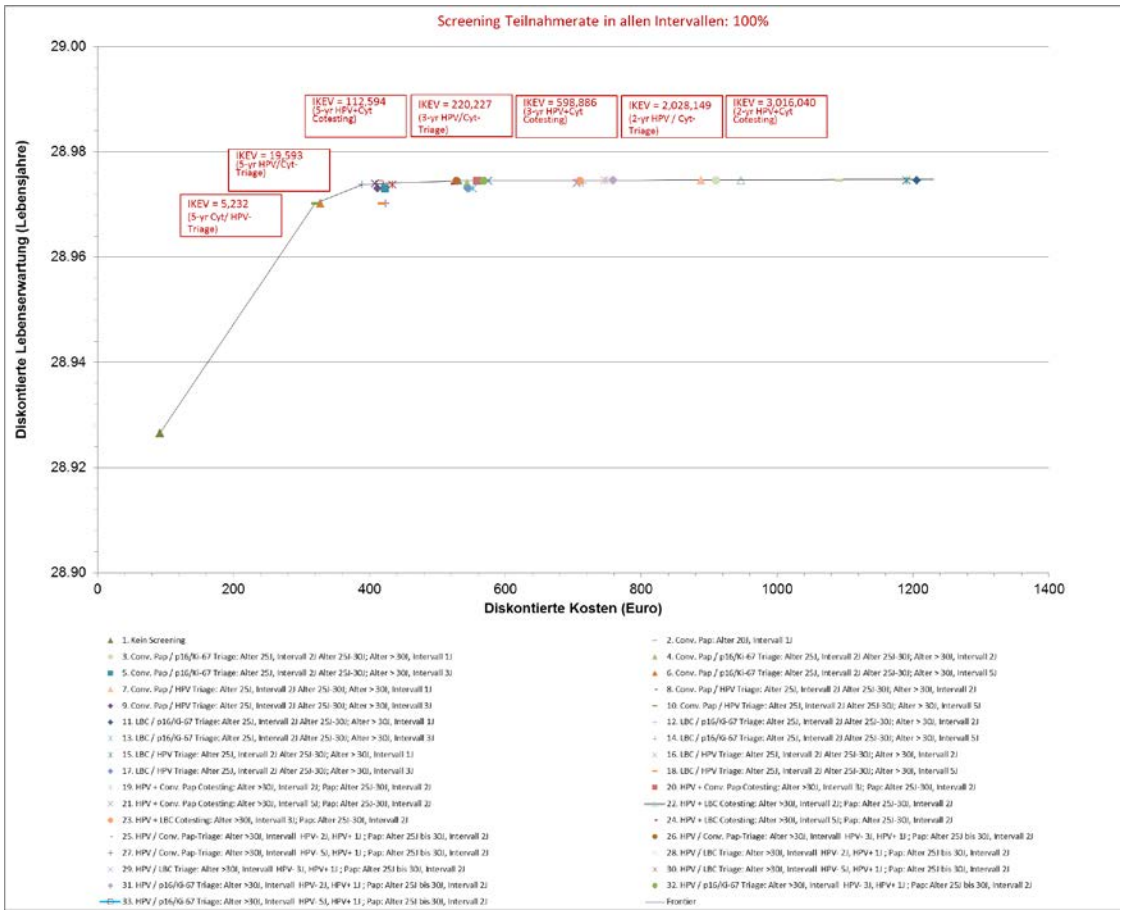
In women certainly attending with a screening adherence of 100%, 2-yearly and even 3-yearly screening programs are highly likely to be no more cost-effective, and 5-yearly HPV screening with cytology triage can be considered as a cost effective option in this scenario.

Table 25. Sensitivity analysis: 100% screening adherence.

Screening adherence	**100%**	**70-80%**
Strategy	**ICER (Euro/LYG)**	**Base case**
1. Kein Screening		
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	5,232	4,212
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	19,593	9,210
21. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 5J; Pap: Alter 25J-30J, Intervall 2J	112,594	Dom
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	220,227	30,599
20. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 3J; Pap: Alter 25J-30J, Intervall 2J	598,886	Dom
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	2,028,149	107,715
19. HPV + Conv. Pap Cotesting: Alter >30J, Intervall 2J; Pap: Alter 25J-30J, Intervall 2J	3,016,040	Dom
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	Dom	531,379

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated

Figure 26. Sensitivity analysis: 100% screening adherence.



Cancer Treatment Costs

Table 24 shows the incremental cost-effectiveness ratios (in Euro / LYG) for the non-dominated strategies, when alternative colposcopy accuracy data are used. Figure 25 shows the cost-effectiveness frontiers for the scenario with alternative sensitivity and specificity values for colposcopy.

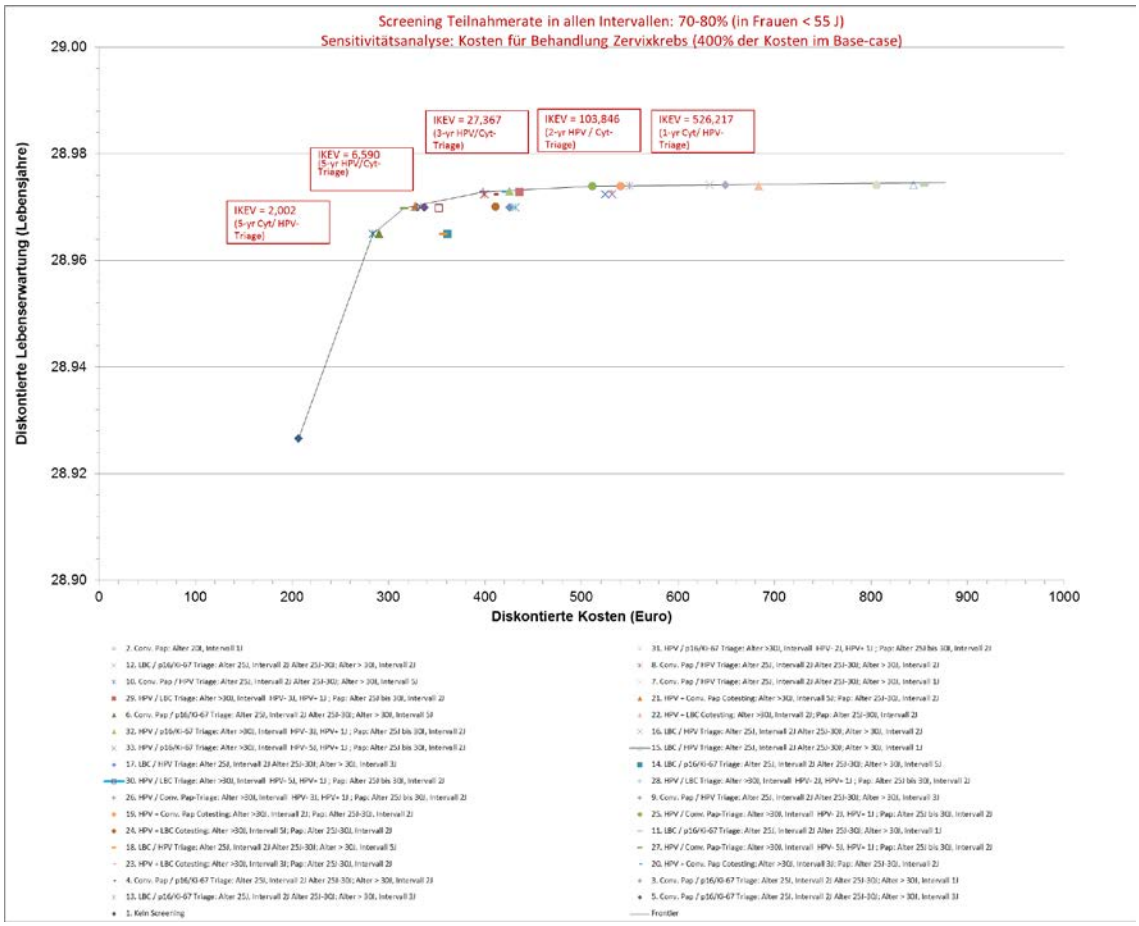
The ranking remained the same with the variation of cancer treatment costs. The ICERs of the different strategies decreased. However, in the scenario with increased cancer treatment costs, triennial HPV with cytology triage remains the cost-effective screening option.

Table 26. Sensitivity analysis: cancer treatment costs increased to 4-fold of the base case values.

Cancer treatment costs (Euro) for FIGO stage 1 - 4.	**18,715 - 29,387**	**4,679 - 7,347**
Strategy	**ICER (Euro/LYG)**	**Base case**
1. Kein Screening		
10. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 5J	4,349	4,212
27. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 5J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	8,597	9,210
26. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 3J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	26,201	30,599
25. HPV / Conv. Pap-Triage: Alter >30J, Intervall HPV- 2J, HPV+ 1J ; Pap: Alter 25J bis 30J, Intervall 2J	88,251	107,715
7. Conv. Pap / HPV Triage: Alter 25J, Intervall 2J Alter 25J-30J; Alter > 30J, Intervall 1J	407,378	531,379

HPV: human papilloma virus test, Pap: Papanicolaou cytology test, ICER: incremental cost-effectiveness ratio, LYG: life years gained, Dom: dominated.

Figure 27. Sensitivity analysis: increased cancer treatment costs



7 Discussion of Model Features and Limitations

This evidence report describes the decision-analytic study for cervical cancer screening to evaluate the benefits, harms and cost-effectiveness of different screening strategies in order to inform the development of the German evidence-based S3 clinical guideline “Prevention of Cervical Cancer”.

We performed evidence-based benefit-harm analyses and cost-effectiveness analyses comparing several cervical cancer screening strategies. In order to synthesize all best available evidence, we performed a decision analysis incorporating evidence on epidemiologic parameters, benefits, harms and costs. The decision-analytic model is designed to be applied in the context of comparative effectiveness analysis and economic evaluation analysis in order to inform evidence-based clinical guideline development. We performed comprehensive sensitivity analyses to evaluate the uncertainty of our results.

We followed international guidelines of decision-analytic modeling (2-6, 7). Nevertheless, as all decision-analytic modeling studies, this evaluation informing a clinical guideline has several limitations.

First, a published and validated model has been adapted to the context of the S3 guideline, and therefore, it was not possible to include all aspects covered or discussed in the S3 guideline into the decision-analytic framework of this analysis. For example, we did not perform formal decision analyses on the optimization of the length of the screening interval for women in the age of 25-30 years.

Second, there were no empirical quality-of-life data, which could have been additionally implemented into the model. As such, long-term effectiveness was based on life expectancy (measured in life years) instead of quality-adjusted life expectancy (measured in quality-adjusted life years, QALYs). Since screening results in a relatively small average gain in life expectancy, changes in quality-of-life due to psychological distress associated with the communication of screening results or adverse events of pre-cancer treatment may significantly affect the estimated harm-benefit ratios and/or cost-effectiveness ratios (46, 47).

Third, due to a lack of detailed individual data, age-specific adherence rates were assumed to equal average age-specific adherence rates in every screening round independent of prior screening history. No individual-level data on more complex adherence patterns were

available. In addition, as no information was available on how adherence may change with increasing screening interval, we used the same adherence rate for all strategies and intervals. However, health insurance data on screening adherence show much lower screening adherence within one year compared to a three-year time horizon. As we used 70%-80% screening adherence for all strategies in the analyses, annual screening effects, harms, and costs are likely overestimated, and cannot be compared with real data observed in current annual cytology screening in Germany. In addition, compliance with follow-up of abnormal screening results, diagnosis and treatment was considered to be 100%, which may be not the situation in real life.

Fourth, test sensitivity and specificity data for primary screening test were based upon results from meta-analysis including data from randomized clinical trials. However, sensitivity and specificity in real world settings may be significantly reduced, particularly for cytology. In addition, for lesions with specific morphologic conditions, test performance of repeated tests may be lower than for the first test. As this aspect affects cytology-based strategies more than HPV-based strategies, it is likely that particularly the benefits of cytology-based screening strategies with 1-year or 2-year screening intervals are overestimated, and in reality result in a worse benefit-harm balance and cost-effectiveness ratios than reported in the base-case analyses. We have considered this aspect in a sensitivity analysis lowering test performances.

Fifth, we assumed no false-positive biopsy results, and therefore, no false-positive conizations (i.e., conization in women with no lesion, but a positive test result). However, studies comparing cone biopsies to biopsy results are showing false positive rates. In addition, we assumed only conizations in women with CIN 1 if the lesion progressed to CIN 2, but not if the lesion persisted without progression. Therefore, our analyses results on harms (total conizations and conizations below CIN3) may underestimate harm in all strategies.

Sixth, our decision model did not consider heterogeneity of the population with respect to different HPV types and did not include separate states for women treated for precancerous lesions. This leads to a bias in the model against HPV screening (48-50).

Seventh, only direct medical costs from the perspective of the health care system were considered and inpatient costs were likely slightly underestimated. Therefore, HPV screening may be slightly more cost effective as shown in our analyses.

Eighth, model parameters have been calibrated to specific studies in a German population with limited sample size (42). Alternatively, larger samples used for European populations could be used, in particular, when HPV vaccination started to show effects. For instance, the International Agency for Research on Cancer (IARC) und the Information Centre on HPV and Cancer (ICO) are currently preparing a European database, which also includes age-specific prevalences form larger observational studies.

Overall, the comprehensive sensitivity analyses performed in this study showed robust results. Although numbers changed, the overall implications with respect to the guiding information for the clinical S3 guideline did not change substantially.

Future research is needed to acquire evidence-based information on individual-level adherence patterns and the impact of screening results on quality-of-life. In addition, as the introduction of HPV vaccination may result in lower future HPV incidence and consequently lower prevalence of CIN and cervical cancer, this may also change the accuracy of screening tests for detecting cervical lesions. Further modelling studies including long-term data from vaccinated women in Germany are recommended to fill this research gap.

8 References

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