

The German Cervical Cancer Screening Model: development and validation of a decision-analytic model for cervical cancer screening in Germany

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Background: We sought to develop and validate a decision-analytic model for the natural history of cervical cancer for the German health care context and to apply it to cervical cancer screening. **Methods:** We developed a Markov model for the natural history of cervical cancer and cervical cancer screening in the German health care context. The model reflects current German practice standards for screening, diagnostic follow-up and treatment regarding cervical cancer and its precursors. Data for disease progression and cervical cancer survival were obtained from the literature and German cancer registries. Accuracy of Papanicolaou (Pap) testing was based on meta-analyses. We performed internal and external model validation using observed epidemiological data for unscreened women from different German cancer registries. The model predicts life expectancy, incidence of detected cervical cancer cases, lifetime cervical cancer risks and mortality. **Results:** The model predicted a lifetime cervical cancer risk of 3.0% and a lifetime cervical cancer mortality of 1.0%, with a peak cancer incidence of 84/100 000 at age 51 years. These results were similar to observed data from German cancer registries, German literature data and results from other international models. Based on our model, annual Pap screening could prevent 98.7% of diagnosed cancer cases and 99.6% of deaths due to cervical cancer in women completely adherent to screening and compliant to treatment. Extending the screening interval from 1 year to 2, 3 or 5 years resulted in reduced screening effectiveness. **Conclusions:** This model provides a tool for evaluating the long-term effectiveness of different cervical cancer screening tests and strategies.

Keywords: cervical cancer, decision analysis, Markov model, screening

Cervical cancer is the second most common cancer in women worldwide.¹ In Germany approximately 6600 women are diagnosed with cervical cancer every year and the cervical cancer incidence and mortality was estimated to be 13.8/100 000 and

3.3/100 000 women (all data standardized for age).^{2,5} Although there have been no randomized clinical trials, there is a wide consensus based on results of historical series, case-control studies and predictions from birth cohort analyses^{3–6} that cervical cytologic screening leads to significant decreases in incidence and mortality. However, considerable controversy remains about the optimal screening frequency, the potential role of new screening or prevention techniques, risk-adapted screening and adherence to screening policy. Prospective randomized studies are ethically difficult to perform, expensive and results would only be obtained in decades. Thus, mathematical modelling has been used in several studies in the USA,^{7–23} the UK²⁴ and The Netherlands²⁵ to address these questions. These models are mostly transition models simulating the natural history of disease, and are widely accepted as valid approaches for epidemiologic projections and guiding cervical cancer screening, diagnosis and treatment decisions.^{26,27} However, transferability of international results to the German health care context is limited because of different screening strategies, cervical cancer epidemiology, clinical practice patterns and health care costs in these countries. To date, no decision-analytic Markov model exists for the specific German health care context.

Therefore, the objective of this study as part of a health technology assessment (HTA) commissioned by the German Agency for Health Technology Assessment at DIMDI/German Federal Ministry of Health was to develop a decision-analytic Markov model for the natural history of cervical cancer for the German health care system. In this paper, we present a model for the natural history of cervical cancer that incorporates German epidemiological data, as well as German clinical practice in

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screening, diagnosis and treatment of cervical cancer and its precursors. The model can be used to assess the potential impact of different screening or preventive strategies.

Methods

The German Cervical Cancer Model Group, an international and interdisciplinary network, was established to: (i) assess clinical practice patterns in Germany; (ii) create a database of German epidemiological, clinical and economic model parameters; and (iii) develop a German decision model for the natural history of cervical cancer based on previously published and validated international models.

In a systematic literature review²⁸ two high quality Markov models^{15,17} for cervical cancer were identified, which were eligible to be transferred and adapted to the German health care context. An international collaboration was established. The model structures and parameters were modified and adapted according to the German health care context. German epidemiological and clinical data were derived from the literature and German sources including German cancer registries (Munich, Saarland and the Common Cancer Registry of the Federal States Berlin/Brandenburg/Mecklenburg-Vorpommern/Sachsen-Anhalt/Sachsen/Thuringen).

In the following section we will describe the model structure and design, the assessment and implementation of model parameter data, the internal and external model validation process and the application of the model to screening evaluation.

Model design

We developed a 16-state Markov model²⁹ simulating the natural disease of cervical carcinogenesis (see figure 1). In this model, a hypothetical cohort of women aged 15 years and older moves in annual cycles through different health states based on cervical cytology and histology during her lifetime. The 16 health states of our model are no cervical lesion (well), benign hysterectomy, mild cervical intraepithelial neoplasia (CIN 1), moderate cervical intraepithelial neoplasia (CIN 2), severe cervical intraepithelial neoplasia/carcinoma *in situ* (CIN 3), undiagnosed and diagnosed invasive cervical cancer Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stages I–IV, cervical cancer survivors 5 years after cervical cancer diagnosis and treatment,

death from cervical cancer and death from other causes. Women may remain in the same health state, progress or regress to another health state, may die from cervical cancer as a function of FIGO-specific survival rates, or may die from other causes as a function of age and gender. Transitions from one state to another are defined by annual transition probabilities derived from published literature^{30–38} and calibrated to German cancer registry data.³⁹

In addition to the natural history model, we implemented the German standard of screening and treatment of precancerous lesions and invasive cancer into the model. The model estimates incidence of detected cervical cancer cases, cervical cancer mortality, lifetime risks of cervical cancer and deaths due to cervical cancer, and remaining life expectancy.

Our model was based on the following assumptions.

Studies using Bethesda classification were converted to the Munich Nomenclature (CIN system) as follows: low-grade squamous intraepithelial lesion into CIN 1, high-grade squamous intraepithelial lesion into CIN 2, CIN 3 and carcinoma *in situ*. The classification category 'atypical squamous cells of undetermined significance' is not transferable into the Munich nomenclature, and was therefore treated as a negative test results.

We considered benign hysterectomy, since removal of the organ at-risk affects the calculation of cervical cancer incidence.

In our model, development of invasive cervical cancer was operationalized to occur through the progression from CIN 1 to CIN 3/carcinoma *in situ* (CIS) lesions. Precancerous lesions may regress to no lesions. However, regression of invasive cervical cancer to precancerous lesions was not considered.

Although we assumed that cervical cancer is caused by human papillomavirus (HPV), we did not implement heterogeneity in HPV-related cervical cancer development.

Precancerous lesions can be detected by screening only, whereas invasive cancer cases can be detected by screening or by symptoms development. Detected precancerous lesions (CIN 1 to CIN 3/CIS) were assumed to be treated according to the German treatment guidelines. Patients with CIN 1/CIN 2 receive cytological control with Papanicolaou (Pap) smear every 3 months. If the lesion is persistent over 12 (CIN 2) or 24 months (CIN 1), Loop Electrosurgical Excision Procedure (LEEP) or cervical conisation are recommended. Patients with CIN 3 receive cytology and undergo colposcopy plus biopsy. If the biopsy result is CIN 3, LEEP or cervical conisation is

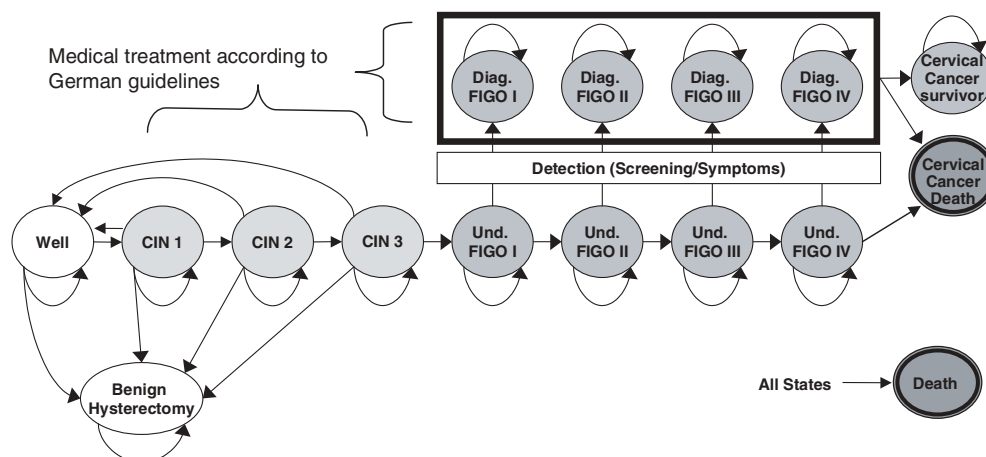


Figure 1 Schematic diagram of the Markov model. A hypothetical cohort of women may acquire different health state within a lifetime based on cervical cytology/histology: no cervical lesion (well), benign hysterectomy (Benign hysterectomy), mild cervical intraepithelial neoplasia (CIN 1), moderate cervical intraepithelial neoplasia (CIN 2), cervical intraepithelial neoplasia/carcinoma *in situ* (CIN 3), undiagnosed invasive cervical cancer FIGO states I–IV (Und. FIGO I–IV), diagnosed invasive cervical cancer FIGO states I–IV (Diag. FIGO I–IV), cervical cancer survivors 5 years after cervical cancer diagnosis and treatment (Cervical Cancer Survivor), death from cervical cancer (Cervical Cancer Death) and death from other causes (Death). Women may remain in the same health state, progress or regress to another health state, may die from cervical cancer as a function of FIGO-specific survival rates or may die from other causes as a function of age and gender

recommended. Women treated for precancerous lesions return to the healthy state, but are still at risk for future disease.

Women diagnosed with cervical cancer stage FIGO I–IV were assumed to be treated according to the German treatment guidelines. The treatment process depends on the TNM (tumour–node–metastases) status and FIGO stage, and includes different diagnostic and pre-treatment procedures, cervical conisation or hysterectomy.

The decision model was programmed using the software DATA Professional for Health Care (TreeAge Software Inc., Williamstown, MA, USA). All statistical analyses regarding model parameters were performed with SAS 8.1 (SAS Institute Inc., Cary, NC, USA).

Model parameters

Natural history of cervical cancer. Natural history parameters for progression and regression of the disease were estimated in two steps. First, epidemiological data were determined from published studies serving as an initial data set. In a second step, the model was empirically calibrated in a hierarchical fashion to fit the age-specific cancer incidence curves observed in unscreened populations.⁴⁰ Epidemiological data from an unscreened population in Germany during 1960–1964 from the German Common Cancer Registry were used for the model calibration. We did not correct for hysterectomy in the calibration, since population-based registries do not make a similar correction.

Natural history data for progression and regression of intraepithelial cervical neoplasia were estimated from several published studies^{30–38} and are described in table 1. We used age-specific probabilities for progression and regression. The probability of developing CIN 1 (step 1) and of progressing from CIN 3 to FIGO I (step 2) were hierarchically calibrated to fit the empirical age-specific cancer incidence curves observed in unscreened populations.

Almost no data exist for the rates of progression from FIGO stage I–IV and for the likelihood of developing symptoms. Therefore, we adopted the approach taken by others.^{8,9,15} In a third step of the hierarchical calibration we derived these parameters by varying the progression rates from FIGO stage I–IV and the symptom presentation rates to obtain a distribution of FIGO stages similar to that of an unscreened population. Distribution of cervical cancer stages were obtained from the German Common Cancer Registry for the years 1964–1966: FIGO I 38.8%, FIGO II 31.6%, FIGO III 24.1% and FIGO IV 5.4% (March 28th, 2002 personal communication Dr. Stabenow, Common Cancer Registry).

Benign hysterectomy. Owing to the lack of age-specific data for benign hysterectomy rates in Germany, we used annual age-specific benign hysterectomy rates reported by Vessey and Villard-Mackintosh⁴¹ for UK during 1985–1989: 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.

Cervical cancer survival and mortality from other causes. Annual cervical cancer survival probabilities at 1, 2, 3, 4 and 5 years post-diagnosis for each FIGO stage were based on original epidemiological data from the Munich Cancer Registry, Germany for the years 1988–1997 (Feb 06th, 2002 personal communication Dr. Engel, Munich Cancer Registry). Five-year survival rates based on these data for FIGO I, II, III and IV were 94.3%, 73.6%, 59.4% and 23.8%, respectively. We assumed no cancer-related mortality after 5 years post-diagnosis and treatment.¹⁵ Mortality owing to causes other than cervical cancer was based on German age-specific all-cause mortality rates for females using German life tables 1997–1999.⁴²

Sensitivity and specificity of cervical cancer smears. We implemented the German standard of screening into the model. Sensitivity and specificity of cervical cancer screening

Table 1 Annual transition probabilities used in the Markov model

From	To	Age (years)	Annual probability	References
No lesion	CIN 1	15–55+	0.0017–0.0521	30–33 in 15, 19
CIN 1	CIN 2	15–34	0.0173	32, 34–36 in 15
		35+	0.0595	
CIN 2	CIN 3		0.0567	36–38
CIN 1	No lesion	15–34	0.1027	32, 34–36 in 15
		35+	0.0645	
CIN 2	No lesion	15–34	0.1027	32, 34–36 in 15
		35+	0.0645	
CIN 3	No lesion	—	0.0567	32, 34–36 in 15
CIN 3	FIGO I ^a	—	0.0410	8, 9, 15, 18, 19
FIGO I ^a	FIGO II ^a	—	0.2015	15
FIGO II ^a	FIGO III ^a	—	0.2592	15
FIGO III ^a	FIGO IV ^a	—	0.3624	15
Undiagnosed	Diagnosed ^b			15
FIGO I	FIGO I	—	0.1098	15
FIGO II	FIGO II	—	0.2150	15
FIGO III	FIGO III	—	0.6120	15
FIGO IV	FIGO IV	—	0.9000	15

CIS included in CIN 3

a: Undiagnosed

b: Diagnosed by symptoms. Adapted to German context

based on Pap testing were obtained from the literature^{14,45} (table 2). Based on the data from a meta-analysis of studies of Pap screening using colposcopy or histology as reference standard¹⁴ Nanda *et al.* published disaggregated Pap test accuracy considering (i) low risk populations, (ii) different cytologic thresholds and (iii) correction for verification bias.⁴³ We used the cytological threshold of low squamous intraepithelial lesions or higher. Pap test sensitivity with 95% confidence intervals (CI) was estimated to be 47.1% (95% CI 44.8–49.4) for CIN 1 and 71.8% (95% CI 67.0–76.2) for CIN 2/3 or invasive cancer. Specificity of Pap test was estimated to be 95.0% (95% CI 94.5–96.4). Table 2 shows test criteria and likelihood of mild or moderate/severe dysplasia as used in the decision model.

Validation

The natural history model with its parameter values was validated in two steps. First, an internal validation was performed comparing the model predictions with observed epidemiological data for an unscreened population from the German Common Cancer Registry for the period 1964–1968, that is, prior to the beginning of the German national screening program. Secondly, an external validation was performed comparing the model predictions for an unscreened population to (i) German data published in the literature, and (ii) observed epidemiological data from the German Cancer Registry Saarland, which were both not used to generate or calibrate

Table 2 Accuracy of Pap test (source: Nanda *et al.*⁴³) and likelihoods of mild and moderate/severe cervical intraepithelial neoplasia (source: Payne *et al.*²⁴)

Health state	Specificity [% (95% CI ^a)]	Sensitivity [% (95% CI ^a)]	Mild CIN (%)	Moderate/severe CIN (%)
No CIN	95.0 (94.5–96.4)		90.0	10.0
CIN 1		47.1 (44.8–49.4)	90.7	9.3
CIN 2		71.8 ^b (67.0–76.2)	59.5	40.5
CIN 3		71.8 ^b (67.0–76.2)	50.0	50.0
Invasive cervix carcinoma		71.8 ^b (67.0–76.2)	60.0	40.0

a: Confidence interval calculated by authors

b: Aggregated data for CIN 2, CIN 3 and invasive carcinoma

the model and reflected an unscreened population. In addition, a brief cross-model validation was performed using modelling results reported in the literature^{12,15,17–19} for settings without screening.

Validation outcomes were peak age (in years) of cervical cancer and its precursors (CIN 1–3/CIS), peak cervical cancer incidence (per 100 000 women), total cervical cancer incidence (per 100 000), the distribution of cervical cancer FIGO I–IV stages (in %), and the lifetime risks (in %) of benign hysterectomy, cervical cancer and death due to cervical cancer.

Model application: effectiveness of Pap screening

As a model application, we evaluated the long-term effectiveness of German cervical cancer screening with Pap testing. Target population was women aged 15 years and older undergoing cervical cancer screening starting at age 20 years according to the German national cancer screening program. We report results for a homogeneous cohort of women with complete adherence to screening and follow-up.

We performed a Markov cohort simulation using a lifetime horizon to compare the strategies no screening, annual Pap screening (basecase), and Pap screening every 2, 3 and 5 years. Evaluated outcomes were incidence of detected cervical cancer cases, cervical cancer mortality and remaining life expectancy.

In sensitivity analyses, we examined the impact of varying Pap sensitivity on these outcomes. For Pap test sensitivity we used lower and upper 95% CIs limits derived from the published literature.⁴³ In a further sensitivity analysis, we used a lower bound of 20.0% Pap test sensitivity as reported in a German routine screening study including 4761 women.⁴⁶

Results

Model predictions and internal validation for unscreened populations

Age-specific and total cervical cancer incidence. The model predicted a peak age of cervical cancer of 51 years with a peak incidence of 84 cervical cancer cases per 100 000 women (table 3). The German Common Cancer Registry reported observed data of similar magnitude for an unscreened German population (March 28th, 2002 personal communication Dr. Stabenow, Common Cancer Registry). The peak age of cervical cancer was within the age group of 55–59 years with a peak incidence of 112 cervical cancer cases per 100 000 women.

Our model predicted a total incidence rate of detected cervical cancer cases of 46 per 100 000 women and year. The German Common Cancer Registry reported the same value for cervical cancer incidence, representing a high internal validity of our model. The model prediction for the distribution of cervical cancer FIGO stages was similar to the observed data (table 3).

Model predictions and external validity for unscreened populations

Lifetime risk of benign hysterectomy. Based on our model, the predicted cumulative risk of benign hysterectomy was 30.5% (table 3). In a recent German survey⁴⁵ every third woman was reported to have had a hysterectomy and only 10% of those for invasive cervical cancer reason, resulting in a cumulative risk of benign hysterectomy of 30.0%, or a deviation of 1.7%.

Age-specific prevalence of cervical cell dysplasia. Our model predicted an average prevalence for CIN 1–3 and CIS of 7.2% with a peak at age 27 years, and an average prevalence for CIN 2/3 of 2.6% (standardized for age) (figure 2).

A German clinical trial⁴⁶ examining 967 women with no cervical cell dysplasia and normal cytology within 1 year before the study began reported a CIN 2/3 prevalence of 6.8% for women under age 35 years and 1.5% for older women, with a peak-age of 20–35 years. The resulting average CIN 2/3 prevalence was 3.9% (not standardized for age). Predicted average CIN 2/3 prevalence differed from observed data in the trial by 33%. However, observed data were not standardized for age and were not obtained from an unscreened population. No observed data for the age-specific distributions of cervical precursors were available for an unscreened population in Germany.

In a cross-model validation, age-specific distributions of precursors were similar to modeling results for an unscreened population reported in the international literature^{15,22,48} (table 3).

Age-specific cervical cancer incidence. Our predicted age-specific cervical cancer incidence curves (data not shown) were similar to other cervical cancer incidence curves of unscreened population reported in the literature. Gustafsson *et al.* described for western European countries between 1950 and 1975 a similar cervical cancer incidence curve with a peak incidence between ages 40 and 50 years with a more rapid decline.⁴⁷

Our model predicted a peak incidence of 84/100 000 at age 51 years (table 3). These results were similar to those reported in the literature^{15,17,21,46,47} as well as to observed data from the German cancer registries. During 1968–1970, the German Cancer Registry Saarland reported a peak incidence at age 53 years.³⁹ Gustafsson *et al.* a peak incidence of 106.6/100 000 in Hamburg/West Germany and 112.3/100 000 in East Germany with a peak-age of 47.5 years (1964–1968).⁴⁹ Our predicted peak incidence was within the range of 67–90 per 100 000 women reported by other international models.^{15,17,21,48} Table 3 shows a summary of model predictions and external validation data.

Lifetime risk of cervical cancer and cervical cancer mortality. Our model predicted a lifetime cervical cancer risk of 3.0% and a lifetime cervical cancer mortality risk of 1.0% (table 3). These results were similar to observed data from the German Cancer Registry Saarland during 1968–1970, estimating a 3.3% lifetime risk for cervical cancer for a woman until the age of 85 years.³⁹ Several modelling studies performed in other countries reported

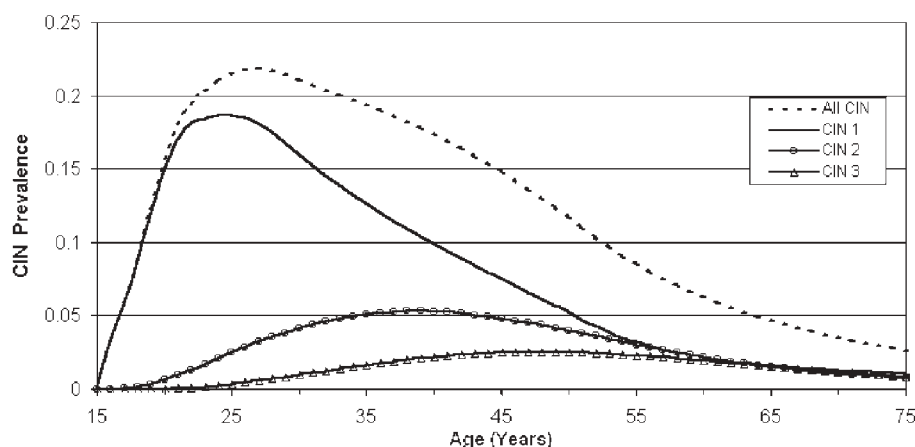
Table 3 Model predictions and validation values for cervical cancer incidence, distribution of FIGO stages, and lifetime risk of cervical cancer

	Model prediction German Cervical Cancer Screening Model	Internal validation Observed German data: Common Cancer Registry (1964–1968)	External validation Observed German data: Cancer Registry Saarland (1968–1970), Brenner <i>et al.</i> , ³⁹ Gustafsson <i>et al.</i> ⁹	Cross-model validation International literature data: Myers <i>et al.</i> ¹⁵
Peak age (years) CIN				
CIN 1	25			28
CIN 2	38			42 ^a
CIN 3	48			42 ^a
Peak age (years) cervix carcinoma	51	55–59	47; 53	48
Peak incidence cervix carcinoma (per 100 000)	84	112	107–112	81
Total incidence cervix carcinoma (per 100 000)	46	46		
Distribution cervix carcinoma FIGO stages (%)				
FIGO I	38.8	38.8	38	46.4
FIGO II	31.6	31.6	27	27.0
FIGO III	24.1	24.1	35 ^b	18.1
FIGO IV	5.45	5.44		8.5
Lifetime risk cervix carcinoma (%)	3.0		3.3 ^c	2.5

a: CIN 2/3 aggregated data

b: FIGO III + IV aggregated data

c: Women until age 85 years

**Figure 2** Age-specific prevalence of CIN. CIN 1 = mild; CIN 2 = moderate; CIN 3 = severe CIN or CIS

a similar lifetime risk of cervical cancer ranging from 2.5% to 3.7%.^{12,15,17–19,21,22,46}

Model application: effectiveness of Pap screening

In our model base-case analysis, we evaluated a hypothetical cohort of women aged 15 years and older completely adhering to annual screening starting with age 20 years until end of life to evaluate the potential of this strategy under ideal adherence. In the absence of screening, the model yielded 3032 diagnosed

cancer cases per 100 000 women, whereas annual Pap screening resulted in only 38 cancer cases per 100 000 women (table 4). Predicted mortality due to cervical cancer was 1004/100 000 for no screening and 3.9/100 000 for annual Pap screening. In other words, annual Pap screening has the potential to prevent 98.7% of diagnosed cancer cases and 99.6% of deaths due to cervical cancer among women completely adherent to this screening strategy and compliant to treatments.

Extending the screening interval resulted in reduced screening effectiveness. Compared with no screening, regular Pap screening every 2, 3 or 5 years had the potential to prevent 94.0%,

Table 4 Absolute and prevented cervical cancer cases and cervical cancer deaths, and life expectancy with Pap screening in screening intervals of 1, 2, 3 and 5 years

	No screening	Pap screening			
		1 year	2 years	3 years	5 years
Absolute cases per 100 000					
Cervical cancer cases	3032	38	180	310	699
Cervical cancer deaths	1004	4	23	53	128
Prevented cases per 100 000 ^a					
Cervical cancer cases	–	2994	2851	2676	2333
Cervical cancer deaths	–	1000	981	951	876
Life expectancy					
Absolute life years	65.80	66.06	66.06	66.05	66.02
Life days gained ^a	–	94.2	91.7	88.0	79.5

a: Versus no screening

88.3% and 76.9% of cervical cancer cases and 97.7%, 94.8% and 87.3% of cancer deaths, respectively. In terms of life expectancy, annual Pap screening saved on average 94 life days, whereas Pap screening every 2, 3 or 5 years saved 92, 88 and 80 life days per woman screened, respectively.

In sensitivity analyses on Pap sensitivity across 95% CIs, lower Pap sensitivity resulted in 0.3% decrease and higher sensitivity in 0.2% increase of life expectancy gained. Prevented cervical cancer cases increased by 0.4% (3007/100 000) with higher Pap sensitivity and decreased by 0.6% (2974/100 000) with lower Pap sensitivity. Prevented cervical cancer deaths increased by 0.1% (1002/100 000) with higher Pap sensitivity and decreased by 0.2% (998/100 000) with lower limit of Pap sensitivity. Using the lower bound of 20% Pap sensitivity prevented known cervical cancer cases decreased by 34.9% (1949/100 000) and prevented deaths due to cervical cancer decreased by 12.6% (875/100 000), respectively.

Discussion

An international and interdisciplinary network, the German Cervical Cancer Model Group, was established and a decision-analytic Markov model for the natural history of cervical carcinogenesis and screening was developed for the German health care context.

The model was internally and externally validated by comparing the model predictions with observed German data from published literature and from German cancer registries. In the absence of screening, the model predicted a lifetime cervical cancer risk of 3.0% with a peak incidence of 84/100 000 at age 51. These results were similar to observed data from German cancer registries,³⁹ as well as German and international data reported in the literature^{12,15,17–19,21,22,46,47} for unscreened populations. Model-predicted age-specific distributions of precursors with an average prevalence of CIN 1–3 and CIS of 7.2% with a peak at age 27 years, matched well with German and international data reported in the literature.^{15,22,44,46}

We applied our model to evaluate the clinical long-term consequences of Pap screening in women completely adherent to screening and treatment compared with no screening using

different screening intervals. Based on these decision analyses in the German health care context, annual Pap screening has the potential to prevent more than 98% of cervical cancer cases and more than 99% of deaths due to cervical cancer, resulting in an average gain in life expectancy of 3 months for each woman regularly participating in the screening program. Our model predicted mortality due to cervical cancer of 3.9/100 000 women. This is in line with a cervical cancer mortality rate of 3.6/100 000 (standardized for age) reported by the Robert-Koch Institute⁵ for the years 1996–1998 in Germany. Our results were also consistent with international data by Eddy⁸ reporting a 90% reduction in cervical cancer incidence with Pap screening every 2 years (our model 94%) and an average gain in life expectancy of 96 days (our model 92 days). Modelling longer screening intervals resulted in lower effectiveness. These results were similar to results reported in health technology assessments conducted in the USA and UK.^{14,24}

Our modelling results imply that Pap screening prevents substantial cervical cancer morbidity and mortality in women adherent to annual screening and follow-up procedures. However, biennial screening may result in similar gains in life expectancy. Cost-effectiveness analyses should be performed for different scenarios regarding screening intervals and screening adherence to determine the optimal screening policy in the German context.

Our decision model has several limitations owing to the availability and uncertainty of the model parameter values, and is based on model assumptions that can be reasonably debated. First, no sufficient up-to-date evidence about the natural history of disease with respect to the progression and regression data for the German context was available. Instead, we obtained these estimates from international studies and adjusted them to observed German epidemiological data from several cancer registries. However, model validation results proved a high internal and external validity when compared to observed epidemiological data in Germany. Secondly, differences in socio-demographic structure, epidemiology and clinical practice patterns across countries make it difficult, if not impossible, to transfer the results of our decision analysis focusing on the German health care context to other countries and health care systems.^{48–50} Nevertheless, the predicted clinical outcomes for Pap screening versus no screening were similar to the results from other industrialized countries.^{8,14,15,24} Thirdly, future research is required in obtaining quality-of-life data for women in different health states of cervical cancer disease and its precursors. Psychological effects of a positive cytology test result should be assessed and included in decision analyses in the future. Fourthly, no sufficient evidence on the patterns on women's adherence to cervical cancer screening in Germany is available. However, subgroups with reduced screening adherence likely include women who participate in screening but not on a regular basis. In future modelling efforts, sensitivity analyses should be performed on adherence to cervical cancer screening.

Finally, our model does not comprehensively capture the heterogeneity in population characteristics. In the absence of detailed information on the nature of the heterogeneity and the underlying or distinguishing risk factors in the population, we assumed a homogeneous population. However, failure to adjust for population heterogeneity may lead to biased model results.^{40,51} For example, we did not consider HPV heterogeneity in the population. Kuntz and Goldie⁵¹ reported that failing to account for the effects of persistent HPV could be important, even if screening for HPV is not the focus of the evaluation. They used a simple cervical cancer screening model to evaluate the potential impact of heterogeneity bias and found that the life expectancy gains were consistently greater in the unadjusted model compared with the adjusted model (positive bias). Nevertheless, in a cross-model validation, our model results

matched well with those from international models accounting for HPV heterogeneity.^{15,18,21,22}

In this paper we presented a comprehensive natural history model for cervical cancer, which was developed as a part of a health technology assessment for the German health care context. As each comprehensive health technology assessment must include a cost-effectiveness analysis, we plan to embed economic parameters into our model, which will allow us to determine the incremental cost-effectiveness ratios of different cervical cancer screening strategies, such as conventional Pap screening, liquid-based or computer-assisted screening. In future research, the model should be adjusted to HPV heterogeneity within the population, in order to evaluate HPV DNA testing as a screening tool or HPV vaccination as a preventive strategy.

Furthermore, our model could be used to address questions such as the optimal frequency of screening, the optimal age to start and stop screening, and the optimal way to diagnose and manage cervical cancer. Future research should address the role of screening adherence and compliance to treatment management strategies as well as risk-adapted screening strategies.

In conclusion, our model provides a valid tool for evaluating the long-term effectiveness of different cervical cancer screening or prevention strategies, such as conventional Pap screening or new screening technologies, for example, liquid-based cytology, computer-assisted smear screening or HPV testing. In addition, the application of the German Cervical Cancer Screening Model now allows to systematically evaluate several more sophisticated research questions such as the optimal screening frequency and starting age, risk-adapted screening in combination with new screening techniques, and the impact of improving screening adherence. As the model was designed to be updated easily as new evidence becomes available, its application will allow deriving recommendations that will guide policy makers, guideline developers and public health officials in clinical decision making and health care resource allocation.

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Key points

- Development and validation of a decision-analytic model for the natural history of cervical cancer and screening in Germany.
- The model projects detected cervical cancer cases, lifetime cervical cancer risk, deaths and remaining life expectancy.
- Predicted natural history results accurately reproduced observed German data for unscreened women derived from cancer registries and literature.
- The model provides a tool for optimizing screening algorithms regarding testing strategy, screening intervals and age ranges.
- The German Cervical Cancer Screening Model can be used to guide policy makers and guideline developers in the assessment of emerging technologies (e.g. HPV testing, HPV vaccination).

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