Cost-Effectiveness of Cervical Cancer Screening: Comparison of Screening Policies

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Background: **Recommended screening policies for cervical cancer differ widely among countries with respect to targeted age range, screening interval, and total number of scheduled screening examinations (i.e., Pap smears). We compared the efficiency of cervical cancer-screening programs by performing a cost-effectiveness analysis of cervical cancer-screening policies from high-income countries.** ***Methods:*** **We used the microsimulation screening analysis (MISCAN) program to model and determine the costs and effects of almost 500 screening policies, some fictitious and some actual (i.e., recommended by national guidelines). The costs (in U.S. dollars) and effects (in years of life gained) were compared for each policy to identify the most efficient policies.** ***Results:*** **There were 15 efficient screening policies (i.e., no alternative policy exists that results in more life-years gained for lower costs). For these policies, which considered two to 40 total scheduled examinations, the age range expanded gradually from 40–52 years to 20–80 years as the screening interval decreased from 12 to 1.5 years. For the efficient policies, the predicted gain in life expectancy ranged from 11.6 to 32.4 days, compared with a gain of 46 days if cervical cancer mortality were eliminated entirely. The average cost-effectiveness ratios increased from $6700 (for the longest screening interval) to $23 900 per life-year gained. For some countries, the recommended screening policies were close to efficient, but the cost-effectiveness could be improved by reducing the number of scheduled examinations, starting them at later ages, or lengthening the screening interval.** ***Conclusions:*** **The basis for the diversity in the screening policies among high-income countries does not appear to relate to the screening policies' cost-effectiveness ratios, which are highly sensitive to the number of Pap smears offered during a lifetime. [J Natl Cancer Inst 2002; 94:193–204]**

The purpose of cervical cancer screening with the Pap smear test is to detect preinvasive cancers and to prevent subsequent death from the disease. Although no randomized, controlled trials on mortality reduction from cervical cancer screening have been performed, there is ample evidence that screening has led to a reduction in cancer-related mortality *(1–4)*. In the high-income countries of Western Europe, North America, and Australia, preventive Pap smear tests are performed on a large scale in organized, often invitation-based, programs and by the personal initiative of individual women and physicians or practitioners. The screening recommendations and official policies in different countries and regions show considerable variation. For example, in The Netherlands and Finland, the recommended number of Pap smears during a woman's lifetime is seven, whereas in Germany and Australia, the recommended number is more than 25. In addition, in the U.K., The Netherlands, and Finland, the recommended time interval between screening examinations is 5 years, whereas in Australia it is 2 years and in Germany it is 1 year. There are also differences in the target age range. For example, in The Netherlands, screening is offered between the ages of 30 and 60 years (before 1996, screening was offered between the ages of 35 and 53 years), whereas in Australia screening is recommended between the ages of 18 and 70 years *(5)*.

How much the differences in the recommendations alter the cost effectiveness of the screening policies is unclear. The method of choice for the evaluation and comparison of different health care policies is cost-effectiveness analysis, which, for cervical cancer screening, involves a comparison of different screening policies that consider screening costs, possible savings in treatment, and potential health effects, such as life-years gained and cervical cancer deaths prevented. Such a comparison of policies would lead to the identification of efficient policies for which no alternative policies currently exist that result in more life-years gained for lower costs. In the rational decision-making process for making cervical cancer-screening recommendations, a policy maker can compare the incremental and/or average costs per life-year gained of the efficient policies with the maximum allowed values or thresholds for the incremental and/or average costs per life-year gained and identify the most efficient screening policy given the available resources.

In this study, the microsimulation screening analysis (MISCAN) model *(6,7)* for cervical cancer screening was used to evaluate and compare almost 500 screening policies that differed with respect to the recommended number of screenings, screening intervals, and targeted age ranges. These screening policies consist of fictitious screening policies, policies used in countries with a cervical screening program or in which screening was recommended in national guidelines *(5,8–13)*, policies recommended in the literature *(14)*, and policies found to be cost-effective in other studies *(2,15–21)*. We estimated the life-years gained and the costs of the policies and identified efficient screening policies. We determined the best policy for different thresholds for the incremental costs per life-year gained. The results were compared with existing policies and recommendations and with policies that have emerged from other cost-effectiveness analyses *(2,15–21)*. Our analysis uses demographic, epidemiologic, screening, and treatment characteristics

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See "Note" following "References."

from The Netherlands. Because these characteristics may be different for other countries, we investigated the extent to which differences in demographic, epidemiologic, screening, and treatment characteristics result in differences in screening recommendations.

METHODS

Policies

The fictitious screening policies considered in this cost-effectiveness analysis are listed in Supplementary Table 1 (available at the Journal's Web site http://jnci.oupjournals.org). We also included screening policies used in countries with cervical screening programs or recommended in national guidelines *(5,8–13)* and screening policies considered in other cost-effectiveness analyses *(2,15–21)*.

MISCAN

Costs and effects for the different screening policies were estimated using MISCAN *(6,7)*. The MISCAN simulation program was developed at the Department of Public Health, Erasmus University Rotterdam, The Netherlands, and has been used to evaluate breast, cervical, colon, and prostate cancer-screening programs. In MISCAN, a comparison is made between the situation with and without screening. A large population (i.e., 40 million women) is generated. This population consists of fictitious individual life histories, in which some of the women may develop cancer and some may die of the disease. This results in an age-specific and time-specific output of cancer incidence and mortality. This fictitious population then undergoes simulated screening. Screening may change some of the life histories. For example, in some life histories, preclinical lesions will be detected by screening, which may prevent further development of the disease and subsequent cancer-related death. The aggregated changes in all of the life histories constitute the effectiveness of the screening program. The cervical model specifications used as input for the MISCAN program include the demographic characteristics, the epidemiology and natural history of the disease, the screening characteristics, and the costs. A detailed description of the MISCAN program is given elsewhere *(6,7)*.

Model Specifications: Demography and Epidemiology

The Dutch population at risk for cervical cancer was simulated from demographic data *(22)* and hysterectomy (for reasons other than cervical cancer) rates that were obtained from the National Hospital Admission Registration *(23)*.

The background risk, i.e., the risk of dying of cervical cancer in a situation without screening, of cervical cancer-related mortality was derived from an age–period cohort analysis *(24)*. For our analyses, we assumed that the lifetime background risk of developing cervical cancer (or its progressive precursors) was proportional to the estimated relative level of cervical cancer mortality for each birth cohort. Furthermore, we assumed that there was a fixed ratio in each birth cohort between the lifetime risks of preinvasive disease that will spontaneously regress and preinvasive disease that will progress to cervical cancer. The cumulative incidence of progressive preinvasive cervical cancer by birth cohort was 0.0229 for those born from 1889 through 1918, 0.0235 for those born from 1919 through 1928, 0.0128 for those born from 1929 through 1938, 0.0106 for those born from 1939 through 1948, and 0.0148 for those born from 1949 through 2000.

For our analyses, we considered the reported negative association between attendance to the screening program and risk of cervical cancer *(25–27)* by subdividing the simulated population into two risk strata: 90% of the women were assumed to be potential attenders and were assumed to have a low risk of developing cervical cancer, and the remaining 10% of the population was assumed to be persistent nonattenders. On the basis of results from British Columbia in which the risk of attenders was estimated at 0.74 of the average risk *(27)*, we assumed that the persistent nonattenders have a risk of cervical cancer three times higher than that of the attenders.

The age distribution of the incidence of progressive preinvasive neoplasia was determined with the use of the age components of the mortality derived from the age–period cohort analysis *(24)*, the distribution of the duration of the preclinical stages of the disease, and the duration between clinical diagnosis and death combined with the age-specific lethality from cervical cancer. The age distribution of the incidence of regressive preinvasive neoplasia was calibrated by calculating the difference between observed cervical intraepithelial neoplasia (CIN) detection rates in The Netherlands (derived from the Dutch Network and National Database for Pathology [PALGA] data for the year 1992) and the detection rates of progressive CIN predicted by MISCAN. The resulting age distributions of preinvasive incidence of regressive and progressive disease, respectively, are shown in Supplementary Table 2 (available at the Journal's Web site http://jnci.oupjournals.org).

Preclinical disease is subdivided into four sequential stages (Supplementary Fig. 1; available at the Journal's Web site http://jnci.oupjournals.org): preinvasive (corresponding to CIN; the stage in which the disease is not yet invasive and spontaneous regression may occur) and the three preclinical invasive stages, i.e., the stages in which the disease has become invasive but is not yet detected [International Federation of Gynecology and Obstetrics definitions IA, IB, and II+; *(28)*]. A Weibull distribution was used to assume variation between women in the duration of the different preinvasive and preclinical disease stages *(27)*. The mean duration and the standard deviation of the different stages were 11.8 ± 2.2 years for preinvasive stage CIN, 2.0 ± 0.9 years for preclinical invasive stage IA, and 1.9 ± 0.9 years for preclinical invasive stages IB and II+ combined. Progressive and regressive preinvasive stages were assumed to have the same duration distribution. The mean duration and the standard deviation of the preinvasive stages were estimated from British Columbia screening data that used one combined CIN stage *(27)*. Regressive lesions never become invasive and will return to normal (without evidence of cervical neoplasia) after the preinvasive stage. After progressive preinvasive lesions become macroinvasive (stage IB), some will be clinically diagnosed, whereas others will progress to stage II+ before any symptoms develop. The mean duration of the preclinical invasive stage was based on the ratio of the prevalence to clinical incidence before screening began in British Columbia *(27,29)* and in a Dutch pilot study *(30)*. In the Dutch pilot study, 54% of the invasive cancers detected at the prevalent screen (i.e., the first screening in a previously unscreened population) were diagnosed with stage IA disease; this indicates that the duration of preclinical stage IA compared with preclinical stages IB and II+ is about the same. For our analyses, we assumed [on the basis of

data from Dutch hospital registries *(31)* and from the Norwegian cancer registry *(32)*] that the proportion of clinical cancers that are diagnosed in stage IB decreased linearly from 58% at age 30 years to 26% at age 70 years.

Model Specifications: Screening and Treatment

The simulated screening policies were assumed to start in 1993 and to continue for 27 years until 2020. Screening practices before 1993, however, will influence the effectiveness of the screening program after 1993; therefore, this practice has been included in the simulation of the Dutch situation.

Information on the screening activities before 1993 was obtained from survey data *(24,33,34)*. The attendance rate from 1993 onward was assumed to be 80% until age 50 years and to decrease by 0.5% per year thereafter. Because we assumed that 10% of the population will never attend the screening program, we calculated a probability of 88.9% for the potential attenders, which constituted 90% of the population, to actually respond to a scheduled screening examination. After age 50 years, the attendance rate was assumed to decrease by 0.5% per year. This is in accordance with the percentage of women in The Netherlands who had a Pap smear from 1990 through 1994.

The sensitivity of the Pap smear for different disease stages is 80% for preinvasive CIN *(27)*, 85% for preclinical invasive stages IA and IB, and 90% for preclinical invasive stage II+.

False-positive test results indicate the specificity of the Pap smear. We assumed that 0.06% of screening attenders were referred for a colposcopy and a biopsy after which no cervical neoplasia was found and that 6.2% of screening attenders will, on average, have 1.8 repeat smears because of borderline test results after their primary smear before they return to the regular screening schedule (PALGA 1992).

For the simulation model, the percentage of women surviving after a clinical diagnosis of cancer was assumed to be age dependent and stage dependent on the basis of Dutch incidence and mortality figures from the prescreening period in The Netherlands *(24)*. Cancers clinically detected in stage IB have a more favorable prognosis than cancers detected in stage II+, and women aged 30–50 years who are diagnosed with stage II+ disease have a higher probability of surviving than women diagnosed with the same disease when younger than 30 years or older than 50 years (Supplementary Table 3 available at the Journal's Web site http://jnci.oupjournals.org).

Screen-detected preinvasive lesions were assumed to lead to a 100% cure rate. For screen-detected invasive cancers, the survival was modeled as a reduction in the risk of dying of cervical cancer compared with that of dying of clinically diagnosed cancer. This reduction was assumed to be 80% for screen-detected stage IA disease, a percentage that was found to reproduce the reported 97% 5-year relative survival for this stage *(35)*. For screen-detected stage II+ disease, the reduction was fixed at 20%, resulting from a comparison of the stage distribution within stage II+ in a period with little screening (1970–1975) to the stage distribution within screen-detected II+ cases *(30)*. For screen-detected stage IB disease, the reduction was assumed to be 40%, an intermediate value.

Model Specifications: Costs

The costs of a screening program (Supplementary Table 4 available at the Journal's Web site http://jnci.oupjounals.org) were divided into fixed costs and variable costs. Fixed costs are associated with coordinating and evaluating a cervical cancer-screening program. Variable costs are divided into invitation costs and screening costs. Screening costs include time and travel costs for the woman, costs of smear taking, costs of cytologic evaluation, costs of registration in the PALGA, and the costs of 5.3% (estimated from PALGA data for the year 1992) of the smears that are repeated because of inadequate smears or smears without endocervical cells *(36,37)*.

The costs of diagnostic and treatment procedures for the different disease stages and the costs of treatment and palliative care for advanced cervical cancer in the last phase before dying of cervical cancer were derived from cost studies in The Netherlands *(24,36,38,39)*.

Cost-Effectiveness Analysis

In this study, MISCAN was used to predict costs and effects for organized screening programs for a 27-year period. We assumed a hypothetic situation in which the organized program is the only screening program and in which no opportunistic screening (i.e., spontaneous screening for other than medical reasons) occurs. The simulated effects are accounted for until all simulated women who could have benefited from the program have died. The costs are presented in U.S. dollars (1 U.S. dollar = 2 Dutch florins). The effects are presented in days of life gained per woman per year of the screening program. The cost-effectiveness calculations are conducted from the societal perspective.

To identify efficient screening policies, we compared the simulated costs of and life-years gained from each policy. A policy was considered to be efficient when there was no alternative policy resulting in more life-years gained for the same or lower costs (simple dominance) and when there was no combination of two other screening policies that gained more life-years for the same costs (extended dominance) *(40,41)*.

The effects per woman during her lifetime were derived by multiplying the number of days gained per woman per year of the screening program by the average life expectancy of a woman in The Netherlands, which is 80 years *(42)*. In the calculation of incremental and/or average cost-effectiveness ratios, both costs and effects were discounted at a rate of 3% to convert future costs and health effects to their present value [i.e., dollars expended or health effects experienced n years in the future are discounted by a factor of $1/(1.03)^n$ *(41)*], as recommended by the Panel on Cost Effectiveness in Health and Medicine.

Because of the nature of microsimulations, estimates for costs and effects are affected by random fluctuation. We calculated this fluctuation to be less than 2% of the estimated value of the cost-effectiveness ratio and up to 35% for the incremental cost-effectiveness ratio. Therefore, to reduce the influence of random fluctuation, the incremental cost-effectiveness ratio was estimated by enlarging the simulated population 10 times to 400 million women.

Sensitivity Analysis

A one-way sensitivity analysis was performed on background incidence, attendance, sensitivity (proportion of false-negative tests) and specificity of the screening test, and costs (fixed costs, screening costs, and assessment and treatment costs). The background incidence and fixed costs, screening costs, and treatment costs were halved and doubled to obtain the low values and high values, respectively, used in the sensitivity analysis. To deter-

mine attendance, the lack of attendance values were halved and doubled to obtain the high estimates and low estimates, respectively. To determine the sensitivity of the screening test, we halved and doubled the proportion of false-negative results for all stages to obtain the high estimates and low estimates, respectively. To determine the specificity of the screening test, we obtained the high values by halving the percentage of repeat smears because of borderline test results and the proportion of referrals for biopsy after which no cervical neoplasia was found, and the low values were obtained by doubling the baseline estimates for these parameters.

RESULTS

Costs and Effects of Screening Policies

From nearly 500 screening policies, there was a broad range of combinations of predicted costs and effects as measured by life-years gained (Fig. 1). Per 1 000 000 women of the general population, the costs varied between 0.5 million and 9.5 million U.S. dollars, and the effects ranged from 50 life-years to 350 life-years gained per year of the screening program.

Next, after deleting those that were not efficient, we obtained the efficient screening policies for which no alternative policy exists that result in more life-years gained for lower costs. There were 15 efficient screening policies, and together they represented the efficient frontier (Fig. 2). The age range of efficient screening policies increased from age 40–52 years for policies that recommend two examinations during a woman's lifetime to age 20–80 years for those that recommend more than 20 examinations. In general, a more intensive screening policy was one that recommended that screening start at a younger age, end at an older age, and have a shorter interval between examinations (Table 1). For the efficient policies, the effects of the total screening program on life expectancy ranged from 11.6 days for those that recommend two scheduled examinations during a woman's lifetime to 32.4 days for those that recommend 40 scheduled examinations. We estimated that total elimination of cervical cancer would yield a gain in life expectancy of 46 days.

According to the law of diminishing returns, if the number of scheduled examinations in a screening program were increased, the increase in the number of life-years gained would slow (Table 1). When a detailed assessment of the costs of a screening program was compared with that of the costs of no screening, screening costs were in excess of the costs of diagnostic testing and treatment of preinvasive disease detected by screening combined and were only partially compensated for by the savings incurred from preventing invasive carcinoma and advanced disease (Table 2). Because the costs of coordinating and evaluating the screening program were assumed to be independent of the number of scheduled examinations, and because a scale effect (i.e., the costs per smear are lower if more smears are performed) was assumed for the costs per smear, the screening costs increased less than proportionally with the number of scheduled examinations. Moreover, when moving toward more intensive policies, the incremental cost-effectiveness ratio increased because the incremental effects rapidly diminished (Table 1). For a policy maker, if the decision regarding a policy depends only on a maximal allowed value or threshold value for the incremental costs per life-year gained, then for reference values of $15 000, $30 000, and $60 000, screening policies with five, 10, and 20 scheduled examinations, respectively, and screening intervals of 9, 5, and 3 years, respectively, are optimal.

Sensitivity Analysis

Differences in demographic, epidemiologic, and screening characteristics, such as background incidence, attendance, sensitivity and specificity of the screening test, and cost, may lead to different choices in efficient screening policies. The influences of these differences were investigated in a sensitivity analysis (Table 3). A higher background incidence, i.e., the incidence of invasive cancer in the hypothetic situation where there has never been screening, led to higher effects of a screening policy because the effects were proportional to the incidence of cervical cancer (*see* Table 3). This resulted in a more favorable incremental cost-effectiveness ratio, and consequently, more intensive screening policies were feasible given a threshold value for the incremental cost-effectiveness ratio.

Differences in either the percentage of women who will at-

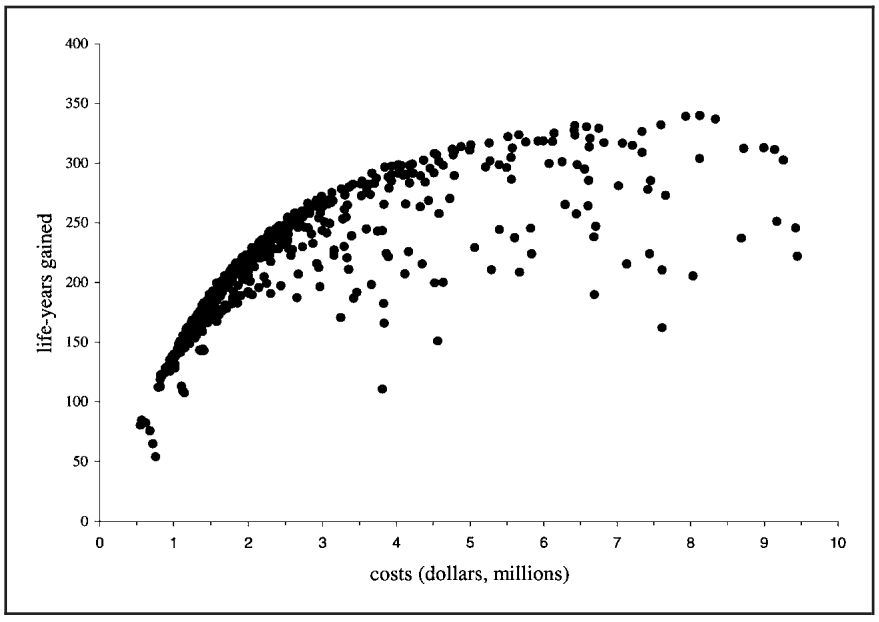

Fig. 1. Costs (in millions of U.S. dollars) and effects (life-years gained) per 1 000 000 women in a simulated general population per year for nearly 500 simulated screening policies (each represented by a **dot**) differing with respect to age range, screening interval, and number of scheduled screening examinations in a lifetime. The analysis considered a 3% discount rate to convert future costs and health effects to their present values.

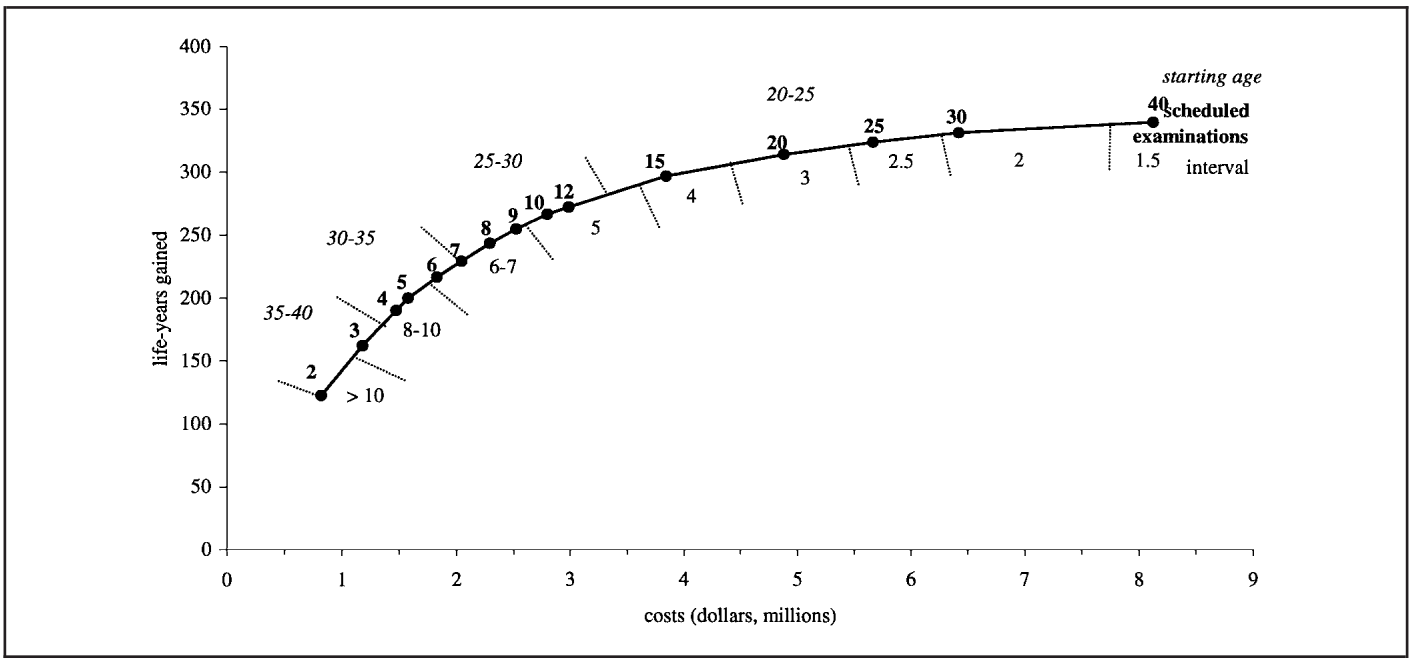

Fig. 2. Schematic representation of the simulated efficient frontier showing the location of optimal starting ages, number of scheduled examinations, and screening intervals. Costs (in millions of U.S. dollars) and effects (life-years gained) are per 1 000 000 women in the simulated general population per year of the screening program. The analysis considered a 3% discount rate to convert future costs and health effects to their present values. The starting ages are shown as a range in years. The interval between scheduled Pap smears is shown in years. **Broken lines** represent the boundaries between the age ranges and scheduled intervals.

Table 1. Efficient policies, estimated by MIcrosimulation SCreening ANalysis (MISCAN)*, characterized by the number of scheduled examinations, screening interval, and age range and expressed as the cost and effects per woman per year of the screening program, the effects of the program per woman during her lifetime, the cost-effectiveness ratio (CER), and the incremental cost effectiveness ratio (ICER)

			Costs	Effects	Effects	CER	ICER†§
No. of scheduled exams	Interval between exams, y	Age range, y	U.S. dollars per woman per year of screening (no discounting)‡	Days gained per woman per year of screening (no discounting)	Days gained per woman during lifetime (no discounting)	Costs (U.S. dollars) per life-year gained (3% discounting)	Costs (U.S. dollars) per life-year gained (3% discounting)
2	12	40–52	0.99	0.14	11.6	6700	6700
3	9	35–53	1.42	0.19	15.5	7300	9100
4	8	32–56	1.79	0.23	18.3	7700	10 200
5	9	32–68	1.94	0.23	18.7	7900	11 800
6	7	32–67	2.27	0.25	20.3	8500	15 200
7	6	32–68	2.55	0.27	21.4	8900	17 300
8	7	27–76	2.86	0.29	22.9	9400	16 800
9	6	27–75	3.17	0.30	23.9	9900	20 800
10	5	27–72	3.54	0.31	25.2	10 600	26 300
12	5	27–82	3.79	0.32	25.4	11 000	32 300
15	4	22–78	4.93	0.35	28.1	13 000	35 000
20	3	22–79	6.35	0.37	29.6	15 500	55 700
25	2½	20–80	7.43	0.38	30.8	17 500	79 500
30	2	22–80	8.49	0.39	31.4	19 400	119 000
40	1½	20–79	10.88	0.41	32.4	23 900	173 700

*CER = cost-effectiveness ratio; ICER = incremental cost-effectiveness ratio; MISCAN = MIcrosimulation SCreening ANalysis *(6,7)*.

†CER was estimated using a fictitious population of 40 million women; ICER was estimated using an enlarged simulated population to reduce random fluctuation.

‡Discounting refers to converting future costs and health effects to their present values.

§The incremental cost-effectiveness ratio is calculated by dividing the difference in costs between the next less intensive efficient screening policy with the current screening policy by the difference in effects between these screening policies. To calculate the ICER for the screening policy with two scheduled examinations the costs and effects of this screening policy are compared with a situation without screening.

tend a recommended screening examination (screening attendance) or sensitivity of the screening test will not only affect the choice of the number of screening examinations to be offered per woman but will also affect the choice of the age range and time interval between the scheduled examinations *(43)*. Higher attendance and/or sensitivity will make longer intervals between screenings and, simultaneously, broader age ranges more favorable in terms of cost-effectiveness because the role for a subsequent screening to detect abnormalities previously missed would be less important (Table 3).

A lower specificity will increase the incremental costs per life-year gained and, therefore, lead to a lower number of scheduled examinations that would be offered per woman to achieve the same incremental cost per life-year gained compared with

Table 2. Detailed overview of the predicted costs and effects per 1 000 000 women of the general population per year of the screening program for the efficient screening policies as estimated by MIcrosimulation SCreening ANalysis (MISCAN), with 5, 10, 20, and 40 scheduled examinations*

No. of scheduled examinations	5	10	20	40
Interval between examinations, y	9	5	3	1½
Age range, y	32–68	27–72	20–77	20–79
No. of Pap smears per year of screening	40 000	78 000	152 000	300 000
Costs† (U.S. dollars, millions)				
Screening	1.74	2.94	5.05	8.66
Repeat smears	0.22	0.42	0.83	1.62
Referred, no cervical intraepithelial neoplasia (CIN)‡	0.01	0.02	0.04	0.09
CIN§	1.12	1.70	2.28	2.54
Invasive carcinoma‡§	−0.58	−0.80	−0.98	−1.07
Advanced disease‖	−0.56	−0.75	−0.88	−0.96
Total costs	1.94	3.53	6.35	10.87
Effects				
Prevented deaths	26	35	41	45
Life-years gained¶	640	862	1022	1110

*MISCAN = MIcrosimulation SCreening ANalysis *(6,7)*. The values are not discounted because no time preference is established.

†Costs determined relative to a situation without screening.

‡Costs of follow-up and treatment.

§If all invasive cases could be prevented a total U.S. $1.54 million saved, as predicted by MISCAN.

‖Costs of treatment for recurrence and palliative care in women who die of cervical cancer. Maximum savings on costs of advanced disease total U.S. $1.38 million.

¶The days gained per woman per year of screening can be calculated by multiplying the number of life-years gained by 365/1 000 000.

the baseline situation in which Dutch characteristics are incorporated. The choice of the number of scheduled examinations depends on the costs of medical procedures (including screening itself) that are generated or prevented by screening. If the costs of Pap smears, assessment, and treatment of false-positive results and CIN generated by screening are higher than those assumed in the baseline situation, then the cost-effectiveness ratio of screening will be unfavorably influenced. In contrast, higher costs for treatment of invasive cancers and advanced disease, some of which are prevented by screening, will lower the incremental and/or average cost-effectiveness ratio. The fixed costs for coordinating and evaluating a cervical screening program do not influence the incremental costs per life-year gained. However, the average costs per life-year gained will increase if the fixed costs are higher.

International Comparison

We next compared the screening policies from countries with cervical cancer-screening programs or national guidelines, with the assumption that their demographic, epidemiologic, screening, and treatment characteristics were similar to those in The Netherlands. As shown in Fig. 3, several of the screening policies are remarkably close to the efficient frontier. However, for several screening policies, such as those from Sweden, Denmark, the U.K. (16 scheduled examinations), the United States, and Australia, alternative policies could be recommended to reduce costs for the same amount of life-years gained or to improve effectiveness while keeping the costs the same. These alternative policies are situated in the upper-left quadrant of the marking for a screening policy of a country in Fig. 3. For example, the area in which more cost-effective screening policies are situated for the United States is identified in Fig. 3 by a broken line. It can be seen in Fig. 3 that the policy for screening every 4 years between ages 22 and 78 years with 15 examinations has the same effects for much lower cost (yearly almost $1 million less) than the recommendations issued by the U.S. Preventive Task Force *(10)* for screening every 3 years between ages 18 and 66 years with 17 scheduled examinations. If, however, a more intensive policy is committed to (the U.S. Preventive Task Force policy is conservative compared with recommendations from other U.S. authorities and current U.S. practice that recommends annual screening), the efficient screening policies with 20–30 examinations and an interval of 2–3 years starting after age 20 years are more cost effective than current practice.

To investigate whether the wide diversity in screening recommendations and official policies among countries originates from differences in the epidemiology of cervical cancer or price level, we compared the incidence of cervical cancer and price levels among countries. If the background incidence is higher in a country than it is in The Netherlands, then the effects of a screening policy would be proportionally higher than those calculated in this analysis, whereas the total costs would stay at the same level. If the price level in a country is lower than it is in The Netherlands, then the total costs of a screening policy would be proportionally lower than those calculated in this analysis. The differences in background incidence of cervical cancer and/or price level will result in more favorable cost-effectiveness estimates than those calculated for The Netherlands (and vice versa, if the background incidence is lower and/or the costs are higher), which may lead to the choice of an efficient screening policy with a higher number of scheduled examinations despite having the same threshold value of the incremental and/or average cost-effectiveness ratio. Differences in incidence and/or price level may, therefore, explain the diversity in the number of scheduled examinations among different countries.

We obtained the background incidence of cervical cancer for each country *(44–46)*. We calculated the price levels for each country by dividing the health care-specific purchasing power parities *(47)*, which adjust the exchange rates for different countries to the health care-specific price levels by the current exchange rates. By comparing the incidence and the price levels to those of The Netherlands, we obtained relative incidence and relative price levels, respectively. These values were then plotted (Fig. 4, A). The solid line represents the situation in which the relative incidence is equal to the relative price level. For the countries that fell above the line (Denmark and the United States, assuming a high background incidence to be representa-

Table 3. Sensitivity analysis: Incremental cost-effectiveness ratios, expressed as U.S. dollars per life-year gained, with 3% discounting to convert future costs and health effects to present values*

No. of scheduled Pap smears	5		10		20		40	
Interval, y	9		5		3		1½	
Age range, y	32–68		27–72		20–77		20–79	
	low†	high	low	high	low	high	low	high
Background incidence	24 400	5100	49 800	11 400	124 300	26 800	331 700	83 600
Attendance	14 500	10 800	16 200	33 300	33 300	81 500	80 100	315 400
Sensitivity of screening test	19 200	9300	19 200	32 000	41 700	66 500	117 300	191 000
Specificity of screening test	13 500	11 000	30 100	24 400	64 300	51 400	206 300	157 400
Screening costs	7000	21 400	16 100	46 700	34 800	97 600	107 200	306 600
Treatment costs, CIN and false positives‡	10 200	15 100	23 700	31 500	51 400	64 400	167 300	186 600
Treatment costs, invasive cancers	13 100	9200	27 700	23 400	57 200	52 700	175 200	170 600
Baseline§	11 800		26 300		55 700		173 700	

*Sensitivity analysis is defined as investigations that isolate key parameters involved in the cost-effectiveness analysis that indicate the degree of influence each key parameter has on the outcome of the analyses. Incremental cost-effectiveness ratios are calculated by comparing the costs and effects of a screening policy with five scheduled examinations to one with four scheduled examinations, 10 scheduled examinations to one with nine scheduled examinations, 20 scheduled examinations to one with 15 scheduled examinations, and 40 scheduled examinations to one with 30 scheduled examinations.

†The background incidence (defined as the incidence in a situation without screening) and fixed costs, screening costs, and treatment costs were halved and doubled to obtain the low values and high values, respectively. To determine attendance, the lack of attendance values were halved and doubled to obtain the high estimates and low estimates, respectively. To determine the sensitivity of the screening test, the proportion of false-negative results for all stages was halved and doubled to obtain the high estimates and low estimates, respectively. The high values for the specificity of the screening test were obtained by halving the percentage of repeat smears because of borderline test results and the proportion of attending women that are referred for a colposcopy and a biopsy after which no cervical neoplasia is found. The low values for the specificity of the screening test were obtained by doubling the baseline estimates for these parameters.

‡CIN = cervical intraepithelial neoplasia.

§The baseline estimates for the background incidence for women willing to participate in screening were 0.0229 for those born from 1889 through 1918; 0.0235 for those born from 1919 through 1928; 0.128 for those born from 1929 through 1938; 0.0106 for those born from 1939 through 1948; and 0.0148 for those born from 1949 through 2000. For attendance the baseline estimate was 80%. The sensitivity was assumed to be 80% for preinvasive CIN, 85% for preclinical invasive stages IA and IB, and 90% for preclinical invasive stage II+ at baseline. The specificity assumed that 0.06% of attending women are referred for a colposcopy and a biopsy after which no cervical neoplasia is found, and that 6.2% of attending women will, on average, have 1.8 repeat smears because of borderline test results after their primary smear and before they return to the regular screening schedule. The baseline estimates for the screening costs decrease from U.S. $32 per smear if 80 000 smears were taken annually to U.S. $26 per smear if 2 500 000 smears were taken annually. The invitation costs were U.S. $1 per invitation at baseline. The baseline estimates for the costs of diagnosis and treatment of CIN and false positive results are U.S. $1950 and U.S. $485, respectively. The costs for diagnosis and treatment of invasive cancers at baseline are U.S. $5315, U.S. $11 265, U.S. $10 620, and U.S. $9705 for diagnosis and treatment of invasive cancers stage IA, IB, screen-detected II+, and clinically diagnosed II+, respectively. The costs for treatment (including palliative care) for advanced cervical cancer are age dependent; U.S. $30 800 for women aged less than 50 years, U.S. $21 955 for women aged between 50 and 70 years, and U.S. $9345 for women aged more than 70 years at baseline.

tive), the cost-effectiveness estimates of a policy will be more favorable than those estimates in The Netherlands. Consequently, more intensive screening policies will stay below a certain threshold value of the incremental and/or average cost-effectiveness ratio. For the countries that fell below the line (Australia, the U.K., Iceland, Finland, Sweden, and the United States, assuming a low background incidence), having a relatively low incidence and/or a higher price level, the cost-effectiveness estimates will be less favorable than those in The Netherlands.

We next plotted the combination of incidence and price level for the different countries against the incremental cost-effectiveness ratios for each of the respective screening policies (Fig. 4, B). If the differences in intensity of screening among countries can be explained by differences in incidence and/or price level, all screening policies would be situated on a straight line through the origin when plotted. However, it can be concluded from Fig. 4, B, that the diversity in screening policies, which range from recommending seven to 27 scheduled examinations, cannot be explained by differences in incidence level or price level.

Finally, we calculated the costs and effects of screening policies evaluated in other cost-effectiveness analyses *(2,15–21)* with our MISCAN model (Fig. 5). Most policies appeared to be close to our efficient frontier (Fig. 5). The screening policies with intervals between screening examinations varying by age that were found to be efficient by Gustafsson and Adami *(16)* are close to our efficient frontier, as were those with fixed intervals (screening every 7 years between ages 30 and 58 years). Eddy *(15)* investigated screening every 3 years between ages 20 and 74 years, alternative ages to start screening (17, 23, or 26 years), and alternative screening intervals (every 2 or 4 years) and concluded that a minimal screening policy of every 3 years between ages 20 and 65 years was cost efficient. However, this minimal policy and screening every 3 years between ages 29 and 74 years are less than efficient according to our model (Fig. 5). For this number of scheduled examinations (16 in both cases), an interval of screening every 4 years would be more efficient (*see* Fig. 2). McCrory et al. *(19)* calculated the costs and effects for three screening policies based on conventional Pap smears that started at age 18 years and had a screening interval of every 1, 2, or 3 years. The screening policies with a screening interval of every 2 or 3 years, which we included in our analysis, appeared to be close to the efficient frontier. The screening policy with a 1-year interval was omitted, as no screening policies with more than 40 scheduled examinations were included in our analyses. Although

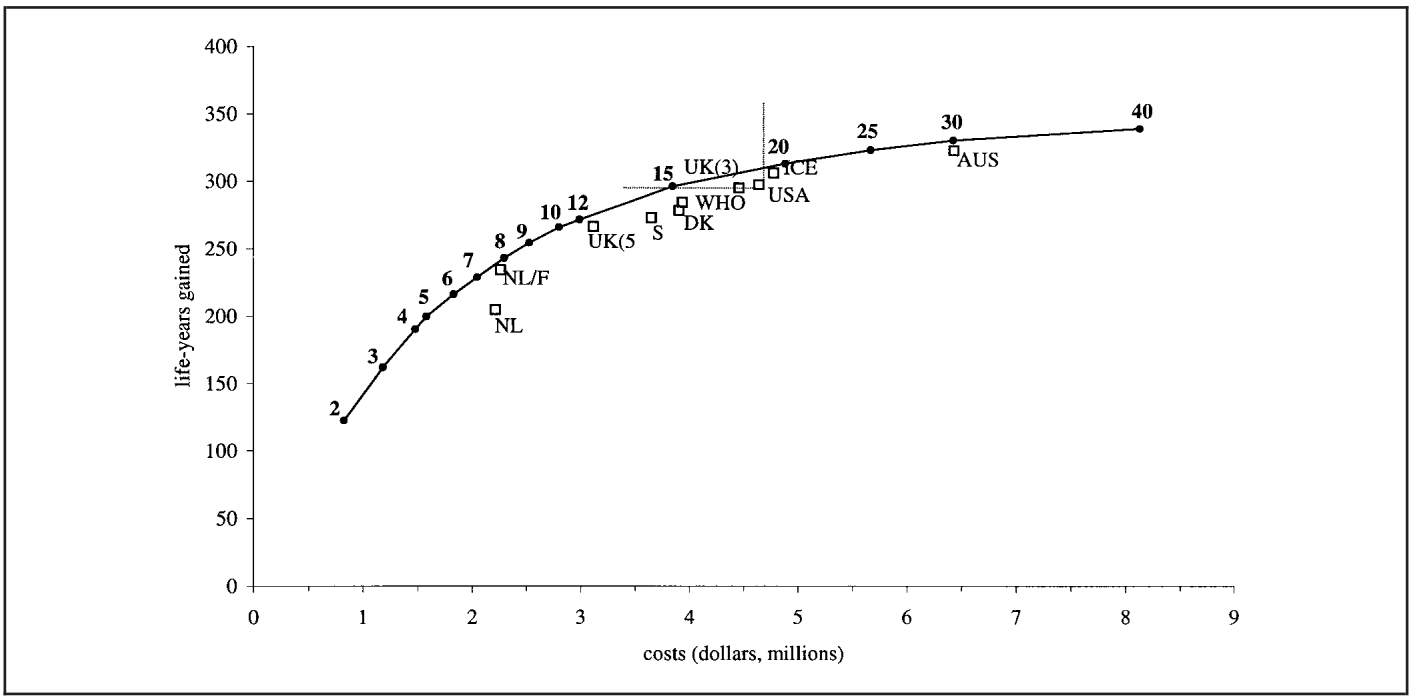

Fig. 3. Comparison of the costs (in millions of U.S. dollars) and effects (life-years gained) per 1 000 000 women in the general population per year of screening for screening policies used in countries with a cervical screening program or program recommended in national guidelines and the simulated efficient frontier, with 3% discounting. Discounting refers to converting future costs and health effects to their present values. The **solid line** represents the simulated efficient frontier. The numbers of scheduled lifetime Pap smears are identified with **solid filled circles.** NL/F = The Netherlands from 1996/Finland *(8)* (7/5/30–60, where 7 is the number of scheduled Pap smears, 5 is the screening interval in years, and 30–60 is the age range); NL = The Netherlands before 1996 (7/3/35–53); DK = Denmark *(9)*, (13/3/23–59); S = Sweden *(13)* (12/25/25–58); ICE = Iceland *(12)* (19/2½/25–70); UK(3) = United Kingdom *(11)* (16/3/20–65); UK(5) = United Kingdom *(11)* (10/5/20–65); US = United States *(10)* (17/3/18–66); AUS = Australia *(5)* (27/2/18–70); WHO = World Health Organization/Eurogin *(14)* (14/3/25–64).

the screening policy also may have appeared to be quite close to the efficient frontier, the incremental and/or average cost-effectiveness will be far outside the range that we considered to be acceptable. The screening policies considered by Waugh *(21)* (screening every 3 years between ages 20 and 59 years and screening every 5 years between ages 20 and 60 years) and Sherlaw-Johnson *(20)* (screening every 3 years between ages 18 and 64 years) and some of the screening policies considered optimal by Gyrd-Hansen *(17)* (varying from five scheduled examinations between ages 30 and 50 years to 28 scheduled examinations between ages 25 and 69 years) were not efficient according to our model.

DISCUSSION

The results show that efficient screening policies for cervical cancer can be characterized by an average screening age of about 50 years. This means that an intensive screening policy would begin at a younger age, end at an older age, and have a shorter interval between the scheduled examinations.

With the use of the MISCAN program, we determined a predicted gain in life expectancy of 46 days if cervical cancer is eliminated. This gain is small compared with the predicted increase in life expectancy of other diseases, such as the approximately 1.5 years if coronary heart disease were eliminated in women *(48)*, and is directly related to the relatively low mortality rate from cervical cancer. However, it is more relevant to compare the gain in life expectancies with different health interventions because most health interventions can only partly eliminate the disease. Also, elimination or near elimination of cervical cancer through screening does not seem possible considering the persistent level of nonattendance of women at high risk for cervical cancer. Because we based our model on the Dutch cervical cancer-screening figures, we assumed an attendance of about 80%. Half of the remaining 20% are persistent nonattenders. The nonattenders were assumed to be at high risk for cervical cancer and accounted for 25% of the cervical cancer mortality, putting the upper limit of attainable gain in life expectancy by cervical cancer screening at 75% of 46 days or a total of 34 days.

Our predictions show that the efficient screening policies that range from two to 40 scheduled examinations result in a gain in life expectancy from 12 to 32 days. Wright and Weinstein *(49)* reviewed gains in life expectancy from a variety of health interventions and found estimates on a gain in life expectancy of 0.8 months for women aged 50–60 years who are offered biennial mammography and of 8 months for women aged 35 years who quit cigarette smoking. Our estimates for the effects of cervical cancer screening are at the lower side of this range. However, in addition to the effects, costs also must be considered when evaluating diverse health interventions. Cost-effectiveness ratios as estimated in this study express the trade-off between costs and effects of interventions *(50)*.

There are several limitations associated with cost-effectiveness analyses, including random fluctuation and outcome uncertainty *(41)*. Random fluctuation complicates the determination of the efficient screening policies because repeat estimations of costs and effects may yield different estimates for the costs and effects that result in small differences in screening

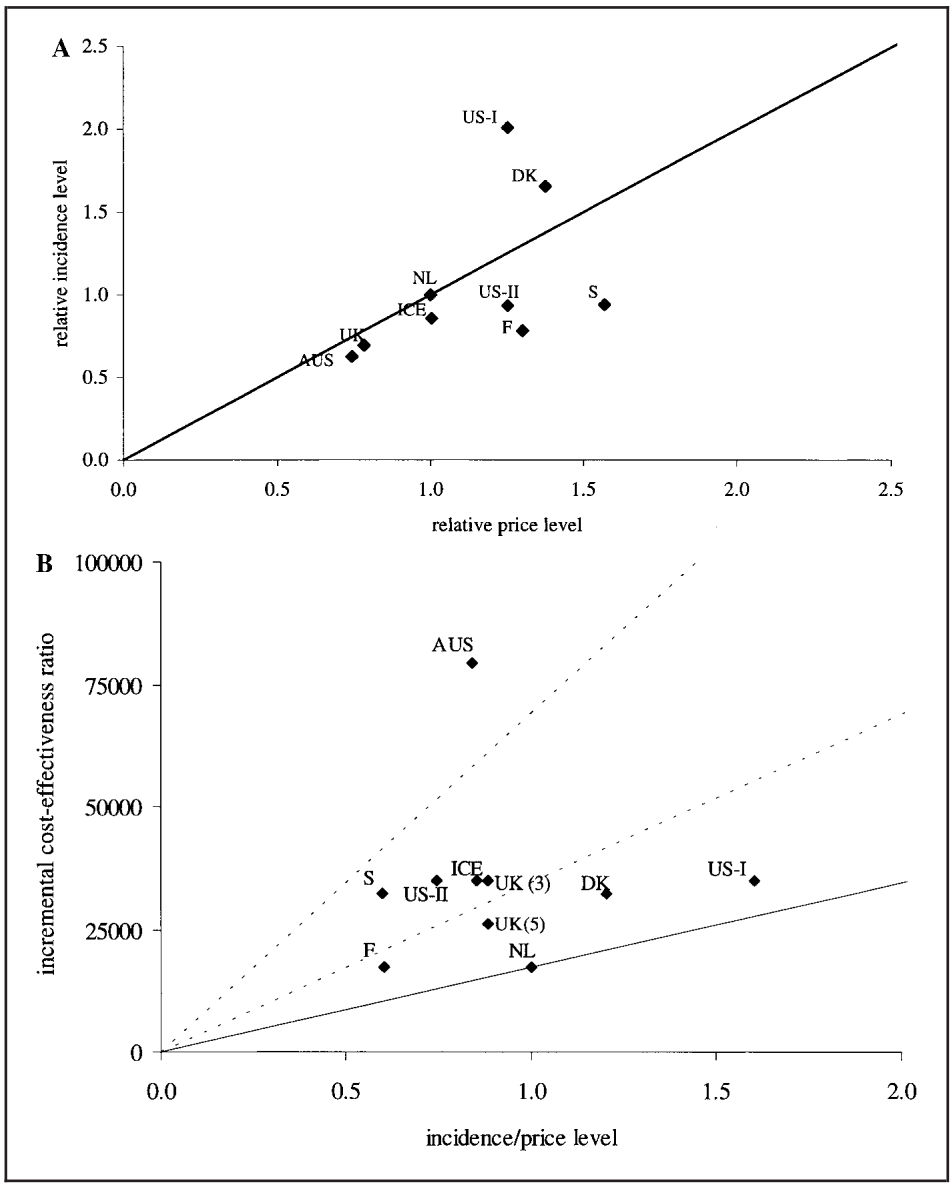

Fig. 4. A) Comparison of the incidence of cervical cancer and health care-specific price levels of seven countries (Australia, Denmark, Finland, Iceland, Sweden, the United States, and the U.K.) relative to The Netherlands. The relative incidence level is calculated by dividing the incidence in a situation before screening by the Dutch incidence in a situation without screening. The relative price level is calculated by dividing the price level of a country by the Dutch price level. Price levels are calculated by dividing health care-specific price levels by the exchange rates. **B)** Ratios of incidence of cervical cancer to price level relative to The Netherlands and incremental cost-effectiveness ratios of cervical screening policies used or recommended in Australia, Denmark, Finland, Iceland, Sweden, the United States, and the U.K. The **solid line** represents all situations with the same incremental cost-effectiveness ratio as The Netherlands, after correction for incidence and price level. The **dotted lines** indicate all situations with two (**lower line**) or four (**upper line**) times the incremental cost-effectiveness ratio of The Netherlands. For the incremental cost-effectiveness ratios of screening policies used or recommended, comparisons are made between the efficient screening policies with the same number of scheduled examinations. AUS = Australia; DK = Denmark; F = Finland; ICE = Iceland; S = Sweden; US-I = United States, Second National Cancer Survey 1947; US-II = US-Connecticut Tumor Registry; UK = United Kingdom; UK (3) = UK screening every 3 years; UK(5) = UK screening every 5 years.

policies determined to be efficient. This was illustrated by the screening policy including seven scheduled examinations between ages 27 and 68 years, which was found to be efficient in our initial predictions but not after enlarging the simulated population.

Outcome uncertainty is related to both parameter and model uncertainty. Parameter uncertainty is the uncertainty about the true values of the input parameters, whereas model uncertainty involves the way these parameters are modeled. An example of model uncertainty is that we made the assumption that costs for coordinating and evaluating a cervical screening program were fixed and thus that these costs were independent of the number of scheduled examinations. Increasing the coordinating and evaluating costs with the number of scheduled examinations will decrease the incremental cost-effectiveness ratio for screening policies with a small number of examinations but will increase the incremental cost-effectiveness ratio for more intensive screening policies.

In addition to the study design limitations, our results would be influenced if quality-adjusted life-years gained were used instead of life-years gained to include any side effects of the intervention. The negative side effects of screening, including those on quality of life, are largely proportional to the number of screening examinations. By contrast, the favorable effects of screening follow the law of diminishing returns. Combining the negative side effects and the favorable effects of screening in terms of quality-adjusted life-years will result in a rapid decrease in the number of incremental quality-adjusted life-years gained for screening policies with an increase in the number of examinations *(24)*, and eventually any additional intensifying screening will decrease the net health effects. Uncertainty analysis and quality-of-life considerations are both subjects of ongoing research.

The present cost-effectiveness estimates are obtained for a model that aimed to be representative of cervical cancer screening in The Netherlands. Different demographic, epidemiologic, and screening characteristics led to changes in the choice of the number of Pap smears offered per woman, the choice of the age range to be screened, and the time period between the scheduled number of Pap smears. However, we found (Fig. 4, B) that the diversity in the number of scheduled examinations in currently used or recommended screening policies, which varied from

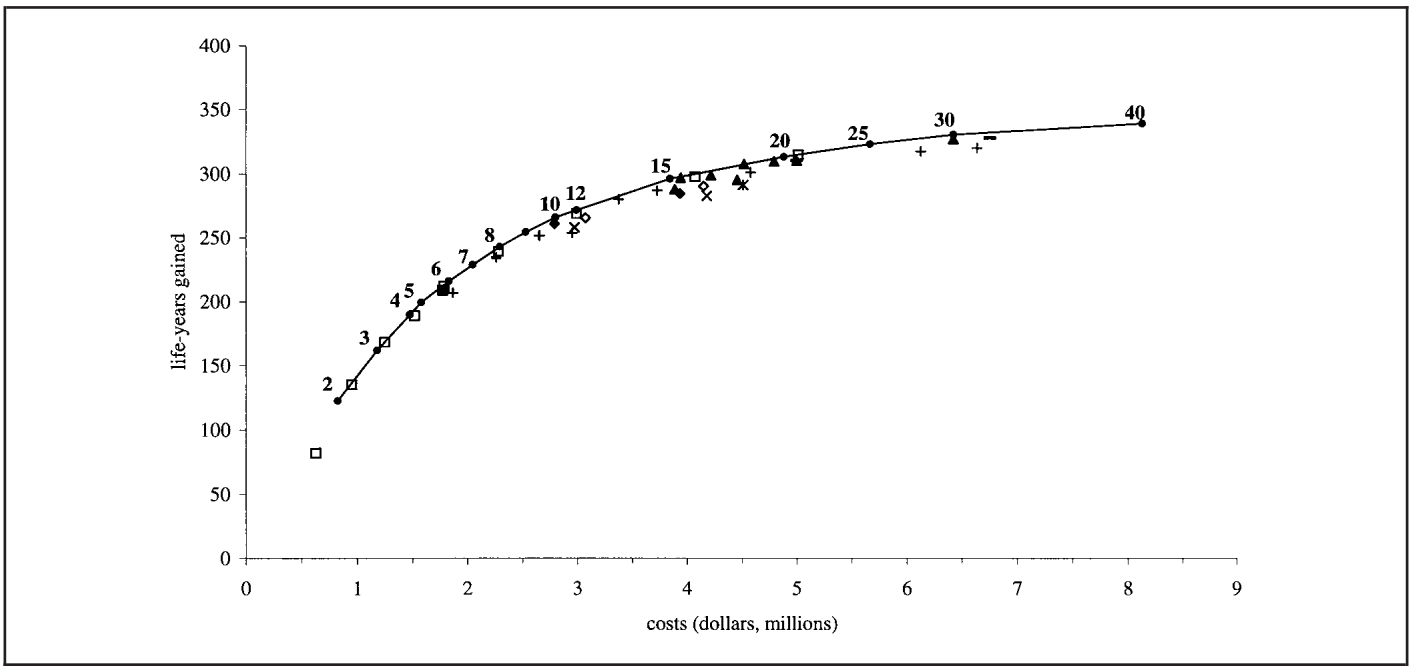

Fig. 5. Comparison of the costs (in millions of U.S. dollars) and effects (life-years gained) per 1 000 000 women in a simulated general population per year of screening for screening policies considered in other cost-effectiveness analyses. Comparison is made with the simulated efficient frontier with 3% discounting. Discounting refers to converting future costs and health effects to their present values. - = Hristova and Hakama *(18)* (7/5/30–60, where 7 is the number of scheduled Pap smears, 5 is the screening interval in years, and 30–60 is the age range); + = Gyrd-Hansen et al. *(17)* (5/5/30–50; 7/5/30–60; 8/5/25–60; 8/4/30–58; 9/4/25–57; 12/4/25–69; 13/4/20–68; 13/4/20–68; 18/3/20–68; 25/2/20–68; 28/2/15–69); ▲ = Eddy *(15)* (16/3/29–74; 15/4/20–76; 17/3/26–74; 16/3/20–65; 18/3/23–74; 19/3/20–74; 20/3/17–74; 28/2/20–74); × = Waugh and Robinson *(21)* (14/3/20–59; 9/5/20–60); * = Sherlaw-Johnson *(20)* (15/3/18–63); ◆ = International Agency for Research on Cancer (IARC) *(2)* (9/5/25–65; 14/3/25–64); ◇ = IARC *(2)* varying intervals indicated by * and all screening ages (10/*/25,26,30,36,40,45,50,55,60,65; 15/*/25,26,29,32,35,38,41,44,47,50,53,56,59,62,65); ■ = Gustafsson and Adami *(16)* (5/7/30–58); □ = Gustafsson and Adami *(16)* varying intervals indicated by * (1/*/37; 2/*/34,45; 3/*/32,40,51; 4/*/31,37,44,57; 5/*/30,35,43,50,60; 7/*/28,33,37,43,49,57,66; 10/*/26,30,33,37,42,46,51,57,63,70; 15/*/23,27,30,32,35,38,41,44,48,51,55,60,64,69,74; 20/*/22,25,28,30,32,34,36,38,40,43,46,49,52,55,58,62,65,69,73,78); – = McCrory *(19)* (20/3/18–75; 30/2/18–76). An upper age for screening of, respectively, 76 and 75 years was assumed, although no upper age limit was mentioned in the study.

seven to 27 examinations, cannot be explained by differences in the incidence of or price level in the countries involved. A factor that may influence the age range is the age-specific incidence of invasive cervical cancer, which reflects the age-specific incidence of progressive CIN. By comparing the age-specific incidence among different populations, Gustafsson et al. *(44)* found that, in addition to differences in the level of cervical cancer incidence, there were two patterns of age-specific incidence. In the first pattern, illustrated by some European countries, including The Netherlands, the peak age-specific incidence of invasive cervical cancer occurs at a younger age and declines rapidly thereafter. In the second pattern, illustrated by the United States, New Zealand, and Asian and African countries, the peak age-specific incidence of invasive cervical cancer occurs at an older age and declines slowly thereafter. Therefore, in countries where the initial peak in age-specific incidence occurs at an older age, there will be a shift in the estimated optimal screening starting age, moving upward, to an older age, and/or to lengthening the screening interval. Thus, when considering the incidence of invasive cervical cancer in the United States and Australia, it is unclear why screening policies that have short screening intervals and that start at a young age are recommended. Possible differences among countries in the implicit threshold values of the acceptable incremental and/or average cost-effectiveness ratio provide no plausible explanation for the diversity in screening policies. The diversity, therefore, originates from other sources, including, for example, the rationality of the recommendation process, the data and evidence used in choosing among policies, or the methods used in evaluating policies. The latter is illustrated by the fact that even though policies evaluated in other cost-effectiveness studies *(24)* were close to our efficient frontier (Fig. 5), the estimated incremental and/or average cost-effectiveness ratios differed considerably among studies *(24)* and may, subsequently, have led to different elected screening policies.

Moreover, our model considers features that were not considered in other cost-effectiveness analyses *(24)*; this may have contributed to the different cost-effectiveness estimates. First, in our model both costs and effects were discounted to the start of screening at a rate of 3% *(41)*. Second, we assumed that nonattendance is associated with an increased risk of cervical cancer *(25–27)*. Third, we accounted for the fact that the population is already screened to a certain extent. Our assumption leads to a lower prevalence of preclinical disease and, consequently, to a lower baseline risk for cervical cancer at the start of the screening program. Therefore, our cost-effectiveness estimates will be less favorable.

The current cost-effectiveness analyses concern high-income countries. However, in low-income countries in Southern America, Africa, and Asia, the incidence and cancer-related death rate from cervical cancer is much greater than the "high" incidence selected in our sensitivity analyses. Although the incidence of cervical cancer can be reduced by a Pap smear-based screening program, such a program is often not feasible in low-income countries because it requires a high degree of organization with cytologic laboratories and personnel. An alternative for

Pap smear screening in developing countries may be aided visual inspection of the cervix, which has a sensitivity similar to Pap smears but a lower specificity *(51,52)*. A specific cost-effectiveness analysis to investigate the possibility of a screening program based on aided visual inspection in low-income countries is warranted.

Although the present analyses are based on Pap smear screening, which is the conventional method for detection of cervical lesions in large-scale settings, there are new methods for the detection of cervical cancer; for example, screening for the presence of oncogenic variants of the human papillomavirus. The cost-effectiveness of screening for human papillomavirus is not yet known *(53)*. Other developments involve new diagnostic technologies in cytopathology, such as liquid-based cytology and computer-aided imaging. In the future, these or other new developments may lead to improvements in test characteristics and/or changes in costs, which would require reconsidering the optimal screening policies. Because women who are regularly screened at the appropriate ages already have a reduced risk of cervical cancer, the gain in cost-effectiveness of cervical cancer screening must arise from reducing the overall costs and simplifying the screening process by reducing the number of false-positive results. The great breakthrough in the latter has to come from methods that are able to distinguish progressive and regressive disease.

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NOTE

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