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Moving towards an organized cervical cancer screening: costs and impact

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Background: HPV screening has been shown to be more cost-effective than cytology screening under most scenarios. Furthermore, it should be offered only in organized programmes with good quality assurance mechanisms. This study analyses the comparative cost of the current policy of opportunistic cytology screening vs. a hypothetical organized programme based on primary HPV screening. **Methods:** Total cervical cancer expenditure was defined as the sum of three cost elements: (i) direct (medical and non-medical) costs, obtained from a calibrated Markov model of the natural history of HPV and cervical cancer; (ii) programmatic costs, estimated based on other organized screening programmes; and (iii) indirect costs, extrapolated from previously published data. **Results:** Organized HPV screening at 5-year intervals costs consistently less across all coverage levels than opportunistic cytology screening at 3-year intervals. The current annual direct medical cost to the public health system of the opportunistic cytology at 40% coverage is estimated at €33.2 per woman screened aged 25–64. Under an organized programme of primary HPV screening at 70% coverage, the cost is estimated to be €18.4 per woman screened aged 25–64. **Conclusion:** Our study concludes that the economic resources currently devoted to providing opportunistic cytology screening to 40% of the target population at 3-year intervals could be more effectively used to screen 70% of the target population at 5-year intervals by switching to an organized programme based on primary HPV screening. This finding is of relevance to other European countries or regions with similar screening policies and health infrastructures.

Introduction

As a part of a comprehensive economic assessment, it is essential to know in advance the total health expenditure of implementing a new intervention that has already shown to be cost-effective.[1] This costing approach is increasingly required by public health decision-makers, along with cost-effectiveness analysis, because predicts the potential impact on the health care system and can be useful for resource or budget planning.[2] Thus, policy-makers could better inform the prioritization of health interventions by knowing the financial resources required to implement each of the available alternatives.[3]

Organized cytology screening programmes are well-established as an effective and efficient means of preventing cervical cancer, whether used alone or, preferably, in combination with the pre-teen human papillomavirus (HPV) vaccine.[4] For its part, opportunistic screening tends to be marked by overscreening of an extensive low-risk population, combined with virtually non-existent screening among higher risk groups.[5] Both organized and opportunistic screening lead to declines in cervical cancer incidence and mortality, though drops are substantially lower and come at a higher cost when following an opportunistic system.[4,6]

In Europe, several countries have national organized programmes to screen for cervical cancer,[7] though others, like Germany, Austria,

Spain and Belgium, have stuck to opportunistic or partially organized screening programmes.[8] Meanwhile, primary HPV DNA testing has emerged as a more effective means of prevention than traditional cytology. It also offers longer-term protection in women over the age of 30, thereby lengthening the screening interval for HPV negative women and improving cost-effectiveness of HPV testing vs. cytology screening.[9] However, despite an increasing body of evidence in favour of primary HPV screening, most European countries tend only to use HPV testing as triage for cytological abnormalities.[8] Successful HPV screening carries the caveat that it must be implemented as part of an organized programme with high coverage and good quality assurance mechanisms.[10] Therefore, given suitable infrastructure, such programmes would allow the same resources to be used more efficiently, covering a larger group of women in countries with some spontaneous or organized activity.[11]

In Spain, the national health system provides universal public health care independently administered by the 17 Autonomous Regions. In the Autonomous Region of Catalonia, cervical cancer screening is opportunistic, unlike population-based breast and colorectal cancer screening that have been organized since 1992 and 2000, respectively.[12] Current guidelines recommend that women aged 25–65 receive a cytology test every 3 years with HPV testing for triage in some specific cases.[13] It is estimated that the Catalan public health system covers around 40% of the target group, while private providers reach a further 30%.[14] The Catalan Department of Health has set up a working committee to develop a new protocol for the incorporation of HPV screening as the primary screening method. Further, in Catalonia, a school-based HPV vaccination programme for girls aged 11–12 years was brought into the immunization schedule in 2008. In 2015–2016 achieved 82.8% coverage for the full three-dose course.[15]

As in many European countries, budget constraints have characterized the public health sector in Spain in recent years. Therefore, being able to calculate the costs of all the available prevention strategies is key to assure that health resources are used as efficiently as possible. This study aims to present an analysis of the economic evidence for switching to a hypothetical organized programme based on primary HPV screening, compared to the current policy of opportunistic cervical screening by cytology test by means of a calibrated simulation model to Catalonia.

Methods

The target population figures were extracted from data compiled by the Government of Catalonia indicating that 979 177 women aged 25–64 were attended at primary health centres, of a total 3 255 325 women aged 10–84 based on a 2015 postcensal estimate.[16]

Type of costs

Total cervical cancer expenditure is defined as the sum of three cost elements for both screening strategies: direct (medical and non-medical), programmatic and indirect costs. Direct medical costs are those associated with the screening of asymptomatic women in the target group, including prevention, diagnosis and follow-up of cervical abnormalities, and the treatment of cancers and precancerous lesions. Direct non-medical costs are related to patient transport. In this study, they have been obtained using a simulation model of the natural history of HPV and cervical cancer, described below.[17] Programmatic costs are those of implementing an organized programme, from preparing and sending invitation letters, information brochures, results letters, reminder calls, to the need for additional administrative staff. They have been estimated based on other such screening programmes in Catalonia.[18] Indirect costs include the productivity loss of the patient associated to morbidity and to premature mortality. Our data have been extrapolated from Oliva *et al.*,[19] using the human-capital approach, which takes the patient's perspective.[20] A societal perspective was adopted, with unit costs indexed to 2017 (Supplementary appendix).

Screening strategies

This work analyzed two screening strategies: the current protocol based on opportunistic cytology screening at 3-year intervals for women aged 25–65,[13] and a hypothetical organized programme based on primary HPV testing at 5-year intervals for women aged 35–64 with cytology triage for HPV-positive women and cytology for women aged 25–34.[11] This last strategy showed to be cost-effective in a previous analysis.[17]

Opportunistic screening at 3-year intervals was based on the fact that, of the women who get themselves checked, 15% schedule repeat visits every year, 15% every 2 years, 50% every 3 years, 15% every 4 years and 5% every 5 years.[14] For the organized screening programme, regular 5-year intervals were assumed for all visits. Coverage was estimated based on adherences of 40%, 70% and 100%.

Structure and calibration of the simulation model

The simulation model used in this study was adapted from a previously validated model of HPV and cervical cancer.[17] Briefly, a discrete-time, stochastic Markov chain model that simulates the natural history of HPV infection and cervical cancer was calibrated to the best epidemiological data available from Catalonia—i.e. age-specific HPV prevalence and cervical cancer incidence. This closed model consists of 12 mutually exclusive health states where the transition probabilities vary by age. It follows a single cohort of 10-year-old girls using 1-year increments until they reach the age of 84, or die. Starting from a matrix calibrated to Spanish data, each model parameter was varied iteratively by the Nelder-Mead search algorithm, which is very efficient and has been recommended in the literature as a suitable option to conduct a calibration process in this context.[21,22] This model allows recording outcomes such as the number of procedures, precancerous lesions, detected cancers and deaths, life expectancy and lifetime costs associated with each strategy. Further information on the epidemiological data used and calibration are provided in the Supplementary appendix.

Analysis

For both screening strategies, total annual costs and annual costs per woman (>9 years old) and per screened woman aged 25–64 were compared. Since the first vaccinated pre-teen girls in Catalonia will not reach screening age until 2022, vaccination was not considered in the base-case scenario. The unit costs for screening and vaccination were estimated from a societal perspective using multiple sources (Supplementary appendix).[15,23] Specifically, this study considered a total cost per cytology of €74.50 and per HPV test of €81.60, figures which include all consumables, equipment, facilities, staff, laboratory transport and patient time costs.

Two one-way sensitivity analysis were performed, one assuming the same unit cost for both cytology and HPV screening, and another assuming the HPV 16/18 vaccination of pre-teen girls at aged 12 with 82.8% coverage.[15] The HPV vaccine tender price is €102.90 for the full three doses.

Lifetime costs are presented both undiscounted, to simulate current values, and discounted at an annual rate of 3% to simulate the reduction of future costs.

Results

A comparison of model predictions with the latest observed data for opportunistic cytology screening in Catalonia at 3-year intervals and

Table 1 Estimated annual cost (direct, programmatic and indirect) of current opportunistic cytology screening vs. an organized programme based on primary HPV screening, both at 40% coverage (€2017)

Cost category	Opportunistic screening with 3y-cytology (40% coverage)		Organized screening with 5y-HPV testing (40% coverage)	
	Undiscounted	Discounted	Undiscounted	Discounted
Total direct cost	€28 050 016	€9 911 396	€18 666 460	€6 478 753
Direct medical cost	€23 044 544	€8 017 296	€16 038 665	€5 443 275
Direct non-medical cost	€5 005 471	€1 894 100	€2 627 795	€1 035 478
Programmatic cost	–	–	€1 140 566	€388 106
Indirect cost	€9 679 273	€3 420 144	€9 807 769	€3 404 079
Total cost	€37 729 288	€13 331 540	€29 614 795	€10 270 938

40% coverage is performed in table S3 of the Supplementary appendix.[14,23]

Impact assessment on the Catalan health budget

For the current opportunistic cytology screening at 3-year intervals and 40% coverage, total direct costs are estimated at €28.0 M annually (€23.0 M medical and €5.0 non-medical; €9.9 M discounted) (table 1), representing 74% of total cervical cancer expenditure. Comparatively, the total direct cost of an organized programme based on primary HPV screening at 5-year intervals and the same coverage is estimated at around €18.7 M (€16.0 M medical and €2.6 non-medical; €6.5 M discounted), representing 63% of total expenditure. In both cases direct medical costs account for over 80% of total direct costs.

Current total cervical cancer expenditure stands at €37.7 M (€13.3 M discounted), compared to the €29.6 M (€10.3 M discounted) it would cost to implement the organized programme. These figures include the costs of productivity loss, estimated at over €9.7 M in both cases and accounting for 26% of current total expenditure and 33% of total expenditure under the proposed programme. In the case of the latter, it also includes the programmatic cost, which accounts for just 3.9% of total expenditure. Thus, at 40% coverage, total expenditure decreases by 21.5% when moving from the current opportunistic cytology screening to an organized primary HPV screening. This drop is mainly attributable to the 33.5% decrease in direct costs, given that costs of productivity loss remain stable and programmatic costs are only incurred in the latter instance.

The effect of raising coverage on the costs is shown in figure 1. For instance, when coverage is raised to 70%, total expenditure under the current system increases to €51.3 M (€18.8 M discounted). Under an organized programme based on HPV screening, 70% coverages gives a total expenditure of €37.7 M (€13.6 M discounted), rising to €44.8 M (€16.9 M discounted) at 100% coverage. Organized HPV screening at 5-year intervals is therefore consistently less expensive across than opportunistic cytology screening at 3-year intervals. Indeed, current expenditure in Catalonia would cover 71.4% of women of target age if spent on organized HPV screening.

The current annual direct medical cost to the Catalan public health system per woman is estimated at €7.1, increasing to €33.2 if only women of target age screened are taken into account (figure 2). Under an organized programme, even if coverage is rasen to 70%, the annual direct medical cost per woman screened is estimated at €6.9, increasing to just €18.4 per woman of target age screened.

Table 2 summarises the results of the sensitivity analysis. Direct costs are found to be largely insensitive to the addition of the pre-teen HPV vaccination at 82.8% coverage, and much the same between the equal cost of HPV screening and traditional cytology.

The complete results for all cost categories, at different coverage rates, for discounted and undiscounted total costs, per woman (> 9 years old) and per woman aged 25–64 screened are available in the Supplementary appendix.

Discussion

According to the EU Advisory Committee on Cancer Prevention, cancer screening in Europe should be offered only in organized programmes with quality assurance at all levels.[24] Evidence shows that participation and equity of access could be improved with this approach.[25] Additionally, several modelling studies, including a model calibrated to Spain, have shown that HPV screening is more cost-effective than cytology screening under most scenarios.[9,17] Our study concludes that, by switching to an organized programme of primary HPV screening at 5-year intervals, the same economic resources as currently used to screen 40% of women in the target age group in Catalonia could be used more efficiently to provide slightly over 70% coverage. This conclusion would be even more favourable had we factored the pre-teen HPV vaccination into the base-case scenario, given the fewer infections and the higher sensitivity of the HPV test. Further, in HPV-vaccinated populations, the initial screening age should be raised and the screening intervals extended,[17] resulting in even lower overall expenditure.

The current opportunistic protocol in Catalonia covers 40% of women by conventional cytology screening every 3 years. This work shows that the total direct cost to the public health system for cytology screening is €28.0 M, including screening, follow-up and treatment. This corresponds to around €8.6 per woman and €40.4 per woman aged 25–64 screened. This study estimates that switching to an organized programme of primary HPV screening at 5-year intervals and the same 40% coverage would leave total direct costs at 18.7 M. This amounts to €5.7 per woman and €26.9 per woman aged 25–64 screened. This cost would increase to €26.8 M if coverage were raised to 70%, corresponding to €8.2 per women and €22.1 per woman aged 25–64 screened. Increasing coverage to 70% under the current protocol would generate a huge burden on public finances, causing direct medical costs to increase by >60%. Meanwhile, the same resources spent under the current protocol at 40% coverage would cover 71% of the target female population in Catalonia under an organized programme of HPV screening. A policy that scaled up coverage to a hypothetical 100% would increase the cost of HPV screening by just 5–10%, depending on what cost categories were included. Direct costs account for the bulk of total expenditure in both strategies, though more so under the current opportunistic protocol (74% vs. 55%). Switching to an organized programme based on HPV screening at 40% coverage would bring annual savings in direct costs of 9.3 M€. Costs of productivity loss remain largely stable across both strategies, decreasing progressively as coverage increases from 40% to 100% (from 29% to

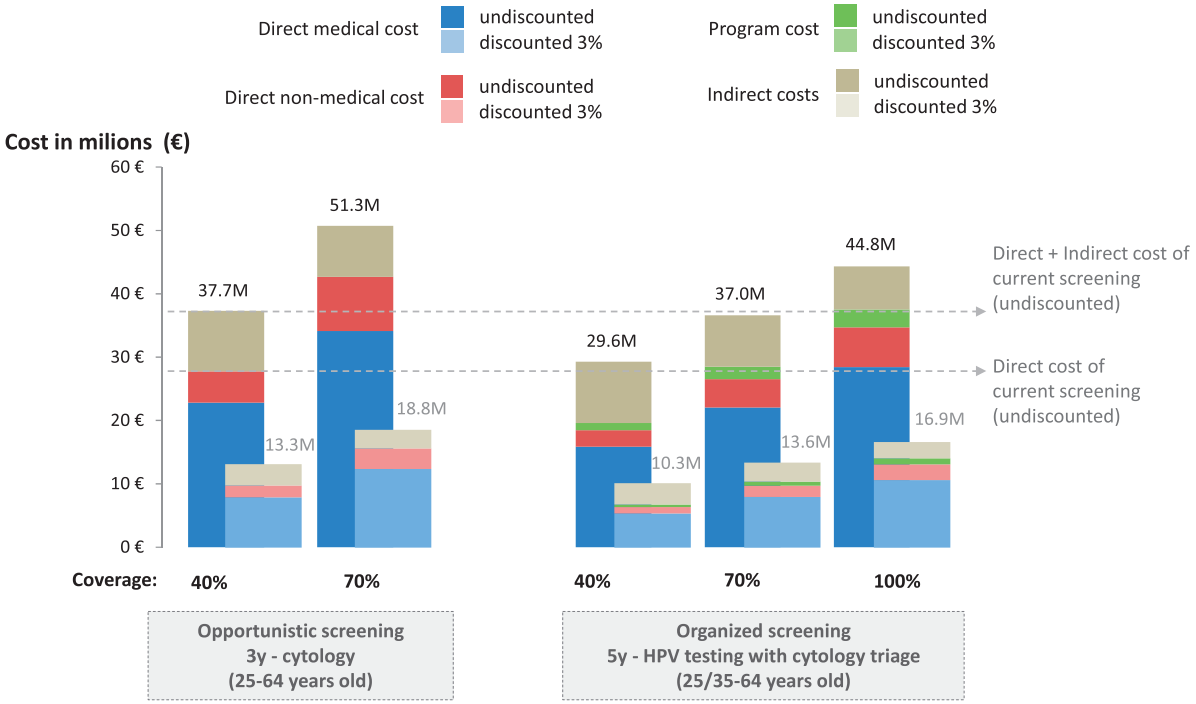

Figure 1 Estimated annual cost of current opportunistic cytology screening and organized HPV primary screening at different coverage rates

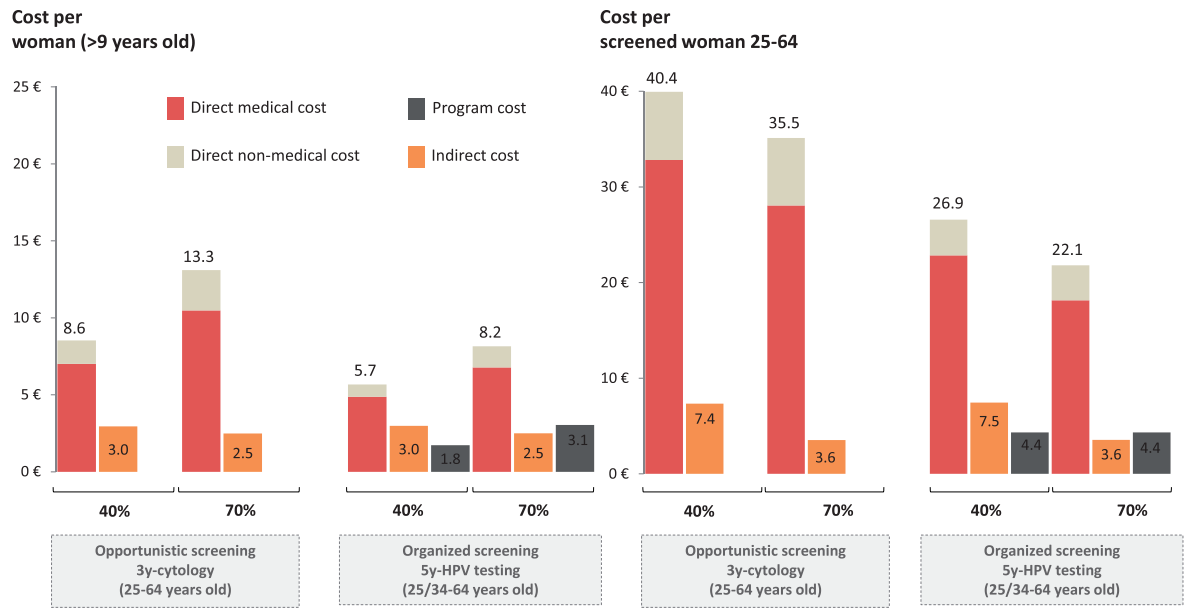

Figure 2 Estimated annual cost per adult woman or screened woman aged 25–64 years of current opportunistic cytology screening and organized HPV primary screening at different coverage rates

13% of total expenditure for HPV screening). This is because costs of productivity loss correlate to morbidity and mortality: the higher the coverage, the lower the number of incident cases and deaths resulting from cervical cancer. For programmatic costs, the opposite is true, with higher costs incurred as coverage is increased. An organized HPV screening at 40% coverage would require in excess of €1.1 M in programmatic costs. These findings suggest that the costs of implementing primary HPV screening as part of an organized programme of 5-yearly interventions would be probably repaid within a few years and lead to annual savings of 22% in subsequent years, including productivity losses.

Our study is the first in Europe to assess the total lifetime expenditure of an opportunistic cytology screening vs. an organized programme based on HPV screening within the same population. The information already available in this regard for Spain was limited to a cross-sectional study performed in the Autonomous Region of Cantabria, which calculated the cost of opportunistic cytology screening for the period 2006–2011.[26] The direct costs were reported as €567 567, which works out at €19.40 per woman screened. This somewhat lower than our own calculations suggest, but the authors do mention that the cost of primary care, specialist visits, outpatient care and treatment were not included.

Table 2 Sensitivity analysis for the estimated annual direct cost of the current opportunistic cytology screening vs. an organized programme based on primary HPV testing, at 40% and 70% coverage (€2017)

Direct cost	Opportunistic screening with 3y-cytology		Organized screening with 5y-HPV testing	
	40% coverage	70% coverage	40% coverage	70% coverage
Undiscounted				
Base case	€28 050 016	€43 137 236	€18 666 460	€26 805 323
HPV test cost = cytology cost	–	–	€17 991 626	€25 623 688
+ Vaccination (82.8% coverage)	€28 545 267	€43 802 132	€18 229 951	€26 454 664
Discounted				
Base case	€9 911 396	€15 819 725	€6 478 753	€9 859 336
HPV test cost = cytology cost	–	–	€6 249 123	€9 457 284
+ Vaccination (82.8% coverage)	€12 810 341	€18 731 144	€8 701 969	€12 074 360

Costs of productivity loss are reported at 40% of the total annual expenditure. In 2014, the same group also calculated the cost of an organized screening programme for different frequency and coverage scenarios, though the primary screening method was cytology, not HPV testing.[27]

Just one simulation model in Germany and two cost analyses in Mexico and the United States have calculated cervical cancer cost from the payer perspective (direct costs) in relation to screening strategies based on primary HPV testing.[28–30] In Germany different HPV screening scenarios, all with 5-year screening intervals, were compared to annual cytology screening with a time horizon of 6 or 10 years. Direct costs were consistently lower with HPV screening than with cytology. The annual cost for HPV screening with cytology triage was €117 M, compared to €177 M for cytology screening. This constitutes an annual saving of €60 M (33.9%). When the compliance rate for HPV screening was set at a constant 80%, cytology screening achieved comparable outcomes when compliance rates were raised to just 64% in some scenarios. In practice, very few countries recommend a screening interval of 1 year, with the majority recommending intervals of 3 to 5 years. Considering a time horizon of 3 or 5 years, the authors in Mexico also conclude that primary HPV screening costs less in all scenarios than conventional cytology. The direct cost stood at US$98.9 M for conventional cytology and US$97.9 M for HPV testing with cytology triage, assuming a total of 5.6 M women screened (32% of women aged 35–64). In the US, researchers used a 1-year time horizon model, giving an annual direct cost per screened woman aged 30–65 of $41 for cytology at 3-year intervals. For primary HPV screening with HPV16/18 genotyping, the cost is $30 at 5-year intervals and $48 at 3-year intervals. These latter results broadly match the costs obtained in our study per screened woman.

Annual expenditure on cytology screening protocols has been estimated in Europe for Belgium, Finland, France, Germany, Italy, Sweden and the UK, as well as on other continents.[6,30–38] Direct costs per woman vary widely. The variations may be attributable to factors such as the differences in healthcare systems, screening methods (conventional/liquid-based cytology), model outcomes (cervical cancer, other HPV-related diseases) and/or consideration of primary costs. For instance, the study in Finland did not include the cost of treatment.

The recent European financial crisis has spawned economic pressures on national health systems. In Spain the budget allocated to health and social services has been reduced by around 15% over the last few years, with additional budget cuts in some regions.[39] The impact of these measures are yet to be established, though it will likely have adverse effects on determinants of health and health inequalities.[40] Responses to mitigate this impact should include alternative policy interventions with a focus on population health and based on scientific evidence.[39]

Our model does not include HPV triage for the cytology screening scenario, which would likely result in lower costs and, therefore, make the case for primary HPV screening less convincing. That said, the model does not include cost estimates for the prevention and treatment of HPV-related diseases other than cervical cancer either. This factor would help to quantify the real economic burden of HPV and the benefits of HPV vaccination, results which would turn the tables back in favour of the implementation of an organized programme based on HPV testing given vaccinated populations. Mathematical models are based on a large number of assumptions, some of which are more accurate than others. Although existing analyses all point to the same or similar conclusions, model uncertainty may be affecting the outcomes, so results should be considered an approximation. Consequently, further analyses are needed to confirm the findings and existing models have to be renewed regularly as scientific knowledge progresses.

The findings of this study provide valuable information for health decision makers in Catalonia that was not previously available. European countries with a similar screening status and health infrastructures may also find themselves reflected in this study and consider the change to an organized screening with primary HPV testing. We recommend that the new Catalan protocol on cervical cancer incorporate HPV testing as the primary screening method. It should also include guidelines to enable its implementation as part of an organized programme without overloading the system and drawing excessively on the health budget.

Supplementary data

Supplementary data are available at *EURPUB* online.

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Key points

- The same economic resources used under the current system for opportunistic cytology screening at 40% coverage could be used more efficiently to cover 70% of the population by switching to primary HPV testing at 5-year intervals as part of an organized screening programme.
- If vaccination against HPV of pre-teen girls is assumed, primary HPV screening is even further justified, leading to fewer infections and increasing the sensitivity of the HPV test.
- European countries with comparable policies of opportunistic cytology screening and adequate health infrastructures may find their own cases reflected in this assessment and be persuaded of the benefits of switching to a policy of organized screening by primary HPV testing.

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The Screening Illustrator: separating the effects of lead-time and overdiagnosis in mammography screening

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Background: Mammography screening increases incidence because cancers are detected earlier in time and because of overdiagnosis. We developed an Excel-based model to visualize the expected increase from lead-time amplified by increasing background incidence. Subsequently, we added overdiagnosis to the model. **Methods:** We constructed two hypothetical populations of women aged 50–79 in 5-year age and calendar groups: one with screening for women aged 50–69 and one without. The user enters information on population at risk, number of breast cancers, trends in background incidence, average length of lead-time and, optionally, overdiagnosis. The model computes incidence rate ratios (IRRs) comparing incidence changes with screening to changes without in open and closed cohorts. **Results:** We entered information from Norway from 1990 to 1994, the period preceding the gradual introduction of a national mammography screening programme. As expected, the Screening Illustrator showed prevalence peaks and compensatory drops. Only the closed cohort approach remained unaffected by increasing background incidence. The model showed a 20% sustained increase in incidence (IRR: 1.20) from lead-time and increasing background incidence in the open cohort approach for women aged 50–69. However, real life Norwegian data show a corresponding 38% increase. For the model to achieve the observed incidence, 10–14% overdiagnosis had to be added. **Conclusion:** The observed breast cancer incidence increase in Norway after screening implementation could not be obtained from an average lead-time of 2.5 years and empirical background incidence trends, but had to incorporate overdiagnosis.

Introduction

The aim of mammography screening is to detect breast cancer earlier in time. Lead-time is the time interval between screening diagnosis and clinical diagnosis, had the woman not been screened.[1] Introduction of mammography screening leads to a sustained increase in breast cancer incidence, because cancers are detected earlier.[2] Overdiagnosis occurs when mammography screening detects breast cancers that would not have presented with symptoms during a woman's remaining lifetime.[3] Overdiagnosis adds to the sustained increase in breast cancer incidence after screening introduction. Separating the intended effect of lead-time on incidence from the excess increase due to overdiagnosis is complex.

One approach to assess overdiagnosis is to follow a 'closed cohort' that is a group of women followed from the time they enter the screening programme and until screening ends plus the maximal length of lead-time, where screening no longer affects their incidence (figure 1). Since cancers are diagnosed earlier within a cohort, the cumulative incidence with screening will equal the cumulative incidence without screening.[3] Hence, excess breast cancers at end of follow-up with screening by definition represent overdiagnosis. Another approach is to follow an 'open cohort' that is a group of screening-age women followed over periods of calendar time, but individual women are not necessarily followed during their entire screening history. Since some cancers that would have been diagnosed above the upper-age limit without screening are diagnosed below with screening, the average incidence in screening-age women will be higher than without screening. If the open cohort is expanded to include women above the upper-age limit corresponding to the maximal length of lead-time, the average incidence with screening may approach the incidence without, depending on trends in background incidence. Hence, overdiagnosis is more difficult to distinguish from the expected incidence increase in open cohorts.

We define trends in background breast cancer incidence as the naturally occurring change in incidence over time without screening