Screening for cervical cancer – an evidence-based approach

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Summary

Introduction: The Papanicolau (Pap) smear is widely accepted by both the public and health authorities as a useful tool for detection of cervical cancer and its precursors. In Israel only opportunistic screening exists and still the incidence of invasive cervical cancer is among the lowest in the world.

Objectives: To examine the existing evidence for the effectiveness of cervical cancer screening by Pap smears; to apply the findings to Israeli data, and to assess the implications for the current cervical cancer screening policy.

Methods: Search of *Medline* (1966-June 2003) and the Cochrane Library for relevant systematic reviews, controlled trials and cohort studies.

Results: There have been no trials of screening for cervical cancer and its precursors and therefore, no direct evidence that screening improves outcomes. A single retrospective cohort study estimated the age-adjusted RR for invasive cervical cancer in women with at least one Pap smear, whether normal or abnormal, compared to women with no smear at 0.4 (95% CI 0.2-0.9). In Israel some 27,800 (range: 20,800-167,000) women need to be screened in order to prevent one case of cervical cancer. The cost of preventing a single case of invasive cervical is approximately 1.288 million NIS (range: 1.643-13.193 million NIS).

Conclusions: An evidence-based approach to the question of the effectiveness of cervical cancer screening using Pap smears has yielded weak evidence. Based on this weak evidence and rough estimations of the effectiveness and cost of mass screening for cervical cancer in Israel, we conclude that the current policy should be maintained.

Key words: Cervical cancer; Screening; Pap; Evidence-based medicine; Number needed to screen (NNS).

Introduction

Since the development of the Papanicolau smear (Pap) in the 1940s and the implementation of the first screening programs in the 1960s, the Pap smear has been widely accepted by both the public and health authorities around the world as a useful practice for detection of cervical cancer and its precursors.

The coverage of organized screening program varies from country to country. In Denmark, 90% of the target population is screened, in England 84%, in most Swedish counties between 50 to 70%, while the organized screening programs in Luxemburg and Spain cover some 40% of the target population [1].

Due to the widespread acceptance of the Pap smear and subsequent ethical considerations, the effect of cervical cancer screening on relevant outcomes, i.e. averall mortality rates, disease-specific mortality rates and incidence rates of invasive cervical cancer, as well as severity of disease at the time of diagnosis have never been studied in a randomized controlled trial.

Only opportunistic screening exists in Israel although women 35-54 years old are entitled to free cytological testing by Pap smears once every three years, by law. According to a survey conducted in 1998 that included 1,700 women, only 23% of the women aged 21-44 reported having a Pap smear taken in the past year and 54% reported never having undergone a Pap smear. In women 45-74 years old the proportions were 22% and 50%, respectively [2].

The incidence of invasive cervical cancer in Jewish women and in Israel is among the lowest in the world. In 2000, the crude incidence rate among Jewish women was 5.8 per 100,000, in 1999, 6.0, and in 1998, 7.12. The respective rates (per 100,000 women) among the non-Jewish population were 1.4, 2.5 and 2.3 [3].

In light of the low incidence of cervical cancer in Israel, the Israeli Gynecologic-Oncology Society recommended against mass routine screening in 1981 [4]. This position included a recommendation to focus efforts on targeting high-risk groups and is still supported by many professionals. Others argue against restricting screening to high-risk groups claiming that risk targeting is not a practical option as 70% of the population would have to be screened in order to detect 90% of cervical cancer cases [5]. It has also been argued that an organized and centrally controlled and monitored screening program is necessary for effective population screening and that funding could be made available [6].

The purpose of this analysis was to examine the existing evidence for the effectiveness of cervical cancer screening by Pap smears. In addition we were interested in applying these findings to Israeli data, assessing the implications for the cervical cancer screening policy in Israel.

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In order to appraise the research concerning the effectiveness of cervical cancer screening we used principles of evidence-based medicine. Evidence-based medicine centers on three major questions:

What are the clinical outcomes of interest?

A priori agreement as to the relevant outcomes should be achieved when evaluating the evidence of a clearly defined research question (regarding the intervention, target population and relevant outcomes). These outcomes should, first and foremost, reflect the target population's interests.

Is the research good enough to support a decision on whether or not to implement an intervention?

The hierarchy of evidence is determined by the potential of different study designs to eliminate bias. Systematic reviews of randomized controlled trials have become widely accepted as providing the best evidence and on an individual study level, randomized controlled trials (RCTs) are regarded as the gold standard of study design.

However well conducted RCTs are often not feasible because of ethical, practical or resource constraints. When such is the case we must rely on observational studies. These studies are classified to a lower level of evidence due to their potential to introduce bias.

Is the research transferable to the potential recipients of the intervention?

Evidence-based decisions concerning the value of a given intervention are usually based on studies carried out in a different setting. In order to assess the transferability of the existing evidence, attention should be given to relevant characteristics of the population such as disease rates or compliance with diagnostic and therapeutic regimes, the socio-cultural context, and the characteristics of the intervention itself [7].

In light of these principles, we formulated the following research question:

What are the effects of screening all women who are or have been sexually active and who have a cervix up till the age of 65-70 for cervical cancer using Pap smears, on overall mortality (primary outcome), disease related mortality, incidence of invasive cervical cancer and screening related harm (secondary outcomes)?

Methods

Literature search strategy

We initially carried out a search of *Medline* (1966 through June 2003) and the Cochrane Library for randomized controlled trials designed to evaluate cervical cancer screening using Pap smears. Although this search retrieved 71 studies, none of them were randomized controlled trials to evaluate cervical cancer screening using Pap smears. We subsequently searched for systematic reviews of cohort or case-control studies.

Two hundred and two items were retrieved. Two researchers independently reviewed the titles and abstracts of the articles identified and excluded those that did not meet eligibility criteria. If the reviewers disagreed, we carried the article in question forward to the next stage in which we then reviewed the full article and made a final decision about inclusion or exclusion. None of the retrieved items met our criteria and so we conducted a search for individual cohort studies. Although guidelines for appraising evidence about clinical interventions do not discriminate between evidence obtained from different observational study designs (mainly between cohort and case-control studies), we limited our search to cohort studies based on their greater potential to eliminate bias [8].

In a cohort study, a group of healthy people is identified and followed-up for a given period of time in order to ascertain the occurrence of health-related events. The cohort subjects are classified according to exposure status and the incidence of the health outcome is compared across exposure categories. In a prospective cohort study the cohort is assembled at the present time and is followed while in a retrospective cohort study the cohort is assembled in the past and "followed-up" to the present time [9].

This search retrieved 457 items that were reviewed in the same fashion as the results of the previous search. The large majority of the identified items were studies of mortality and incidence of cervical cancer trends before and after introducing screening for cervical cancer in a given population and so did not meet our criteria. However, we did identify a single cohort study that matched our definition [10].

Results

The retrospective cohort study conducted by Stenkvist *et al.* had the advantage of utilizing the Swedish population and cancer registries. The characteristics of these registries allowed the authors to obtain the complete individual history of screening activity and morbidity for some 207,000 women residing in three counties in 1971-1981, with no loss to follow-up.

Based on the reported annual incidence of invasive cervical cancer, the age-adjusted relative risk (RR) for invasive cervical cancer in women with at least one Pap smear, whether normal or abnormal, compared to women with no smear was 0.4. The confidence interval for the RR was not originally reported but using the data provided it was computed at: 95% CI: 0.2-0.9. No data on overall mortality, disease-related mortality or screening-related harm was provided.

We performed a sensitivity analysis to estimate the "numbers needed to screen" in order to identify a single case of invasive cervical cancer in Israel, based on the risk estimate obtained from Stenkvist *et al.'s* study.

Table 1. — *Numbers needed to screen by relative risk (RR) and incidence rate.*

Incidence rate	RR = 0.2*	RR = 0.4**	RR = 0.9*
3/100,000	41,700	51,500	333,300
4/100,000	31,250	41,700	250,000
5/100,000	25,000	33,300	200,000
6/100,000	20,800	**27,800**	167,000
7/100,000	18,000	23,800	143,000
8/100,000	15,600	20,800	125,000

* 95% CI limits for RR from Stenkvist's study; ** RR from Stenkvist's study.

As we had no knowledge of the screening history of the invasive cervical cancer cases, we used a range of incidence rates and calculated the "numbers needed to screen" using the RR of 0.4 computed from the Swedish study, as well as the lower and upper 95% CI boundaries (Table 1).

Based on a RR of 0.4 and an incidence rate of six per 100,000 (the rate in Israel in 2000), we estimate that some 27,800 Israeli women would have to be screened in order to prevent one case of invasive cervical cancer. Assuming the price of a Pap smear is 79 NIS [11], the prevention of one case of cervical cancer would cost over 2 million NIS.

Discussion

Evidence

The evidence supporting population screening for cervical cancer and its precursors by Pap smears is weak. The effectiveness of the intervention has never been addressed by RCTs and our search yielded only one retrospective cohort study. In addition, this study does not address overall mortality or disease-related mortality and screening-related harms. However the risk estimate provided by the single cohort study is in close concordance to the risk estimates of various case-control studies conducted in different countries and using different criteria for the selection of cases and controls. The overall pooled risk based on four case-control studies was 0.42 for women with one smear and 0.20 for two or more past smears [12].

Ideally a randomized control trial, the "gold standard" of evidence-based medicine should be carried out in order to address the effectiveness of cervical cancer screening using Pap smears. However there are obstacles to carrying out such a trial.

Ethical considerations: Screening for cervical cancer by Pap smears is one of the few preventive interventions to receive an "A" recommendation(1) from the US Preventive Services Task Force (USPSTF) in the absence of randomized trials demonstrating effectiveness [13]. As an accepted practice it would be questionable from an ethical point of view to withhold cervical cancer screening from a given population. This obstacle could be overcome by a trial in which the control group would continue to be screened in accordance with existing practices, while an intensive effort to increase screening would be made in the intervention group.

Sample size: due to the rarity of the defined outcomes (mortality, disease-related mortality and invasive cervical cancer), a clinical trial of the effectiveness of screening for cervical cancer would have to be extremely large. Assuming the Israeli incidence rate, a trial studying the effect of screening on the incidence of invasive cervical cancer would require recruiting over one million women and a long follow-up period. Studying the effect of cervical cancer screening on overall or disease-related mortality would require an even larger sample size.

In addition, the most pragmatic design would be a cluster randomization trial, the clusters being either clinics or settlements. This would again result in the need to increase the sample size. Contamination, i.e. continuation of existing screening practices in the control group, would again contribute to the necessity to recruit a large number of participants (whether women or clusters).

Due to these limitations and the existing evidence of the effectiveness of cervical cancer screening obtained from various observational studies, it is doubtful that such a trial will be initiated.

Israeli Policy

When considering Israeli reality and the ongoing debate as to the most appropriate screening policy, there are several options: performing a randomized controlled trial in order to test the effectiveness and cost effectiveness of cervical cancer screening in Israel, canceling free cervical cancer screening, continuing the existing practice (women 35-54 are entitled to a Pap smear at three-year intervals), targeting high-risk groups, and finally implementing a routine mass screening program.

As already noted, a randomized controlled trial does not seem feasible in Israel and complete cessation of free screening would probably not be acceptable to any of the major stakeholders (policy makers, public and health professionals).

The option of targeting high-risk groups is probably not a viable one either. In order to classify high-risk groups, we would have to identify a single or combination of risk factors that defines a large portion of potential cervical cancer cases and yet is exclusive enough to pertain to a relatively small portion of the population. Such a risk factor or combination of risk factors does not exist [4, 14].

Let us now turn to the option of organized mass screening for cervical cancer and its precursor program in Israel. According to our estimates, 27,800 (range: 20,800-167,000) would have to be screened in order to prevent a single case of invasive cervical cancer, at a cost of over two million NIS (1.643-13.193 million NIS). The cost estimate is a conservative one as it does not include the costs of diagnostic procedures such as colposcopies and biopsies or the cost of multiple smears per woman.

Furthermore, our estimates do not take into account screening-related harms. The incidence of premalignant lesions in Israeli women is comparable to other Western countries but the incidence of cervical cancer is substantially lower. One possible reason is a low conversion rate of premalignant to malignant lesions [15]. If this is the case, the adverse affects of screening for cervical cancer and its precursors in Israel could be significant.

In conclusion, an evidence-based approach to the question of the effectiveness of cervical cancer screening using Pap smears has yielded weak evidence – one retrospective cohort study that did not address the primary outcome, but only one of several secondary outcomes.

Based on our estimate of the numbers needed to screen and the cost of preventing a single case of cervical cancer and the relative weak evidence of the effectiveness of routine cervical cancer screening, we conclude that implementing such an organized program in Israel is not recommended. In light of the practical difficulties that arise in regard to targeting high-risk groups, we cannot recommend any change in Israeli cervical cancer screening policy.

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