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Screening for Cervical Cancer—Should the Routine be Challenged?

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Despite the extensiveness of cervical cancer screening programs, certain major issues are still at stake: (a) substantial false negative rates are common, mostly due to impaired test quality, (b) the optimal length of interval between screenings is uncertain, being a function of available resources and the physicians' attitude, (c) the postmenopausal population, in which incidence is highest, is inadequately tapped. Efforts must be made to optimise the process through more stringent control measures, and a more comprehensive cover of the target population.

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INTRODUCTION

THE RATIONALE for cervical cancer screening programs is based on the notion that early detection reduces significantly the incidence of, and mortality from, invasive disease [1, 2]. Yet, despite the wide acceptance of these programs several related issues are still debatable. A major issue is the accuracy of the test. The inherently high rate of false negatives may confer a false confidence to the woman, positive or suspicious readings do not always lead to an immediate action by the physician, while a repeat test, even at a short interval, may be erroneously negative [3–6]. On a different level, even though the Papanicolaou (PAP) smear is considered an innocuous procedure, it may entail physical and mental sequelae [7–9].

Efficacy

The key issue is the rate and extent of progress from precursor lesions to carcinoma *in situ* (CIS) and to invasive cervical cancer. This information is based primarily on inference. Only a few studies attempted to answer this question prospectively, none of them controlled. The occasional treatment of *in situ* lesions by hysterectomy [10], coupled with the high rate of hysterectomies among U.S. women in general, also preclude a better understanding of the problem.

Koss *et al.* [11, 12] claimed, on the basis of a 13-year follow-up study, that CIS is a precursor of invasive cervical cancer, but constitutes an unstable entity which may be modified by biopsy, drugs or delivery trauma, and even, albeit rarely, disappear spontaneously. Less advanced lesions (i.e. atypia or dysplasia) may also develop into CIS or invasive cervical cancer, but these precursor lesions have a very slow evolution. Richard and Barron [13] showed that dysplasia, if untreated and not biopsied, may progress to CIS in a significant proportion of cases, and that the precursor lesions have a stepwise inter-relationship. Stern and Neely [14] noted a 12% progression to CIS in patients with dysplasia, 40% regression and 48% persistence. Several other investigators have shown that the precursor lesions have a stepwise inter-relationship [15–20], but the exact rate, time and extent of progression to full-blown invasive cervical cancer remain uncertain, which is due at least in part to the aggressive approach following screening.

No randomised trials have been undertaken to assess the true value of cervical cancer screening programs. Major support comes from time trends to concurrent decreasing incidence and mortality [21–31], and case-controlled studies that compare screening histories of women with invasive cervical cancer to women presenting with less advanced forms of the disease [32–39]. If taken at face value, the decreasing rates of cervical cancer look very impressive: 72% decline of mortality in British Columbia [22], 75% decline in incidence in Sweden [40], and 50% in the Netherlands [41]. However, a similar world-wide decline has been noted in the incidence of gastric cancer [42], so that these observations may reflect an overall pattern of a decreased incidence of diseases related to low socio-economic status, independently of the screening process. By the same token, the lack of change in the pattern of cervical cancer in Norway, where no organised programs have been undertaken nationally, in comparison with the apparent success in the other Scandinavian countries—Sweden [43], Denmark [44], and Finland [45]—is compatible with findings that in those sections of Norway where a screening program was conducted, the disease did not subside [46]. The lack of change in Britain [47] and New Zealand [48], coupled with increased mortality rates in younger age groups [49], do not support causality.

Case–control studies show an apparently lower risk of invasive cervical cancer in screened women, with a gradient related to the number of previous screenings [39, 50, 51]. Although these findings seem more valid than time-trend correlations, they may reflect the presence of confounders associated with compliance, access to screening, and other aspects of health care utilisation [52].

Essentially, the efficacy of the PAP smear should be examined within the framework of three components: the patient, the medical personnel and the laboratory [53–58].

The patient

The role of the woman evolves around compliance, biological status and clinical pathology. Delayed diagnosis may stem from denial or ignorance, related to health promotion efforts [59–61] that depict cervical cancer as a disease affecting young, highly sexually active women. The semi-stigma of promiscuity and emphasis on multi-partner experience may similarly deter many

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women from complying with a screening program. The role of a promiscous male partner of a one-man-woman in the disease aetiology is also rarely underscored. Therefore, it is not surprising that only a minority of postmenopausal women participate in organised screening programs [62–66]. In reality, the New York State cancer registry data show that almost 45% of women with cervical cancer were 50 years of age or older at diagnosis, and many of these had probably spent most of their reproductive life in a non-permissive society.

Several host factors affect the quality of the smear and lead to an incorrect diagnosis: a concurrent vaginal infection [67–69], previous trauma to the vaginal wall, and the woman's hormonal (menstrual) status. Among elderly women atrophic changes may mask the presence of abnormal cervical cells. Only rarely are all these parameters ascertained or reported on the patient's record. Similarly, women are seldom instructed by their physicians to abstain from intercourse and/or douching prior to the test. An extensive review of pertinent literature conducted in the course of the present study revealed that reference to the menstrual cycle, contraceptive measures and/or other related clinical conditions of the woman are reported less than 5% of the time.

The medical personnel

The attitudes and experience of the medical personnel involved in the screening process play a major role in the efficacy of the procedure [70–71]. Furthermore, the standards of the physician are usually inter-related with the proficiency of the laboratory where the slide is processed, since high quality laboratories may refuse to examine unsatisfactory slides. This factor will become of even greater importance when the legislation concerning the Bethesda System reporting of PAP smears [72] is implemented.

The collection of the smear requires appropriate training [73–75]. To attain a satisfactory slide [76], one must acquire enough endocervical cells [77–79], rather than harvesting the vaginal pool [80], use an appropriate instrument of cell collection [81–83], maintain the procedure gently to avoid trauma to the desquamated cells, but not too gently to deprive exfoliation [84], and ensure correct and rapid fixation, as well as a rapid and safe transfer to the laboratory. This may not be the case when students or newly arrived house staff perform it. The interpretation of the report, and further action undertaken by the physician in consequence—colposcopy, biopsy and/or treatment, if necessary [85–88]–are also major determinants affecting the outcome.

Lack of consciousness regarding the adequacy of smear collection can be illustrated by the fact that, out of the publications reporting false negative findings in cervical cancer screenings examined in the course of this review, the professional identity of the collector was mentioned in only 13%, the source of the smear was given in 27% of the papers, and the specifications of the instrument were detailed in 37%.

The laboratory

Factors associated with laboratory work that must be considered in this context are those that may contribute to an erroneous reading of a PAP smear. These would include inadequate sampling, confounding pathology, poor slide quality (e.g. trapping of cells, inadequate fixation, insufficient number of cells), and low proficiency.

It is virtually impossible to achieve 100% sensitivity and 100% specificity in a biological test [89], and the point of compromise must be attained in concordance with the potential clinical outcome [90]. Although a false-positive determination may theoretically lead to an unnecessary hysterectomy in a young woman, rarely will the physician proceed to surgical treatment without colposcopy and biopsy. Since the probability for *three* such successive errors is extremely low, the main adverse outcome of a false-positive PAP smear determination is distress and anguish. In contrast, a false-negative determination of cervical cancer can be life threatening, due to delay of available treatment.

The rate of false-negative determinations has been widely quoted in the literature, both in real life situations (i.e. among women with invasive cancer treated at the same medical center where a negative PAP smear result was obtained in the past [53, 54, 91–99]); and under experimental conditions (i.e. repeat or simultaneous reading of slides [100–106]). The magnitude of such errors has reached up to 70%. However, these rates are incomparable for a number of reasons:

1. There is a marked variation in the criteria employed by different investigators with regard to both the numerator and the denominator; for instance, invasive cervical cancer vs. CIS, dysplasia or atypia; CIS vs. dysplasia or atypia, etc. Occasionally, distinctions are made between severe, moderate and mild dysplasia, and rates are computed for under-reading by one or two categories, such as marked vs. moderate dysplasia, or mild dysplasia vs. inflammation.
2. A "publication bias": the literature is weighted by errors made in examinations of women with unfortunate sequelae, while women who continue their normal healthy life are rarely reported.
3. The literature tends to focus on the fraction of women with cervical cancer that are detected by the PAP test. Therefore, the rates of false-negative results in cervical cancer screening, as usually given, are based on women having the disease, seen within certain selected medical system organisations, who developed invasive cervical cancer and whose smears were reviewed retrospectively. However, the ultimate denominator of the diagnosed women is the total number of women in that centre, or more appropriately, the total number of women in the population who participated in the screening program. Thus, if recomputed from this perspective, the proportion of false negatives comes down to 1%, or even less than that.

Still, a false-negative test implies that a woman who could have been detected at an early stage of her disease was not diagnosed until much later, sometimes only when she reached an incurable stage. This leads, inevitably, to the question of the optimal interval between screenings [107–109]. Not infrequently can one find a statement that in a particular patient the course of the disease must have been rapid, since on review the PAP smear was negative a year or more prior to diagnosis [110, 111]. A statement of this kind is inconsequential since it implies that cancer must become evident in the selected sample, at the moment the disease has been initiated. Obviously, an existing cancer could have been missed on the smear.

Opinions regarding the optimal screening interval vary [74, 103, 112–116]. Lack of adequate data on the rate of progression from dysplasia to CIS and from CIS to invasive cervical cancer [86, 117], coupled with repeated observations that up to 50% of dysplasia cases may regress [118], and the plausibility that some women with CIS will not eventually progress to invasive cervical cancer, make any attempt to design a mathematical model to optimise the frequency of screening a hypothetical effort [18, 119–121]. Taking into consideration the woman's sexual history

is erroneous, since there are no data to indicate that women with experience of multiple partners (a term that changes rapidly with sexual mores) have a more fulminant disease course than celibate ones. Consequently, cost becomes a major factor in the decision process concerning an optimal interval.

COST

The assessment of cost efficiency [122–124] is highly dependent on most of the issues discussed above, including the optimal time interval between screenings. Indeed, the cost of one smear may be valued at only $30, but the real question is how many smears have to be taken to alter the course of the disease. Some investigators who claim that 40 000 smears have to be taken to detect one invasive cervical cancer [125], reach the high point of $200 000–400 000 per life saved [126].

Let us take a simple but real example. It is frequently recommended that screening should start shortly after the woman becomes sexually active [127–129], and continue throughout menopause [62, 64, 130, 131]. In New York State, there are approximately 7.5 million women between the ages of 20 and 74. In 1987, close to 1000 new cases of invasive cervical cancer were diagnosed in the state, and approximately 500 women died from cervical cancer. If we choose a more conservative approach, and set a screening interval at 3 years, the minimal cost at $30 a smear, would total $75 million/year for screening. If we take the more aggressive approach of yearly screening, the expenditure would triple.

These estimates are minimal. They do not include the cost of subsequent repeated smears, or of colposcopy and biopsy of healthy women with suspicious cell findings. It may be of interest to quote Eddy's [121] recent concurrence that screening of women, aged 20 to 75 years, once in 3 years, will increase the life expectancy by 96 days and that screening beyond age 65 will add only 3 days to the life expectancy.

ADMINISTRATIVE CONTROL

Historically, clinical laboratories in the U.S.A. have had a long tradition of regulation [132]. Within this context, certain measures have already been undertaken to optimise the quality of cervical cancer screening, but they have not been systematically enforced.

Thus far, the emphasis has been primarily on proficiency [133–137], a process that entails deciphering slides by the cytotechnologists, and the pathologist in charge. Failure requires retraining, and may lead to loss of registration. Yet this can not be the exclusive measure undertaken. A proficiency test that is based on 10 slides, and allows individuals to pass who incorrectly identify at most one slide, has a high probability of error through chance alone. Specifically, we can expect over one-third of cytotechnologists, who routinely misclassify 20% of the slides they read, to pass this test by chance alone, and 5% of those who routinely misclassify 40% to pass by chance alone. Thus, even if what may be equivalent to type I (α) error (failing a competent technologist) is low, the type II (β) error (i.e. passing an incompetent technologist) is quite high.

These control measures have been strengthened by regulations that require that negative slides be kept for 5 years, and positive slides for 10, setting a limit of 80–130 slides per day to be read by one cytotechnologist (the range being a function of the rank and additional work by the cytotechnologist). However, keeping the slides for 5 years is insufficient when the backlog of reporting and processing a case at the cancer registry may take 3–4 years.

The inadequate criteria for a slide labelled positive led to the recent formulation of the Bethesda System, which is meant to provide a unified approach. Another major advantage of implementing the Bethesda System [72, 138, 139] may be the requirement for the laboratory to label inadequate slides as unsatisfactory, thus making the laboratory responsible for the adequacy of the slides. Implementation and enforcment of a more stringent evaluation program of the laboratories could provide better leverage for quality control. This could be achieved if the following, or similar, measures are considered: (a) laboratories should be required to report the total number of women examined during each calender year, providing a denominator for computing the proportion of positive determinations by each laboratory. (b) A maximal response period must be defined for performance of the test, and for transmitting the results to the patient. In addition, laboratories should be required to obtain relevant demographic data that will enable subsequent linkage with cancer registries.

Since more supervision would mean a higher expenditure, we now enter a new vicious cycle, whereby in order to make the test more efficacious, we may be selecting out the very high risk population; possibly the one segment where the test is cost effective, even though at intervals nobody can afford.

PROSPECT

Since screening for cervical cancer is presently considered part and parcel of good medical practice, no public health official will take the risk of starting a clinical trial to prove its value. On a different level, the issue has a semi-political flavour and attracts strong media reaction: cervical cancer is prevalent in women belonging to low socio-economic class, and provision of primary care to a deprived population is considered a major task of health agencies. In consequence, despite the lack of adequate assessment, cervical cancer screening is strongly propagated, even at the price of an additional load on the health budget.

Thus, the questions of whether we need cervical screening, especially at public expense, and whether we can afford to continue cervical screening while deferring other health priorities, become theoretical. The evolving practical issue is what should be done to optimise the process and reduce its cost.

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Commission of the European Communities "Europe Against Cancer" Programme European School of Oncology Advisory Report Cancer Treatment in the Elderly

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Within the EC approximately one million cases of cancer are diagnosed every year. At present, more than 55% of cancers occur in subjects aged over 65 years. There has been little clinical attention to the problem of neoplasia in the elderly. They are not receiving the same standard of specialised oncological care as younger patients. Other diseases (co-morbidity conditions) associated with cancer, and influencing its treatment and outcomes are not being properly considered. Information on surgery, radiotherapy and chemotherapy in younger patients exists for all cancers and could be adapted for the elderly. Controversial aspects of neoplasia in the elderly concern the intensity of chemotherapy, extent of surgery and the relative roles of specialised cancer centres, community hospitals and primary care providers. Future research should aim to replace subjective opinions on presence of frailty with objective instruments such as the multidimensional geriatric assessment scale. New trials could then seek to improve treatment in well-defined populations in terms of both efficacy and quality of life. Funding priorities should firstly consider that clinical trials for tumours in the elderly must be organised from cancer institutes and specialised referral centres in collaboration with geriatricians, primary care and community hospital physicians. Continuing education of doctors should be supported. A document such as this with appropriate modifications might be used as an initial message on neoplasia in the elderly to be published for information to clinicians and the public throughout Europe. Specific measures of quality assurance need financial support to evaluate the improvements in patterns of care. The 10 points of the 'Europe Against Cancer Guidelines' need re-emphasising.
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INTRODUCTION

This document has been prepared for the EC Medical Commission to provide information on the problem of cancer in the elderly, with present and future needs for treatment and education, in order for the EC to provide recommendations to the Member States. The main object of this document is to underline that chronological age is not a reliable indicator of frailty and thus cannot be used for selecting the most appropriate therapeutic strategy for cancer in the elderly. Concomitantly, this report has been conceived for parallel dissemination to European public health officers and possibly to all medical doctors.