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Screening history in women with cervical cancer in a Danish population-based screening program

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ABSTRACT

Objective. The aim of this study was to explore the screening histories of all cervical cancers in a Danish screening population. The intention was to decide suboptimal sides of the screening program and to evaluate the significance of routine screening in the development of cervical cancer.

Methods. The study describes the results of a quality control audit, performed on all new cervical cancer cases diagnosed in the years 2008–2009 at two major Danish screening-centers. All relevant cytological and histological cervical samples were reviewed.

Results. 202.534 cytological samples were evaluated in the study period, while 112 women were diagnosed with cervical cancer. The histological diagnoses comprised: 62 (55.4%) squamous cell carcinomas, 20 (17.9%) microinvasive squamous cell carcinomas, 25 (22.3%) adenocarcinomas and 5 cancers of different histology. The mean age of study subjects was 46.6 years. 51 (45.5%) women had deficient screening histories, while 45 (40.2%) women had followed the screening recommendations and had normal cervical samples in review. 11 (9.8%) women were diagnosed with false negative cytology, 2 women had false negative histological tests, while pathological review was not feasible for 3 subjects.

Conclusions. More than 45% of the cervical cancer cases in our study were due to deficient cervical screening, stressing the importance of increasing the screening-uptake and coverage. 40% interval cancers emphasize the relevance of further cervical testing of women with relevant symptoms, despite of prior normal cervical samples. Finally, 9.8% false negative cytological samples are consistent with previous reports, but still a part of the screening program that should be improved.

Introduction

Cervical cytological screening, as developed by George Papanicolau in the 1940s [1], has been described as one of the most successful screening tools for cancer disease in the history of medicine [2]. Several investigators have shown that population based cytological screening has been responsible for a significant decrease in the incidence of cervical cancer [3].

The original cervical smear technique has now been improved with new cytological sample instruments and liquid based screening technology. In addition automated systems have been introduced to make the screening procedures more efficient. In spite of this, it is widely agreed that all cervical cytological screening methods have serious limitations, in particular there are reports of low test-sensitivity [4]. Cuzick et al. report test sensitivity as low as 53% [5]. Gay et al. report a false negative rate of 20% with conventional smear technique, and in concurrence with other investigators, find preparation and sampling errors to account for the greater part of these false negative samples [6].

As in other Scandinavian countries, a population-based screening program was introduced in Denmark in the 1960s [7]. The Danish National Board of Health recommended that all women between 23 and 59 years of age should be offered a cervical cytological test free of charge every third year. The program was revised in the year 2007 and cytological testing is now recommended every third year to women between 23 and 50 years of age and hereafter every fifth year until the age of 65 [8]. Furthermore, until 2007 the regional Danish health providers were only recommended to offer cervical screening to its female population. Now this is a mandatory part of the national health program. In spite of this, screening-uptake and coverage in the study period of 2008 and 2009 in the region of Greater Copenhagen, Denmark was only 56% and 76%, respectively. This is consistent with reports from neighboring countries with similar populations [9,10].

It has been reported that close to 50% of women with cervical cancer diagnosis have adequate screening histories within 5 years of disease detection [11]. The aim of this study was to compare this report with data from a Danish population-based screening program,

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and to evaluate the significance of routine cervical cytological screening on the development of cervical malignancy.

Materials and methods

With the intention of testing quality and accuracy of the population-based cervical cytological screening program, The Regional Steering Committee for Cervical Cancer Screening in Greater Copenhagen, Denmark, implemented a pilot project with routine audit of all newly diagnosed cervical cancer cases in the year 2008 [8]. This study describes the results of the audit from the years 2008 and 2009 from two screening-centers in greater Copenhagen; the Department of Pathology at Hvidovre University Hospital and the Department of Pathology at Hillerød University Hospital. The two centers provide cytopathological service for a population of approximately 960.000 inhabitants and approximately 323.000 women between 23 and 65 years of age, and evaluate close to 100.000 cytological and 15.000 histological cervical specimens each year.

Audit protocol

The pilot project includes re-evaluation and investigation of all earlier normal cytological and/or normal histological samples within 5.5 years of disease detection. Furthermore, the relevant physicians are informed of audit results. In the future, additional review of patients charts and final reporting to a central body is planned.

All relevant cytological samples are re-evaluated both by the individual who made the original diagnosis (cyto-technician or cyto-pathologist) and by an independent cyto-pathologist. In case of discrepancy between the two re-evaluations, an additional independent cyto-pathologist is consulted and final diagnosis is determined by majority decision. If this cannot be established, a consensus diagnosis is found by joint microscopy and conference-decision. All relevant histological samples are re-evaluated by the individual who made the original diagnosis (always a pathologist) and an independent pathologist. In case of discrepancy between the two evaluations, an additional independent pathologist is consulted. A final diagnosis is decided by majority decision. If this cannot be established, a consensus diagnosis is found by joint microscopy and conference-decision. The relevant gynecologist is informed regarding final audit-results in each specific case.

The audit aims at categorizing the cancer cases in the following groups: 'Deficient screening history', 'False negative cytology', 'False negative histology', 'Regular screening history' and 'Review not possible'. 'Deficient screening history' is defined as no cervical cytological screening performed within 3.5 years of cancer diagnosis for women up to 50 years of age, within 5.5 years of diagnosis for women between 50 and 65 years of age and no screening test performed between 55 and 65 years of age for women over the recommended screening age. 'False negative cytology' is defined as "normal" cytological sample prior to cancer diagnosis with post-audit diagnosis of High-grade Squamous Intraepithelial Lesion (HSIL) or worse, while 'False negative histology' is defined as "normal" histological sample prior to cancer diagnosis with post-audit diagnosis of Cervical Intraepithelial Neoplasia grade 2 or worse (CIN2+). 'Regular screening history' is defined as having followed the screening recommendations as decided by the Danish National Board of Health, meaning that there were a registered cytological sample within 3.5 years of cancer diagnosis for women up to 50 years of age, within 5.5 years of diagnosis for women between 50 and 65 years of age and at least one cytological test performed between 55 and 65 years of age for women over the recommended screening age. Furthermore, women in this category had of course no false negative cytological or histological samples found in the audit process.

In Denmark, most cervical cytological samples are collected by general practitioners, while only a few are obtained by gynecologists. Cervical histological specimens are typically collected by gynecologists, either in a hospital setting or in private practice.

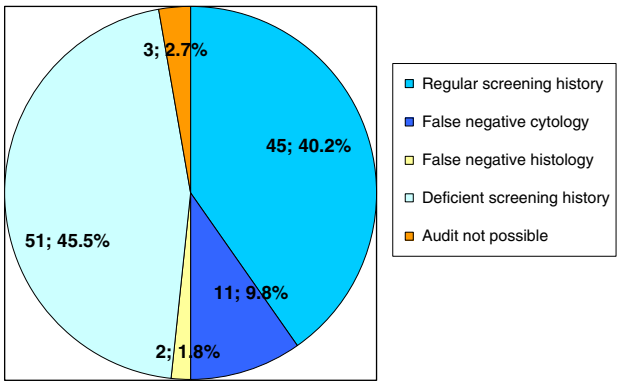

Fig. 1. Distribution of screening histories in 112 cases of cervical cancer, absolute numbers and percentage.

For this study, the authors have undertaken a retrospective analysis of audit data of all new cases of invasive cervical cancers diagnosed in 2008 and 2009 in two Danish screening-centers. Both centers are of considerable size, and in the 2 year of the study-period the centers received 202.534 cervical cytological samples and 27.146 histological specimens. Both departments use the Cervex-Brush® system (Rovers Medical Devices, B.V., NL-5347 KV Oss, The Netherlands) for cervical cytological sampling and SurePath® liquid based cytology and SlideWizard computer screening system for cervical cytological processing (BD-TriPath Imaging®, Inc., Burlington, NC, USA). In addition, both departments use automated cytological screening systems (FocalPoint® automated analyzer, BD-TriPath Imaging®, Inc., Burlington, NC, USA), which has been shown to improve both screening sensitivity and productivity [12]. From a nationwide computerized pathology register (The Danish National Pathology Data bank) that contains diagnosis of all pathological material evaluated in Denmark, information on all relevant cervical histology- and cytology-material could be retrieved. In principle, all pathology laboratories in Denmark report to this computerized system, which registers cervical tests taken in all settings: primary cytological samples within the screening-program, opportunistic screening and control specimens. The study includes all diagnosed cervical cancers in the region, and so includes cases that have been detected both as a result of population-based screening, opportunistic testing and as a result of symptomatic disease.

Statistical analysis with comparisons of categorical variables including screening history and histological diagnosis were performed by means of Fishers exact test. To adjust for age differences in the groups Mantel–Haenzels test was used. Only results with $p<0.05$ were considered statistically significant.

Results

A total number of 112 women were diagnosed with an invasive cervical cancer in the 2-year period. The mean age of the women in the study was 46.6 ± 15.8 years (range 23–91 years.

Screening history

The screening history of the women in the study was defined as all cervical pathological samples registered 5.5 years prior to disease detection for women within the screening age,[1] and as all cervical pathological samples registered up to 10 years prior to cessation of screening for women older than the recommended screening age.[1]

[1] The screening program as recommended by The Danish National Board of Health was revised in the year 2007. The age-limit for screening was changed from 59 to 65 years of age.