Elderly Women Above Screening Age Diagnosed with Cervical Cancer Have a Worse Prognosis

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Abstract. *Aim: To analyze the cervical screening history in women with cervical cancer and their outcome. Design: All women diagnosed with cervical cancer between January 2009 and December 2010 in the South Sweden region were included in the audit. Materials and Methods: Cervical cancer was registered in 165 women in 2009 and 2010. Their screening history was analyzed, and was classified as normal or imperfect. The method of discovering the cancer was either by symptoms or by screening. The main outcome measured was overall survival in cervical cancer related to cervical screening history. Results: Women above 65 years of age were more frequently diagnosed with advanced-stage disease (The International Federation of Gynecology and Obstetrics II-IV) (n=36 out of 43; 84%) compared to women below 65 years of age (n=35 out of 122; 29%) (p<0.001). All patients diagnosed by the cervical screening program were still alive (30/30) at the median follow-up time (36 months), showing better overall survival compared to women below screening age in whom cancer was discovered due to symptoms (68/98; p<0.001). Cox proportional hazards model showed that women beyond screening age (>65 years old) with normal screening history had a worse prognosis, with a hazard ratio of 4.8 (95% confidence interval=1.9-12.1, p=0.001), and women (>65 years old) who had not followed the screening program had a hazard ratio of 5.9 (95% confidence interval I 2.4-14.6, p<0.001), compared to women under 65 years old who had followed the screening program. Conclusion: Cervical cancer in women above the age of 65 years is discovered at advanced stages of the disease and their prognosis is poor.*

Every year, 420 Swedish women are diagnosed with cervical cancer, which is a preventable disease (1). The cervical screening program was introduced in Sweden in the late 1960s in order to detect and treat dysplastic lesions preceding cervical cancer (2). Not all invited women attend the recommended cervical screening program. Moreover, there is a lower and upper age-limit for the screening, which varies to some extent in the 20 counties in Sweden. In Skane, in the South Sweden region (Skane, Blekinge and Kronoberg), women are invited to screening tests every third year between the ages of 23 and 50, and every fifth year between the ages of 51 to 60, (in Skane to 65 years of age). The compliance with the screening program in South Sweden for women below 50 years of age varies between 68%-73% depending on where the women live. For the age-group 51-65 years, the compliance varies between 55-73%. Since cervical cancer can be prevented by the screening procedure, the challenge is to reach non-attending women. A number of studies, many from the Netherlands, have been performed to analyze the screening history of women with cervical cancer (3-5). These have shown that women who do not attend regular screening risk a diagnosis of cervical cancer at a later stage of the disease (5). In the Netherlands, half of the women with cervical cancer were never screened due to older age or non-attendance (3).

The aim of the present study was to analyze the cervical screening history in women with cervical cancer and their outcome in the South Sweden region. All women diagnosed with cervical cancer between January 2009 and December 2010 were included in the audit, which analysed their previous screening history.

Materials and Methods

Cervical cancer was diagnosed and 165 women were included in the regional cancer register in the South Sweden region between January 2009 and December 2010. Analyses of all previous cytological tests were performed. Correctly-screened patients had two valid tests within the prescribed screening interval: every third year between the ages of 23 and 50, and every fifth year between the ages of 51 to 65. In the South Sweden region, the county of Skane stops screening at 65 years (population 1,230,000 inhabitants), whereas the Kronoberg and Blekinge (population 330,000 inhabitants) counties stop screening at 60 years of age. The compliance with the screening in the counties are somewhat different. In Blekinge and Kronoberg, women older than 57 years have a coverage of 55.4-60.6%, but in Skane, the coverage is 72.8% amongst the same age group. The younger women

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Table I. *Histopathological diagnoses in relation to stage in patients with cervical cancer.*

Stage	Squamous cell carcinoma		Adenocarcinoma*		Total
	n	%	n	%	n
Ia	29	76%	9	24%	38
Ib	32	57%	24	43%	56
II	26	74%	9	26%	35
III	15	88%	2	12%	17
IV	16	84%	3	16%	19
Total	117	71%	47	29%	165

*Including one patient with stage Ib disease with adenosquamous histology.

Table II. *The International Federation of Gynecology and Obstetrics stage in relation to the age of the patient at diagnosis.*

Stage	Age (years)			
	Mean	SD	Median	Range
Ia	45	15.2	41	24-84
Ib	46	14.5	44	22-93
II	59	15.6	61	27-87
III	70	16.9	74	38-94
IV	64	19.0	67	34-94

have a coverage of 69.8% in Skane, and 68.3-72.5% in Blekinge and Kronoberg. These data come from the control group of cervical cancer screening in the South Sweden region, year 2012 (6). The longest accepted correct screening interval in the study was 3.5 years for women aged between 23-50 years and 5.5 years for women aged between 51-65 (in Blekinge and Kronoberg to 60 years) years. Invasive cancer detected by screening was defined as an abnormal smear test recorded 1-6 months before diagnosis. All other patients received their diagnosis of cervical cancer based on symptoms documented in the patients' medical record.

The patients who had passed the screening age were considered to have a normal screening history if the last two screening samples were without dysplasia and taken within the correct timespan. The women were considered to have a correct screening history if they followed the guidelines which applied when they were at the recommended age. The screening tests used both regular Pap smear and liquid-based cytology and were conducted according to local clinical guidelines in the different counties.

The study was approved by the Regional Ethical committee (Dnr 2009/345).

Statistical analyses. Data were controlled for normality with Levene's test. Parametric data are presented as mean±standard deviation (SD) within parenthesis. Student's *t*-test was used for analysis of descriptive parametric data. A Chi-square test or Fisher's exact test was used when appropriate for analysis of grouped data. All comparisons were two-sided and a *p*-value <0.05 was considered statistically significant. The survival statistics were prepared using the Cox proportional hazard model. Assumptions of proportional hazards were verified graphically. For a graphical presentation of overall survival, the Kaplan–Meier method was used. Analysis was performed using IBM Statistical Package for Social Sciences (SPSS) 21.0 (SPSS Inc., Chicago, IL, USA).

Results

The histology of the cervical cancer in the 165 women was squamous cell carcinoma in 71% and adenocarcinoma in 29% of the cases (Table I). In advanced FIGO stages II-IV, squamous cell carcinoma seemed more frequent compared to adenocarcinoma but the difference was not statistically significant (comparison between stage Ia-Ib *vs*. II-IV) (Table I).

The mean age at diagnosis was 53 years (SD=18 years, range=22-94 years); in the adenocarcinoma group the mean age was 46 years (SD=14) and for the squamous carcinoma group it was slightly higher at 55 years (SD=19 years) ($p>0.05$) (Table II). One-quarter of the women (n=43) were above 65 years of age at diagnosis, and one-third of the women (n=56) were older than 60 years of age (Figure 1). In the women above 65 years of age, 18 (42%) had a normal screening history. In four women above 65 years of age, the last screening test had not been normal and the follow-up was not according to guidelines. The screening-detected patients (n=30; 18%) all had stage I a-b disease, except for one patient with stage II (Figure 2). The pattern of FIGO stages in women of screening age was the same whether they had followed the recommended screening program or not. Women above 65 years of age had significantly more often an advanced stage of disease (FIGO II-IV) (n=36 out of 43; 84%) compared to those below 65 years of age (n=35 out of 122; 29%) ($p<0.001$).

The overall survival using Cox regression analysis indicated a significantly worse prognosis for women above screening age (>65 years old) who had not followed the screening program, Hazard Ratio (HR)=5.9 (95% Confidence Interval (CI)=2.4-14.6, $p<0.001$), and for women beyond screening age (>65 years old) with normal screening history, who had an HR of 4.8 (95% CI=1.9-12.1, $p=0.001$), compared to women of screening age who had a recommended cervical smear history (Figure 3). The median survival time in the patients beyond screening age was 39.0 months. The women of screening age who had not had a recommended screening test tended to have a worse prognosis compared to the women with a normal screening history, but the difference was not statistically significant (HR=2, 95% CI=0.8-4.7, $p>0.05$). All patients diagnosed through the cervical screening program were still alive (30/30) with a median follow-up time of 36 months, showing a significantly better overall survival compared to those aged 65 or younger whose disease was discovered due to symptoms (68/98; $p<0.001$).

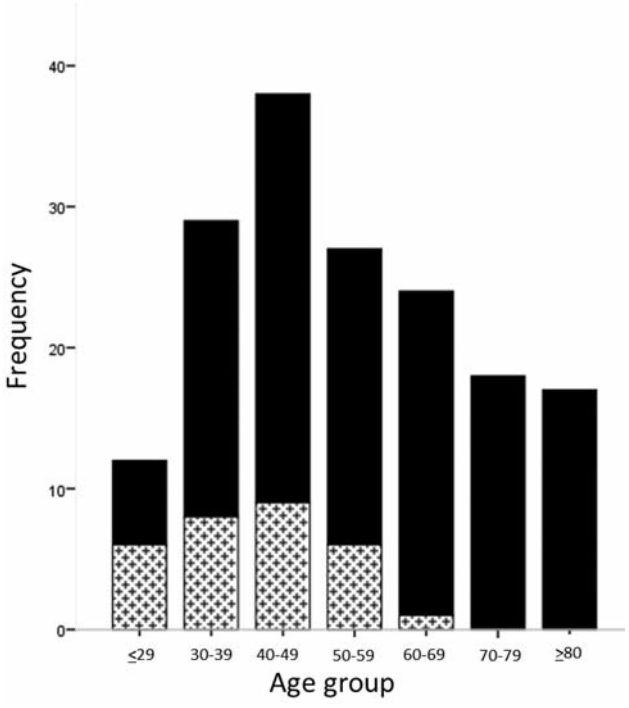

Figure 1. *The number of screen-detected (+) cervical cancer cases and the number of patients with symptoms (black shading) in relation to age. There were 30 (18%) screen-detected patients out of 165. The number of women with symptoms leading to diagnosis was 135 (72%) out of 165 women. The number of women beyond screening age (>65 years) was 43 (26%).*

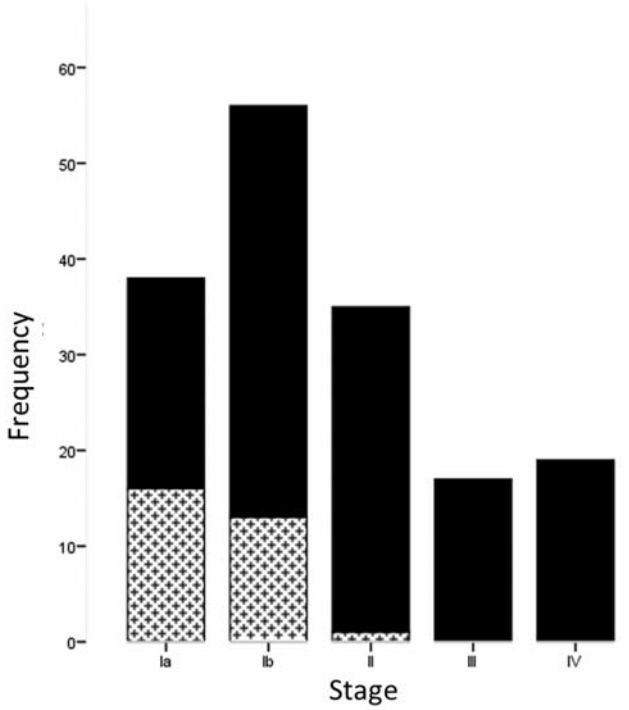

Figure 2. *The number of patients with screen-detected cervical cancer (×) and the number of patients with symptoms (black shading) in relation to the International Federation of Gynecology and Obstetrics stage. All screen-detected women with cervical cancer had disease stage I a-b except for one patient with stage II.*

Discussion

In the present study, 26% of the women who were diagnosed with cervical cancer were above the age of 65 years. The recommended cervical cancer screening system in Sweden covers women aged up to 65 years, which is why our results indicate that more than one-quarter of cancer cases are not detected by the national screening program. In 2011, women in Sweden had an estimated life expectancy of 83.5 years, which means that for one-third of their lives they are not screened (7). The breast cancer screening program ends at 75 years of age. The major causes of death are cardiovascular diseases and malignancies (8). However, a large proportion of women over 65 years are healthy and have an active sexual life (9). They are susceptible for curative treatment for dysplasia and cervical cancer if the disease is discovered at an early stage, as shown by the results from another study (2). The recommended screening programs are ended at 60 to 65 years of age in many countries. The screening program accomplishes substantial risk reduction up to the last smear and some years beyond the last smear (10). However, the efficiency of cytological screening has been shown to be lower in women 50 years or older compared to women of younger age (11). The high-risk Human Papilloma Virus (hr-HPV) test has higher sensitivity (12) than a single cytological test at finding cervical dysplasia, especially in women above 50 years of age (13). A Dutch study of cost-effectiveness indicated that primary HPV screening would be preferred in women over the age of 30 years (14). The somewhat lower specificity of the hr-HPV test compared to liquid-based cytology may be compensated for by also analyzing the hr-HPV-positive samples with normal liquid-based cytology. Incorporating screening with the modern hr-HPV test and triage of hr-HPV-positive women with cytology provides a good balance between maximizing sensitivity and specificity by limiting the number of referrals for colposcopy and conisation (15), especially in post-menopausal women (13, 16, 17).

Since organized screening in Sweden began in the 1960s, the number of women with cervical cancer has decreased. The mean age of diagnosis for cervical cancer has increased to 55 years, and the proportion of elderly women aged 70 years or above has increased from 5.4% to 27.3%, supporting the results of this study (18). It is, therefore, important to

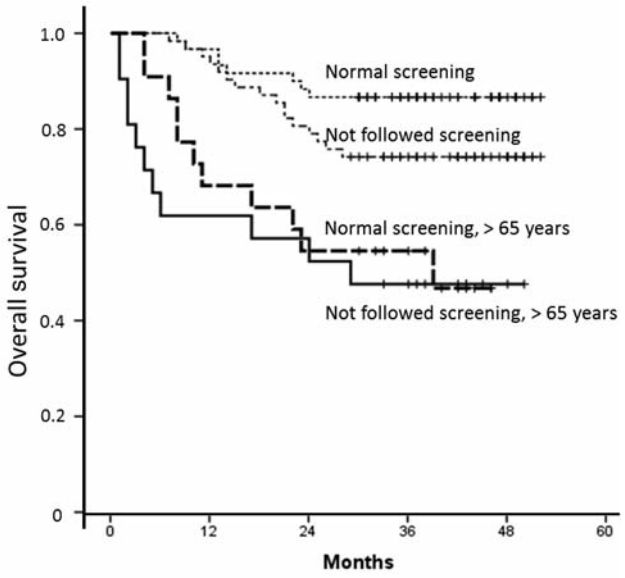

Figure 3. *Kaplan–Meier estimates of survival probabilities for patients with cervical cancer diagnosis related to whether the woman had followed the screening program (n=60, deaths=8), not followed the screening program (n=62, deaths=16) or was beyond the screening age (>65 years old) with normal screening history (n=22, deaths=11) or beyond screening age (>65 years old) not followed the screening program (n=21, deaths=11). Ticks indicate censored patients. Overall survival using the Cox proportional hazards model showed that women beyond screening age who had not followed the screening program had a Hazard Ratio (HR) of 5.9 (95% Confidence Interval (CI)=2.4-14.6, p<0.001), women beyond screening age with normal screening history had an HR of 4.8 (95% CI=1.9-12.1, p=0.001), while the women of screening age who had not followed the recommended screening program had an HR of 2.0 (95% CI=0.9-4.7, p>0.05 compared to women who had followed the screening program. There was no difference in the overall survival between women beyond screening age if they had a normal screening history or not (p=0.6).*

identify the high-risk individuals above screening age, or to extend the screening program to older women. An Italian study shows results parallel to ours. Almost 40% of Italian women with cervical cancer had not had a Pap smear taken. Interestingly, 16% of the cases were above 64 years of age, and thus not included in the screening program (19). In a Dutch study including 401 women with cervical cancer, one-third of the women were outside the screening age, which is consistent with our findings (2).

An adequate compliance in cervical screening programs is 85% according to European guidelines (20). In Sweden, the compliance rate in women 50-60 years of age was 84% but in Skåne was 74% in 2012 (21). In non-attending women, cervical cancer is detected at a more advanced stage, leading to worse prognosis (22), similar to the results in this study. Some commonly stated reasons for not attending cervical screening are "uncomfortable with vaginal examination", "lack of time", "feeling healthy" or "experience of unfriendly health workers" (23). An HPV self-test may be a suitable way to address these issues and increase compliance with cervical screening in both non-attendants and also in elderly women above the screening age. In Finland, the coverage of cervical cancer screening was increased to the desired level of 85% with a self-screening test if a third reminder was sent (24). Recently, we also showed that an HPV self-test increases compliance with the cervical screening program in long-term non-attendant women (23).

The present study confirms that screening-detected cervical cancer is diagnosed at an earlier FIGO stage than is symptom-detected cancer. Andrae *et al*. presented similar results showing a cure proportion of 92% in screening detected cancer (22). Among the symptomatic women, the cases that were discovered between screening intervals (interval cancer) had a higher cure rate compared to cancer in women who were not screened at all, or who were underexposed to screening. The more advanced stages of cancer were more common amongst the under-screened/unscreened persons, as in our study. In a Dutch study, 16% of screened women had advanced stages of cancer, while in the under-screened group, the figure was 48% (5). The cure rate is related to the FIGO stage, but the prognosis is better for screening-detected cancer, even after adjustment for stage (22). Further studies show that women above the age of 50 years are more likely to present with advanced stages compared to women under 50 years of age (25). Women not attending the recommended screening program and women beyond the screening age have a significantly more advanced FIGO stage when diagnosed with cervical cancer. We suggest that the cervical screening program should continue even after 65 years of age similarly to the breast cancer screening program up to 75 years of age. The introduction of cervical screening in elderly women must be assessed by the national quality register in Sweden.

Conclusion

Cervical cancer in women above the age of 65 years is discovered at advanced stages of the disease which is why their prognosis is poor. We propose further discussions and studies extending the current cervical screening program beyond the recommended screening age of 65 years.

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Conflicts of Interest

None of the Authors in this article has any conflict of interest.

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