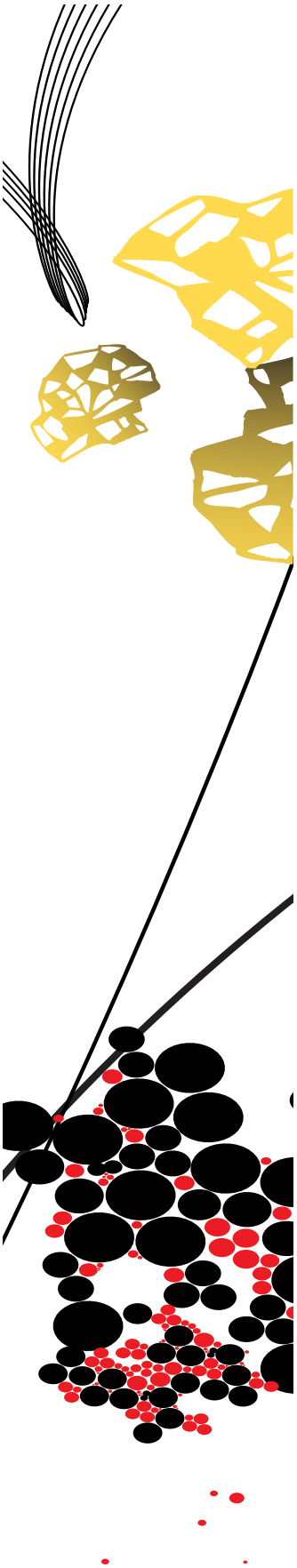

Master thesis

Screening history of women 60 years and older diagnosed with cervical cancer in the Netherlands

Health Sciences
Faculty of Science and Technology (TNW)

Author: Neneh Blömer (s1492233)

First supervisor UT: Prof. dr. S. Siesling
Second supervisor UT: Dr. J.G. van Manen
External supervisor IKNL: Dr. M.A. van der Aa

Date: 13-07-2018

IKNL comprehensive cancer centre the Netherlands

UNIVERSITY OF TWENTE.

SCREENING HISTORY OF WOMEN 60 YEARS AND OLDER DIAGNOSED WITH CERVICAL CANCER IN THE NETHERLANDS

AUTHOR:
N. Blömer[1]

[1] Department of Health Technology & Services Research, Technical Medical Centre, University of Twente, Enschede, the Netherlands

Objective
In the Netherlands, despite a nationwide screening program since the 1980s, invasive cervical cancer has been detected in women of 60 years and older. Diagnosis of an invasive cervical cancer at the post-screening age could be a result of failure in the screening program, failure in detection or inadequate follow up of abnormalities. The aim of this study is to determine the disease occurrence of cervical cancer in relation to the screening histories of women 60 years and older at diagnosis in the Netherlands.

Study design
Women aged 60-84 years diagnosed with cervical cancer in the period 2010 – 2015 were selected from the Netherlands Cancer Registry (N = 787). Smear results were extracted from the Dutch nationwide network and registry of histopathology and cytopathology. Groups with different screening history were compared (Chi-square). Multivariable cox regression analysis was performed to explain possible survival differences between screening histories.

Results
None of the patients participated in all screening rounds, incomplete participation was reported in 39% and 61% had never been screened in the nationwide screening program. Never screened patients more often had low socioeconomic status (35% versus 22%) and advanced stage disease (76% versus 57%) than patients in the incomplete participation group. In the latter, 255 patients (83%) had 1-2 pap smears during the screening period. The interval between the abnormal last smear and date of diagnosis was < 5 years in the majority of patients (69%). No statistical significant difference in survival was found between both groups.

Conclusion
Women who developed cervical cancer at 60 years and older were observed with incomplete participation or were never screened in the screening program. Survival did not differ between these patient groups. However, the treatment for advanced stage disease, which was more common in the never screened group, will probably be associated with higher morbidity.

Introduction

Cervical cancer is the sixth most common female cancer in the Netherlands [1]. Every year, approximately 700 women are diagnosed with cancer of the cervix and approximately 200 women die from this cancer in the Netherlands [1]. These incidence and mortality rates have been declining over the past decades due to changes in sexual behavior and as a result of the introduction of a nationwide screening program, targeting women aged 30 – 60 years at a screening interval of 5 years [2,3]. Although the incidence and mortality rates declined, the number of newly diagnosed cases has remained stable since 2007 [2].

Since the 1980s, cervical screening with pap smear cytology has been offered to all women in the Netherlands through an organized screening program [4]. The aim of this screening program is to reduce the number of women who develop cervical cancer and the number of deaths by detecting abnormalities and treating pre-invasive and early invasive disease [4]. Because the prevalence of pre-invasive cervical lesions declines with age and the rate of progression is considered to be slow, the national screening program starts at the age of 30 and invites women until they become 60 years of age [5]. Women over 60 years with a negative smear history are supposed to have a small risk of developing cervical cancer [5].

Despite this small risk, approximately 200 women older than 60 years are diagnosed with cervical cancer each year in the Netherlands [6]. In the ideal situation, all premalignant lesions should be treated before they progress into invasive cancers [7]. A Dutch study estimated that with a 100% screening coverage, the cases of cervical cancer will only include young women diagnosed before the starting of the program [8]. This raises questions about why invasive cervical cancer in women older than 60 years were not discovered at the premalignant stage [9]. An important factor found in the literature is incomplete or nonparticipation in the screening program [8]. Besides, the diagnosis of an invasive cervical cancer at the post-screening age could be a result of a failure in the screening program, a failure in detection or an inadequate follow up of abnormalities [7].

Previous studies have investigated the screening history of women with invasive cervical cancer in the Netherlands and concluded that the incomplete participation or nonattendance to the screening program is the major reason why the disease still occurs. However, none of these studies focused on women of 60 years and older and who are above the screening age. In 2017, 817 new diagnoses of cervical cancer were identified in the Netherlands [10]. Of these 817 new diagnoses, 219 women (27%) were diagnosed at 60 years or older. Given the aim of the screening program, the incidence of cervical cancer could probably be lower among these group of women.

The aim of this study is to determine the disease occurrence of cervical cancer in relation to the screening histories of women 60 years and older at diagnosis in the Netherlands.

Methods

Patient population

We selected all women aged 60 – 84 diagnosed with cervical cancer in the Netherlands in the period 2010 – 2015 from the Netherlands Cancer Registry (NCR). The NCR is a population-based registry with coverage of all newly diagnosed malignancies in the Netherlands since 1989. Source of notification of new malignancies is the Dutch nationwide network and registry of histopathology and cytopathology (PALGA). Specially trained registration clerks routinely extract patient information from medical records within the hospitals including data on date of birth, age at diagnosis, year of diagnosis, histological subtype, TNM stage, treatment type (anonymous at institutional level), and socioeconomic status (SES). Information on vital status and date of death were obtained from the municipal demographic registries. Data from the NCR was linked to all relevant cytological and histological results from PALGA to obtain the complete smear histories of the included women.

Classification of patients

To analyse the pap smear history, we classified women in three categories based on participation in the screening program (complete participation, incomplete participation and never screened). Complete participation was defined as women who completed all seven screening moments of the screening program in the Netherlands. The group incomplete participation was defined as women who attended at least once but less than seven times the screening program. The never screened group was defined as women who never attended the screening program, however this group could have pap smears outside the screening program.

Mean age at diagnosis was calculated and categorized into five age groups (60 – 64, 65 – 69, 70 – 74, 75 – 79 and 80 – 84). Besides, the histological subtypes of cervical cancer were classified in four subgroups. These subgroups were squamous cell (icd-o codes 8050 – 8085), adeno (icd-o codes 8140 – 8490, 8574), adenosquamous (icd-o code 8560), and other (all other icd-o codes). FIGO stage was categorized in early and advanced (FIGO stage of 1B2, 2A2 – 4). Furthermore, SES scores were provided by the Netherlands Institute for Social Research for each four-digit postal code neighbourhood (SCP, 2012). SES was grouped into three categories (high, middle and low).

In the screening program, there were maximum seven screening moments (age 30, 35, 40, 45, 50, 55 and 60). A screening result was defined as normal if no follow up action was required. Normal results included negative or no dysplastic abnormalities, known as pap 1. Abnormal screening results were defined as abnormalities requiring a change in follow up. These smears were reported as pap 2 or higher. We also calculated the interval between the last normal or abnormal smear and date of diagnosis, and categorized this in < 5 years, 5 – 10 years and > 10 years. For some analyses, the outcome of the highest pap smear was used for women who had multiple pap smears.

Besides, a subcategory was made for women who performed pap smears between age 50 – 60 and who were diagnosed with cervical cancer between age 60 – 70. In this ten-year period, there were maximum three screening moments (age 50, 55 and 60). In this way, we investigated the outcomes of the most recent pap smears performed before women aged 60 – 70 were diagnosed with cervical cancer and with that taking into account the development period of cervical cancer, which is in general ten to fifteen years [11].

In addition, the abnormal smears were classified in whether they had an adequate follow up, which is divided in yes, or no. We defined adequate follow up in case a positive smear (pap 2 or higher) was obtained and follow up such as a repeat smear, colposcopy, loop electrosurgical excision, cervical biopsy, vaginal biopsy, cone biopsy or endocervical curettage was performed within 6 – 12 months.

Statistical analysis

Pearson's chi-square tests were used to compare categorical variables. Kaplan-Meier survival analysis was used to compare survival rates between women who had an incomplete participation in the screening program and women who were never screened in the screening program. Furthermore, hazard ratios (HR's) were computed using univariate and multivariable Cox regression, adjusted for age at diagnosis, SES, histological subtype, FIGO stage and type of treatment. Stata Statistical Software (Version 14.2) was used to perform all analyses.

Results

Patient population

We selected 787 women aged 60 – 84 with cervical cancer diagnosed from January 2010, through December 2015, from the NCR. Table 1 shows the characteristics of the patient population. The mean age at diagnosis was 68 years (SD = 5.51). Most of the women were diagnosed between 60 – 64 years

(32%) and had medium SES (40%). The most common histological subtypes were squamous cell carcinoma (71%) and adenocarcinoma (21%). Most of the cervical cancer diagnoses (63%) were detected at an advanced stage. Treatment with chemo-radiation was most common (35%) in this group.

None of the patients attended all seven screening moments of the screening program. Most women (61%) were never screened in the screening program and 309 (39%) women did not complete the total screening program. The mean age at diagnosis was higher in the never screened group compared to the incomplete participation group (66 years versus 70 years, $P = <0.001$). The number of women with a low SES was higher in the never screened group compared to the incomplete participation group (35% versus 22%, $P = <0$ .001). The most common histological subtype was squamous cell in both groups, but this percentage was significantly higher in the never screened group compared to incomplete participation (76% versus. 65%, $P = 0.003$). Nonattendance to screening was associated more often with advanced stages of cervical cancer at diagnosis compared to incomplete participation (76% versus 57%, $P = <0.001$). The number of women who had surgery as treatment type was higher in the incomplete participation group than in the never screened group (40% versus 25%, $P = <0.001$).

Screening characteristics of the patient population

Table 2 shows the screening characteristics of women with an incomplete participation in the screening program. Of the 309 women with an incomplete participation, we found that most of them 255 (83%) attended to screening only one or two times. Most of the performed smear results were normal (74%). Furthermore, we found most of the women with an abnormal smear result had a pap 3A (8%). The follow up after an abnormal smear was for most women adequate (88%). We found most of the women had an interval between the normal last smear and the date of diagnosis of five to ten years (41%). For the abnormal last smear and date of diagnosis had most women (69%) a five-year interval.

Patient and screening characteristics of women with a screening history between age 50 – 60 and diagnosed with cervical cancer between age 60 – 70

Given that most women (83%) in the incomplete participation group had one or two pap smear(s) and most of them (63%) were diagnosed with cervical cancer between age 60 – 70, we further examined if these pap smears were performed in the potential development period (between age 50 – 60). Table 3 shows the patient and screening characteristics of women with screening histories between age 50 – 60 and diagnosed with cervical cancer between age 60 – 70. Of the 309 women with an incomplete participation in the screening process, 223 of them were screened between age 50 – 60. Most women (53%) were diagnosed with cervical cancer between age 60 – 64. Squamous cell carcinoma (68%) was most common in this group and most women (53%) were diagnosed with advanced stage disease. In most of the women (44%) two pap smears were performed in this period, most of being normal (69%). For women with an abnormal pap smear, 22 (10%) had a pap 3A. We found the interval between the normal last smear and date of diagnosis was for most women (53%) five to ten years. Besides, most women (74%) had an interval of five years between the abnormal last smear and date of diagnosis.

Patient and pap smear characteristics of women with pap smears outside the screening program

Because we found pap smears of women outside the screening program performed between age 30 – 60 in PALGA, we further examined this group's pap smear history. Table 4 shows patient and pap smear characteristics of women who had no pap smears within the screening program, but who had pap smears outside the screening program between age 30 – 60. Of the 478 never screened women in the regular screening program, we found 86 of them had at least one pap smear outside this screening program. The mean age at diagnosis was 65 years (SD = 5.58). Most women (44%) had medium SES.

Most women (52%) were diagnosed with cervical cancer between age 60 – 64. Furthermore, most women (71%) developed squamous cell cancer and 63 women (73%) were diagnosed at an advanced stage. The majority (74%) had one or two pap smear(s). Most of them being abnormal (69%) and most of the women (28%) having pap 2.

Survival in relation to participation in screening program

Figure 1 shows the survival rates for incomplete participation patients and never screened patients in the screening program. The five-year survival rate for women with an incomplete participation in the screening program was 62% (55 – 68 95% CI) and 47% (42 – 52 95% CI) for women who were never screened.

Table 5 shows the results of the univariate and multivariable survival analyses. In the univariate analysis, survival of the incomplete participation patients was significantly better than the never screened patients. After adjustment for confounders in the multivariable analysis, this difference disappears (adjusted HR = 0.94 (073 – 1.21) for never screened patients compared with incomplete participation patients (as shown in figure 2).

Discussion

The aim of this study was to determine the disease occurrence of cervical cancer in relation to the screening histories of women 60 years and older at diagnosis in the Netherlands in the period 2010 – 2015. All women who developed cervical cancer at 60 years and older were incomplete (39%) or never screened (61%) in the screening program. This finding is similar to results from other studies of cervical cancer in women with access to screening [8,12-15]. However, this study differs from those studies in that we included only patients diagnosed with cervical cancer at 60 years or older, the time setting and the investigated screening history prior to diagnosis.

The percentage of women who were never screened is high, especially compared with the uptake rates of the screening program in the Netherlands, which varied between 64.4% and 66.2% in the period of 2012 - 2015 [16]. Uptake rates are based on five-yearly participation numbers and therefore do not indicate whether the same women participate in every screening moment. An interesting finding found in the literature is that the pap smear uptake could vary between socio-demographic groups [17]. Women from higher social classes are more willing to attend cervical screening, while women from lower social classes feel more embarrassed and less obliged to attend [17]. We found that the never screened group more often had low SES than the incomplete participation group.

The cases with an interval between the normal last smear and date of diagnosis of < 5 year are remarkable because of the long development period of cervical cancer [18]. After infection with hrHPV types, CIN-1 and CIN-2 abnormalities can develop relative quickly after two to three years [18]. From that point it takes at least ten years before abnormalities develop into invasive cervical cancer [18]. This suggests false negative outcomes of pap cytology. However, there could be other reasons for this finding. Several studies show the limited sensitivity of irregular pap smears for pap cytology and therefore pap smears must be repeated frequently to achieve programmatic effectiveness [11,19]. Because most women in this study performed only one or two of the seven pap smears, this could be the reason why not all cervical cancers and its precursors were detected within the screening program. Furthermore, cervical carcinomas were detected in women with suspicious smears in their screening history, which suggests that adequate follow up and treatment are important and it emphasize the need for future studies to investigate in clinical factors that may be predictors for patients [20].

Older women without pap smears in the screening history showed higher FIGO stages compared with older women who had pap smears in the screening history [21]. Besides, two other studies show that never screened women are at higher risk of worse prognosis due to the higher FIGO stages compared to screened women [22,23]. These results are in accordance with our study results. After adjustment for confounders in the multivariable analysis there is no significant difference in survival between never screened women and incomplete participation women. The reason for this could be related to different distribution of characteristics between never screened patients and incomplete participation patients or due to effective treatments. Nevertheless, it is shown that patients with advanced stage disease suffered more often from higher morbidity due to invasive treatments than patients with early stage disease [24]. Besides, women with early stages of cervical cancer have higher quality of life (QOL) scores months after treatment than women with advanced stages of cervical cancer [25].

A strong point of this study is the available data, which was abstracted from medical records in an environment in which clinical information routinely is documented by specially trained registration clerks within the closed systems of PALGA and NCR, in this way avoiding reliance on self-reported patient information. Besides, as far as we know, this is the first study in the Netherlands that investigated the screening histories of women diagnosed with cervical cancer aged 60 years and older, allowing us to study a specific age category.

Since we took the pap smears performed in the national screening program, a limitation of our study could be that the actual number of performed pap smears in the incomplete participation could be higher than we have reported. The focus of this study was on the effect of nationwide screening and therefore we decided only to count and investigate pap smears performed within the screening program. Due to abnormal pap smears found within the screening program or to pap smears performed on medical indication, it is possible that women are not seen at regular screening moments for a while. Follow up research takes place outside the screening program. A consequence of this decision is that the actual number of performed pap smears could be higher. Besides, we are aware of the new screening program for cervical cancer, which is introduced in the Netherlands in 2017 [26]. This screening program uses high-risk human papilloma virus (hrHPV) screening instead op pap cytology as primary method to detect cervical cancer and its precursors in women aged 30 – 60 years [27]. However, this change in the screening program does not affect the importance of this research.

To conclude, our results indicate that all women who developed cervical cancer between age 60 – 84 were incomplete or never screened in the screening program. Interventions to increase the participation to the screening program among women with no or irregular pap smears could be the potential solution to decrease the incidence of cervical cancer in the Netherlands. Furthermore, survival did not differ between incomplete participation patients and never screened patients. However, the treatment for advanced stage disease, which was more common in the never screened group, will probably be associated with higher morbidity.

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Tables

Table 1. Characteristics of the patient population*†

Characteristics	Total population N = 787 (100%) N (%)	Incomplete participation N = 309 (39%) N (%)	Never screened N = 478 (61%) N (%)	*P*
Age at diagnosis				< 0.001
• Mean (years, SD)	68 (5.51)	66 (4.52)	70 (5.60)	
• 60 – 64	249 (32)	133 (43)	116 (24)	
• 65 – 69	215 (27)	104 (34)	111 (23)	
• 70 – 74	189 (24)	59 (19)	130 (27)	
• 75 – 79	132 (17)	13 (4)	119 (25)	
• 80 – 84	2 (0)	0 (0)	2 (0)	
SES				< 0.001
• High	234 (30)	105 (34)	129 (27)	
• Medium	313 (40)	135 (44)	178 (37)	
• Low	235 (30)	68 (22)	167 (35)	
• Unknown	5 (1)	1 (0)	4 (1)	
Histological subtype				0.003
• Squamous cell	562 (71)	201 (65)	361 (76)	
• Adeno	162 (21)	84 (27)	78 (16)	
• Adenosquamous	24 (3)	10 (3)	14 (3)	
• Other	39 (5)	14 (5)	25 (5)	
FIGO stage				< 0.001
• Early	232 (30)	131 (42)	101 (21)	
• Advanced	538 (68)	176 (57)	362 (76)	
• Unknown	17 (2)	2 (1)	15 (3)	
Type of treatment				< 0.001
• Surgery	242 (31)	124 (40)	118 (25)	
• Chemo-radiation	275 (35)	111 (36)	164 (34)	
• Radiotherapy	142 (18)	39 (13)	103 (22)	
• Other	38 (5)	14 (5)	24 (5)	
• No treatment	90 (11)	21 (7)	69 (14)	

* Complete participation column is missing because none of the included patients completed all seven screening moments of the screening program.

† Some row percentages do not total 100% because of rounding.

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Table 2. Screening characteristics of women with an incomplete participation in the screening program

Characteristics	N = 309 N (%)
Number of screening moments	
• 1 – 2	255 (83)
• 3 – 4	53 (17)
• 5 – 6	1 (0)
Smear result	
• Normal	228 (74)
• Abnormal	81 (26)
Pap 2	18 (6)
Pap 3A	26 (8)
Pap 3B	18 (6)
Pap 4	9 (3)
Pap 5	10 (3)
Follow up adequate	
• Yes	71 (88)
• No	10 (12)
Interval normal last smear – diagnosis (N = 241)	
• < 5 year	54 (22)
• 5 – 10 years	98 (41)
• > 10 year	89 (37)
Interval abnormal last smear– diagnosis (N = 68)	
• < 5 year	47 (69)
• 5 – 10 years	12 (18)
• > 10 year	9 (13)

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Table 3. Patient and screening characteristics of women with a screening history between age 50 – 60 and diagnosed with cervical cancer between age 60 – 70

Characteristics	N = 223 N (%)
Age at diagnosis	
Mean (years, SD)	64 (3.26)
• 60 – 64	118 (53)
• 65 – 70	105 (47)
Histological subtype	
• Squamous cell	151 (68)
• Adeno	53 (24)
• Adenosquamous	7 (3)
• Other	12 (5)
FIGO stage	
• Early	102 (46)
• Advanced	119 (53)
• Unknown	2 (1)
Number of screening moments	
• 1	83 (37)
• 2	98 (44)
• 3	42 (19)
Smear result	
• Normal	154 (69)
• Abnormal	69 (31)
Pap 2	14 (6)
Pap 3A	22 (10)
Pap 3B	15 (7)
Pap 4	9 (4)
Pap 5	9 (4)
Interval normal last smear – diagnosis (N = 162)	
• < 5 year	49 (30)
• 5 – 10 years	86 (53)
• > 10 year	27 (17)
Interval abnormal last smear – diagnosis (N = 61)	
• < 5 year	45 (74)
• 5 – 10 years	11 (18)
• > 10 year	5 (8)

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Table 4. Patient and pap smear characteristics of women who were never screened in regular screening program but with pap smears outside the screening program

Characteristics	N = 86 N (%)
Age at diagnosis	
• Mean (years, SD)	65 (5.58)
• 60 – 64	45 (52)
• 65 – 69	22 (26)
• 70 – 74	10 (12)
• 75 – 79	9 (10)
• 80 – 84	0 (0)
SES	
• High	23 (27)
• Medium	38 (44)
• Low	24 (28)
• Unknown	1 (1)
Histological subtype	
• Squamous cell	61 (71)
• Adeno	18 (21)
• Adenosquamous	5 (6)
• Other	2 (2)
FIGO stage	
• Early	21 (24)
• Advanced	63 (73)
• Unknown	2 (2)
Number of pap smears	
• 1 – 2	64 (74)
• 3 – 4	11 (13)
• 5 – 6	5 (6)
• 7 – 15	6 (7)
Smear result	
• Normal	27 (31)
• Abnormal	59 (69)
Pap 2	24 (28)
Pap 3A	8 (9)
Pap 3B	12 (14)
Pap 4	3 (4)
Pap 5	12 (14)

Table 5. The univariate and multivariable Cox regression analyses of prognostic factors and screened in the screening program for incomplete participation patients and never screened patients

Prognostic factors	Univariate HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
Screened in screening program				
• Never	1.00 (ref)		1.00 (ref)	
• Incomplete	0.61 (0.48-0.77)	< 0.001	0.94 (0.73-1.21)	0.643
Age at diagnosis	1.06 (1.04-1.08)	< 0.001	1.04 (1.02-1.07)	< 0.001
SES				
• High	1.00 (ref)		1.00 (ref)	
• Medium	0.82 (0.63-1.08)	0.157	0.82 (0.62-1.08)	0.152
• Low	1.14 (0.86-1.49)	0.363	1.16 (0.88-1.53)	0.292
Histological subtype				
• Squamous cell	1.00 (ref)		1.00 (ref)	
• Adeno	1.56 (1.20-2.03)	0.001	1.49 (1.13-1.97)	0.004
• Adenosquamous	0.62 (0.28-1.40)	0.254	0.91 (0.40-2.07)	0.827
• Other	1.88 (1.22-2.89)	0.004	1.56 (0.99-2.44)	0.055
FIGO stage				
• Early	1.00 (ref)		1.00 (ref)	
• Advanced	4.80 (3.37-6.86)	< 0.001	3.32 (2.18-5.04)	<0.001
• Unknown	7.67 (3.78-15.59)	< 0.001	2.13 (0.99-4.56)	0.052
Type of treatment				
• Surgery	1.00 (ref)		1.00 (ref)	
• Chemo-radiation	2.22 (1.55-3.18)	< 0.001	1.15 (0.76-1.75)	0.504
• Radiotherapy	4.15 (2.84-6.07)	< 0.001	2.17 (1.42-3.33)	< 0.001
• Other	6.61 (4.05-10.80)	< 0.001	3.27 (1.89-5.67)	< 0.001
• No treatment	33.59 (22.69-49.74)	< 0.001	16.72 (10.79-25.93)	< 0.001

Title: SCREENING HISTORY OF WOMEN 60 YEARS AND OLDER DIAGNOSED WITH CERVICAL CANCER IN THE NETHERLANDS

Figure captions

Fig. 1. Kaplan-Meier survival rates for incomplete participation patients and never screened patients in the screening program

Fig. 2. Cox regression survival rates for incomplete participation patients and never screened patients in the screening program, adjusted for age at diagnosis, SES, histological subtype, FIGO stage and type of treatment

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Figures

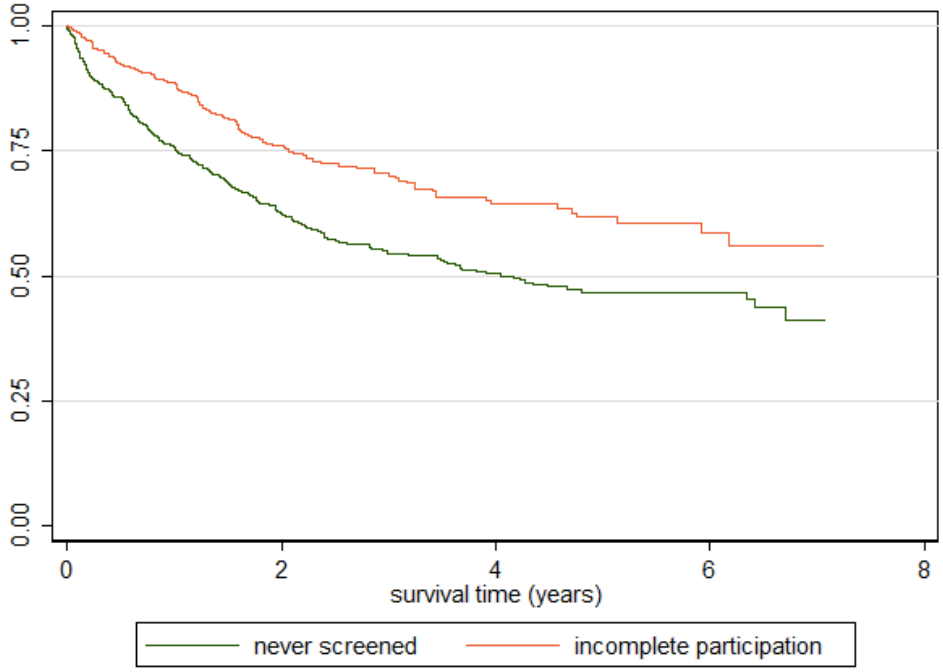

Figure 1

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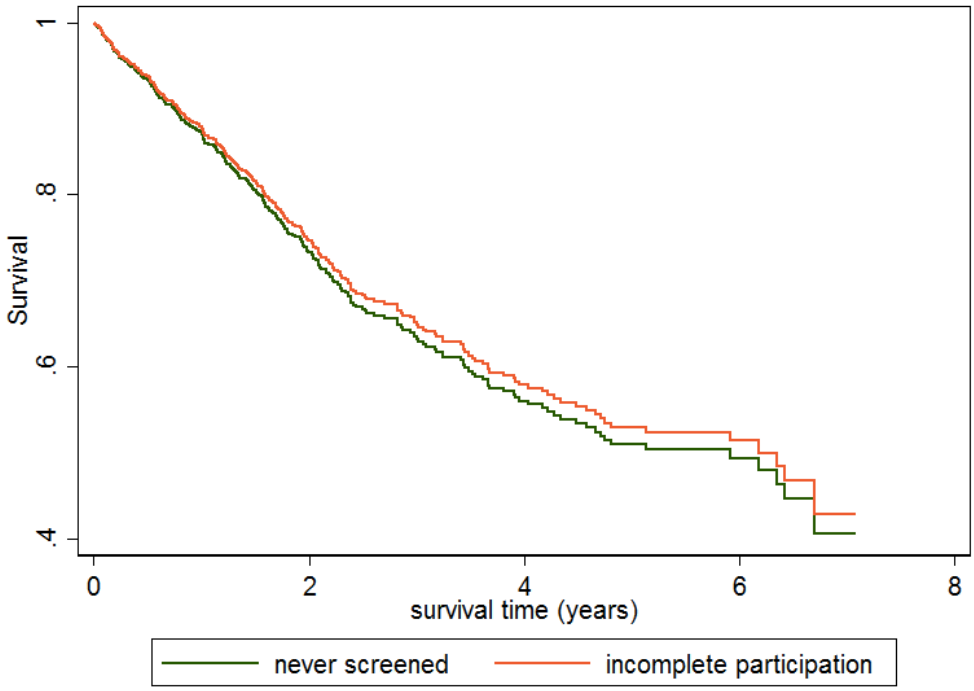

Figure 2