Gynecologic Oncology 147 (2017) 601–606

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Impact of organized and opportunistic Pap testing on the risk of cervical cancer in young women – A case-control study from Finland

Petra Makkonen [a,b,*], Sirpa Heinävaara [a,c], Tytti Sarkeala [a], Ahti Anttila [a]

[a] The Finnish Cancer Registry, Finland
[b] Faculty of Medicine, University of Helsinki, Finland
[c] Department of Public Health, University of Helsinki, Finland

HIGHLIGHTS

- The effect of screening on the risk of cervical cancer diminishes by decreasing age.
- Data on opportunistic testing was also available.
- Under the age of 25 Pap testing appeared to have no impact.
- A clear preventive effect was observed among women tested at age 35–39 years.
- Organized screening is more effective than opportunistic testing.

ARTICLE INFO

Article history:
Received 4 July 2017
Received in revised form 7 September 2017
Accepted 12 September 2017
Available online 21 September 2017

Keywords:
Cervix uteri
Cancer incidence
Screening
Effectiveness
Outcome

ABSTRACT

Objective. Effectiveness of organized cervical cancer screening has been shown in several studies. However, screening among women aged <25 years has been suggested to have little or no impact on the risk of cervical cancer. Also the significance of opportunistic testing in preventing cervical cancer is unclear. The aim of this study was to clarify the effect of opportunistic testing and organized screening on the risk of cervical cancer among young Finnish women.

Methods. In the Finnish Cancer Registry there were 284 cervical cancer cases diagnosed and tested below the age of 40 in 2004–2009. Screening histories and data on opportunistic testing for these women and their 1698 age-matched controls were derived from databases of the Mass Screening Registry and The National Institute for Health and Welfare from 1997 onward. OR's and 95% CI's for the association of cervical cancer diagnosis and participation in organized screening and opportunistic testing were estimated using unconditional logistic regression. Results were corrected for self-selection bias and attendance rate.

Results. Among women aged under 25, OR of cervical cancer for any Pap test taken 0.5–5.5 years before diagnosis was 1.25 (95% CI 0.46–3.43). Attending only organized screening at age 25–39 resulted in OR 0.52 (0.36–0.77), attending only opportunistic testing in OR 0.86 (0.60–1.25) and attending both in OR 0.48 (0.29–0.79).

Conclusion. Opportunistic testing showed no clear additional benefit on preventing cervical cancer. The study also supports findings on a smaller effect of screening in younger age groups.

1. Introduction

Effectiveness of organized cervical cancer screening has been shown in several studies [1] [2], [3], but it may be dependent on age. Screening under 30 years old women has been generally shown to have only little impact on the risk of cervical cancer whereas a clear risk reduction has been observed in women aged 40 years or over [4–9].

A well-organized screening program is considered to be more effective in cancer prevention than opportunistic testing. Further, it results in lower costs and less harm [10]. [2], [11],In well-organized population-based screening, all women are followed from the invitation and test to the potential treatment, and all data of steps are registered. These data are essential for monitoring and evaluation of the quality and effectiveness of screening. In opportunistic testing, these benefits are often lost due to incomplete follow-up and lack of registration. Also the

* Corresponding author at: Finnish Cancer Registry, Unioninkatu 22, 00130 Helsinki, Finland.
E-mail address: petra.makkonen@cancer.fi (P. Makkonen).

https://doi.org/10.1016/j.ygyno.2017.09.010

suitable age range and testing interval may not be clearly defined or followed.

A human papilloma virus (HPV) infection is a necessary factor in the development of precancerous epithelial lesions and further cervical cancer [12–14]. Both HPV infections and mild cell atypia are known to be very prevalent but also transient at young age [15–17]. Pap testing therefore detects a significant number of mild abnormalities and even precancerous lesions which are likely to be regressive [18]. Excessive testing at young age thus causes not only more unnecessary testing and related psychological stress but also overtreatment of precancerous lesions which increases the risk for treatment related complications in reproductive health [2]. In Finland extensive opportunistic testing practice is particularly common in young women with low risk of cervical cancer [19,20].

The aim of the study is to evaluate age-specific effects of Pap testing among women aged <40 years using registry-based case-control data. We also assess differences in the preventive effects of opportunistic and organized testing against cervical cancer.

2. Material and methods

The organized screening program for cervical cancer in Finland was initiated in 1963. Municipalities are responsible for organizing the screening and delivering the results to the national Mass Screening Registry. All women aged 30–60 years are invited to screening with personal letter every five years. Some municipalities have extended invitations to 25 and/or 65-year olds. Opportunistic Pap testing has emerged later, after the onset of the organized screening program, but is currently extensive.

All women aged 13–99 years diagnosed with cervical cancer in 2000–2009 were identified as cases from the Finnish Cancer Registry and their age-matched controls were retrieved from the Population registry [8]. Screening histories prior to cases' diagnoses for all invited cases and controls were obtained from 1991 onwards from the Mass Screening Registry for organized screening. These data were created in 2012 and included 1546 cases and 9276 controls [8]. For the current study, we linked these data with available data on opportunistic testing prior to cases' diagnosis from the research database collected and maintained by The National Institute for Health and Welfare (THL). The THL research database includes data from the Social Insurance Institution of Finland (1997–2008) with Pap smears reimbursed in the private sector covering the whole country. Other data sources of the THL database are regional: data from the Finnish Student Health Service (2000–2008) includes Pap smears taken in the student health care covering the university towns, and data from the Southern Finland, i.e. from Turku region (2002–2009) and the capital region (2000–2009), include Pap smears taken in the public primary health care services. Diagnostic Pap tests, i.e. tests taken within the six-month period before cases' diagnoses were excluded. All data were linked with unique personal identifier as a key.

We restricted the data to cases aged <40 years at the time of a preventive Pap test and their respective controls. The preventive Pap test was defined to take place at least six months before the diagnosis of cervical cancer. Only women with the latest invitation for organized screening in 1997 or later were included in the study due to lack of opportunistic data before that year. To ensure adequate screening history only cases diagnosed from 2004 onwards and their respective controls were included. Overall, our study included 284 cases and 1698 controls, altogether 1982 women (Fig. 1). Women under the age of 30 composed approximately 28% of the whole study population. There were only 23 cases tested under the age of 25 (Table 1). Among them, two cases were diagnosed under the age of 15 and rest of them over the age of 20. Subgroup analyses were performed by morphology (squamous cell carcinoma and adenocarcinoma) and stage (carcinomas with Figo stage at least IB).

We estimated the association between the risk of cervical cancer and protective Pap testing using unconditional logistic regression adjusted for year of birth. Pap smears taken during the same month were counted only once since subsequent tests were regarded as retests due to a failure in the previous test. We examined a time period of 10 years

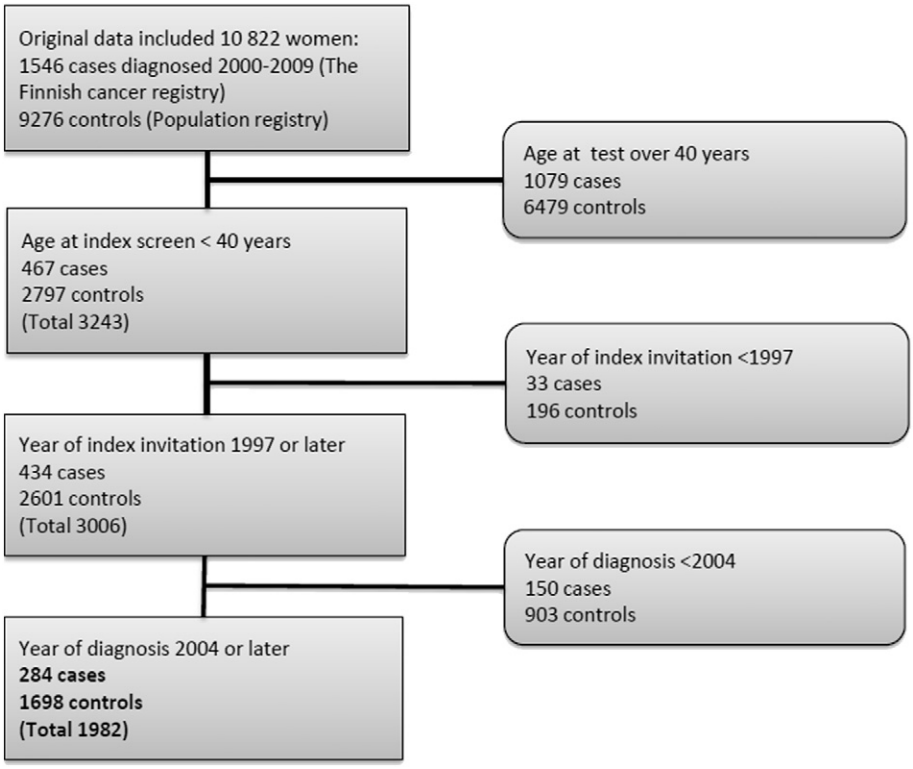

Fig. 1. Accumulation of cases and controls.

Table 1
Age distribution and the availability of organized and opportunistic data for cases and controls by age at testing.

Age at testing	Cases N (%)	Controls N (%)	Total N (%)
<25	23 (8.1)	147 (8.7)	170 (8.6)
25–29	61 (21.5)	330 (19.4)	391 (19.7)
30–34	91 (32.0)	591 (34.8)	682 (34.4)
35–39	109 (38.4)	630 (34.8)	739 (37.3)
All/<40	284 (100.0)	1698 (100.0)	1982 (100.0)
No test/NA 0.5–10.5 years before diagnosis[1]			
<25	15 (65.2)	93 (63.3)	108 (63.5)
25–29	28 (45.9)	136 (41.2)	164 (41.9)
30–34	32 (35.1)	144 (24.3)	176 (25.8)
35–39	36 (33.0)	105 (16.7)	148 (20.0)
All/<40	111 (39.0)	478 (28.2)	589 (29.7)

Invited to organized screening 0.5–10.5 years before diagnosis[a]	Cases N (%)	Controls N (%)	Total N (%)
<25	0 (0.0)	6 (4.1)	6 (3.5)
25–29	22 (36.0)	99 (30.0)	121 (30.9)
30–34	73 (80.2)	503 (85.1)	576 (84.5)
35–39	94 (86.2)	584 (92.7)	678 (91.7)
All/<40	189 (66.5)	1192 (70.2)	1381 (69.7)

Participated to organized screening 0.5–10.5 years before diagnosis[a]	Cases N (%)	Controls N (%)	Total N (%)
<25	0 (0.0)	1 (0.7)	1 (0.0)
25–29	6 (9.8)	40 (12.4)	46 (12.0)
30–34	40 (44.0)	316 (55.2)	355 (53.7)
35–39	56 (51.4)	442 (69.7)	496 (67.0)
All/<40	102 (35.9)	799 (47.5)	898 (45.9)

Participated to opportunistic testing 0.5–10.5 years before diagnosis[a]	Cases N (%)	Controls N (%)	Total N (%)
<25	8 (34.8)	54 (36.7)	62 (36.5)
25–29	29 (47.5)	174 (52.7)	203 (51.9)
30–34	37 (40.7)	282 (47.7)	319 (46.8)
35–39	40 (36.7)	270 (42.9)	310 (41.9)
All/<40	114 (40.1)	780 (45.9)	894 (45.1)

[a] Percentages are presented as proportions of the age group concerned.

(more accurately 0.5–10.5 years) before cases' diagnosis which was further divided in two 5-year periods (0.5–5.5 and 5.5–10.5 years). In the primary analyses any Pap test taken (yes/no) during the first 5-year period before the cases diagnosis was used as a primary exposure. To assess differences in the preventive effects of opportunistic and organized testing in that 5-year period, Pap tests were categorized into four categories (no tests, only an organized test, only an opportunistic test, both organized and opportunistic test) which were used as a secondary exposure. The latter analysis included only women who could have received an invitation to organized screening, i.e. those aged at least 25 years at testing. In the secondary analyses, Pap tests taken during a 10-year period before the cases' diagnosis were used as an exposure. The reference group (baseline) in all analyses was women with no test or information not available within the 0.5–10.5 time period before cases' diagnosis.

Results were corrected for self-selection by applying a formula from Duffy et al. [21] The correction factor 1.19 was obtained from Lönnberg et al. [8] and attendance rate 75% was estimated from our data.

2.1. Sensitivity analyses

Comprehensive data on opportunistic tests was available only for the southern parts of the country. We therefore evaluated whether the incompleteness of opportunistic data affected on results and conclusions. For that, women were categorized into two groups based on their residential municipality at the latest invitation to organized screening prior to cancer diagnosis (women from the southern parts of the country; women from other parts of the country). The completeness indicator based on this regional categorization was included in the models with its interaction with primary and secondary exposures. Analyses were also conducted by restricting the data only for the southern parts of Finland and data was assessed also by individual years during the study period.

The true correction factor for self-selection is not known. We therefore explored also the effect of other plausible correction factors, 1.1 and 1.3, on Results.

Age distributions among women participating in organized screening and opportunistic testing vary from each other and the preventive impact of Pap test on the risk of cervical cancer seems to be dependent on age. For that reason we also evaluated whether age categorized into 5-year groups interacts with the effects of the mode of testing (secondary exposure).

In sensitivity analyses exact logistic regression was used instead of unconditional logistic regression if the number of women in a certain group was lower than five.

Stata version 14.0 was used in all the analyses.

3. Results

In the time period of 0.5–10.5 years before the cases' diagnosis 128 (45%) of the cases and 852 (50%) of the controls had had one or two Pap tests taken (further results not presented). 45 (16%) of the cases and 368 (22%) of the controls had had three or more Pap tests. The baseline, women with no test or information not available within the 0.5–10.5 time period before cases' diagnosis, consisted of 111 (39%) cases and 478 (28%) controls (Table 1). 67% of the cases and 70% of the controls had received an invitation for organized screening and data on opportunistic tests was available for 40% of the cases and 46% of the controls. Among women aged below 30 years, the coverage of the organized invitations was poor. In older age groups the coverage was approximately 80–90%. The coverage of opportunistic testing was highest among women aged 25–29 years (52%). A clear majority of the cancer cases were stage IA (43%) or IB-IIA (36%) whereas advanced stage IIB^{+} was rare (11%) (Table 2). Regarding morphology, squamous

Table 2
Stage and morphology distributions for all cases.

Figo stage	Cases N (%)
IA	122 (43.0)
IB-IIA	102 (35.9)
IIB^{+}	32 (11.3)
Unknown	28 (9.9)
Total	284 (100.0)
Morphology	**Cases N (%)**
Squamous cell carcinoma	191 (67.3)
Adenocarcinoma	69 (24.3)
Others	24 (8.5)
Total	284 (100.0)
Morphology stage Ia excluded	
Squamous cell carcinoma	91 (32.0)
Adenocarcinoma	50 (17.6)
Others	21 (7.3)
Total	162 (57.0)

Table 3
Associations between organized and opportunistic testing 0.5–5.5 years before diagnosis and the risk for cervical cancer by five-year age group.

Age at testing	Cases tested Y/N[a]	Controls tested Y/N[a]	Crude OR (95% CI)	Corrected OR (95% CI)[b]
<25	8/15	54/93	0.98 (0.36–2.70)	1.25 (0.46–3.43)
25–29	30/28	175/136	0.82 (0.47–1.45)	1.04 (0.60–1.84)
30–34	51/32	414/144	0.56 (0.35–0.90)	0.71 (0.44–1.14)
35–39	54/36	454/105	0.34 (0.21–0.54)	0.43 (0.27–0.69)
<30	38/43	229/229	0.68 (0.48–0.97)	1.08 (0.66–1.78)
<40	143/111	1097/478	0.54 (0.40–0.71)	0.70 (0.51–0.90)
Stage IA excluded				
<25	2/9	30/46	0.33 (0.03–2.05)[c]	0.42 (0.04–2.60)
25–29	14/12	78/61	0.91 (0.39–2.12)	1.16 (0.50–2.69)
30–34	25/20	221/75	0.45 (0.23–0.86)	0.57 (0.29–1.09)
35–39	38/25	311/75	0.32 (0.18–0.56)	0.41 (0.23–0.71)
<30	16/21	108/107	0.73 (0.35–1.52)	0.93 (0.44–1.93)
<40	79/66	640/250	0.43 (0.30–0.63)	0.55 (0.38–0.80)
By morphology				
SCC[d]				
<25	4/9	30/52	0.88 (0.17–3.75)[c]	1.11 (0.22–4.76)
25–29	19/18	115/96	0.88 (0.43–1.76)	1.12 (0.55–2.23)
30–34	30/26	277/106	0.44 (0.25–0.78)	0.56 (0.32–0.99)
35–39	37/24	315/80	0.39 (0.22–0.69)	0.49 (0.28–0.88)
<30	23/27	145/148	0.86 (0.46–1.59)	1.09 (0.58–2.02)
<40	90/77	737/334	0.51 (0.36–0.72)	0.65 (0.46–0.91)
Stg Ia exc. <40	43/36	365/144	0.46 (0.28–0.75)	0.58 (0.36–0.95)
Adenocarcinoma				
<25	3/3	13/21	1.64 (0.18–14.69)[c]	2.08 (0.23–18.66)
25–29	8/6	43/27	0.67 (0.20–2.32)	0.85 (0.25–2.95)
30–34	16/4	101/30	1.28 (0.39–4.20)	1.62 (0.50–5.34)
35–39	16/7	113/22	0.41 (0.15–1.13)	0.41 (0.52–1.44)
<30	11/9	56/48	0.91 (0.33–2.53)	0.91 (1.16–3.21)
<40	43/20	270/100	0.80 (0.43–1.46)	1.08 (0.55–1.85)
Stg Ia exc. <40	29/16	197/68	0.59 (0.29–1.20)	0.75 (0.37–1.52)

[a] Number of cases and controls with invitation and exposed to Pap testing yes/no.
[b] Corrected using self-selection bias factor 1.19 and attendance rate 0.75.
[c] Estimated using exact logistic regression.
[d] Squamous cell carcinoma.

cell carcinoma was more pronounced than adenocarcinoma (67% and 24%, respectively).

Compared to women with no test or information on testing, any Pap test 0.5–5.5 years before the diagnosis reduced the risk of cervical cancer at age <40 years by 30% (OR corrected for self-selection of 0.70 with 95% CI 0.51–0.90, Table 3). The preventive effect increased by age being statistically significant only at ages 35–39 years (OR 0.43 with 95% CI 0.27–0.69). The subgroup-analyses by morphology included 167 cases with SCC and 63 with adenocarcinoma (Table 3). The OR of any Pap test for SCC was 0.65 (95% CI 0.46–0.91). For adenocarcinoma there was no impact (OR 1.08, (95% CI 0.55–1.85). Further, a subanalysis restricted to cancers with Figo stage at least IB with 145 cases resulted in OR of 0.55 (95% CI 0.38–0.80). The strengthening preventive effect of Pap testing by increasing age was seen also in all subgroup-analyses, though the number of cases was small especially in the younger age groups.

In the secondary analyses for ages 25–39 years, OR for attending only organized screening was 0.52 (95% CI 0.36–0.77). The corresponding OR for attending both organized and opportunistic testing was 0.48 (95% CI 0.29–0.79) (Table 4). There was no difference in the risk of cervical cancer between women attending both organized screening and opportunistic testing and women attending only organized screening ($p = 0.77$). OR for attending only opportunistic testing was 0.86 (95% CI 0.60–1.25) (Table 4).

When comparing the preventive effects of Pap testing by the 5-year time periods, any Pap smear taken in 0.5–5.5 years before the diagnosis resulted in OR of 0.72 (0.95% CI 0.52–1.00) (Table 5). Additional Pap smear taken 5.5–10.5 years before the diagnosis didn't increase the effect ($p = 0.50$). Pap tests taken only 5.5–10.5 years before the diagnosis didn't protect against cervical cancer (OR 1.26 with 95% CI 0.79–1.98).

3.1. Sensitivity analyses

In the sensitivity analyses, the effect of Pap testing for the risk of cervical cancer did not differ substantially between the southern parts of Finland and the rest of the country. For the southern Finland alone, OR of any Pap test for the risk of cervical cancer was 0.58 (95% CI 0.30–1.08) based on 69 cases and 456 controls (Supplementary Table 1). The analyses, however, emphasized some differences between the impacts of organized screening and opportunistic testing on the risk of cervical cancer. For the southern Finland alone, the effect of having only had an opportunistic testing remained constant and non-significant (OR 0.84 with 95% CI 0.42–1.69). Attending only organized screening or both organized screening and opportunistic testing resulted in OR of 0.30 (95% CI 0.11–0.86) and 0.22 (95% CI 0.09–0.55), respectively; i.e. these effects were stronger compared to the effects regarding the whole country (Supplementary Table 2).

Table 4
Association between the mode of testing and the risk of cervical cancer 0.5–5.5-years before diagnosis in women tested at ages 25–39.

Mode of Pap testing	Cases no. %	Controls no. %	Crude OR (95% CI)	Corrected OR (95% CI)[a]
No test/NA[b]	96 (45.3)	385 (29.5)	1	1
Only organized	41 (19.3)	383 (29.3)	0.41 (0.28–0.61)	0.52 (0.36–0.77)
Only opportunistic	52 (24.5)	306 (23.4)	0.68 (0.47–0.98)	0.86 (0.60–1.25)
Both	23 (10.8)	233 (17.8)	0.38 (0.23–0.62)	0.48 (0.29–0.79)
Total[c]	212 (100)	1307 (100)		

[a] Corrected using self-selection bias factor 1.19 and attendance rate 0.75.
[b] Not available.
[c] Restricted to age 25–39 years, 49 cases and 244 controls had a Pap test only in 5.5–10.5 years before diagnosis and therefore they were excluded in the analysis.

Table 5
Associations between the period of testing and the risk of cervical cancer in the study population.

Time period before diagnosis					
0.5–5.5	5.5–10.5	Cases No. %	Controls No. %	Crude OR (95% CI)	Corrected OR (95% CI)[a]
No/NA[b]	No/NA[b]	111 (39.1)	478 (28.2)	1	1
Yes	No/NA[b]	76 (26.8)	555 (32.7)	0.57 (0.41–0.79)	0.72 (0.52–1.00)
No/NA[b]	Yes	30 (10.6)	123 (7.2)	0.99 (0.62–1.56)	1.26 (0.79–1.98)
Yes	Yes	67 (23.6)	542 (31.9)	0.50 (0.36–0.71)	0.64 (0.46–0.90)
	Total	284 (100)	1698 (100)		

[a] Corrected using self-selection bias factor 1.19 and attendance rate 0.75.
[b] Not available.

We used a correction factor of 1.19 for the correction of self-selection in the analyses, but also explored the effect of factors 1.1 and 1.3 on our results. With all these correction factors the main results remained constant. Among women aged under 30 years, OR of any Pap test for the risk of cervical cancer was 0.86 (95% CI 0.51–1.45) with factor 1.1 and 1.10 (95% CI 0.65–1.83) with factor 1.3, respectively.

Age didn't have an interaction with the mode of testing ($p = 0.26$). Therefore the stronger preventive effect of organized screening compared to that of opportunistic testing couldn't be explained by the differing age distribution.

4. Discussion

According to our results, the effect of screening on the risk of cervical cancer appears to diminish by decreasing age. Any Pap test reduces the risk for cervical cancer in a 5-year period before the diagnosis clearly among women aged 35 to 39 years old, but at younger ages the effect was small. Under the age of 25 Pap testing appeared to have no impact. We also found that opportunistic testing on top of attending organized screening showed no clear additional benefit on preventing cervical cancer. This reinforces the general understanding that for optimal effectiveness cervical cancer screening can and should be offered within an organized program [11].

The strength of our study is that also opportunistic testing was taken into account in evaluating the effect of screening on the risk of cervical cancer. Data regarding opportunistic testing was based on data available from registries and electronical databases in health care, not on a questionnaire. Unfortunately due to lack of national register of opportunistic Pap tests, the availability of opportunistic data was limited and we had fully covering data only for the southern parts of the country.

Principally the sensitivity analyses indicated that the effect of Pap testing was not dependent on the completeness of opportunistic data except regarding the analysis of mode of testing, i.e. when the risk of cervical cancer was compared between women who had attended only organized screening, only opportunistic testing or both. Even so the effect of opportunistic Pap testing remained persistently non-significant while the effect of organized screening actually seemed to strengthen. When the analysis was restricted only to the southern parts of Finland, attending any Pap test reduced the risk of cervical cancer around 50% also in younger age groups of 25–29 and 30–34 years. It is worth noting, though, that confidence intervals were wide and the proportion of cases tested at least once in the five-year time period was large (78% of the cases compared to 79% of the controls aged <30 years, Supplementary Table 1). Nevertheless, due to lack of comprehensive opportunistic data the poor effect of opportunistic testing could be at least partially due to lack of power. The number of cases was small as cervical cancer is a rare disease among young women.

Regarding organized screening, the data available was comprehensive. In younger age groups women are invited for screening from the age 25 or 30 years onwards depending on the residential municipality. The invitational coverage in older age cohorts was almost complete. Reasons for lacking an invitation in age groups 30–40 years were internal immigration, disregard for the national screening age recommendations by the residential municipality, and missing invitational information from the residential municipality (i.e. the real status of invitation was unknown) [8].

Also earlier studies have found similar results compared to ours'. Sasieni et al. [7] showed that screening for cervical cancer in women aged 20–24 has little or no impact on rates of invasive cervical cancer up to age 30. According to Zappa et al. [5] there was a marked increase in the level of protection for women older than 40 years. Yang et al. [22] found that unadjusted relative risk estimates appeared to indicate that Pap tests might be more protective for older than for younger women. On the other hand rather a strong impact irrespective of age was reported in a Swedish study [23] where clear effects of screening were found also at the age of 21 to 29, though results were considered to be influenced at least partly by selection bias [7]. As a response to the critic, the authors showed that the effect persisted among women aged 27–29 if analysis was restricted to stage IB+ cancers whereas not among women aged 23–26 [24].

Lack of opportunistic data is a general problem in studies comparing the impact of an organized screening to opportunistic testing on cervical cancer. There are few studies of this subject and they are primarily descriptive [2]. Nieminen et al. [10] showed that the substantial decrease in the incidence of and mortality due to cervical cancer in Finland is mainly due to the organized screening. Pap smears taken in the organized screening program had a larger effect on invasive cervical carcinoma (adjusted OR 0.38) than a Pap smear taken outside the program (adjusted OR 0.82). However, the risk estimates may have been subject to recall bias as data on personal Pap smear history was collected via a questionnaire.

Reasons for poorer effect of opportunistic testing could be e.g. lack of quality assurance and monitoring, related to lack of organization of services and central registration. Health care providers may not know about tests taken by other providers and no provider has a full responsibility of organizing a proper follow-up. In addition to poorer effect, many cost-effectiveness studies consistently report that organized screening is more cost-effective than opportunistic testing [2]. In Finland, costs produced by opportunistic testing were estimated to be two to three folds higher compared to organized screening [20]. [19],

In many European countries screening for cervical cancer begins at ages 24–25 years and the recommended screening interval can be three years instead of five [4,5]. In other Nordic countries beginning to screen for cervical cancer earlier than Finland and adhering to shorter 3-year screening interval there is no historical decrease in the trends of cervical cancer among women aged under 30 years [2,25]. In Finland, the recommended interval is five years in all age groups. Although participation in organized screening in younger age groups from 25 to 35 is alarmingly low (51–61%), when including Pap tests taken both within and outside the organized program, the 5-year coverage of Pap smears is high 85–90% [19]. Furthermore, it has been evaluated that two thirds of women aged 20–24 years, not yet even eligible for organized screening, are tested outside the organized screening program [19]. However, the incidence of cervical cancer has increased steadily from the 1990′s among 25–39 year old women in Finland despite active Pap testing in these age groups. The first peak in the age-specific incidence rate is at ages 30–39 years [1]. [26], [25],

The increased incidence of cervical cancer among younger women seems not to be due to lack of screening. Perhaps most importantly, etiological risks have also increased over time. Sexual behavior has indeed changed during the last decades and the role of oncogenic sexually transmitted HPV infection might have grown in the development of cervical cancer [2] as the life time number of sexual partners has increased [27] and the age of onset of sexual life has decreased [27]. Further, tobacco smoking, which decreases the clearance of HPV and increases the risk of cervical cancer [28] [29], [30], increased in the 1980′s among young women and stayed on that level before starting to slightly decrease in the 2000′s [31] [32],. Nevertheless we cannot rule out that

more frequent screening could have some effect on the incidence of cervical cancer also in women younger than 35 years. Active testing might result in cervical cancers to be diagnosed at an early phase.

Pap testing seems not to have a clear impact on the risk of cervical cancer at young age, especially considering women aged under 25. In this age group asymptomatic women should not be tested. HPV infection is very common among young women and a majority of the pre-invasive lesions would not progress into invasive cancer even if not diagnosed and if left untreated. There aren't any unambiguous means to distinguish the progressive lesions from the non-progressive ones and the resulting overdiagnosis may be more harmful than beneficial by increasing the risk for complications and psychological stress. Instead of frequent non-organized Pap testing, information and education of the risk factors for cervical cancer and of the importance of attending the organized screening program should be emphasized among women. Also, as vaccines against oncogenic HPVs are now available offering a means to intervene in the HPV epidemic, advocating for the HPV vaccine program should be a priority in adolescent health care.

To conclude, taking into account the high costs of opportunistic testing and related CIN treatments in young women, unnecessary Pap testing in younger age-groups should be avoided. Also practices of health care professionals resulting in excessive opportunistic testing should be revised as health care professionals are in a crucial position in the transition from excessive opportunistic testing to better compliance in organized screening. HPV vaccines have been demonstrated to reduce incidence of precancerous lesions, even though their effect on cervical cancer is not yet available. Though vaccination programs against HPV infections should be a priority in cervical cancer control in young women, screening programs will still remain crucial in the preventive strategy for cervical cancer. Efforts are still needed to define optimal starting ages of organized cervical cancer screening programs, and also by authorities to make the organized program more appealing by improving its profile and practicalities.

A conflict of interest disclosure statement

The authors declare no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2017.09.010.

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