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Mortality of non-participants in cervical screening: Register-based cohort study

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The selective uptake of screening by healthy participants and its impact on the evaluation of screening effectiveness in non-randomized studies have been discussed, but hardly studied. We quantified excess mortality among cervical screening non-participants compared to participants. Based on Danish healthcare registers, we determined women's participation in cervical screening in 1990–1993 (one screening round) and 1990–1997 (two screening rounds). Women were followed until end of 2010. We computed hazard ratios (HR) comparing non-participants' and participants' risk of death, and analyzed the impact of age, calendar period of screening evaluation, screening intensity, length of follow-up and cause of death. After one screening round, the 17-year HR of death in non-participants was 1.61 (95% CI: 1.59–1.63), with an increasing trend over calendar time. After two rounds, regular non-participants had a HR of 2.09 (95% CI: 2.05–2.14) compared to regular participants. The HR for human papillomavirus (HPV)-related cancers other than cervical cancer was 3.80 (95% CI: 2.67–5.41). Younger women, whose coverage rates were higher, had higher all-cause mortality HRs. Women screened more frequently than recommended had the same mortality as those screened as recommended. Acute illness did not seem to be a major reason for non-participation, as the excess risk of death was not higher in the first years following screening evaluation. Non-participants in cervical screening had substantially higher all-cause mortality than participants, and a particularly increased risk of HPV-related causes of death. These results indicate that improper control for the selective uptake of cervical screening may result in overestimating its effectiveness.

Health problems, difficult living conditions, risky lifestyles or insufficient knowledge may explain why some individuals do not participate in cancer screening.[1] The same circumstances might also lead them to have less favorable health outcomes including higher all-cause and cancer-specific mortality than individuals who do participate. This selective uptake poses a problem for an interpretation of the effect of cancer screening, particularly when mortality and related health indicators are compared between participants and non-participants.[2,3] However, the actual differences in the background all-cause mortality have been seldom quantified, particularly for cervical cancer.

As cervical screening detects primarily precancerous lesions, a lower incidence of cervical cancer is usually observed among screened women, which results in a lower mortality from cervical cancer. However, if screening participants have a generally better health, they may also be less prone than non-participants to develop precancerous and cancerous lesions. Selective screening uptake will therefore affect also a comparison of cervical cancer incidence between these two groups. After decades of screening, no unselected unscreened population can be identified and it is therefore not possible to directly evaluate the relative background risk of cervical cancer. Hence, the differences in the background risk can only be approximated indirectly, for example by using mortality data from diseases with the same risk factors, but for which no screening program exists.

We quantified the selective uptake of cervical screening by examining the long-term mortality of women who do not participate compared to those who do. This analysis also allowed us to approximate the differences in the background risk of cervical cancer.

Material and Methods

The national cervical screening guidelines from 1986 recommending all women aged 23–59 to be personally invited

Key words: cervical cancer, screening, cohort study, mortality, participation, selection bias

Additional Supporting Information may be found in the online version of this article.

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What's new?

In countries with routine cancer screening, certain factors are associated with choosing not to participate. These factors are also associated with poorer overall health; however, their impact on all-cause mortality is not clear. In this study, the authors quantified excess mortality among non-participants in cervical-cancer screening in Denmark. Long-term, all-cause mortality was substantially higher in non-participants, as was their risk of dying from HPV-related cancers. These results indicate that improper control for the selective uptake of cervical screening may result in overestimating its effectiveness.

every 3 years were gradually implemented in all of Denmark, with 90% of women covered by the guidelines in 1997.[4] Screening coverage was though comparably high in counties that adopted these guidelines late and those that adopted them earlier.[5] Since 2007, the guidelines have recommended 3-yearly screening at age 23–49 years, and 5-yearly screening at age 50–65 years. For Danish residents, we retrieved data on cervical cytology samples from the Danish Pathology Data Bank (Patobank; covering samples that were read by hospital, and increasingly also private, laboratories),[6] the National Health Service Register (NHSR; covering samples taken or evaluated in primary care)[7] and the National Patient Register (NPR; partially covering samples taken in hospitals).[8] The registration of samples in the Patobank began on small scale in the 1970s and first covered hospital laboratories. We can consider that by combining the registers the ascertainment of cytological samples has been nationally virtually complete since the NHSR was set up in 1990. To avoid double-counting of samples after merging the registers, we followed a protocol described elsewhere.[9]

Women's vital information and residency status in Denmark were retrieved from the Danish Civil Registration System (CRS), set up in 1968.[10] Causes of death were retrieved from the Danish Cause of Death register, which has been using the ICD-10 classification since 1994.[11] The small number of deaths (1.1%) not included in this register were retrieved from the CRS. All data were retrieved from the beginning of registration until December 31, 2010. The registers were linked using the Danish unique personal identification numbers.

Statistical analysis

To account for reasonable delays in attending cervical screening regularly, a woman was considered to be participating if she had at least one cytological sample taken in 4 years (definition of one screening round). We assessed screening participation during one screening round taking place between January 1, 1990 and December 31, 1993 (one-round analysis), and separately during two adjacent screening rounds taking place between January 1, 1990 and December 31, 1997 (two-round analysis). We restricted our analyses to women recommended for screening throughout the entire evaluated screening rounds. Therefore, the study population consisted of all female residents aged 23–55 years on January 1, 1990 and alive on December 31, 1993 for the one-round analysis, and those aged 23–51 years on January 1, 1990 and alive on December 31, 1997 for the two-round analysis. Women with gaps in residence in Denmark longer than one month while screening participation was being evaluated were excluded, as we had no information on their cervical screening abroad.

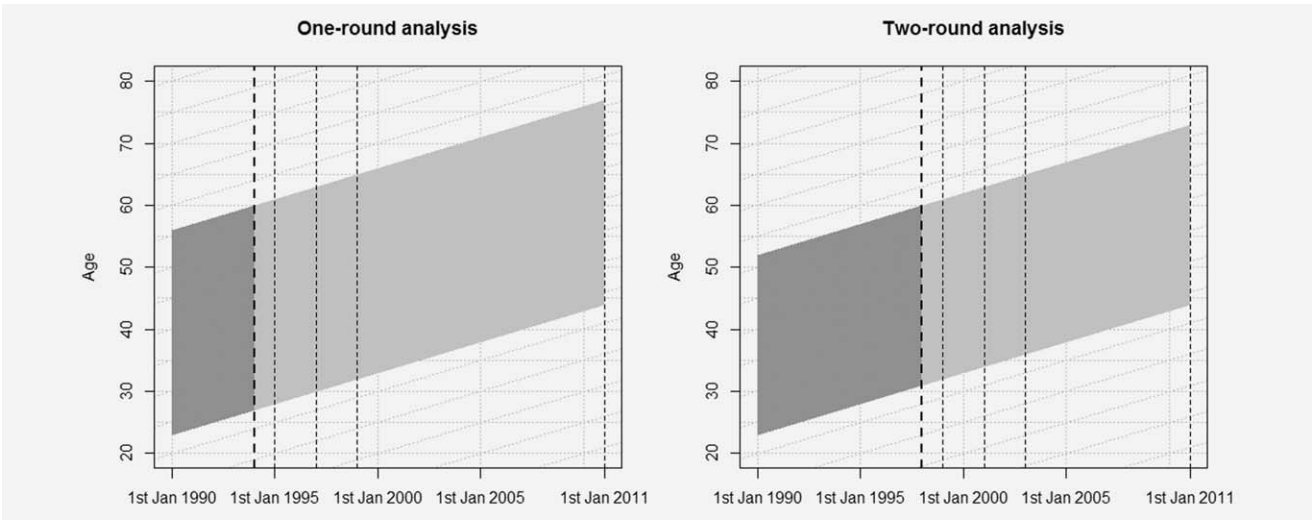

Figure 1. Lexis diagrams of the study. Darker shade—period during which participation in screening was evaluated; lighter shade—follow-up period; – – –: end of screening evaluation period and beginning of follow-up, - - -: various ends of follow-up (corresponding to 1, 3, 5 and the maximum available number of years of follow-up).

Women were followed from January 1, 1994 (one-round analysis) or January 1, 1998 (two-round analysis) until death from any cause, emigration from Denmark (unless the woman eventually migrated back) or end of follow-up on December 31, 2010, whichever came first (Fig. 1).

We used hazard ratios (HR) from Cox proportional hazard models as measures of the relative risk of dying, comparing non-participants to participants during the follow-up period. Attained age was used as timescale to control for the effect of age.[12] Screening participation was included in the model as a qualitative predictor. In the one-round analysis, HRs compared non-participants to those screened at least once. In the two-round analysis, HRs compared (*i*) women never screened in the two evaluated rounds (regular non-participants) to those screened in both screening rounds (regular participants) and (*ii*) women screened once (in the first or the second but not both rounds, *i.e.* irregular participants) to regular participants. We pooled all irregular participants regardless of whether they were screened in the first or the second round because their HRs were similar (results not reported). Since hazard rates are not estimable from Cox models, absolute mortality rates were calculated as number of deaths divided by woman-years at risk.

We tested the robustness of our results using sensitivity analyses. Firstly, the impact of the length of follow-up on the HRs was analyzed by restricting it to 1, 3 and 5 years.[13] Secondly, to assess whether the relationship between screening participation and subsequent all-cause mortality was changing over calendar time, we repeated the one-round analysis by evaluating screening participation also in 1994–1997, 1998–2001 and 2002–2005, and followed women aged 23–55 at the beginning of each round for 5 years (*i.e.*, maximum follow-up available after the screening period 2002–2005). Thirdly, the impact of screening intensity among participants was analyzed in the one-round analysis by considering the number of distinct calendar years in which a woman had cytology taken. In this analysis, women screened in 3 or 4 distinct years were considered as being screened considerably more frequently than recommended, whereas women screened either in 1 or 2 out of 4 distinct years were considered screened as frequently as recommended given the 3-year screening interval. Fourthly, the two-round analysis was repeated using cause-specific deaths as endpoints, following broad categories of the ICD-10 classification. Results using a more detailed classification are presented in the Supporting Information Appendix. Women dying from a cause different from the cause of interest were censored at their time of death, giving a correct estimate of the HRs.[14]

The relative background risk of dying from cervical cancer in participants and non-participants was approximated by the mortality from diseases with the same risk factors as cervical cancer and for which no screening program exists. We focused on two well-described major risk factors for cervical cancer, human papillomavirus (HPV) infection[15] and tobacco smoking.[16] We assessed the risk of death from other HPV-associated cancers[17] (*i.e.*, those with $\geq$30% of tumors found to contain HPV DNA) or from diseases most strongly associated with smoking[18] (*i.e.*, those with an estimated attributable fraction $\geq$30%).

Ethical approval

According to Danish legislation, notification to the Danish Data Inspection Agency serves as ethical approval of register-based research projects in which no contact is made to patients, their relatives or treating physicians. The project has notification number 2010-41-5594.

Results

On January 1, 1990, 1,184,841 women aged 23–55 lived in Denmark, from whom 10,463 (0.9%) died and 17,707 (1.5%) emigrated before 1994. The one-round analysis therefore included 1,156,671 women. During the subsequent 17-year follow-up, 92,201 (8.0%) women died [Table 1(a)]. The two-round analysis included 1,030,786 women aged 23 to 51 on January 1, 1990 and remaining alive by December 31, 1997, among whom 57,105 (5.5%) died during the 13-year follow-up [Table 1(b)].

All-cause mortality

There was a significant association between screening participation and risk of death in the following years. In the one-round analysis, the relative risk of dying in the following 17 years was 1.61 times higher (HR = 1.61, 95% CI: 1.59–1.63) for non-participants compared to participants [Table 2(a)]. When exposure to screening was evaluated over two screening rounds, the relative risk was HR = 2.09 (95% CI: 2.05–2.14) for regular non-participants, and HR = 1.54 (95% CI: 1.51–1.57) for irregular participants, compared to regular participants [Table 2(b)].

HRs were increased in all age groups. For example, after one screening round the HR was 1.47 (95% CI: 1.44–1.50) in non-participating compared to participating women aged 50–55, and 2.07 (95% CI: 1.93–2.21) in those aged 23–29. After two screening rounds, the HR for regular non-participants compared to regular participants at age 50–51 years was 1.80 (95% CI: 1.71–1.89), and 3.13 (95% CI: 2.85–3.44) for women aged 23–29. However, age-specific HRs should be compared with caution. They may reflect differences in participation rates [*e.g.*, in the one-round analysis, 39.4% of women aged 50–55 years were unscreened, compared with 12.9% among 23 to 29-year olds, Table 2(a)], and differences in screening before 1990, which are not entirely identifiable in the available data.

Restricting the length of follow-up to 5 years, the HRs were similar to those computed with the full follow-up. In the one-round analysis, the 5- and 17-year HRs were equal, 1.60 (95% CI: 1.55–1.65) and 1.61 (95% CI: 1.59–1.63) respectively. Very similar results were found in the two-round analysis. The results for follow-up restricted to 1 year and 3 years also remained very close (results not reported).

In line with improved remaining life expectancy observed at any age in the period 1994–2010,[19] both participants and non-participants showed decreasing mortality rates in recent

Table 1. One-round and two-round analyses: numbers of women at risk, deaths, migrations from Denmark, and all-cause mortality rates

(a) One-round analysis						
Age group (years)[1]	Resident women, *N* (%)	Died 1990–1993, *N* (%)	Immigrated 1990–1993, *N* (%)	Study population in one-round analysis, *N* (%)	Died 1994–2010, *N* (%)	All-cause mortality rate (per 100,000 wy)
All	1,184,841 (100%)	10,463 (0.9%)[2]	17,707 (1.5%)[3]	1,156,671 (100%)	92,201 (8.0%)[4]	487.4
23–29	274,874 (100%)	514 (0.2%)	9,491 (3.5%)	264,869 (100%)	4,535 (1.7%)	102.3
30–39	363,428 (100%)	1,592 (0.4%)	5,001 (1.4%)	356,835 (100%)	15,785 (4.4%)	266.1
40–49	376,446 (100%)	4,177 (1.1%)	2,651 (0.7%)	369,618 (100%)	37,506 (10.1%)	625.3
50–55	170,093 (100%)	4,180 (2.5%)	564 (0.3%)	165,349 (100%)	34,375 (20.8%)	1344.8

(b) Two-round analysis						
Age group (years)[1]	Resident women, *N* (%)	Died 1990–1997, *N* (%)	Immigrated 1990–1997, *N* (%)	Study population in two-round analysis *N* (%)	Died 1998–2010, *N* (%)	All-cause mortality rate (per 100,000 wy)
All	1,074,713 (100%)	17,752 (1.7%)	26,175 (2.4%)	1,030,786 (100%)	57,105 (5.5%)	438.1
23–29	274,874 (100%)	1,164 (0.4%)	14,179 (5.2%)	259,531 (100%)	3,857 (1.5%)	115.6
30–39	363,428 (100%)	3,845 (1.1%)	7,515 (2.1%)	352,068 (100%)	13,477 (3.8%)	300.2
40–49	376,446 (100%)	10,053 (2.7%)	4,108 (1.1%)	362,285 (100%)	31,557 (8.7%)	698.3
50–51	59,965(100%)	2,690 (4.5%)	373 (0.6%)	56,902 (100%)	8,214 (14.4%)	1190.0

wy = woman-years at risk.
[1]Age on January 1, 1990.
[2]40.1% were screened between January 1, 1990 and the date of death.
[3]60.2% were screened while present in Denmark from January 1, 1990 onwards until emigration before December 31, 1993.
[4]61.8% were screened in 1990–1993. Among other women in follow-up, 79.1% were screened in 1990–1993.

years. However, the decrease was larger among participants, and the HRs between non-participants and participants increased with the recency of the screening rounds, with HRs increasing from HR = 1.60 (95% CI: 1.55–1.65) to HR = 1.81 (95% CI: 1.76–1.87), HR = 1.92 (95% CI: 1.86–1.98) and HR = 2.12 (95% CI: 2.05–2.19), after the screening periods 1990–1993, 1994–1997, 1998–2001 and 2002–2005, respectively (Table 3).

Women screened twice in 4 years, which would be in strict accordance with the recommended 3-year screening interval, had a lower mortality than those screened only once in 4 years, HR = 0.87 (95% CI: 0.86–0.89). Women screened $\geq$3 times in 4 years, which means more frequently than recommended, had similarly lower mortality than those screened twice in 4 years, HR = 0.86 (95% CI: 0.84–0.88).

Cause-specific mortality

Non-participants' relative risks of death varied by cause. The overall risk of cancer death (any site) was increased both in regular non-participants, HR = 1.62 (95% CI: 1.57–1.67), and in irregular participants, HR = 1.31 (95% CI: 1.27–1.34), compared to regular participants, but less so than for all-cause mortality (Table 4). Substantial variation according to cancer site was observed (Supporting Information Appendix). The relative risk of death from external causes was also increased less than for all causes (HR = 1.91, 95% CI: 1.73–2.11 in never-participant women), with a rather low relative risk for the risk of suicide (in never participants: HR = 1.34, 95% CI: 1.13–1.59, Supporting Information Appendix). On the contrary, HRs higher than that for all causes were found in regular non-participants for deaths from cardiovascular disease (HR = 2.45, 95% CI: 2.32–2.59), and the effect was consistent for all types of cardiovascular diseases (Supporting Information Appendix). High relative risks in regular non-participants were also observed for the risk of dying from respiratory diseases (HR = 2.48, 95% CI: 2.29–2.68) or digestive diseases (HR = 2.91, 95% CI: 2.68–3.15). The risk of death from diseases such as infectious, endocrine (of which deaths from diabetes constituted 68%) and mental diseases was also strongly increased in non-participant women.

Not surprisingly, the risk of cervical cancer death was very high in regular non-participants (HR = 7.91, 95% CI: 6.62–9.46), and in irregular participants (HR = 2.23, 95% CI: 1.81–2.73). High HRs were also found for other HPV-associated cancers in regular non-participants and irregular participants, with HR = 3.80 (95% CI: 2.67–5.41), and HR = 1.84 (95% CI: 1.36–2.79) respectively (Table 4). The risk of dying from strongly smoking-associated diseases was increased, but slightly less so than for all-cause mortality, with HR = 1.81 (95% CI: 1.72–1.90) in regular non-participants, and HR = 1.44 (95% CI: 1.38–1.51) in irregular participants.

Discussion

Danish women not participating in cervical screening had a 1.5–2 times higher risk of death from any cause compared to participating women. The high relative risks were not

Table 2. Relative risk of dying from any cause after one or two screening rounds

a) One-round analysis						b) Two-round analysis					
	% Screened in 1990–1993	17-year follow-up (1994–2010)			5-year follow-up (1994–1998)		% Screened in 1990–1997	13-year follow-up (1998–2010)			5-year follow-up (1998–2002)
Age group (years)[1]		*N* women/ *N* deaths	Mortality rate[2]	HR (95% CI)	HR (95% CI)	Age group (years)[1]		*N* women/ *N* deaths	Mortality rate[2]	HR (95% CI)	HR (95% CI)
All	No 21.9%	253,232/ 34,821	863.3	1.61 (1.59–1.63)	1.60 (1.55–1.65)	All	NS 10.2%	105,558/ 12,353	952.8	2.09 (2.05–2.14)	2.12 (2.04–2.21)
	Yes 78.1%	903,439/ 57,380	385.5	1 (ref)	1 (ref)		IS 20.1%	207,492/ 14,976	575.5	1.54 (1.51–1.57)	1.57 (1.51–1.63)
							RS 69.7%	717,736/ 29,776	326.0	1 (ref)	1 (ref)
23–29	No 12.9%	34,156/ 1,063	187.6	2.07 (1.93–2.21)	1.96 (1.67–2.31)	23–29	NS 5.3%	13,828/518	295.3	3.13 (2.85–3.44)	3.51 (2.96–4.17)
	Yes 87.1%	230,713/ 3,472	89.8	1 (ref)	1 (ref)		IS 17.8%	46,261/954	161.0	1.75 (1.62–1.89)	1.80 (1.56–2.07)
							RS 76.9%	199,442/ 2,385	92.9	1 (ref)	1 (ref)
30–39	No 17.2%	61,261/ 4,271	424.6	1.78 (1.72–1.84)	1.84 (1.70–2.00)	30–39	NS 7.7%	27,120/ 2,068	608.9	2.43 (2.32–2.55)	2.56 (2.34–2.80)
	Yes 82.8%	295,574/ 11,514	233.7	1 (ref)	1 (ref)		IS 18.5%	65,002/ 3,313	402.3	1.63 (1.57–1.70)	1.71 (1.58–1.84)
							RS 73.8%	259,946/ 8,096	243.4	1 (ref)	1 (ref)
40–49	No 25.5%	94,303/ 13,249	881.2	1.60 (1.56–1.63)	1.57 (1.50–1.65)	40–49	NS 14.4%	52,074/ 7,281	1149.2	1.99 (1.94–2.05)	2.00 (1.90–2.00)
	Yes 74.5%	275,315/ 24,257	539.7	1 (ref)	1 (ref)		IS 22.8%	82,478/ 8,514	834.2	1.50 (1.46–1.54)	1.53 (1.46–1.61)
							RS 62.8%	227,733/ 15,762	550.2	1 (ref)	1 (ref)
50–55	No 39.4%	63,512/ 16,238	1695.8	1.47 (1.44–1.50)	1.52 (1.45–1.59)	50–51	NS 22.0%	12,536/ 2,486	1681.4	1.80 (1.71–1.89)	1.84 (1.68–2.01)
	Yes 61.6%	10,837/ 18,137	1134.5	1 (ref)	1 (ref)		IS 24.2%	13,751/ 2,195	1325.8	1.42 (1.34–1.49)	1.37 (1.25–1.51)
							RS 53.8%	30,615/ 3,533	937.5	1 (ref)	1 (ref)

CI = confidence interval; HR = hazard ratio. NS: never screened (regular non-participants), IS: irregularly screened (irregular participants), RS: regularly screened (regular participants).
[1]Age on January 1, 1990.
[2]Per 100,000 woman-years at risk.

Table 3. Relative risks of dying from any cause after 4 one-round screening periods: 1990–1993, 1994–1997, 1998–2001 and 2002–2005, for women aged 23–55 years at the beginning of the respective calendar period. One-round analysis

Calendar periods of screening evaluation and follow-up	Percent screened		*N* women/*N* deaths	Mortality rate[1]	HR (95% CI)
Screening evaluation: 1990–1993, Follow-up: 1994–1998	No	21.9%	253,232/7,070	566.9	1.60 (1.55–1.65)
	Yes	78.1%	903,439/11,038	246.1	1 (ref)
Screening evaluation: 1994–1997, Follow-up: 1998–2002	No	20.3%	241,726/6,434	540.6	1.81 (1.76–1.87)
	Yes	79.7%	951,205/10,820	229.2	1 (ref)
Screening evaluation: 1998–2001, Follow-up: 2002–2006	No	20.6%	253,235/6,497	521.7	1.92 (1.86–1.98)
	Yes	79.4%	974,125/10,285	212.8	1 (ref)
Screening evaluation: 2002–2005, Follow-up: 2006–2010	No	20.9%	254,096/6,285	503.3	2.12 (2.05–2.19)
	Yes	79.1%	964,295/9,152	191.4	1 (ref)

CI = confidence interval; HR = hazard ratio.
[1]Per 100,000 woman-years at risk.

confined to the first years following screening; the gap in mortality was in fact maintained over almost two decades. This suggests that the observed effect cannot be entirely explained by an immediate impact of acute medical conditions preventing women from attending screening, but may also be related to *e.g.* a cumulative impact of unhealthy living conditions or lifestyle on mortality. Non-participants had an almost 4-fold risk of death from causes, other than cervical cancer, associated with HPV infections (for comparison, non-participants had a 1.6-fold risk of death from all cancers). Although not all anal, vaginal, vulvar, tonsil and oropharyngeal cancers are caused by HPV, the on-average 4-fold risk for this group of cancers suggests that non-participants have a higher-than-average background risk of cervical cancer.

The observed gradient in the relationship between screening attendance and future mortality was consistent. Firstly, women not at all screened in two rounds had a higher mortality than those screened irregularly, who in turn had a higher mortality than those screened regularly. Secondly, the higher the coverage rate, the higher were the observed relative risks for non-participants, meaning that non-participating in screening might correspond well to poorest overall health status.

As observed in the early studies from Nordic countries and Canada, cervical cancer incidence and mortality have decreased dramatically after the introduction of cervical screening.[20–22] As shown in our study, those who remain unscreened appear to be women with a high background risk of cervical cancer. These results suggest that the incidence and mortality from cervical cancer could be further reduced by motivating non-participants to undergo screening. Our results point to the importance of undertaking randomized controlled trials before implementation of screening programs. However, with cervical screening being a well-established part of healthcare, it is in most countries at present not anymore possible to undertake randomized controlled trials on cervical screening.

Our cohort study was population-based, including more than one million Danish women followed for up to 17 years. The data were retrieved from well-maintained registers, linked on an individual basis. The assessment of screening participation could not suffer from recall bias.

We measured selective uptake of screening computed for the period following one or two screening rounds. Since women who died during the screening evaluation period were excluded, those included in our cohorts were on average slightly healthier than the total population alive on January 1, 1990. Hence, even higher HR might have been observed during the screening evaluation period. However, among women excluded from the study due to either death or emigration during the studied screening round, 40 and 60%, respectively, had been screened prior to their death/emigration. This compares to 62 and 79%, respectively, among women included in the study that died or emigrated during the follow-up period. Given the shorter length of observation for the excluded than for the included women, these numbers do not point to a strong selection bias.

In Denmark it is not possible to distinguish between screening samples and those taken for medical indication. Women with cytology taken for the latter reason were considered as screened in our analysis, although in reality their sample did not reflect a regular screening behavior. However, these samples probably represent a relatively small proportion of all samples. This also has implications for the interpretation of the calculated HR for dying from cervical cancer, HR = 7.91 (95% CI: 6.62–9.46). Because unscreened women with symptomatic and lethal cervical cancer would be erroneously considered as screened, the HR was probably underestimated, particularly in the first years of the follow-up period. Since Denmark has used cervical screening for decades, the background relative risk of cervical cancer could only be indirectly estimated, *e.g.* based on diseases sharing the same cofactors. If having a smear taken because of symptoms is also a predictor of an increased risk of dying from other causes of death (particularly gynecologic cancers), our estimates of the mortality differences according to participation would be conservative also for those causes of death.

Table 4. Relative risks by cause of death, for women aged 23 to 55 years on January 1, 1990. Two-round analysis

Cause of death (*N* deaths)	ICD-10 codes	Screening	N deaths	% deaths	HR (95% CI)
Overall (*N* = 57,105)	All codes	NS	12,353	21.6%	2.09 (2.05–2.14)[1]
		IS	14,976	26.2%	1.54 (1.51–1.57)[1]
		RS	29,776	52.1%	1 (ref)
Infectious and parasitic diseases (*N* = 562)	A00-B99	NS	137	24.4%	2.57 (2.09–3.16)
		IS	148	26.3%	1.66 (1.36–2.03)
		RS	277	49.3%	1 (ref)
Cancers (*N* = 28,552)	C00-C97	NS	5,325	18.7%	1.62 (1.57–1.67)[2]
		IS	7,007	24.5%	1.31 (1.27–1.34)[2]
		RS	16,220	56.8%	1 (ref)
Endocrine, nutritional and metabolic diseases (*N* = 1,607)	E00-E90	NS	529	32.9%	4.50 (4.00–5.07)
		IS	473	29.4%	2.42 (2.14–2.73)
		RS	605	37.6%	1 (ref)
Mental and behavioral disorders (*N* = 1,833)	F00-F99	NS	476	26.0%	3.25 (2.89–3.64)
		IS	532	29.0%	2.07 (1.85–2.31)
		RS	825	45.0%	1 (ref)
Diseases of the nervous and sensory systems (*N* = 1,617)	G00-H95	NS	380	23.5%	2.61 (2.30–.96)
		IS	480	29.7%	1.98 (1.76–.22)
		RS	757	46.8%	1 (ref)
Cardiovascular diseases (*N* = 7,872)	I00-I99	NS	1,935	24.6%	2.45 (2.32–.59)
		IS	2,130	27.1%	1.68 (1.60–.78)
		RS	3,807	48.4%	1 (ref)
Respiratory diseases (*N* = 3,820)	J00-J99	NS	1,013	26.5%	2.48 (2.29–.68)
		IS	1,033	27.0%	1.67 (1.55–.80)
		RS	1,774	46.4%	1 (ref)
Digestive diseases (*N* = 3,972)	K00-K93	NS	956	24.1%	2.91 (2.68–.15)
		IS	1,218	30.7%	2.15 (2.00–.31)
		RS	1,798	45.3%	1 (ref)
External causes (*N* = 3,155)	V00-Y99	NS	516	16.4%	1.91 (1.73–2.11)
		IS	828	26.2%	1.58 (1.45–1.71)
		RS	1,811	57.4%	1 (ref)
Unknown, missing[3] or other causes (*N* = 4,115)	Other codes	NS	1,086	26.4%	2.95 (2.74–3.18)
		IS	1,127	27.4%	1.83 (1.70–1.97)
		RS	1,902	46.2%	1 (ref)
Cervical cancer (*N* = 663)	C53	NS	274	41.3%	7.91 (6.62–9.46)
		IS	152	22.9%	2.23 (1.81–2.73)
		RS	237	35.7%	1 (ref)
Smoking-associated diseases[4] (*N* = 10,418)	C00-C14, C33-C34, J40-J44, J47	NS	2,186	20.9%	1.81 (1.72–1.90)
		IS	2,723	26.1%	1.44 (1.38–1.51)
		RS	5,509	52.9%	1 (ref)

Table 4. Relative risks by cause of death, for women aged 23 to 55 years on January 1, 1990. Two-round analysis (Continued)

Cause of death (*N* deaths)	ICD-10 codes	Screening	N deaths	% deaths	HR (95% CI)
HPV-associated cancers[5] (*N* = 55)	C09, C10, C21, C51, C52	NS	67	26.3%	3.80 (2.67–5.41)
		IS	73	28.6%	1.84 (1.36–2.79)
		RS	115	45.1%	1 (ref)

CI = confidence interval; HR = hazard ratio; HPV = Human Papillomavirus; ICD = International Classification of Diseases, NS = never screened (regular non-participants), IS = irregularly screened (irregular participants), RS = regularly screened (regular participants).
[1]Excluding deaths from cervical cancer: NS: HR = 2.05 (2.01–2.10), IS: HR = 1.53 (1.50–1.56).
[2]Excluding deaths from cervical cancer: NS: HR = 1.56 (1.51–1.61), IS: HR = 1.30 (1.26–1.33).
[3]635 deaths were retrieved from the Civil Registration System since they were not registered in the Cause of Death Register, representing 24.7% of the missing causes of death and 1.1% of the total number of deaths.
[4]Including: lung cancer (fraction attributable to smoking = 70%), chronic obstructive pulmonary disease (fraction attributable to smoking = 62%), upper aerodigestive cancer (fraction attributable to smoking = 39%).[18]
[5]Including: anal cancer (% tumors containing HPV DNA = 84%), vaginal cancer (% tumors containing HPV DNA = 77%), vulvar cancer (% tumors containing HPV DNA = 40%), tonsil cancer (% tumors containing HPV DNA = 90%), oropharyngeal cancer (% tumors containing HPV DNA = 36%).18

Another potential source of misclassification is the Cause of Death Register. Even in high-quality registers such as the one in Denmark, the classification of causes of death is assumed not to be absolutely reliable. Misclassification and missing data may occur because autopsies are nowadays seldom performed.[11,23] However, the relative risk is not affected if screened and unscreened women are equally subject to misclassification of their cause of death,[24] which might not be an unreasonable assumption.

Few studies have previously quantified selective uptake in cancer screening. In a Japanese study[3] of 63,541 women aged 30–79, a lower 15-year all-cause mortality was found in women who self-reported to be screened for cervical cancer in the year before the study, with a point estimate of HR = 0.73 (95% CI: 0.68–0.78). In a study of cancer-related mortality by participation in breast cancer screening,[25] the patterns were very similar to ours. For example, that study found no increased risk of death from cancers of the skin, pancreas and brain. Mortality following non-participation in other routine cancer screening has been evaluated in Japan, but with smaller samples of population and self-reporting of screening histories.[26]

The consistent and stable excess all-cause mortality found in non-participants may be explained in part by socio-economic differences compared to participants. We found substantially lower relative risks of dying from cancer than from cardiovascular diseases. In the Danish population at large, all-cause mortality is higher in lower socio-economic groups, but the disparity is wider for deaths from cardiovascular diseases.[27] As observed in other countries, including Nordic countries, the lowest socio-economic groups also tend to have the highest rates of non-participation in cervical screening.[28] Nordic countries have a rather high level of health inequality related to socio-economic factors,[29] despite healthcare access being mainly free of charge. Other risk factors associated with lower socio-economic status such as smoking and obesity were found to be associated with lower screening attendance,[28,30] and higher risk of death from cardiovascular diseases.[31,32] It would be interesting to disentangle the effect of each of these factors on the mortality of Danish non-participants. However, this was beyond the scope of our analysis, which aimed to quantify their cumulative effect.

We found that non-participants had a strongly increased risk of dying from HPV-associated diseases other than cervical cancer, which suggests that they might also have a high background risk of cervical cancer. However, our study design does not allow for concluding on whether the contribution of HPV-associated factors to this risk is stronger than that of lifestyle-associated risk factors, or whether these factors interact. For the case of cervical cancer, this distinction is difficult to establish because the cancer's etiology is a combination of HPV-associated, host-associated and lifestyle-associated factors including screening participation, and these are often correlated. For example, the number of sexual partners, use of condoms and smoking are all part of lifestyle, and strongly associated with HPV infection and cervical screening.[28] Moreover, it is methodologically challenging to assess HPV prevalence in an unscreened population. Self-sampling studies, however, suggest that HPV prevalence is higher in non-participants[33] than in participants,[34] which could explain the high relative risks we found for HPV-associated cancer deaths. Finally, since HPV-associated cancers, other than cervical cancer, are not all caused by HPV, our indirect estimate should be interpreted cautiously. It should be noted, however, that the mortality risk in non-participants was in particular high for cancers most frequently associated with HPV (>75% of tumors containing HPV DNA): tonsil cancer (90%), HR = 3.8 (95% CI: 2.1–6.7) (this increased risk may not be fully explained by smoking, as among non-participants the HR for lung cancer was only 1.6 (95% CI: 1.5–1.7)), anal cancer (84%), HR = 2.1 (95% CI: 1.1–3.9) and vaginal cancer (77%), HR = 5.1 (95% CI: 1.6–16.2) (Supporting Information Appendix).

In several developed countries such as the US, self-reported coverage rates[35] are higher than in Denmark. Given the observed inverse relationship between screening participation and future mortality, we speculate that the non-participants' HRs of dying would be higher in those countries than in Denmark.

Our results could help interpret studies of relative survival between screened and unscreened cervical cancer patients[2,36] where a longer survival has typically been observed among screened patients. Although patients with a cancer detected by screening are probably a selected group of screened women in the sense that they cumulate more risk factors for cervical cancer than the general population, knowing that a woman attended screening may indicate that she has other characteristics related to better survival, for example a more favorable socio-economic status.[37] In this case, a longer survival in screened women might not only be a consequence of the tumor's biological characteristics specific to screen-detected cases, but also to some extent of the women's generally better health status.

In conclusion, Danish women not participating in cervical screening had higher all-cause mortality, including mortality from causes of death associated with HPV-infection. This pattern indicates that improper control for the selective uptake in the monitoring of cervical cancer screening may result in overestimating its effectiveness.

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