Acta Oncologica, 2015; 54: 1136–1143

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ORIGINAL ARTICLE

Hysterectomy and its impact on the calculated incidence of cervical cancer and screening coverage in Denmark

JANNI UYEN HOA LAM, ELSEBETH LYNGE, SISSE HELLE NJOR & MATEJKA REBOLJ

Department of Public Health, University of Copenhagen, Copenhagen, Denmark

ABSTRACT

Background. The incidence rates of cervical cancer and the coverage in cervical cancer screening are usually reported by including in the denominator all women from the general population. However, after hysterectomy women are not at risk anymore of developing cervical cancer. Therefore, it makes sense to determine the indicators also for the true at-risk populations. We described the frequency of total hysterectomy in Denmark and its impact on the calculated incidence of cervical cancer and the screening coverage.

Material and methods. With data from five Danish population-based registries, the incidence rate of cervical cancer and the screening coverage for women aged 23–64 years on 31 December 2010 were calculated with and without adjustments for hysterectomies undertaken for reasons other than cervical cancer. They were calculated as the number of cases divided by 1) the total number of woman-years from the general population; and 2) the at-risk population after exclusion of post-hysterectomy woman-years. Cases were defined as women with cervical cancer (incidence), or as women screened in the recommended interval, with or without adjustment for hysterectomies (coverage).

Results and conclusions. In 2010, the all-age prevalence of hysterectomy was estimated at 6%, and ≥16% at age ≥65. This translated into an overall 6% increase in the incidence rate of cervical cancer, from 12.8 (unadjusted) to 13.5 (adjusted) per 100 000 woman-years. The screening coverage increased from 76% (unadjusted) to 79% (adjusted).

In Denmark, hysterectomies do not have a large overall impact on the calculated cancer incidence and screening coverage. Nevertheless, at ≥65 years adjusted rates would increase by almost 20% compared to unadjusted rates. This suggests that calculating disease risks per organ-years may have a role in understanding the true burden of the disease in a population at risk of developing that disease.

Hysterectomy is a frequent gynaecological surgical procedure [1]. The removal of the cervix uteri along with the corpus uteri protects women from developing cervical cancer. Women hysterectomised for reasons other than cervical cancer can therefore cease the routine cervical cancer screening [2–4].

Nevertheless, the official cervical cancer statistics are usually reported without correction for women without cervix uteri, leading to an underestimate of the rates in the true at-risk population [5]. Already in 1977, Lyon and Gardner estimated, using self-reported hysterectomy data from the USA that the cervical cancer mortality rates for 1960–1973 increased by 25–40% after accounting for hysterectomy [6]. However, the difference between unadjusted and adjusted cervical cancer mortality rates in the late 1960s/early 1970s in England and Wales was more modest, at most 10% in some birth cohorts [7]. In 1983, using self-reported data, Andersen et al. estimated that the prevalence of hysterectomy in Danish women was only 6% and saw no "decisive effect" on adjusting the calculated incidence rates of uterine cancers. However, with an increasing frequency of hysterectomy, they recommended that the trends continue being monitored [8]. Recently, a report was published from the USA [9] suggesting that an adjustment for hysterectomies has a decisive (60%) effect on the calculated cervical cancer incidence rates. It is important to determine whether the findings can be generalised to other countries.

Correspondence: J. Lam, Department of Pathology, Copenhagen University Hospital Hvidovre, Kettegård Allé 30, 2650 Hvidovre, Denmark. Tel: +45 38 622265. E-mail: janni.uyen.hoa.lam@regionh.dk

(Received 12 November 2014; accepted 3 February 2015)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/0284186X.2015.1016625

Another reason to determine the size of the true at-risk population is to monitor the quality of cervical cancer screening programmes. The screening coverage is one of the most essential screening process indicators. Given the limited value of screening after hysterectomy for reasons other than cervical cancer [2–4], an estimate of the screening coverage in the true at-risk population might be informative. Indeed, the Danish cervical cancer screening programme monitoring group (DKLS) called for an estimate of the hysterectomy-adjusted screening coverage [10].

We studied the impact of hysterectomies on the calculated cervical cancer incidence and screening coverage in Denmark using recent population-based data from nationwide registers.

Material and methods

Data sources

The data were retrieved from five nationwide registers: the Danish Civil Registration System (containing information on the vital status of all Danish residents since 1968), the National Patient Register (inpatient admissions since 1977 and outpatient admissions since 1995), the Danish Cancer Register (established in 1943), the National Health Service Register (NHSR; health care services, including cervical cancer screening, in primary care since 1990), and the Danish Pathology Data Bank (Patobank; cytological and histological specimens evaluated in hospital pathology laboratories, complete since 1997, increasingly also including samples evaluated by private pathology practices). All hysterectomy data were retrieved from the NPR. All screening information was retrieved from the Patobank and the NHSR. The data were retrieved from the beginning of registration until 31 December 2010, and were linked using the Danish unique personal identification number. According to Danish legislation, notification to the Danish Data Protection Agency serves as ethical approval of register-based research projects in which no contact is made to patients, their relatives, or physicians. This project has notification number 2010-41-5594.

Statistical analysis

The hysterectomy data were available from 1977 onwards. As hysterectomies below age 25 have been extremely rare, we assumed that the data were complete for cohorts born in 1952 or later. Subtotal hysterectomies were not counted because thereafter the woman remained at risk of cervical cancer. With the main focus of the analysis being on the changes to the population at risk that are unrelated to cervical cancer, the analysis included hysterectomies for reasons other than cervical cancer. These reasons were not available for our study in full but included, e.g. benign diagnoses and non-cervical uterine cancers; for 1988–1998, it was reported that 81% of all hysterectomies had a benign diagnosis [11]. We defined a hysterectomy undertaken because of cervical cancer as all instances where a cervical cancer diagnosis was registered up to three months before to one month after the hysterectomy date. Unless otherwise specified, the term "hysterectomy" was hereafter used for a radical or total hysterectomy undertaken for reasons other than cervical cancer. Finally, during their residence abroad, if any, women were assumed not to have undergone a hysterectomy.

Incidence rates of hysterectomy were calculated as the number of hysterectomies divided by the number of woman-years at risk (WY). WY were counted from 1 January 1977 or from the date the woman started residing in Denmark, whichever came last, until the date of hysterectomy, emigration, death, or 31 December 2010, whichever came first. To compare these rates over calendar years, they were standardised to the Danish female population with cervix uteri in 2000.

We calculated the proportion of women with a hysterectomy on 31 December 2010. For birth cohorts 1939–2010, it was calculated as the observed numbers of women with a hysterectomy by 31 December 2010, divided by the number of women alive on 31 December 2010. For women born before 1939, the proportion with a hysterectomy started decreasing in the registered data (not shown). Given that in the past, women underwent a hysterectomy at a younger average age than nowadays [12], with a plausible risk of a hysterectomy already before 1977, we assumed that (at least) the same proportion of women from birth cohorts born before 1939 underwent a hysterectomy as cohorts born in 1939–1942.

Age-specific incidence rates of cervical cancer in 2010 were calculated as the number of new cancer cases in 2010 divided by the number of WY in 2010. Unadjusted WY were counted from 1 January 2010 or from the date the woman started residing in Denmark, whichever came last, until the date of emigration, death, or 31 December 2010, whichever came first. As a result of incomplete hysterectomy data for the oldest women, we estimated the number of hysterectomy-adjusted WY for year 2010 for each age i as follows: [1-proportion of women at age i with a hysterectomy before 31 December 2010] $\times$ unadjusted WY. The proportion of women born before 1939 with a hysterectomy was set at the highest observed proportion for the younger birth cohorts. Finally, the proportion increase at age i in the cervical cancer incidence rate after hysterectomy

adjustment was calculated as [1/(1-proportion of women at age *i* with a hysterectomy before 31 December 2010)-1].

To follow the screening coverage definitions used by the DKLS [10], we calculated the proportion of women alive on 31 December 2010 who had at least one cytological sample (whether for screening or other reason) in the preceding 3.5 years if aged 23–49 years (recommended interval: 3 years), or in the preceding 5.5 years if aged 50–64 years (recommended interval: 5 years). For calculation of hysterectomy-adjusted screening coverage, we excluded women with a hysterectomy before 31 December 2010 from both the numerators and the denominators.

Results

In 1977–2010, 195 048 hysterectomies were registered for Danish residents. Of these, 6289 (3.2%) were undertaken for cervical cancer, and 247 (0.1%) were duplicate registrations. The remaining 188 512 hysterectomies were included in the analysis.

Relying on the hysterectomy data registered since 1977, about 5% of all WY at risk were in 2010 lived after a hysterectomy (Table I). The increasing percentages of WY after a hysterectomy though probably reflect an increasing completeness of the hysterectomy data rather than an increasing prevalence of hysterectomy. This seems a reasonable conclusion since the incidence of hysterectomy actually decreased by 31% between 1977 (282.7 per 100 000 WY) and 2010 (194.2 per 100 000 WY, Figure 1).

The proportion of women alive at the end of 2010 with a prior hysterectomy increased continuously with age, and was 11% for birth cohort 1952 (58 years; Table II). For women born before 1952, the proportion with a hysterectomy continued to increase even with the incomplete data, and reached 16% for birth cohorts 1939–1942. Assuming that 16% of women born before 1939 underwent a hysterectomy by end of 2010, we finally estimated that in 2010, 6% of women at any age underwent a hysterectomy (7% at $\geq$ 20 years).

Table I. Number of hysterectomies, total number of woman-years at risk unadjusted for hysterectomies, and hysterectomy-adjusted number of woman-years at risk, in Denmark in 1977–2010.

Calendar year	Number of hysterectomies	All woman-years	Woman-years before a registered hysterectomy	Proportion of woman-years after a registered hysterectomy
1977	6374	2 569 211	2 565 783	0.1%
1978	6575	2 578 788	2 569 155	0.4%
1979	6516	2 587 017	2 570 944	0.6%
1980	6295	2 600 288	2 578 035	0.9%
1981	6634	2 593 920	2 565 637	1.1%
1982	6368	2 594 573	2 560 188	1.3%
1983	6649	2 594 637	2 554 151	1.6%
1984	6370	2 601 273	2 554 663	1.8%
1985	5697	2 594 484	2 542 815	2.0%
1986	5985	2 596 968	2 540 179	2.2%
1987	5693	2 600 235	2 538 400	2.4%
1988	5680	2 608 477	2 541 575	2.6%
1989	5414	2 603 206	2 531 947	2.7%
1990	5673	2 607 234	2 531 467	2.9%
1991	5275	2 613 916	2 533 758	3.1%
1992	5078	2 628 610	2 544 236	3.2%
1993	4729	2 629 940	2 542 068	3.3%
1994	4771	2 637 336	2 546 084	3.5%
1995	4532	2 648 871	2 554 261	3.6%
1996	4645	2 670 869	2 572 873	3.7%
1997	4656	2 674 137	2 573 398	3.8%
1998	4582	2 683 616	2 579 775	3.9%
1999	4688	2 691 970	2 585 193	4.0%
2000	4802	2 708 342	2 598 304	4.1%
2001	5125	2 710 369	2 597 569	4.2%
2002	5665	2 719 102	2 602 833	4.3%
2003	5627	2 725 430	2 605 601	4.4%
2004	5393	2 739 577	2 616 026	4.5%
2005	5484	2 739 530	2 613 176	4.6%
2006	5482	2 748 008	2 618 436	4.7%
2007	5620	2 758 539	2 625 907	4.8%
2008	5336	2 780 349	2 644 483	4.9%
2009	5747	2 786 627	2 648 112	5.0%
2010	5352	2 798 324	2 656 896	5.1%

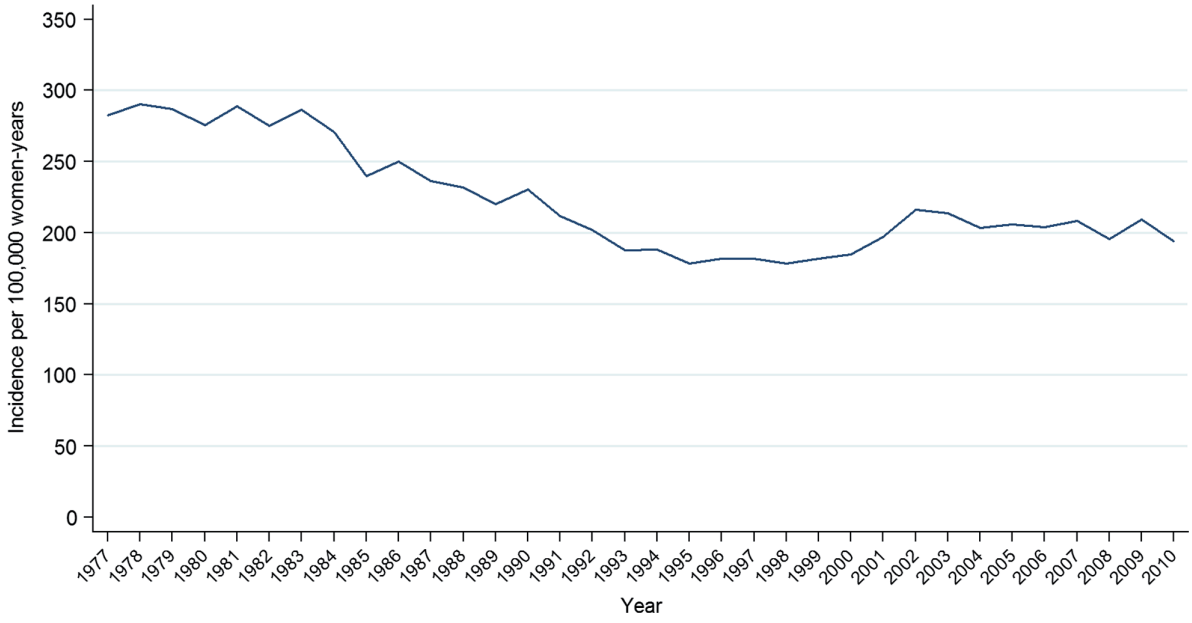

Figure 1. Age-adjusted incidence of hysterectomy, per 100 000 woman-years at risk, in Denmark in 1977–2010. Standard population: Danish female population with cervix uteri in 2000. Woman-years after a prior hysterectomy were excluded from the denominators.

The incidence of hysterectomy has been decreasing for the younger birth cohorts, compared to the older birth cohorts, until they turn about 50 years (Table III). The decrease was particularly strong (more than 10-fold) below age 35 years. At age 50–64 years, all birth cohorts had a roughly similar risk of a hysterectomy. At age $\geq$ 65 years, however, the incidence of hysterectomy was much higher (double to quadruple) in the younger than in the older birth cohorts.

By excluding hysterectomised women from the denominators, the change in the incidence of cervical cancer was below 1% for women aged $\leq$ 36 years. The difference remained at below 5% for women aged $\leq$ 46 years, and reached 10% at age 53 years. At age 63 years, the difference, based on incomplete data, reached $>$ 15%, and continued to rise to approximately 18–19% thereafter (with incomplete hysterectomy data for birth cohorts 1951–1939, and assuming a 16% cumulative risk of a hysterectomy for women born before 1939). For all ages combined, the difference between the unadjusted and adjusted incidence rates was 6%. The resulting age-specific differences between the unadjusted and hysterectomy-adjusted incidence rates of cervical cancer were presented in Figure 2. The differences between adjusted and unadjusted screening coverage were slightly smaller than was the case for the incidence of cervical cancer (Figure 3).

Discussion

Nowadays, total and radical hysterectomies are much less frequently undertaken in Denmark compared to three decades ago. This is particularly the case below age 50 years, leaving more women at risk of developing cervical cancer. This change might have occurred, to some extent, because in the early 1990s cervix-sparing subtotal hysterectomies became more common [11], and one of the presumed advantages of subtotal hysterectomies (now disputed) was preservation of sexual function [13]. The highest hysterectomy rates were found in women around menopause. For women above the age of 65 years, the hysterectomy rates have increased. Although we confirmed earlier Danish findings by Andersen et al. [8] who concluded that the overall difference between hysterectomy-adjusted and unadjusted cancer incidence rates is negligible (6% in our study), nevertheless estimated differences of just below 20% could be observed for older women.

On the population level, this means that the unadjusted crude cervical cancer incidence rate of 12.8 per 100 000 WY in 2010 would correspond to a hysterectomy-adjusted rate of 13.5 per 100 000 WY. Danish women are invited for cervical cancer screening until age 65 years. Women at age $>$ 65 years though have some of the highest age-specific incidence and mortality rates of cervical cancer. Our study demonstrated that the incidence rates in the at-risk elderly population are even higher than the official statistics. The crude unadjusted cervical cancer incidence rate in women aged 65–74 years was 13.5 per 100 000 WY, whereas in the true at-risk population, it was 16.0 per 100 000 WY. For women aged $\geq$ 75 years, the rates were 20.8 and 24.8 per 100 000 WY, respectively. Therefore, the question is

Table II. Proportion of women with a hysterectomy on 31 December 2010, by birth cohort.

Birth cohort	Age on 31 December 2010 (years)	Number alive on 31 December 2010	Number with a hysterectomy before 31 December 2010	Proportion with hysterectomy by 31 December 2010	Estimated change in the cervical cancer incidence rate
1939	71	24 215	3772	16%	18%
1940	70	25 834	3973	15%	18%
1941	69	26 814	4182	16%	18%
1942	68	30 255	4749	16%	19%
1943	67	32 626	4985	15%	18%
1944	66	35 431	5336	15%	18%
1945	65	37 365	5695	15%	18%
1946	64	39 024	5650	14%	17%
1947	63	38 271	5302	14%	16%
1948	62	36 213	4686	13%	15%
1949	61	34 821	4457	13%	15%
1950	60	35 204	4177	12%	13%
1951	59	33 906	3826	11%	13%
1952	58	34 799	3689	11%	12%
1953	57	35 493	3591	10%	11%
1954	56	35 163	3476	10%	11%
1955	55	35 598	3291	9%	10%
1956	54	36 290	3362	9%	10%
1957	53	36 033	3238	9%	10%
1958	52	36 316	3045	8%	9%
1959	51	36 288	2855	8%	9%
1960	50	37 716	2827	7%	8%
1961	49	37 806	2615	7%	7%
1962	48	38 869	2424	6%	7%
1963	47	41 136	2253	5%	6%
1964	46	41 758	2001	5%	5%
1965	45	43 035	1850	4%	4%
1966	44	44 329	1654	4%	4%
1967	43	41 389	1272	3%	3%
1968	42	38 493	954	2%	3%
1969	41	37 344	796	2%	2%
1970	40	37 697	658	2%	2%
1971	39	39 112	567	1%	1%
1972	38	39 966	443	1%	1%
1973	37	38 215	369	1%	1%
1974	36	38 314	254	1%	1%
1975	35	38 992	219	1%	1%
1901–2010	–	2 806 657	157 728[a]	6%	6%

[a]Estimated number. Observed numbers used for birth cohorts 1939–2010. For birth cohorts 1901–1938 (observed data not reported here), we assumed that 16% had a hysterectomy by 31 December 2010. The proportion of women with a hysterectomy for birth cohorts from 1976 or later were $< 0.5\%$ (not reported here).

whether asymptomatic elderly women might benefit from continued cervical cancer screening by having CIN detected and treated, or having a cervical cancer diagnosed at an earlier stage when survival rates are higher. The upper age at which screening should cease has been debated widely [14,15]. Apart from difficulties in the interpretation of cytology in postmenopausal women, the strongest argument against continued screening has been a relatively low number of remaining life years, and competing co-morbidities. However, with an increasing longevity of the current birth cohorts, of whom significant proportions are still in good health, the optimal upper age may have changed. Ideally, it should be determined anew in a rigorously performed cost-effectiveness analysis.

The screening coverage of the targeted population, 23–64 years, increased from 76% before, to 79% after the adjustment. Unadjusted, no age group reached the recommended 85% screening coverage [10]. The adjusted screening coverage came close to 85% among women in their 50s, but for women aged up to 40 years the change was, as expected, negligible. Screening coverage was particularly low below 30 years, 59% at 23–24 years, and 73% at 25–29 years. In Denmark, cervical cancer screening is free of charge, and women receive personal invitations with two reminders. To increase their screening participation, other methods will need to be considered. Of these, self-sampling for human papillomavirus (HPV) appears potentially

Table III. Age- and birth cohort-specific incidence rates of hysterectomy in Denmark, per 100 000 woman years at risk. Based on data retrieved for years 1977–2010. Woman-years after a prior hysterectomy were excluded from the denominators.

Age (years)	Birth cohort (calendar years)										
	<1910	1910–1919	1920–1929	1930–1939	1940–1949	1950–1959	1960–1969	1970–1979	1980–1989	1990–1999	≥2000
≤4								0.0	0.3	0.1	0.1
5–9							0.0	0.0	0.1	0.0	0.0
10–14							0.2	0.1	0.1	0.0	0.0
15–19						3.1	0.9	0.2	0.8	0.5	
20–24						17.3	4.6	2.3	1.4	0.0	
25–29					190.9	86.3	23.9	15.8	11.2		
30–34					335.3	166.1	79.0	77.8	23.4		
35–39				719.5	532.8	280.1	224.1	200.8			
40–44				871.5	735.6	475.3	491.3	322.5			
45–49			888.8	880.8	719.7	639.6	662.0				
50–54			513.2	481.8	450.4	451.7	522.6				
55–59		259.3	288.8	246.0	313.4	264.8					
60–64		246.5	268.4	258.7	300.1	242.1					
65–69	163.2	233.6	252.7	296.0	331.0						
70–74	176.9	217.3	243.9	297.4	310.1						
75–79	140.8	167.3	228.0	281.2							
80–84	90.5	127.7	179.8	311.3							
≥85	32.4	68.5	125.2								

effective, and is currently being piloted in the Capital Region [16–19].

The most recent study from the USA estimated that the hysterectomy-adjusted incidence rate of cervical cancer was 18.6 per 100 000, roughly 60% higher than the unadjusted rate of 11.7 per 100 000 [9]. This is not surprising given the high cumulative risk of hysterectomy in the USA, estimated at around 20% in women in their late 40s, around 40% by their early 60s, and peaking at just below 50% by the early 80s [9]. In Germany in 2000, the overall prevalence of hysterectomy was 16%, with a peak prevalence of 41%; consequently, the adjusted incidence rates of cervical cancer were 11% higher in women aged

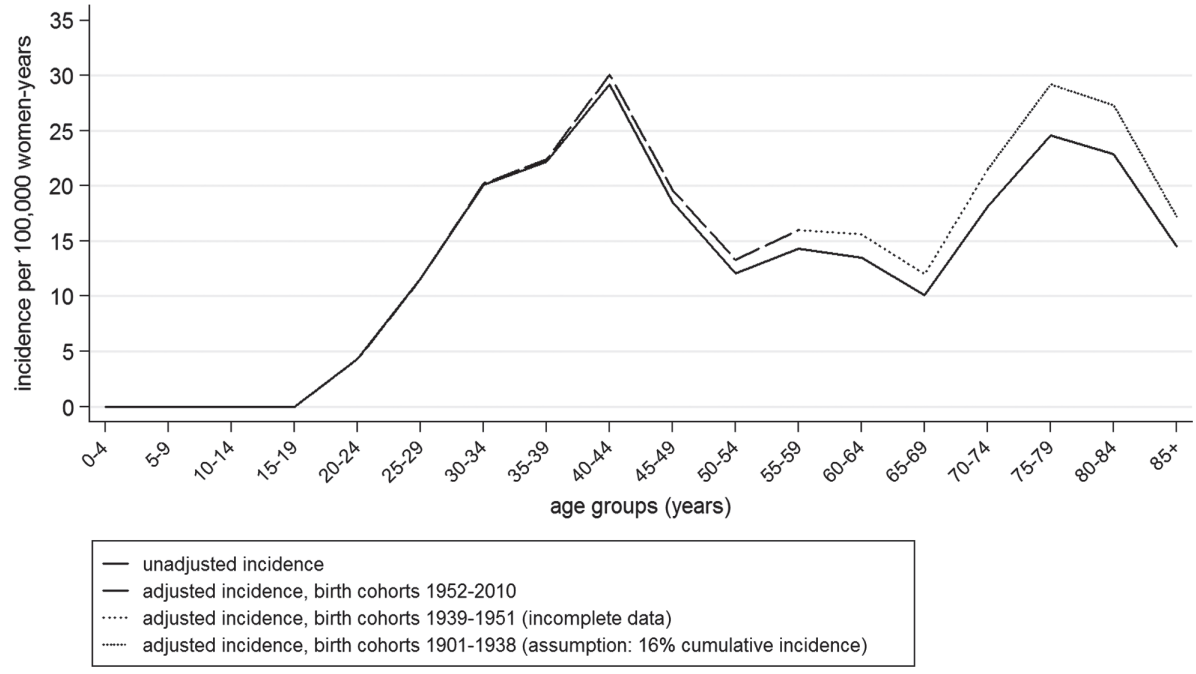

Figure 2. Effect of hysterectomies on the calculated incidence of cervical cancer: unadjusted and hysterectomy-adjusted age-specific incidence rates for women alive on 31 December 2010. All ages: 12.8 per 100 000 woman-years at risk (unadjusted), and 13.5 per 100 000 woman-years at risk (adjusted). Hysterectomy-adjusted incidence rates of cervical cancer were calculated using the observed proportion of hysterectomy in women born in 1939 or later (age ≤ 71 years on 31 December 2010), with incomplete data for women born between 1939 and 1951. For women born before 1939, we assumed a constant 16% proportion of hysterectomy.

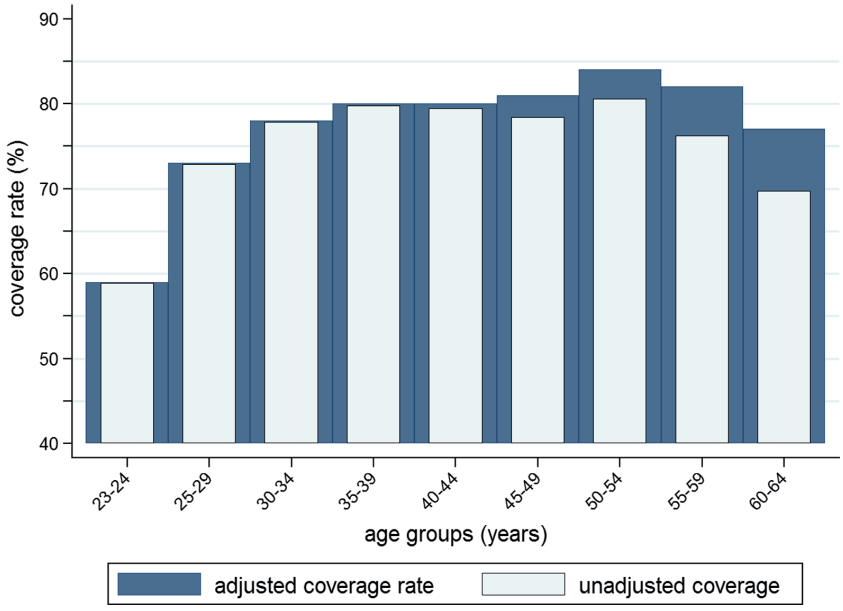

Figure 3. Effect of hysterectomies on the calculated cervical cancer screening coverage: unadjusted and hysterectomy-adjusted age-specific screening coverage for women aged 23–64 years alive on 31 December 2010. Unadjusted overall screening coverage (23–64 years): 76%, adjusted: 79%. Hysterectomy-adjusted screening coverage was calculated using the observed proportion of women with a hysterectomy, with incomplete data for women born between 1946 (age 64 years) and 1951 (age 59 years).

< 65 years (10.3 vs. 11.4 per 100 000 WY), and 67% higher in older women (16.5 vs. 27.5 per 100 000 WY). In Finland, the adjusted overall incidence of cervical cancer in the 1990s was about 11% higher than the unadjusted rate, with an 18% difference in women aged 50–59 years (7.6 vs. 6.5 per 100 000 WY) [20]. In England and Wales, the calculated overall incidence of cervical cancer in 1992 increased by 14% (14.4 vs. 12.6 per 100 000 WY) [21]. However, different time periods, data sources, inclusion criteria, and assumptions suggest caution in comparing these results. In any case, it is clear that the risk of women to undergo a hysterectomy depends on which country they live in. Therefore, the importance of accounting for hysterectomies in calculating cervical cancer statistics may be country-specific, and should be supported by local data.

In 1983, Andersen et al. estimated for Denmark that the proportion of women with a hysterectomy was increasing until age around 60 years (cohorts born around 1923), when it reached ca. 12%, and decreased thereafter [8]. However, that study was small (n = 1058), used self-reported data, and could not cover the recent increases in hysterectomies in older women. Other authors more recently studied the frequency of hysterectomy in the Danish population [11,12,22]. Those studies differed from ours in the definitions of both their numerators and denominators. Regarding numerators, the recent studies were based on hysterectomies for benign reasons including all subtotal hysterectomies (22% of all hysterectomies for benign reasons in 1998) [11], and probably included relatively few radical hysterectomies. In our study, hysterectomies that were undertaken as treatment for cancers that were not cervical (often undertaken as radical hysterectomies) were retained in the numerators because in Denmark, these women may cease with cervical cancer screening [4]. Regarding denominators, earlier studies included total populations, whereas we included only women with cervix uteri, and the standard populations to compare trends were also different.

Unlike several other studies that relied on self-reported hysterectomy information [6,8,9,23], our data were retrieved from national registers and could therefore not suffer from subjective recall. Hysterectomies registered as clearly subtotal were excluded from the analysis. Nevertheless, some subtotal laparoscopic hysterectomies probably remained in the selection, as they could not be distinguished in the register data from the total laparoscopic hysterectomies. Laparoscopic hysterectomies started being registered in 1995. They accounted for only around 6% of all hysterectomies for benign reasons by 2009, and thereafter their numbers increased [12]. As the NPR has been considered satisfactorily complete in registration of hysterectomies [24,25], the likelihood of misclassification of WY into pre- and post-hysterectomy must have been small, except in migrants (who represent up to 10% of the female population based on the proportion of women not born in Denmark) and older women. With 34 years of registration covered in our analysis, the data were insufficient to estimate the true proportion of women

with a hysterectomy at age >58 years in 2010. For the eldest birth cohorts, we assumed that 16% of women underwent a hysterectomy based on the proportions observed for cohorts born in 1939 or later. With an increasing incidence of hysterectomy in older women, this extrapolation might have led to a conservative estimate.

In conclusion, unlike in some other countries, hysterectomies do not have a large overall impact on the calculated Danish cervical cancer incidence and screening coverage. Nevertheless, in women aged 70 years or above, the hysterectomy-adjusted rates would increase by up to approximately 20% compared to the unadjusted rates. This suggests that calculating disease risks per organ-years may have a role in understanding the true burden of the disease in a population at risk of developing that disease.

Acknowledgements

SHN and MR were supported by the Danish Strategic Research Council (grant number: 10–092793). The funder had no role in the study design, in the collection, analysis, and interpretation of the data, in the writing of the report, and in the decision to submit the article for publication. The researchers worked independently of the funders.

Declaration of interest: JUHL and SHN declare no conflicts of interest. EL and MR participate in a trial evaluating four HPV assays involving collaboration with Genomica, Hologic/Gen-Probe, Roche, and Qiagen. EL has served as an unpaid advisor to Hologic/Gen-Probe and Norchip. MR and her former employer received honoraria from Qiagen for lectures on her behalf. None of the authors was compensated for their work on this project, holds stock, or received bonuses from any of the manufacturers.

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