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Increasing incidence and survival of corpus uteri cancer in Estonia over the past two decades

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ABSTRACT

Background: Corpus uteri cancer has become the fourth most common female cancer in Europe. In Estonia, the prevalence of obesity is increasing, and corpus uteri cancer survival has been relatively low. The aim of the study was to evaluate incidence, mortality and survival trends of corpus uteri cancer in Estonia by age, stage and histological subtypes with an emphasis on surgical treatment.

Methods: Estonian Cancer Registry data on incident cases of corpus uteri cancer were used to examine incidence trends (1995–2016) and calculate relative survival ratios (RSR) (1996–2016). Cases were classified by morphology and FIGO stage. Causes of Death Registry data were used to analyse corrected mortality (1995–2017).

Results: A total of 4281 cases were diagnosed in 1996–2016. A significant increase was seen in age-standardized incidence from 2009, while mortality remained stable throughout the study period. Significant increases were observed for type I cancers and age groups ≥65 years. Overall age-standardized 5-year RSR improved from 70% in 1996–2002 to 78% in 2010–2016. Survival increased for type I cancers, all age groups and all stages (significantly for stage IV). The proportion of surgically treated cases increased significantly from 85% to 89%, with the largest increases seen in older age groups and later stages.

Discussion: The rising corpus uteri cancer incidence in Estonia is driven by the type I cancer trend. Survival gain for later stages and older age groups likely reflected more frequent surgical treatment. To reduce mortality, further efforts are necessary to ensure appropriate care for all patients.

1. Introduction

Corpus uteri cancer was the most common gynecological malignancy in Estonia in 2015 (age-standardized (world) incidence rate (ASIR) 17/100 000 per year) [1]. Globally, the respective rate varies considerably, from below 5/100 000 in some regions of Africa and Asia to over 20/100 000 in Europe and North America [2]. In Europe, corpus uteri cancer is the fourth most common cancer in women (ASIR 16/100 000 per year) [2]. A recent analysis showed decreasing mortality in most European countries for women born before 1940, but not for later birth cohorts [3]. Corpus uteri cancer survival is relatively good: the European average 5-year relative survival in EUROCARE-5 (2000–2007) was 76% (70% in Estonia) [4]. In the US, the latest 5-year survival (2008–2014) was as high as 81% [5]. In the treatment of corpus uteri cancer, multidisciplinary approach has been adopted, whereas surgical treatment has remained the cornerstone of treatment [6].

The majority of corpus uteri cancers consist of endometrial cancers (EC) that are divided into two main subtypes, based on tumour aetiology, histology, prognosis and biomarkers [7,8]. Type I EC is associated with being overweight and obesity and includes mostly endometrioid histology. The etiological factors of type II have not been well established. These tumours have non-endometrioid histology and are mostly oestrogen independent [7,8].

Being overweight has been established as one of the main risk factors for EC [9]. Nulliparity, oestrogen-alone hormone replacement therapy and diabetes as a consequence of being overweight have also shown an unfavourable effect on EC incidence [10].

Abbreviations: APC, annual percent change; ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; CI, confidence interval; EC, endometrial cancer; ECR, Estonian Cancer Registry; NOS, not otherwise specified; RSR, relative survival ratio

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Table 1
Incident cases of corpus uteri cancer by age, morphology and stage in Estonia, 1996–2016.

	Total		1996–2002		2003–2009		2010–2016		
	No	%	No	%	No	%	No	%	p-value[a]
Total	4281	100	1322	100	1366	100	1593	100	
Microscopic verification	4185	98	1297	98	1336	97	1552	97	0.217
Death certificate only	9	0	2	0	0	0	7	0	0.163
Autopsy	29	1	9	1	12	1	8	1	0.528
Age at diagnosis (years)									
< 55	866	20	302	23	277	20	287	18	0.001
55–64	1202	28	404	31	370	27	428	27	0.028
65–74	1298	30	416	31	424	31	458	29	0.111
≥75	915	21	200	15	295	22	420	26	< 0.001
Morphology									
Type 1	3268	76	859	65	1062	78	1347	85	< 0.001
Type 2	478	11	224	17	148	11	106	7	< 0.001
Other	535	12	239	18	156	11	140	9	< 0.001
FIGO stage[b]									
I	2614	61	822	63	749	55	1043	66	0.058
II	466	11	144	11	216	16	106	7	< 0.001
III	479	11	130	10	174	13	175	11	0.307
IV	414	10	148	11	131	10	135	8	0.010
Unknown	272	6	67	5	84	6	121	8	0.006
Surgery done[b]	3672	86	1109	85	1158	86	1405	89	< 0.001

[a] two-sided p-value comparing proportions from first to last period.
[b] death certificate only and autopsy cases excluded.

In view of the increasing prevalence of obesity [11] and previously reported relatively low survival compared to other European countries [4], an in-depth analysis of the epidemiological trends of corpus uteri cancer in Estonia was warranted.

The aim of the study was to evaluate the incidence, mortality and survival trends of corpus uteri cancer in Estonia by age, stage and histological subtypes with an emphasis on surgical treatment.

2. Materials and methods

Data on incident cases of corpus uteri cancer (International Classification of Diseases, 10th Edition, code C54) diagnosed in 1996–2016 were obtained from the Estonian Cancer Registry (ECR), a population-based registry that covers the whole country with a population of 1.3 million (2011 census) and has data since 1968. Age at diagnosis was categorized into four groups: < 55, 55–64, 65–74 and ≥ 75 years. Morphology was classified into three types based on International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3): type I (mainly endometrial adenocarcinoma, endometrioid carcinoma, mucinous carcinomas); type II (mainly serous carcinomas, clear cell carcinomas, carcinosarcomas); other (sarcomas, other and unspecified histologic types, and cases with no microscopic verification (n = 96)). Pathological or clinical stage reported by clinicians and/or pathologists on notification forms according to the Union for International Cancer Control TNM classification for malignant tumours was coded to International Federation of Gynecology and Obstetrics (FIGO) (2009) stage. All patients with surgical treatment reported to the ECR, regardless of intention, were considered as surgically treated. The passive nature of reporting did not allow to distinguish between "surgical treatment not done" and "surgical treatment not reported". Two-sided p-values were used to compare proportions.

For survival analysis, we used data on all cases of corpus uteri cancer diagnosed in Estonia during 1996–2016, regardless of cancer sequence. The patients were followed up for vital status until December 31, 2016 via linkage with the Estonian Population Registry; in case of death or emigration, the respective date was ascertained. The linkage was done using unique personal identification numbers. Death certificate only cases and those diagnosed at autopsy were excluded from survival analyses. Patients who were diagnosed and died on the same day were included with one day of survival time.

Relative survival ratios (RSR) with 95% confidence intervals (CI) were calculated as the ratio of the observed survival to the expected survival of the underlying general population. The latter estimate was calculated according to the Ederer II [12] method using national life tables for the female population stratified by single year of age and calendar year. Cohort analysis was used to estimate five-year RSRs for patients diagnosed in 1996–2002 and 2003–2009. Period analysis was used for 2010–2016. The International Cancer Survival Standards were used for age-standardizing overall RSRs [13]. All calculations were conducted with STATA 14.1 (StataCorp LP, College Stations TX USA); survival analysis was performed using the *strs* module.

Age-standardized (world standard [14]) and age-specific incidence trends were analysed for 1995–2016 and mortality trends for 1995-2017. Data on corpus uteri cancer deaths were obtained from the Causes of Death Registry; population denominator data from Statistics Estonia.

In interpreting mortality trends, causes of death recorded as uterine cancer not otherwise specified (NOS) can be a major obstacle [3,15]. To correct for these errors, we used the reallocation rule suggested by Loos et al, under the assumption that cause of death NOS was allocated at random and the proportion of NOS of all uterine cancers was ≤25% [3,15].

Joinpoint analysis with Joinpoint Regression Program (version 4.1.1.1) from the Surveillance Research Program of the US National Cancer Institute (http://surveillance.cancer.gov/joinpoint/) was used to model the rates and calculate the estimated annual percent change (APC) with 95% CI. The default maximum number of joinpoints recommended by the program for the number of datapoints available in our study was five; permutation test was used to assess the statistical significance of the APCs, where APC is significantly different from zero at alpha = 0.05.

The study protocol was approved by the Tallinn Medical Research Ethics Committee.

3. Results

In total, 4281 cases of corpus uteri cancer were diagnosed in Estonia in 1996–2016 (Table 1). The overall percentage of microscopic verification was 98% and this quality indicator remained stable over the study period. Mean age at diagnosis increased from 63 years in

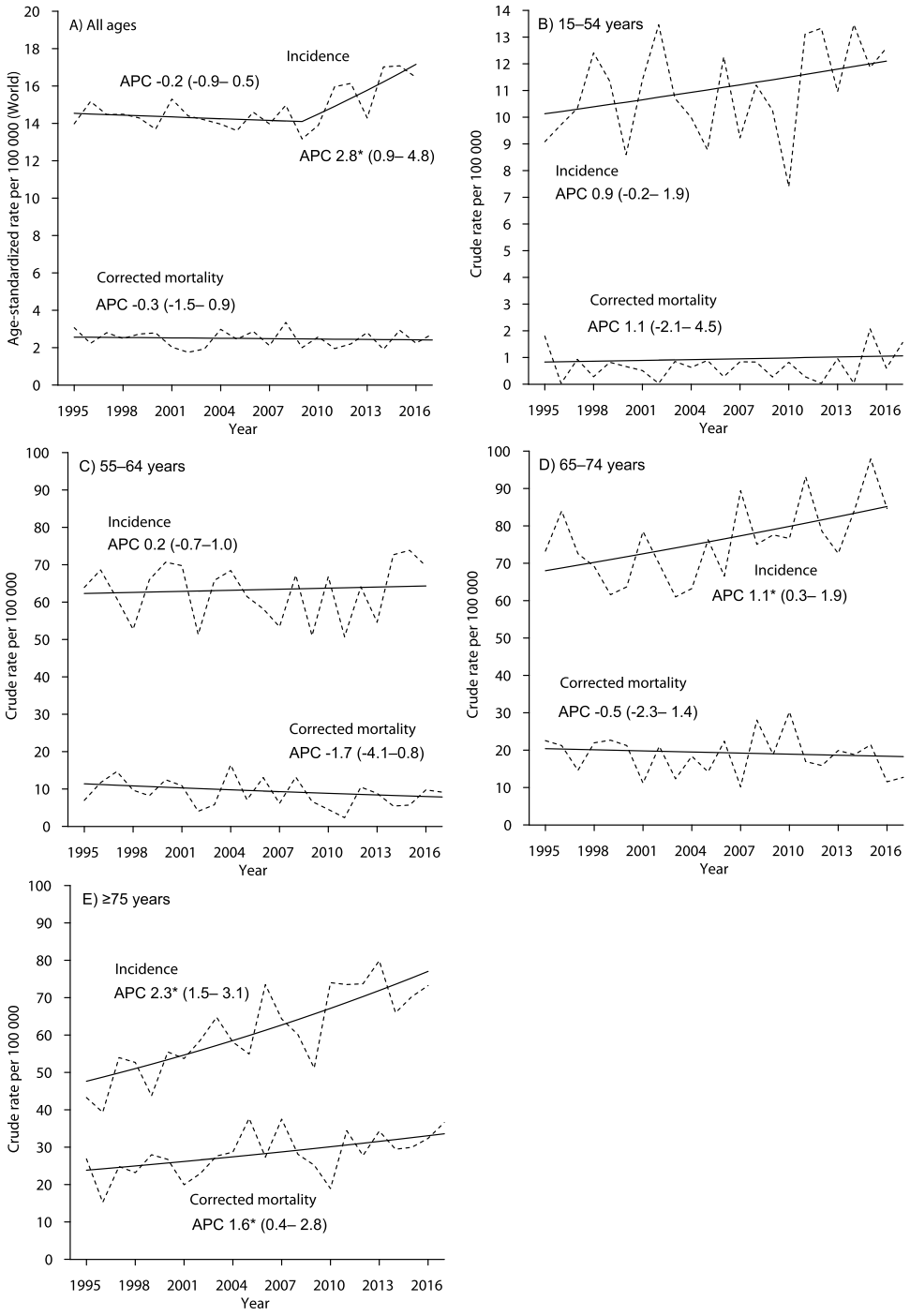

Fig. 1. Observed (dotted line) and modelled (solid line) rates and annual percentage change (APC) for trends in incidence (1995–2016) and corrected mortality (1995–2017) of corpus uteri cancer in Estonia. A): All ages; B): age 15–54 years; C): age 55–64 years; D): age 65–74 years; E): age ≥75 years. *The APC is significantly different from zero at alpha = 0.05.

1996–2002 to 66 years in 2010–2016. The proportion of women age ≥75 years increased from 15% to 26%. Type I cancers accounted for 65% of the cases in the earliest period and 85% in the latest period. The proportions of type II and other cancers decreased accordingly. Stage distribution showed a trend towards earlier stages as the proportion of stage IV decreased from 11% to 8%. The proportion of surgically treated cases increased significantly from 85% to 89%.

For all ages combined, corpus uteri cancer incidence rates were stable from 1996 to 2009, then increased at a rate of 2.8% per year from 2009 to 2016 (Fig. 1A). Over the study period, a slight increase in incidence (APC 0.9) in age group 15–54 (Fig. 1B) and stable incidence in age group 55–64 (Fig. 1C) were observed. In age groups 65–74 (Fig. 1D) and ≥75 years (Fig. 1E), significant increase was seen over the entire study period (APC 1.1 and 2.3, respectively).

By histology, type I cancers showed a significant increase (APC 2.4), while the ASIR of type II and other tumours decreased significantly (APC -6.2 and -4.3, respectively) (Fig. 2).

The overall age-standardized corrected mortality showed a stable trend (APC 0.3) over the study period (Fig. 1A). The youngest age group 15–54 showed slightly increasing trend (APC 1.1) with small number of cases per year (Fig. 1B). Modestly declining and stable mortality trends were observed for age groups 55–64 (Fig. 1C) and 65–74 (Fig. 1D),

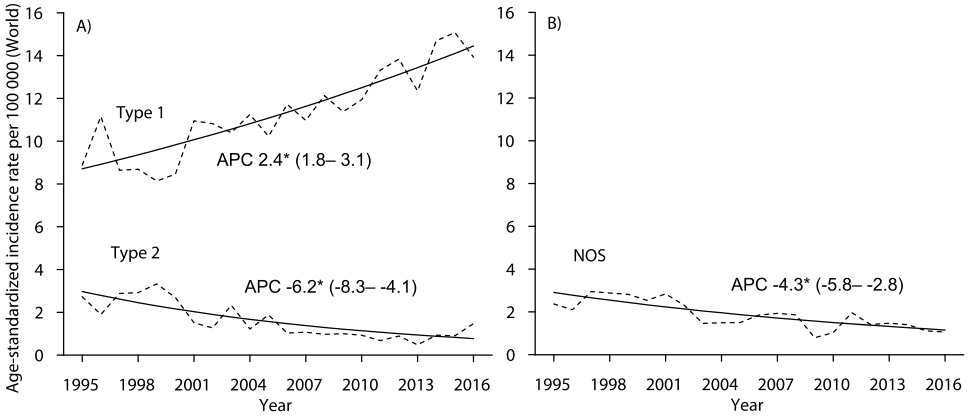

Fig. 2. Observed (dotted line) and modelled (solid line) rates and annual percentage change (APC) for trends in incidence (1995–2016) of corpus uteri cancer in Estonia by histological subtypes. A): Type I and Type II; B): not otherwise specified (NOS). *The APC is significantly different from zero at alpha = 0.05.

Table 2
Five-year relative survival ratio (RSR) for corpus uteri cancer by age, morphology and stage in Estonia, 1996–2016.

	1996–2002		2003–2009		2010–2016		
	5-year RSR	95% CI	5-year RSR	95% CI	5-year RSR	95% CI	Change[a]
Total	75	72–77	73	70–76	79	77–82	+4
Total (age-standardized)	70	65–74	70	66–74	78	76–81	**+8**
Age at diagnosis (years)							
< 55	89	84–92	89	84–92	95	92–98	+6
55–64	81	76–85	78	73–82	84	79–87	+3
65–74	66	60–71	72	66–77	76	71–80	+10
≥75	56	45–66	52	44–60	66	58–73	+10
Morphology (age-standardized)							
Type 1	79	74–84	80	76–83	85	82–88	+6
Type 2	63	54–70	42	33–49	49	38–59	−14
Other	52	45–59	40	32–48	34	28–41	−18
FIGO stage (age-standardized)							
I	88	82–92	88	83–92	95	90–97	+7
II	73	60–82	75	67–82	81	70–88	+8
III	52	39–63	49	42–56	57	49–64	+5
IV	11	7–18	15	10–22	27	19–36	**+16**
Unknown	45	32–58	53	42–63	53	44–60	+8
Surgery done (age-standardized)	82	77–86	79	76–83	86	83–89	+4

[a] From first to last period; statistically significant findings in bold.

respectively. A significant increase was seen in the eldest age group (APC 1.6) (Fig. 1E). The total number of deaths (corrected) was 46 in 1995 and 57 in 2017.

The overall age-standardized 5-year RSR increased significantly from 70% in 1996–2002 to 78% in 2010–2016 (Table 2). Larger increase was seen in older age groups. The gap between the oldest and youngest age group remained 29 percentage units in 2010–2016. Type I cancers showed a slight increase in 5-year RSR from 79% to 85% and type II cases showed a decrease from 63% to 49%. By stage, the improvement in survival was significant for stage IV (from 11% to 27%). The 5-year RSR for surgically treated patients reached 86% in 2010–2016.

The proportion of surgically treated patients increased significantly for age groups 65–74 and ≥75, for type I cancers and for all stages except stage II (Table 3), reaching or exceeding 90% for all age groups except patients age ≥75 years, and all stages except stage IV.

Table 3
Proportion of surgically treated corpus uteri cancer patients by age, morphology and stage, Estonia 1996–2016.

	Total	1996–2002	2003–2009	2010–2016	p-value[a]
Age at diagnosis (years)					
< 55	94	94	92	94	0.733
55–64	93	93	93	94	0.528
65–74	86	82	86	90	< 0.001
≥75	71	58	69	79	< 0.001
Morphology					
Type 1	91	89	90	92	0.005
Type 2	85	86	84	85	0.832
Other	62	69	54	60	0.084
FIGO stage					
I	95	93	94	96	0.018
II	91	89	91	93	0.223
III	90	86	87	95	0.004
IV	55	49	53	65	0.010

[a] two-sided p-value comparing proportions from first to last period.

4. Discussion

The study showed a significant increase in overall incidence of

corpus uteri cancer in Estonia since 2009. This trend derives from patterns seen in type I EC incidence and those of elderly women. Mortality has been stable over the study period. Relative survival improved for type I EC as well as for all age and stage groups. A significant increase was seen in the proportion of surgically treated patients, particularly among older women and later stages.

The main strength of the study was the use of high-quality data from a nation-wide cancer registry. We were able to categorise stage according to the FIGO classification. Stage-specific survival estimates may be somewhat influenced by stage migration due to a more thorough diagnostic workup in the later periods. More advanced pathological diagnostics i.e. immunohistochemistry have made diagnosis more accurate over time and the misdiagnosis of ovarian or endometrial serous carcinomas and undifferentiated carcinomas has probably decreased. Therefore, the incidence and survival of type II EC was likely overestimated in the 1990s. Possible misclassification of corpus uteri cancer as unspecified should be considered, but the total number of incident cancer cases coded as "Uterus, NOS" (ICD-O-3 C55.9) was only 50 over the study period. As one weakness of the study, we were not able to take into account the proportion of hysterectomised women in the population. The annual hysterectomy rate in Estonia decreased from 239 per 100 000 in 2004 to 205 per 100 000 in 2011 [16]. The majority (76%) of hysterectomies were performed among women aged 35–54, mostly due to leiomyomas (64%), female genital prolapse (9%) and endometriosis (9%) [16]. The incidence rates of corpus uteri cancer may thus be somewhat underestimated.

Among risk factors of EC [10], the increasing prevalence of being overweight and obesity are considered as the main reasons for the increasing burden of this cancer. Recent Global Burden of Disease estimates showed that the prevalence of obesity in Estonian women age 20 years and over increased from 19% in 1980 to 26% in 2015 [17]. Excess body weight leads to alterations in sex hormones' metabolism and hyperestrogenemia is found to be a risk factor for the development of EC both in premenopausal and postmenopausal age [18].

The overall incidence trend in Estonia has been driven by the increasing incidence of type I EC, while the incidence of type II EC has decreased. Diverse trends by EC subtypes were first described in the UK in 2007 [19] and the rising pattern of type I EC was suggested to be associated with the rising prevalence of obesity.

The distribution of EC by histologic type (85% type I in 2010–2016) is similar to previous findings in Denmark [20] and Norway [21]. However, the trend of type II cancers has shown a slightly increasing pattern in both Nordic countries [20,21], contrary to our findings. The evolved pathological diagnostics might play a role here as mentioned above.

The age-specific incidence trends seen in Estonia are consistent with those observed in other countries, with larger increases in older women [19,22]. The incidence in women of fertile age has been stable over the recent decades in Estonia and elsewhere [22,23]. These findings are in line with the growing proportion of elderly women as the number of cases in age group ≥75 years has nearly doubled over the study period. Older women tend to present with more aggressive histological subtypes (type II EC) and more advanced stages at diagnosis [24,25]. Indeed, the proportion of type II EC (2010–2016) was 2% in age group < 55 and 8% in age groups 65 and older; and the proportion of stage IV disease increased from 4% in the youngest to 10% in the oldest age group (data not shown).

The shift towards earlier stages was probably associated with the increasing proportion of type I EC. Type I and type II EC have clinically different behaviour. Irregular vaginal bleeding is commonly the first sign of type I disease [8] that contributes to an early diagnosis. Type II EC generally has no specific symptoms at the early stage, which results in almost half of the cancers being diagnosed at more advanced stages [26]. In 2010–2016, 21% and 23% of type II cancers were diagnosed at stages III and IV, respectively (11% and 6% of type I, data not shown).

In most European countries, mortality of corpus uteri cancer has been continuously declining over the past decades, despite increasing incidence, due to better access to health care, safer surgery and more frequent use of chemotherapy [3]. The reasons why corpus uteri cancer mortality has not started to decline in Estonia should be studied further.

Corpus uteri cancer survival improved significantly over the study period and the 5-year RSR reached 78% in 2010–2016. It still remained lower than the latest estimates observed in Norway (84%), Denmark (83%) [27] or in the US (81%) [5]. Type I EC cancers had more favourable prognosis and the 5-year RSR of 85% in 2010–2016 was equal to that seen in the Netherlands (2005–2009) [28]. The latest survival difference between two EC types (36 percentage units) was similar to the finding in Norway (38 percentage units in 2001–2009) [20] and can be explained by the tumours' clinical behaviour [26]. The survival increase of type I EC could be well explained by more accessible and more affordable treatment modalities. The Norwegian study found the latest treatment-related changes to be an independent prognostic factor for improved survival [21]. The decrease in type II EC survival in Estonia was unexpected and likely due to the diagnostic difficulties mentioned above. The latest 5-year RSR of 46% is comparable to previously published data from the UK [19] and Norway [21].

Younger women tend to have better corpus uteri cancer survival. The latest 5-year RSR of 95% in age group < 55 years is comparable to the estimates seen in the Nordic countries (between 88–96%) [27]. The majority of cancers developing at that age are type I EC and their clinical behaviour and medical management at early stages lead to prolonged survival [29]. For age groups 65–74 and ≥ 75 years, the 5-year survival estimates in Estonia in 2010–2016 (76% and 66%) remained lower than those observed in the Netherlands in 2005–2009 (81% and 76%) [28], despite an increase of 10 percentage units in both age groups. Data from the Nordic countries show an improvement of survival of older women over the past two decades and the latest estimates for 5-year relative survival are between 77–83% for women age 70–79 years and between 70–82% for women age 80–89 years [27]. Older women present with higher proportions of type II and more high-grade type I EC which have a dismal prognosis compared to type I cancers with low and moderate grade histologies [25]. Advanced age and comorbidities might limit clinical management of the disease due to poor treatment tolerance and unacceptable toxicities, which may lead to poorer treatment outcomes and higher mortality [30,31]. Estonian women with cancer were shown to have more comorbidities than their counterparts from several other European countries [32]. Early stage low grade EC patients have been shown to be more likely to die due to cardiovascular disease rather than cancer itself [33]. Better management of comorbidities would probably contribute to further survival gain.

Stage I 5-year RSR (95%) in Estonia is comparable to countries with high quality cancer care such as Norway (86%) [21] and the US (95%) [5]. In this study, the latest 5-year RSR was 57% for stage III and 27% for stage IV. The respective estimates were 38% and 9% in Norway [21]. Improved clinical management – modern surgical techniques and the availability of radiotherapy and chemotherapy – have likely had a favourable impact on the survival for advanced stages.

Surgery has been proven to be the strongest clinical prognostic factor for EC patients [34]. Unfortunately, we did not have information about the intent of treatment. Even though the aim of surgical treatment should be radical surgery or optimal cytoreduction at later stages, it has been found that any surgical attempt with hysterectomy is a favourable prognostic factor regardless of stage, age and histology [34,35]. Laparoscopic surgery has become a standard approach for early EC, constituting 54% of radical hysterectomies performed in Estonia in 2017 (data not shown). Our study observed a large increase in surgical treatment, especially among older age groups and later stages, suggesting an association with improved survival among these patient groups. Better preoperative assessment and management of comorbidities have likely played a role in increased surgical treatment rates.

A more detailed analysis of corpus uteri cancer management in

Estonia is warranted. Adherence to international guidelines for the management of endometrial hyperplasia [36] has not been studied in Estonia; better adherence would contribute to the prevention and early detection of corpus uteri cancer. More attention should be paid to following nation-wide standardised patient pathways to ensure appropriate waiting times [37]. A detailed analysis of the use of multimodality treatment according to international guidelines would help to clarify the reasons behind the observed trends in survival and mortality.

5. Conclusions

The recent strong rise in incidence was mainly driven by the changes in type I EC and older age groups. The increasing burden of obesity in Estonia is the most likely reason behind these trends and thus, continuing efforts are necessary to tackle obesity and to increase the awareness of corpus uteri cancer risk associated with obesity. The importance of regular gynaecological check-ups, also in the postmenopausal age, should be emphasised to encourage early detection. Survival gains were most likely associated with increased surgical activity, and more efficient management of comorbidities, particularly in older age groups and later stages. Nevertheless, mortality has not yet turned to decline. Further steps should be taken to reduce corpus uteri cancer mortality in Estonia.

Authorship contribution statement

KO, KI and PV designed the study, KO drafted the manuscript, KI and AB performed statistical analysis, AB prepared the graphics, KO, PV, KI, AB interpreted the results. All authors (KO, PV, KI, AB and HE) critically revised the manuscript for intellectual content and approved the final manuscript.

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Declaration of Competing Interest

None declared.

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