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Prognostic impact and causality of age on oncological outcomes in women with endometrial cancer: a multimethod analysis of the randomised PORTEC-1, PORTEC-2, and PORTEC-3 trials

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Summary

Background Numerous studies have shown that older women with endometrial cancer have a higher risk of recurrence and cancer-related death. However, it remains unclear whether older age is a causal prognostic factor, or whether other risk factors become increasingly common with age. We aimed to address this question with a unique multimethod study design using state-of-the-art statistical and causal inference techniques on datasets of three large, randomised trials.

Methods In this multimethod analysis, data from 1801 women participating in the randomised PORTEC-1, PORTEC-2, and PORTEC-3 trials were used for statistical analyses and causal inference. The cohort included 714 patients with intermediate-risk endometrial cancer, 427 patients with high-intermediate risk endometrial cancer, and 660 patients with high-risk endometrial cancer. Associations of age with clinicopathological and molecular features were analysed using non-parametric tests. Multivariable competing risk analyses were performed to determine the independent prognostic value of age. To analyse age as a causal prognostic variable, a deep learning causal inference model called AutoCI was used.

Findings Median follow-up as estimated using the reversed Kaplan-Meier method was 12·3 years (95% CI 11·9–12·6) for PORTEC-1, 10·5 years (10·2–10·7) for PORTEC-2, and 6·1 years (5·9–6·3) for PORTEC-3. Both overall recurrence and endometrial cancer-specific death significantly increased with age. Moreover, older women had a higher frequency of deep myometrial invasion, serous tumour histology, and p53-abnormal tumours. Age was an independent risk factor for both overall recurrence (hazard ratio [HR] 1·02 per year, 95% CI 1·01–1·04; p=0·0012) and endometrial cancer-specific death (HR 1·03 per year, 1·01–1·05; p=0·0012) and was identified as a significant causal variable.

Interpretation This study showed that advanced age was associated with more aggressive tumour features in women with endometrial cancer, and was independently and causally related to worse oncological outcomes. Therefore, our findings suggest that older women with endometrial cancer should not be excluded from diagnostic assessments, molecular testing, and adjuvant therapy based on their age alone.

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Introduction

Endometrial cancer is the sixth most common cancer in women worldwide, and its incidence is rising. This is in part due to ageing of the population, because endometrial cancer is mostly a disease of postmenopausal women. For decades, it has been known that older women with endometrial cancer have a poorer prognosis than younger women. 70% of deaths from endometrial cancer occur in women older than 65 years.[1] However, it remains unclear whether advanced age is an independent risk factor for cancer-specific death or whether other risk factors become increasingly common with older age. This knowledge gap might have contributed to the fact that age is not incorporated in most risk stratification systems for endometrial cancer.

To assess the prognostic impact of age, only endometrial cancer-specific outcomes need to be evaluated, because advanced age is causally associated with reduced overall survival. Nonetheless, many studies only evaluate the association between age and overall survival.[2] Moreover, studies that do investigate recurrence or endometrial cancer-specific survival often do not account for competing causes of death, which are more common in older women, possibly leading to an

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Research in context

Evidence before this study

A systematic literature search was performed in PubMed to identify original studies investigating the impact of calendar age by multivariable analysis on oncological outcomes in women with endometrial cancer. A search string based on MeSH terms and text words for the following elements was built: endometrial cancer AND age AND risk factors AND survival analysis. The search was performed on April 13, 2022. 783 articles were found, of which 108 were selected. Of those articles, five were from randomised controlled trials and 103 from prospective and retrospective cohort studies. As investigating the prognostic impact of age was not the primary objective of most studies, differences between the younger and older women in tumour characteristics and treatment were commonly observed. As a result, the question of whether endometrial cancer is intrinsically more aggressive in older patients has so far remained unanswered. Only one of the 108 included studies examined the risk of age in the context of the endometrial cancer molecular classification, which has proven prognostic impact. No studies were found that investigated the impact of age in women of all risk groups of endometrial cancer in the context of the molecular classification. Lastly, little consensus was observed between studies on the use of any cutoffs for age. About a third of the studies analysed age as a continuous variable, another third chose a cutoff value of 60 years, and the remaining studies chose a variety of cutoffs. A few studies have modelled the age–risk association and proposed different cutoffs at 55, 61, 63, and 65 years. These results make it questionable as to whether there is a single value for which the tipping point of increased risk is best represented, or whether the increased risk of age should be regarded as a continuous variable, which could be simplified by subdivision into groups of, for example, 10 years. Thus, a comprehensive study of the association between age and tumour characteristics and oncological outcomes in endometrial cancer has not yet been performed.

Added value of this study

To our knowledge, this is the first study that identified age as an independent prognostic risk factor for overall recurrence and endometrial cancer-specific death, corrected for all known clinicopathological and molecular characteristics. For the first time, age is established as a causal risk factor for worse oncological outcomes in women with endometrial cancer. Analyses showed that the risk of recurrence and cancer-specific death steadily increased up to the age of 80 years.

Implications of all the available evidence

These findings highlight the need for full diagnostic assessment of all patients, young and old, as knowing the extent of the disease and its molecular classification is crucial for predicting the risk of recurrence and death. As our findings suggest that the risk of worse oncological outcomes keeps increasing with age, older women should not be excluded from adjuvant therapy based on age alone. Future research into the pathophysiological mechanisms behind the increased risk of age is warranted.

overestimation of the impact of advanced age on prognosis.

Poorer oncological outcomes in older women with endometrial cancer could have several causes. One might be less intensive treatment. Due to comorbidities and frailty, older women are less likely to receive aggressive surgical treatment and adjuvant therapy.[3] Moreover, age alone might be considered a reason for treatment de-escalation by some physicians.[4] Hence, results of studies where treatment is given at the discretion of the physician are potentially biased. Another cause of poorer oncological outcomes in older women might be more aggressive tumour characteristics. Increasing age has been linked to a higher prevalence of serous histology, deep myometrial invasion, and high tumour grade.[4,5]

To determine whether advanced age is an independent risk factor for recurrence and cancer-related death, a comprehensive analysis correcting for all established clinicopathological and molecular risk factors is needed. To date, some studies have corrected for the established clinicopathological risk factors,[6,7] but the risk contribution of age has not been comprehensively investigated in the context of molecular classification, which has proven prognostic value.[5,8]

If age proves to be a significant independent risk factor, then quantification of the prognostic impact across age groups becomes relevant. Some studies have simplified the continuous nature of ageing into categories or even dichotomised using a cutoff value. Often, a cutoff of 60 years is used,[9,10] but no validation studies to support this arbitrary cutoff have been published.

All studies that have investigated the prognostic impact of age in endometrial cancer so far are limited by their use of methods based on statistical correlation, rather than causation. Causal inference using deep learning has been developed and tested on endometrial cancer datasets.[11] Under the assumption of a structural causal model,[12] this automated causal inference (AutoCI) technique identifies causal variables, which provides a causal re-interpretation that is supplementary to the standard statistical analysis.

Here, we address the question of whether age is an independent risk factor for endometrial cancer-specific outcomes in the context of clinicopathological and molecular characteristics, with a unique multimethod study design using state-of-the-art statistical and causal inference techniques on datasets from three large, randomised trials. We aimed to determine how endometrial cancer characteristics differ between

younger and older women, and whether advanced age is independently and causally related to worse oncological outcomes. Because there is currently no consensus in the literature on a cutoff for age, we modelled the age–risk association to determine whether a relevant threshold for older age can be defined.

Methods

Study design and cohorts

In this multimethod analysis, data from the randomised PORTEC-1, PORTEC-2, and PORTEC-3 trials were used for statistical analyses and causal inference. Design and results of all three trials have been published.[13–15]

Briefly, between June 25, 1990, and Nov 28, 1997, PORTEC-1 included 714 women with early stage, intermediate risk endometrioid endometrial cancer, and randomly allocated them adjuvant external beam radiotherapy (EBRT) or no adjuvant therapy. Inclusion criteria were postoperative International Federation of Gynecology and Obstetrics (FIGO) 1988 stage I disease that was either grade 1 with deep (≥50%) myometrial invasion, grade 2, or grade 3 with less than 50% myometrial invasion. EBRT was administered to the pelvic region according to a standardised protocol. The total dose was 46 Gy using 2 Gy daily fractions, 5 days a week. The radiation was delivered by anteroposterior and posteroanterior parallel ports, or a three-field technique, or a four-field box technique. Patients were stratified by radiation oncology centre and depth of myometrial invasion (<50% *vs* ≥50%).

The PORTEC-2 trial included 427 women from May 27, 2002, to Sept 25, 2006, with endometrioid endometrial cancer with high-intermediate risk features, who were randomly allocated to either EBRT or vaginal brachytherapy. Inclusion criteria were age above 60 years and FIGO 1988 stage IC and grade 1–2 disease; age above 60 years and stage IB, grade 3 disease; or any age with stage IIA disease (except grade 3 disease with >50% myometrial invasion). Patients allocated to EBRT received the same dose as in PORTEC-1 (46 Gy using 2 Gy daily fractions, 5 days a week). However, it was delivered through computerised treatment planning with three-dimensional conformal or multiple field techniques, with individual shielding in all fields. Vaginal brachytherapy was delivered with a vaginal cylinder with either a low-dose or high-dose rate with a dose equivalent to 45–50 Gy to the vaginal mucosa. Patients were stratified by participating centre, stage, brachytherapy (low-dose *vs* high-dose rate), and patient age (<60 years *vs* ≥60 years).

The PORTEC-3 trial recruited 660 women between Nov 23, 2006, and Dec 20, 2013, with high-risk stage I–III endometrial cancer who were randomly allocated to chemoradiation or EBRT. The PORTEC-3 entry criteria were FIGO 2009 stage IA, grade 3 endometrioid endometrial cancer with lymphovascular space invasion (LVSI); stage IB, grade 3 endometrioid endometrial cancer; stage II–IIIC endometrioid endometrial cancer; or stage I–III endometrial cancer with serous or clear cell histology. EBRT was given to a total dose of 48·6 Gy, using 1·8 Gy fractions, 5 days a week. The clinical target volume included the proximal vagina, parametrial tissues, and internal, external, and common iliac lymph node regions up to the upper S1 level (the level of promontory). The clinical target volume was extended for lymph node involvement. In case of cervical involvement, a brachytherapy boost was given. Patients allocated to chemoradiation also received two cycles of intravenous cisplatin 50 mg/m² in the first and fourth week of EBRT, followed by four cycles of intravenous carboplatin AUC5 and paclitaxel 175 mg/m² at 21-day intervals. Patients in the PORTEC-3 trial were stratified by participating centre, lymphadenectomy, stage, and histology.

All three trial protocols were approved by the Dutch Cancer Society and the medical ethics committees at participating centres. All patients provided informed consent.

Procedures

Standard follow-up in all three trials consisted of obtaining patient history with special emphasis on treatment-related morbidity, and a physical and pelvic examination. A chest radiograph, blood count, and chemistry tests were to be obtained annually. All other forms of follow-up, such as vaginal smears or biopsy samples, were only taken on indication.

In the PORTEC-1 and PORTEC-2 trials, central pathology review on whole slides of formalin-fixed paraffin-embedded tumour tissue was done after randomisation to assess stage (FIGO 1988), histotype, grade, and LVSI. For both studies, LVSI, defined as the presence of tumour cells within endothelial-lined channels outside of the main tumour, was scored using a three-tiered quantification system (none *vs* focal *vs* substantial). In the PORTEC-3 trial, up-front central pathology review was performed to assess stage (FIGO 2009), histotype, grade, and LVSI (two-tiered: absent *vs* present). For the current study, all cases included in the PORTEC-1 and PORTEC-2 trials were restaged according to FIGO 2009 using prospectively registered variables on tumour invasion and extension from the trial databases. The LVSI variable was aligned across the trials by dichotomisation into absent (none and focal for PORTEC-1 and PORTEC-2 patients) versus present (substantial for PORTEC-1 and PORTEC-2). Assignment of the molecular class of endometrial cancer was performed according to the WHO 2020 classification of female genital tumours, with assigners masked to histotype and clinical outcome. More details can be found in the appendix (p 3).

See Online for appendix

Outcomes

Uniform registration of oncological endpoints was performed across the three PORTEC trials. Primary endpoints for the current study were overall recurrence and endometrial cancer-specific death. Secondary

	PORTEC-1 (n=714)	PORTEC-2 (n=427)	PORTEC-3 (n=660)	Total (n=1801)
Age at randomisation, years	66 (59–73)	69 (65–75)	62 (56–68)	66 (60–72)
<60 years	200 (28·0%)	32 (7·5%)	268 (40·6%)	500 (27·8%)
60–70 years	271 (38·0%)	200 (46·8%)	295 (44·7%)	766 (42·5%)
>70 years	243 (34·0%)	195 (45·7%)	97 (14·7%)	535 (29·7%)
Lymphadenectomy				
Not performed	714 (100%)	427 (100%)	281 (42·6%)	1422 (79·0%)
Performed	0	0	379 (57·4%)	379 (21·0%)
Randomly allocated treatment				
None	360 (50·4%)*	0	0 (0%)	360 (20·0%)
Brachytherapy	0	213 (49·9%)†	0 (0%)	213 (11·8%)
External beam radiotherapy	354 (49·6%)*	214 (50·1%)†	330 (50·0%)‡§	898 (49·9%)
Chemoradiation	0	0	330 (50·0%)‡¶	330 (18·3%)
Stage (FIGO 2009)				
IA	294 (41·2%)	71 (16·6%)	78 (11·8%)	443 (24·6%)
IB	420 (58·8%)	351 (82·2%)	117 (17·7%)	888 (49·3%)
II	0	2 (0·5%)	170 (25·8%)	172 (9·6%)
III	0	3 (0·7%)	295 (44·7%)	298 (16·5%)
Histotype and grade				
Grade 1–2 endometrioid endometrial cancer	601 (84·2%)	374 (87·6%)	257 (38·9%)	1232 (68·4%)
Grade 3 endometrioid endometrial cancer	95 (13·3%)	41 (9·6%)	185 (28·0%)	321 (17·8%)
Non-endometrioid endometrial cancer	18 (2·5%)	12 (2·8%)	218 (33·0%)	248 (13·8%)
Lymphovascular space invasion				
Absent	537 (75·2%)	373 (87·4%)	271 (41·4%)	1181 (65·6%)
Present	26 (3·6%)	20 (4·7%)	389 (58·9%)	435 (24·2%)
Missing	151 (8·4%)	34 (8·0%)	0	185 (10·3%)
Molecular class				
POLE-mutated	42 (5·9%)	24 (5·6%)	51 (7·7%)	117 (6·5%)
Mismatch-repair deficient	137 (19·2%)	110 (25·8%)	139 (21·1%)	386 (21·4%)
p53 abnormal	40 (5·6%)	30 (7·0%)	99 (15·0%)	169 (9·4%)
No specific molecular profile	265 (37·1%)	232 (54·3%)	122 (18·5%)	619 (34·4%)
Missing	230 (32·2%)	31 (7·3%)	249 (37·7%)	510 (28·3%)
Oestrogen receptor status‖				
Negative	29 (4·1%)	18 (4·2%)	93 (14·1%)	140 (7·8%)
Positive	396 (55·5%)	385 (90·2%)	295 (44·7%)	1076 (59·7%)
Missing	289 (40·5%)	24 (5·6%)	272 (41·2%)	585 (32·5%)

Data are n (%) or median (IQR). *For the PORTEC-1 trial, 369 patients received no adjuvant treatment and 345 patients received external beam radiotherapy. †For the PORTEC-2 trial, 3 patients received no adjuvant treatment, 215 received brachytherapy, and 209 received external beam radiotherapy. ‡For the PORTEC-3 trial, 333 patients received external beam radiotherapy and 327 patients received chemoradiation. §158 patients received a vaginal brachytherapy boost, alongside their external beam radiotherapy. ¶151 patients received a vaginal brachytherapy boost, alongside their chemoradiation. ‖>10% nuclear oestrogen receptor expression was considered oestrogen receptor-positive.

Table 1: **Patient and tumour characteristics by PORTEC trial**

endpoints were distant metastasis, locoregional recurrence, pelvic recurrence, and vaginal recurrence. Locoregional recurrence includes both vaginal and pelvic recurrence events.

For the **smcfcs package in R** see https://cran.r-project.org/package=smcfcs

Statistical analysis

Statistical analyses were performed using SPSS version 29.0 and R version 4.3.0. Associations of age with clinicopathological and molecular features were analysed using non-parametric tests (the Mann-Whitney *U* and Kruskal-Wallis tests). For this analysis, patient age was divided into three commonly used age categories with enough patients in each subgroup: less than 60 years (n=500), 60–70 years (n=766), and more than 70 years (n=535).

Median follow-up was estimated with the reversed Kaplan-Meier method. Time-to-event was calculated from the date of randomisation to the date of recurrence, or to the date of death due to endometrial cancer. Patients who had no event were censored at the date of death due to other causes than endometrial cancer, or date of last follow-up for those alive. For the outcome endometrial cancer-specific death, the competing event was death due to other causes than endometrial cancer. For the outcomes overall recurrence and distant metastasis, the competing event was death due to any cause. For the outcomes locoregional, pelvic, and vaginal recurrence, the competing events were both death due to any cause and distant metastasis.

Cause-specific cumulative incidence functions were calculated according to the Aalen-Johansen method, as described by Putter and colleagues.[16]

Multivariable competing risk analyses were performed to determine the independent prognostic value of age as a continuous variable on the cause-specific hazard. Analyses were corrected for any confounding and differences in the composition of the three trial populations by including the following pre-defined established risk factors: FIGO 2009 stage, histotype, grade, LVSI, molecular class, and adjuvant treatment. For pelvic and vaginal recurrence, the correction for confounding was limited to stage, LVSI, molecular class, and adjuvant treatment due to the lower number of events. In addition, all models were stratified by trial (baseline hazards differ according to strata [ie, trials]) to correct for any cohort effects. The proportional hazards assumption was tested using the method of Therneau and Grabsch,[17] implemented in the cox.zph() function in R. Model fit was evaluated through time-dependent area under the receiver-operating characteristic curve (AUC) at 5-year follow-up and Brier scores for all outcomes.

Covariate data were missing in 510 (28·3%) of 1801 patients overall (230 [32·2%] of 714 in PORTEC-1, 31 [7·3%] of 427 in PORTEC-2, and 249 [37·7%] of 660 in PORTEC-3) for the molecular classification, and in 185 (10·3%) of 1801 patients for LVSI (151 [21·1%] of 714 in PORTEC-1, 34 [8·0%] of 427 in PORTEC-2, and none in PORTEC-3), and were imputed by multiple imputation using smcfcs under the missing-at-random assumption.[18,19] A sensitivity analysis using the final model for overall recurrence was performed on the non-imputed data to determine the impact of the imputation itself.

To assess linearity of the effect of age, natural splines with 3 degrees of freedom were used. Statistical significance was accepted at p values <0·01 (rather than

0·05 to limit the risk of type I error when analysing a large dataset), always using two-sided tests.

We used the automated causal inference (AutoCI) method as previously described,[11] to achieve an in-depth understanding of patient age as a causal prognostic variable for endometrial cancer clinical outcomes.

After the automatic search among differentiable layers to generate a type-safe (ie, executable) neural network, AutoCI showcased the causal variable identification given multiple interventional trials (eg, PORTEC-1 and PORTEC-2). Among several executable neural networks, researchers[11] obtained the best accuracy of identifying causal variables for toy experiments by using the two-layer architecture—ie, the combination of a multilayer perceptron and a causal weight layer (CW):

$$\mathrm{CW}_{\theta}(x)=\mathrm{mask}*\mathrm{sigmoid}(\theta)*x$$

Where mask is a binary 0-1 vector, θ a learnable weight vector normalised by sigmoid function, x is the input, and $*$ represents element-wise multiplication. Importantly, this two-layer model further outperforms the series of invariant causal prediction methods for the PORTEC experiments.[20]

Motivated by these previous findings, we here used the two-layer design and carried out the model training for the causal investigation of age variable among the PORTEC-1, PORTEC-2, and PORTEC-3 cohorts.

Following the recommendation from the AutoCI study,[11] we trained the two-layer model using the Adam optimiser at a learning rate of 0·02. The batch size was set to be 64 throughout the entire training process. More implementation detail can be found in our GitHub library.

For analysis of the causal association of patient age with clinical outcomes, we grouped the data samples into three categories: age less than 60 years, 60–70 years, and more than 70 years. The age group less than 60 years was used as the reference group. The other two age categories were both individually compared with this reference group. We then fed the age, clinicopathological, molecular, and adjuvant treatment variables to the neural network and supervised the model training with the Cox partial likelihood loss.[21] More information on the loss function can be found in our GitHub library. Depending on how the hypothetical exclusion of a given variable would have impacted the likelihood computation, measured with the maximum of Fréchet inception distance on PORTEC-1, PORTEC-2, and PORTEC-3 data samples, we determined its causal association to the relevant endometrial cancer outcome.[22]

To achieve reliable causal identification and hazard ratio (HR) computation, we conducted each experiment by repeatedly and randomly launching the training process 16 times for each endpoint of interest. As there is no consensus on the exact number of random seeds required for retraining the model, 16 epochs was chosen to strike a balance between training reproducibility and efficiency. Due to the non-linear nature of the neural network, we then used the (mean) gradient of input variables to compute the HR. Subsequently, the 95% CI and p value are reported based on the gradients collected from training the model 16 times. An in-depth explanation can be found in the appendix (pp 3–4).

	<60 years (n=500)	60–70 years (n=766)	>70 years (n=535)	p value
Randomly allocated treatment	..	..	..	<0·0001*
None	107 (21·4%)	135 (17·6%)	118 (22·1%)	..
Brachytherapy	16 (3·2%)	93 (12·1%)	104 (19·4%)	..
External beam radiotherapy	249 (49·8%)	386 (50·4%)	263 (49·2%)	..
Chemoradiation	128 (25·6%)	152 (19·8%)	50 (9·3%)	..
Stage (FIGO 2009)	..	..	..	<0·0001*
IA	150 (30·0%)	177 (23·1%)	116 (21·7%)	..
IB	153 (30·6%)	383 (50·0%)	352 (65·8%)	..
II	70 (14·0%)	83 (10·8%)	19 (3·6%)	..
III	127 (25·4%)	123 (16·1%)	48 (9·0%)	..
Histotype and grade	..	..	..	<0·0001*
Grade 1–2 endometrioid endometrial cancer	318 (63·6%)	512 (66·8%)	402 (75·1%)	..
Grade 3 endometrioid endometrial cancer	113 (22·6%)	139 (18·1%)	69 (12·9%)	..
Serous endometrial cancer	30 (6·0%)	58 (7·6%)	37 (6·9%)	..
Clear cell endometrial cancer	24 (4·8%)	28 (3·7%)	14 (2·6%)	..
Other†	15 (3·0%)	29 (3·8%)	13 (2·4%)	..
Myometrial invasion‡	..	..	..	<0·0001§
<50%	231 (46·4%)	241 (31·5%)	132 (24·7%)	
≥50%	267 (53·6%)	524 (68·5%)	403 (75·3%)	
LVSI¶	..	..	..	<0·0001§
None or focal‖	288 (64·6%)	495 (71·4%)	398 (83·4%)	..
Substantial or any	158 (35·4%)	198 (28·6%)	79 (16·6%)	..
Molecular class**	..	..	..	<0·0001*
POLE-mutated	63 (18·6%)	33 (6·1%)	21 (5·2%)	..
Mismatch-repair deficient	108 (31·9%)	160 (29·4%)	118 (29·0%)	..
p53 abnormal	23 (6·8%)	87 (16·0%)	59 (14·5%)	..
No specific molecular profile	145 (42·8%)	265 (48·6%)	209 (51·4%)	..
Oestrogen receptor status††	..	..	..	0·79§
Negative	32 (10·8%)	68 (13·0%)	40 (10·1%)	..
Positive‡‡	265 (89·2%)	454 (87·0%)	357 (89·9%)	..

Data are n (%). FIGO=International Federation of Gynecology and Obstetrics. LVSI=lymphovascular space invasion. *Kruskal-Wallis test. †Other: mixed endometrioid and clear cell endometrial cancer, or mixed serous and clear cell endometrial cancer, or mucinous adenocarcinoma, or carcinosarcoma, or undifferentiated. ‡3 missing. §Mann-Whitney *U* test. ¶185 missing. ‖For the PORTEC-1 and PORTEC-2 trials, LVSI was scored using a three-tiered system (none, focal, or substantial LVSI); for the PORTEC-3 trial, LVSI was scored as none or any; for this analysis, LVSI was dichotomised into none or focal *vs* substantial or any. **510 missing. ††585 missing. ‡‡>10% nuclear oestrogen receptor expression was considered oestrogen receptor-positive.

Table 2: **Clinicopathological and molecular characteristics by age in the combined cohort**

Role of the funding source

There was no funding source for this study.

Results

All 1801 women of the intention-to-treat populations of the PORTEC-1, PORTEC-2, and PORTEC-3 trials were

For the **multilayer perceptron** see https://github.com/CTPLab/AutoCI/blob/master/HOUDINI/Library/NN.py#L73

For the **causal weight layer** see https://github.com/CTPLab/AutoCI/blob/master/HOUDINI/Library/NN.py#L48

For the **implementation detail** see https://github.com/CTPLab/AutoCI/blob/master/HOUDINI/Interpreter/Interpreter.py

For the **loss function** see https://github.com/CTPLab/AutoCI/blob/master/HOUDINI/Library/Loss.py

included in this analysis (table 1; appendix p 2). Overall, their median age was 66 years (IQR 60–72; range 27–90). Most patients were between 50 years and 80 years of age, with only 92 (5·1%) younger than 50 years and 73 (4·0%) older than 80 years. There were some differences in age between the trials. 243 (34·0%) of 714 women included in PORTEC-1 were older than 70 years. In PORTEC-2, 195 (45·7%) of 427 patients were older than 70 years, whereas, in the PORTEC-3 trial (which involved chemotherapy), only 97 (14·7%) of 660 patients were older than 70 years. The association of age with clinicopathological and molecular characteristics of endometrial cancer is shown in table 2.

Overall, fewer older patients in these studies had stage II and III disease (table 2). 1136 (99·6%) of 1141 women included in the PORTEC-1 and PORTEC-2 trials had stage I disease (appendix pp 5–6), and no significant association between age and stage was shown in PORTEC-3 (appendix p 7). Deep myometrial invasion was significantly more frequent in older women than in younger women (267 [53·6%] of 498 for <60 years, 524 [68·5%] of 765 for 60–70 years, 403 [75·3%] of 535 for >70 years; p<0·0001; table 2).

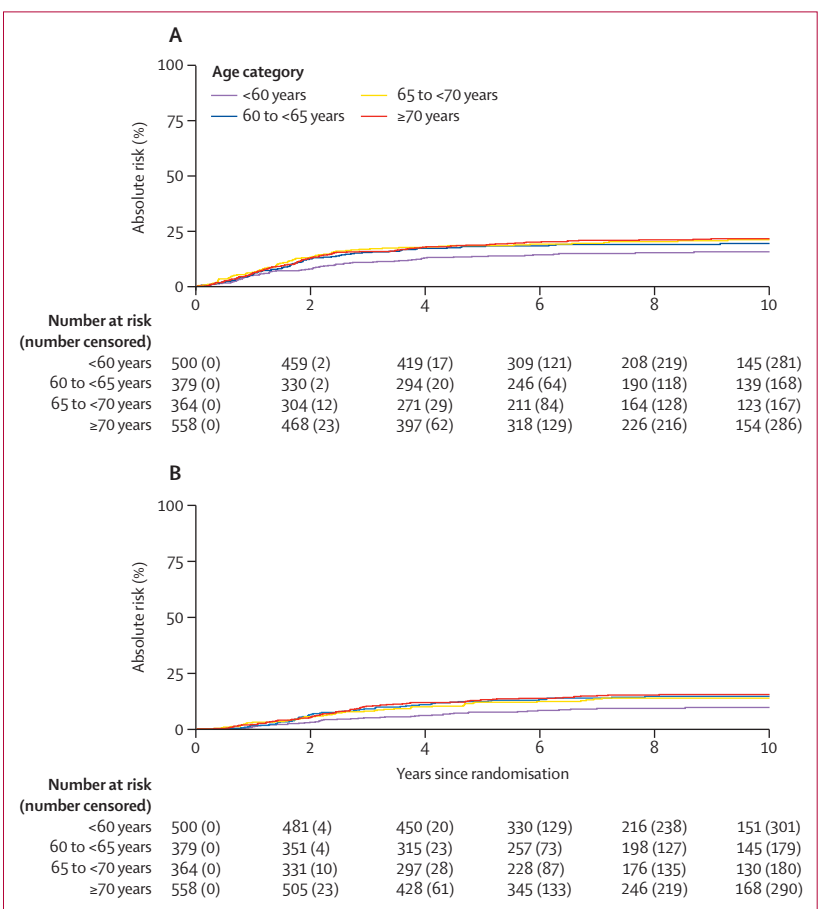

Figure 1: **Cumulative incidence of overall recurrence and endometrial cancer-specific death by age group**
(A) Cumulative incidence of overall recurrence by age group. (B) Cumulative incidence of endometrial cancer-specific death by age group.

A significant difference across the age groups was found in histology and tumour grade in the pooled analysis. Analysis by trial showed that grade 3 endometrioid endometrial carcinoma was not more common among older women in PORTEC-1 and PORTEC-2 (appendix pp 5–6). However, non-endometrioid histotypes were more common with increasing age in PORTEC-3, specifically serous endometrial cancer (25 [9·3%] of 268 for <60 years, 54 [18·3%] of 295 for 60–70 years, 26 [26·8%] of 97 for >70 years; appendix p 7).

In the analysis of the three combined trials, substantial LVSI was found less often in older patients. LVSI was rare (46 [4·8%] of 956) in PORTEC-1 and PORTEC-2, and in the analyses of each trial separately, no significant association between age and LVSI was found (appendix pp 5–7).

Analyses showed a significant difference in molecular classification between the different age groups (table 2). With increasing age, there was a decrease in frequency of *POLE*-mutated tumours, while frequency of p53-abnormal tumours increased. This difference was most striking between the group younger than 60 years and the group aged 60–70 years. The proportion of mismatch-repair deficient and no-specific-molecular-profile tumours was stable across age groups (table 2). The distribution of age for each molecular class can be found in the appendix (p 8).

No significant association was observed between age and oestrogen receptor status in the combined cohorts or in the PORTEC-1 and PORTEC-2 trials alone. However, oestrogen receptor-negative tumours were more common with increasing age in PORTEC-3 (23 [14·4%] of 160 for <60 years, 52 [30·1%] of 173 for 60–70 years, 18 [32·7%] of 55 for >70 years; p<0·0001; appendix p 7).

In the PORTEC trials, patients were randomly assigned (1:1) to adjuvant treatment and no differences in randomly allocated and received adjuvant treatment were observed between the age groups. Most patients completed their treatment in the PORTEC-1 (710 [99·4%] of 714) and PORTEC-2 (423 [99·1%] of 427) trials, with no differences between the age groups. In PORTEC-3, 52 (15·8%) of 330 patients did not complete chemotherapy (0–4 of the six cycles). Non-completion of chemotherapy was more common in older patients: 16 (12·5%) of 128 women younger than 60 years, 24 (15·8%) of 152 women aged 60–70 years, and 12 (24·0%) of 50 women older than 70 years; however, this association was not significant (p=0·073).

Median follow-up was 12·3 years (95% CI 11·9–12·6) in PORTEC-1, 10·5 years (10·2–10·7) in PORTEC-2, and 6·1 years (5·9–6·3) in PORTEC-3. Both overall recurrence and endometrial cancer-specific death significantly increased with age, with the largest differences observed between the group younger than 60 years and the other age groups (figure 1). Cumulative

incidence of all other oncological outcomes can be found in the appendix (p 9).

To evaluate the prognostic impact of age, multivariable competing risk models were built for all outcomes and the AUCs ranged from 0·78 to 0·83. Details and other performance metrics can be found in the appendix (p 10). The multivariable competing risk analyses showed that age was an independent risk factor for overall recurrence with a cause-specific HR of 1·02 per year (95% CI 1·01–1·04; p=0·0012), corrected for stage, histotype and grade, LVSI, molecular class, and adjuvant treatment. Sensitivity analysis (without imputation of missing data) showed an HR of 1·03 per year (95% CI 1·01–1·05, p=0·0002). Age also had an independent prognostic value for endometrial cancer-specific death (HR 1·03, 1·01–1·05; p=0·0012) and locoregional recurrence (HR 1·02, 1·00–1·05; p=0·030). Age was found to be an independent risk factor for vaginal recurrence (HR 1·05, 1·01–1·08; p=0·0059), corrected for stage (I–II *vs* III), LVSI, molecular class, and adjuvant treatment (none *vs* any type of adjuvant treatment), but not for distant metastasis or pelvic recurrence (data not shown).

	Hazard ratio (95% CI)	p value
Overall recurrence*		
<60 years	1 (ref)	..
60–70 years	1·39 (1·36–1·42)	<0·0001
>70 years	1·89 (1·81–1·98)	<0·0001
Endometrial cancer-specific death*		
<60 years	1 (ref)	..
60–70 years	1·53 (1·47–1·59)	<0·0001
>70 years	2·31 (2·13–2·51)	<0·0001
Distant metastasis*		
<60 years	1 (ref)	..
60–70 years	1·19 (1·13–1·26)	<0·0001
>70 years	1·42 (1·27–1·58)	<0·0001
Locoregional recurrence*		
<60 years	1 (ref)	..
60–70 years	1·72 (1·68–1·77)	<0·0001
>70 years	2·79 (2·67–2·91)	<0·0001
Pelvic recurrence†		
<60 years	1 (ref)	..
60–70 years	1·45 (1·38–1·53)	<0·0001
>70 years	2·11 (1·90–2·35)	<0·0001
Vaginal recurrence†		
<60 years	1 (ref)	..
60–70 years	1·59 (1·54–1·64)	<0·0001
>70 years	2·50 (2·32–2·70)	<0·0001

*Corrected for stage, histotype and grade, lymphovascular space invasion, molecular classification, and adjuvant treatment. †Corrected for: stage (I–II *vs* III), lymphovascular space invasion, molecular classification, and adjuvant treatment (none *vs* any type of adjuvant treatment).

Table 3: **Prognostic impact of age using multivariable causal inference analysis**

These results were supported by AutoCI analyses, which identified age as a significant causal variable alongside all established clinicopathological and molecular risk factors for overall recurrence, endometrial cancer-specific death, and all other oncological outcomes (table 3).

To assess the course of the risk increasing with age, the competing risk models were used to visualise the association between age and the cause-specific hazard rates of overall recurrence and endometrial cancer-specific death, as an HR, relative to age 60 years (figure 2). The rates of both primary outcomes of recurrence and endometrial cancer-specific death increase steadily with an approximately linear course between the ages of 50 years and 80 years. A similar association between increased risk and age was observed for all secondary outcomes, although less strong (appendix p 11).

In causal inference analysis, the correlation between age and both primary outcomes showed an accelerating increase of the cause-specific hazard rate with age tending towards an exponential relationship (figure 2C, D). A

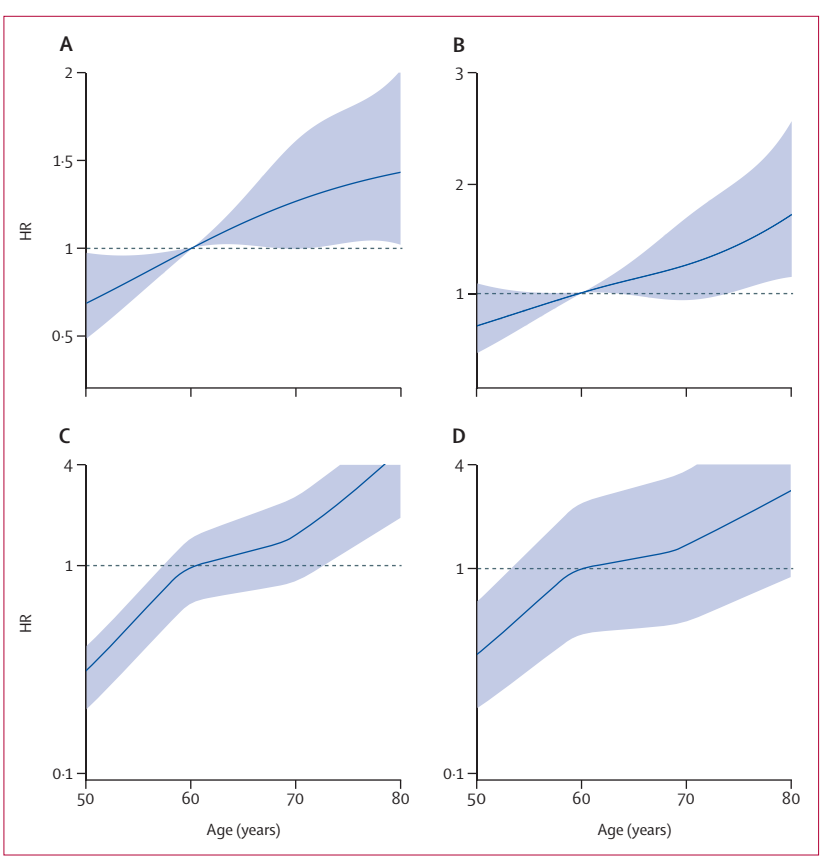

Figure 2: **Association between age and overall recurrence and endometrial cancer-specific death**
Only data between age 50 years and 80 years are presented due to uncertainty in the data outside this range (small numbers of patients aged <50 years and >80 years). (A) Correlation of age with the risk of overall recurrence by statistical inference. (B) Correlation of age with the risk of endometrial cancer-specific death by statistical inference. (C) Causal association of age with the risk of overall recurrence by automated causal inference (AutoCI). (D) Causal association of age with the risk of endometrial cancer-specific death by AutoCI. Shaded areas represent 95% CIs. Dashed lines show the reference (HR=1). HR=hazard ratio.

similar pattern, albeit less strong, was observed for all secondary outcomes (appendix p 12).

Discussion

In this pooled analysis of the randomised PORTEC-1, PORTEC-2, and PORTEC-3 trials, advanced age was associated with more aggressive tumour features, and independently and causally related to worse oncological outcomes. The risk of recurrence and endometrial cancer-specific death steadily increased up to the age of 80 years.

We also found that older women had a higher frequency of deep myometrial invasion, serous tumour histology, and p53-abnormal tumours, as seen by others.[2,4,5,7] However, in this study the correlation between older age and more aggressive tumour characteristics does not entirely explain the poorer oncological outcomes in older women. Age was found to be an independent risk factor, after correcting for stage, histotype and grade, LVSI, molecular class, adjuvant treatment, and competing events. Correction for molecular classification was done in two previous studies. Zheng and colleagues[5] found age to be of independent prognostic value, after correcting for *TP53* mutation status and serous histology. Léon-Castillo and colleagues[8] found age to be of independent prognostic value for recurrence-free survival when corrected for molecular group, in an analysis of the PORTEC-3 trial. The current study, using data of all three PORTEC trials, is, to our knowledge, the first that investigates the prognostic impact of age across the whole spectrum of stage I–III endometrial cancer, in the context of the molecular classification.

Our competing risk analyses of the impact of age on the localisation of recurrence showed that older women have a significantly higher hazard of vaginal recurrence, but not pelvic and distant recurrence. The increased risk of vaginal recurrences in older women might be explained by the postmenopausal thinning of the cervix and myometrial wall of the uterus.[23,24] For recurrences in the pelvic lymph nodes and at distant localisations, other risk factors such as aggressive molecular features and LVSI seem to determine the outcome.[25,26] These findings might imply that advanced patient age should mainly be taken into consideration for the decision on adjuvant vaginal brachytherapy. Vaginal brachytherapy is a minimally invasive treatment with few side-effects, and can be offered to most women, including frail older women and those with obesity or comorbidities.[14]

To our knowledge, the causal relationship between age and oncological outcomes in women with endometrial cancer was investigated for the first time in this study. By using the cutting-edge AutoCI method that provides a novel linkage of causal inference and deep learning on three large, randomised trials, we show that the association between age and worse prognosis in endometrial cancer is causal.[11]

Describing the change in risk of adverse oncological outcomes across different age groups is important for translation of these results to clinical practice. Our analyses showed that the probability of adverse oncological outcomes increases steadily between the ages of 50 years and 80 years, after correction for all established risk factors. We estimated an HR of 1·02 per year, which might seem a minor increase in risk, but will probably add up to a clinically relevant difference when comparing similar patients with an age difference of 5–10 years or more. We also performed a systematic literature search (appendix pp 13–16) and found that only Sun and colleagues[27] had published a modelling study on the course of the increasing risk with age in endometrial cancer. They found a similar linear increase of risk with age, with no clear cutoff value. However, the potential for clinical translation of their results is limited, as no correction for confounding was performed. Another study that investigated the age–risk association without proper survival analysis did establish a cutoff value of 63 years.[28] Thus, the risk of adverse outcomes appears to keep increasing with age, and our systematic literature search showed no consensus on a cutoff value in the literature (appendix p 17). This finding is supported by the fact that we found consistent HRs for the risk of adverse outcomes with increasing age in multiple studies that analysed different risk groups.[8,29] All reported HRs were in the range of 2–4% per year, for both high-intermediate risk groups and high-risk groups.

On the basis of these results, it seems arbitrary to decide on a cutoff for age, but a continuous risk factor is inconvenient, as risk groups in treatment guidelines are created using categorial variables. This might be the reason that guideline committees have dichotomised age (eg, at 60 years[30,31]) or decided to leave this risk factor out.[32] In clinical practice, guideline adherence is lower in older patients; they receive surgery less often, especially lymph node dissection and adjuvant radiotherapy and chemotherapy.[33] Therefore, our results are of value for clinical practice, as they do not support exclusion of older women from diagnostic and therapeutic interventions. A comprehensive diagnostic assessment of all patients, young and old, is necessary. Assessment of the extent of disease and molecular classification of the tumour is essential to estimate risk of recurrence and death and guide treatment decisions,[8] including in older women. In older patients, the molecular classification will enable physicians to better determine in whom the risk of recurrence is sufficiently high to justify adjuvant therapy, and give some guidance as to which therapies might be appropriate.[8,34] For example, no adjuvant therapy might be appropriate in *POLE*-mutated endometrial cancer,[35,36] chemotherapy in p53-abnormal endometrial cancer,[8,34] and, in the future, immunotherapy for high-risk mismatch-repair deficient endometrial cancer.[37–41] Geriatric assessments can be useful to better determine individual risks of morbidity and mortality associated

with adjuvant treatment. The results of these two types of assessments and the preferences of the older patient should be considered in a shared decision-making process on adjuvant therapy.

Strengths of this study are the use of three large, randomised trials with high-quality long-term follow-up data and the large number of molecularly classified tumours. The use of a multimodal analysis, based on state-of-the-art statistical and causal inference techniques, is unique and identified age as a causal risk factor. Our study design ensured minimal bias, sufficient statistical power, and high internal validity. However, the results of the univariable analysis on the differences in tumour characteristics between age groups should be interpreted with caution as there are differences in age distribution, tumour characteristics, and the registration of the stage and LVSI variable between the three trials which included different risk spectra. For the main analysis of the prognostic and causal effect of age, this issue is probably limited as multivariable analyses included all currently known confounders, were corrected for cohort effects, and modelled competing causes of death. Nonetheless, some residual confounding might be present due to uncorrected differences between the trials in design and delivery. A downside of using trial data is that participants are not representative of all patients in medical practice. Exclusion criteria for the PORTEC trials included certain comorbidities, such as impaired renal or cardiac function, which are more prevalent in older patients.[13–15] Moreover, patients in the PORTEC-3 trial had to be fit enough to undergo chemoradiotherapy. However, we do not expect that older patients with endometrial cancer who cannot participate in clinical trials have better oncological outcomes than those who can. Another limitation of this study was the small number of patients younger than 50 years and older than 80 years, subgroups for which we prefer not to draw any conclusions.

The pathophysiological mechanisms that explain the increased risk for older women with endometrial cancer are still unclear. To obtain more insight into the relationship between biological age and worse outcomes, the impact of frailty should be assessed in future studies.[42–44] More research into the ways in which cancer control is different in older individuals would be of value as it could yield prognostic refinement or identify more appropriate therapies. One of those mechanisms possibly related to biological age is cellular senescence. Studies have shown a complex relationship between ageing, cellular senescence, and cancer, where cellular senescence seems to play a role in both tumour suppression as well as tumour progression.[45,46] Future research on this topic for endometrial cancer specifically could contribute to understanding the increased risk of older women. Furthermore, recent research has shown a correlation between increasing age and genomic instability of tumours. Chatsirisupachai and colleagues found that age-related genomic differences in tumours were largest in endometrial cancer.[47] These findings could be of interest in further research. Moreover, we hypothesise that another factor influencing the worse prognosis of older women is the decline of the immune system and antitumour response.[48,49] Studies on the prognostic impact of antitumour response have revealed that the presence of tumour-infiltrating lymphocytes or tertiary lymphoid structures are associated with a better prognosis.[50–52] Among patients with breast cancer,[53] younger patients have a significantly higher tumour-infiltrating lymphocyte density than older patients, which might explain in part why older women have a worse prognosis. These findings encourage further exploration of this topic in endometrial cancer specifically.

In conclusion, our study showed that older women with endometrial cancer have worse oncological outcomes, even when they undergo the same treatment as younger women. This is in part explained by more aggressive histopathological and molecular tumour features with advancing age, but an independent and causal negative effect of age remains unexplained. Further research into the biological mechanisms behind ageing to explain the increased risk is warranted. This risk of adverse oncological outcomes associated with ageing gradually increases between 50 years and 80 years without a clear cutoff. Therefore, this study does not support exclusion of older women from diagnostic assessments, molecular testing, and adjuvant therapy based on their age alone.

Contributors

FW, JW, HP, VHK, CLC, and NH were involved in conception and study design. IMJ-S, JJJ, LCHWL, MADH, MAdJ, JWMM, BGW, RAN, AL-C, MEP, LRM, DK, JA, AL, NS, SMdB, HWN, VTHBMS, TB, and CLC were involved in collection and assembly of data. FW, HP, NH, and CLC accessed and verified the raw data. FW, JW, HP, VHK, and NH were responsible for the data analysis and statistical methodology. FW, JW, HP, VHK, and NH were responsible for writing the original manuscript. All authors had access to the presented data and all authors contributed to the manuscript and approved the final version.

Declaration of interests

JW is supported by core funding of the University of Zurich to the Computational and Translational Pathology Lab led by VHK at the Department of Pathology and Molecular Pathology, University Hospital and University of Zurich. RAN has received grants (to institution) from the Dutch Cancer Society, Dutch Research Council, Elekta, Varian, and Accuray; payment or honoraria (to institution) for lectures and presentations from Elekta; and is chair of the Dutch Gynecological Oncology Group. AL-C declares having received payment or honoraria for multiple lectures and presentations. AL has received a PhD student grant from AstraZeneca; honoraria (to institution) for presentations from GSK, AstraZeneca, and MSD; support for attending meetings from OSEimmuno, AstraZeneca, and MSD; and honoraria (to institution) for participation on Data Safety Monitoring Board or Advisory Board from Genmab, AstraZeneca, MSD, and GSK. NS declares having received personal payment for participation in Advisory Boards of Astra-Zeneca–MSD and Glaxo-SmithKline. HWN has received grants or contracts (to institution) from Merck and the Dutch Cancer Society. VHK receives funding by the University of Zurich; has acted as an invited speaker for Sharing Progress in Cancer Care (SPCC) and holds sponsored research agreements with Roche and IAG unrelated to the content of this study; has served as an invited speaker on behalf of Indica Labs unrelated to the content of this study; is on an advisory board of Takeda (unrelated to the content of this study); and is a member of the European Key Opinion

Leader Network in Digital Pathology supported by Roche. CLC has received clinical trial grants for the PORTEC-1, PORTEC-2, and PORTEC-3 trials (to institution) from the Dutch Cancer Society. NH has received unrestricted research grants (to institution) from the Dutch Cancer Society; personal payment for an educational lecture for specialist nurses in oncology (V&VN), unrelated to the current work; has a patent on a deep learning algorithm on endometrial cancer, unrelated to the current work; and is a member of a Data Safety Monitoring Board of the Apollo study (EudraCT number: 2022-002500-21). All other authors declare no competing interests.

Data sharing

The PORTEC dataset analysed in this study is not publicly available due to restrictions by privacy laws. The dataset and tumour material are currently available to the members of the international TransPORTEC consortium, which is open for requests for sharing the data and material after receipt and evaluation of a scientific proposal. Requests should be addressed to the corresponding author, within 15 years from the date of publication. Depending on the specific research proposal, the TransPORTEC consortium will determine when, for how long, for which specific purposes, and under which conditions the requested data can be made available, subject to ethical consent. The code used for the statistical analysis with R, and causal inference analysis with PyTorch, are publicly accessible at https://github.com/CTPLab/AutoCI, which is released under the MIT licence. Syntax for the statistical analyses is also accessible here.

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