

# Further insights into the role of tumour characteristics in survival of young women with epithelial ovarian cancer

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## HIGHLIGHTS

- Overall survival is better in younger than in older women epithelial ovarian cancer.
- Distribution of tumour characteristics differs between age groups.
- Effects of tumour characteristics on survival depend on age.
- Survival rates as reported are useful to personalise counselling on prognosis.

## ARTICLE INFO

### Article history:

Received 3 January 2019

Received in revised form 13 August 2019

Accepted 18 August 2019

Available online 30 August 2019

### Keywords:

Epithelial ovarian cancer

Young age

Survival

Prognostic

Factor

Prognosis

Counselling

## ABSTRACT

**Objective:** Optimizing the counselling of women  $\leq 40$  years with epithelial ovarian cancer (EOC) by investigating the role of young age and tumour characteristics on overall survival (OS).

**Methods:** A retrospective population-based study was done using data of EOC patients diagnosed between 1990 and 2014 registered in the Netherlands Cancer Registry. Descriptive statistics were performed to analyse clinical and tumour characteristics. Five- and 10-year OS rates were calculated using Kaplan Meier curves. To determine prognostic factors, univariable and multivariable survival analyses were performed.

**Results:** 1407 women  $\leq 40$  years and 29,022 women  $> 40$  years old were included. OS was higher for the younger women compared to older group (5-year survival of 65.6% vs. 32.7%, 10-year survival of 57.5% vs. 22.5%, respectively). The younger women had more often a mucinous (36.4%), well-differentiated (31.8%) tumour in early stage of disease (49.9%). Serous tumours (43.0%), high-grade (36.0%) and stage III (47.1%) were most frequently found in the older women. Histology, grade, stage, incidence year, and age group are independent prognostic factors for survival. OS of the young women for several combinations of tumour characteristics were calculated.

**Conclusions:** Age is an independent prognostic factor for OS in EOC patients. Counselling on prognosis could be more individualised in young EOC patients using the tumour characteristics histology, stage and grade.

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## 1. Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynaecological malignancy worldwide [1]. EOC is a collective term for carcinomas of the ovary, peritoneum, and the fallopian tube. These carcinomas are considered one entity because they are presumed to arise from epithelial cells with the same embryological Mullerian origin [2,3]. Lifetime risk of EOC is around 1.3% in the general population of

western countries [4,5]. In general, patients face a poor prognosis due to the fact that they often have an advanced stage of disease at diagnosis. Five-year survival for stage I is 90%, and 13–18% for stage IV [1,4]. The current standard treatment of presumed early-stage EOC is surgical staging. In case of upstaging, adjuvant treatment with six cycles of chemotherapy (paclitaxel/carboplatin) is recommended. For advanced stage EOC, a debulking procedure in combination with chemotherapy is standard treatment. The peak incidence is seen at 65 to 70 years [4,6], and only a small group of women is diagnosed under 40 years of age. Younger women have better overall survival (OS) compared to older women, with the biggest benefit for women diagnosed under 30 years of age [7,8].

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Several differences in clinical and tumour features have been observed between women  $\leq 40$  years with EOC compared to women over 40 years of age. The tumour in younger women is more frequently well-differentiated and diagnosed at an early stage. Also, mucinous and endometrioid histological types are more common [7,9]. All aforementioned studies on age as a prognostic factor in EOC included small groups of patients and are hospital-based studies, and therefore vulnerable to selection bias. Clinical and histological differences are known to influence prognosis and should therefore be taken into account in counselling of young patients with EOC, thereby creating better patient-centred and personalized care.

The aim of the current population-based study is to gain insight in the effect of (combinations of) tumour characteristics on OS in EOC patients of 40 years and younger by analysing a nationwide population. These data can be used to optimally inform this specific patient group about their prospects on survival, even before being treated.

## 2. Patients and methods

### 2.1. Study population

Data from the Netherlands Cancer Registry (Dutch: IKNL) were used. This database contains information on all patients with cancer in the Netherlands, is connected to the nationwide network and registry of histo- and cytopathology (PALGA) and has had nationwide coverage since 1989. Patients diagnosed with ovarian, primary peritoneal, and fallopian tube carcinomas were included. The last update of vital status was obtained from the municipal personal records database on February 1st, 2016. To create a minimal follow-up of 2 years at the time of this research, patients diagnosed between 1990 and 2014 were included. Data of patients with non-epithelial ovarian cancer, with low malignant potential tumours, with probable ovarian metastases instead of primary EOC and cases without pathological confirmation of ovarian cancer were excluded. The few tumours of undifferentiated grade were included in the grade 3 group, because undifferentiated tumours are mostly poorly differentiated. Two age subgroups were created: women of 40 years and younger, and women older than 40 years.

### 2.2. Outcomes

The primary outcome of interest was the effect of age on OS. The secondary outcomes of interest were the clinical and tumour characteristics of women with EOC and their effect on OS, stratified per age group. These characteristics were: FIGO stage [10], tumour grade (according to Silverberg) [11], histology (WHO-classification) [12], and incidence year.

Treatment could not be included as a potential prognostic factor, because the Dutch Cancer Registry did not register details of performed surgeries in the included incidence years (type of surgery, outcome), nor details of chemotherapy given (type, number of cycles).

### 2.3. Statistical analysis

Kaplan-Meier curves were used to demonstrate 5- and 10-year OS for both age groups and a difference in survival was tested for statistical significance using the log-rank test.

Descriptive statistics were performed to look at clinical and tumour characteristics. Differences in characteristics of the two age groups were tested for statistical significance using the Chi-square test.

To identify age (dichotomised) as a prognostic factor and to identify prognostic factors for OS in EOC patients within both age groups, univariable analysis was performed with Cox regression on

continuous variables and with Kaplan-Meier curves and log-rank methods on categorical variables. Whether a factor had an independent effect on OS was calculated by multivariable analysis using Cox proportional hazard models with a backward selection procedure, thereby testing the proportional hazards assumption by using scaled Schoenfeld residuals.

Furthermore, OS was calculated for both younger and older patients stratified by several combinations of histology, grade and stage of disease.

Data were analysed using IBM SPSS Statistics version 22.

## 3. Results

The database contained a total of 31,364 women diagnosed with EOC in the Netherlands between 1990 and 2014. Ninety of them did not have pathologically confirmed ovarian cancer and were therefore excluded. Pathological diagnoses that were not unequivocal EOC were re-evaluated by a pathologist: 106 patients were excluded because the tumour resembled a metastasis rather than a primary ovarian tumour, and 709 turned out to be non-epithelial. A flowchart is shown in Fig. 1. Of all included women ( $n = 30,429$ ), 1407 women (4.6%) were  $\leq 40$  years old at diagnosis and 29,022 women (95.4%) were  $> 40$  years old at diagnosis. Patient and tumour characteristics are demonstrated in Table 1.

OS was significantly higher in the younger age group compared to the older group (5-year survival of 65.6% vs. 32.7%, 10-year survival of 57.5% vs. 22.5%, respectively) (Fig. 2).

In the younger women, mucinous (36.4% vs. 9.0%) and other subtypes including neuroendocrine, small cell and squamous cell tumours (3.7% vs. 1.5%) were more frequently diagnosed than in the older group. Serous (43.0% vs. 34.3%) and adenocarcinoma not otherwise specified (NOS) (32.6% vs. 12.2%) occurred more often in the older group. The number of adenocarcinoma NOS tumours decreased over the years in both age groups, probably due to improved diagnostics and histological classification. Younger women were more often diagnosed in an early stage of disease: 49.9% in stage I, compared to 20.5% in the older group, whereas stage III was more frequently diagnosed in the older age group (47.1% vs. 31.3%). In the younger women, most tumours were well-differentiated (31.8%) in contrast to the older group, where mainly high-grade tumours (36.0%) were detected.

Univariate analysis of prognostic factors for survival showed that histology, stage, grade, incidence year and age subgroup were statistically significant predictors for OS.

After multivariable analysis, these same factors turned out to be independent predictors of OS, both in the total population as within age groups (Table 2). Being  $\leq 40$  years old at diagnosis turned out to be an independent favourable prognostic factor ( $p < 0.001$ ). Within the younger age group, increasing stage had the most dramatic impact on survival (HR 14.56 95% CI 10.52–20.14 for younger women with stage IV compared to younger women with stage I disease). Table 2 is not meant to compare hazard ratios of younger women to those of older women.

Table 3 shows the 5- and 10- year OS for different combinations of tumour characteristics for women of 40 years and younger with EOC. Table 4 shows the 5- and 10-year OS for different combinations of tumour characteristics for women older than 40 years diagnosed with EOC. We did not calculate survival for combinations with less than five people in that subgroup, since those results are very unreliable. If 5- and 10-year survival outcomes are not demonstrated despite that subgroup containing five cases or more, data on follow-up were insufficient to calculate these results. Younger women showed better OS for almost every combination of tumour characteristics. When point estimates of OS were higher in the older group, either differences are very small and/or confidence intervals are very wide. In women  $\leq 40$  years at diagnosis, the

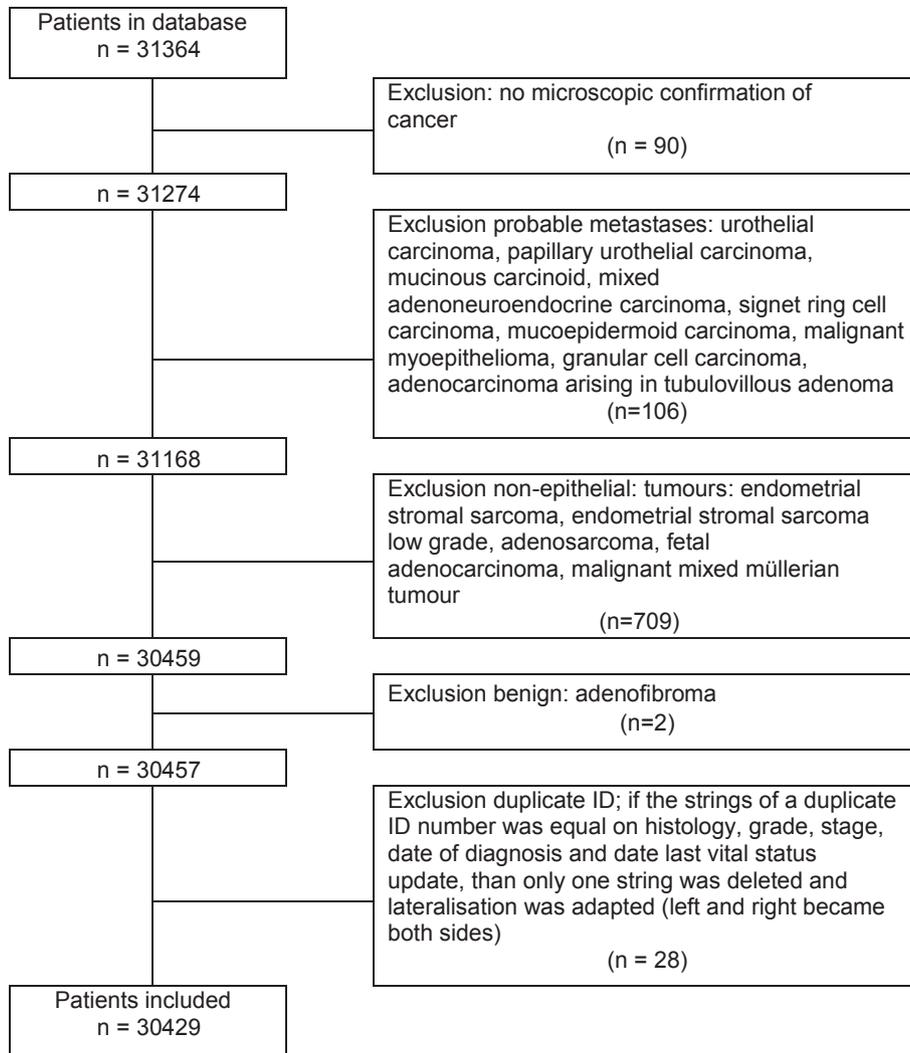


Fig. 1. Flowchart of inclusion of patients diagnosed with EOC in the Netherlands between 1990 and 2014.

**Table 1**  
Patient and tumour characteristics for women with EOC.

	Age group		p-value
	≤40 (N = 1407)	>40 (N = 29,022)	
Age at diagnosis (Median (range))	35 yr (12–40 yr)	66 yr (41–98 yr)	
Histological type (N (% in age-group))			<0.001
Serous	482 (34.3%)	12,479 (43.0%)	
Mucinous	512 (36.4%)	2600 (9.0%)	
Endometrioid	128 (9.1%)	2709 (9.3%)	
Clear cell	62 (4.4%)	1328 (4.6%)	
NOS	171 (12.2%)	9464 (32.6%)	
Other	52 (3.7%) <sup>a</sup>	442 (1.5%)	
Stage (N (% in age group))			<0.001
I	702 (49.9%)	5953 (20.5%)	
II	91 (6.5%)	2491 (8.6%)	
III	441 (31.3%)	13,677 (47.1%)	
IV	110 (7.8%)	3383 (11.7%)	
Unknown	63 (4.5%)	3518 (12.1%)	
Grade (N (% in age group))			<0.001
1	448 (31.8%)	2553 (8.8%)	
2	294 (20.9%)	4909 (16.9%)	
3	266 (18.9%)	10,438 (36.0%)	
Unknown	399 (28.4%)	11,122 (38.3%)	

Abbreviations: NOS not otherwise specified; Other including neuroendocrine, small cell, squamous cell, mesonefric, undifferentiated, mixed subtypes and Brenner tumours; p-value significance frequencies between age groups by chi square test.

<sup>a</sup> Due to rounding up the percentiles to one decimal, the total is >100%.

largest subgroup had a stage I well-differentiated mucinous tumour (14.7%, n = 207) with 5- and 10- year OS of 95% and 94%, respectively. One of the best chances of OS was observed for women with a stage I well-differentiated serous tumour (5- and 10-year OS of

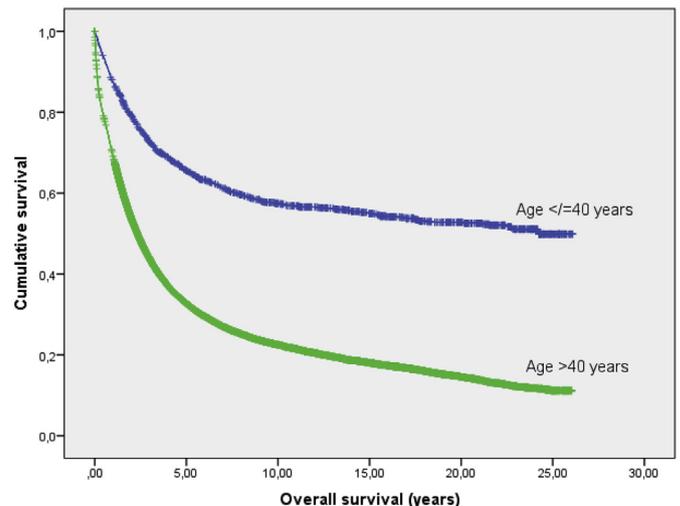


Fig. 2. OS in two age groups of women diagnosed with EOC.

**Table 2**  
Multivariate Cox regression for OS of women with EOC.

	All ages				≤40 years old at diagnosis				>40 years old at diagnosis			
	N	HR <sup>a</sup>	95%CI	p	N	HR <sup>a</sup>	95%CI	p	N	HR <sup>a</sup>	95%CI	p
<b>Histology</b>												
Serous	12,961	1	–	–	482	1	–	–	12,479	1	–	–
Mucinous	3112	1.239	1.173–1.310	<0.001	512	2.03	1.160–2.58	<0.001	2600	1.22	1.15–1.29	<0.001
Endometrioid	2837	0.829	0.784–0.876	<0.001	128	1.03	0.72–1.46	0.887	2709	0.82	0.78–0.87	<0.001
Clear cell	1390	0.960	0.889–1.036	0.289	62	1.85	1.23–2.80	0.003	1328	0.93	0.86–1.01	0.076
NOS	9635	1.620	1.572–1.670	<0.001	171	1.79	1.43–2.25	<0.001	9464	1.61	1.57–1.67	<0.001
Other	494	1.011	0.901–1.134	0.855	52	1.50	0.96–2.34	0.074	442	0.98	0.87–1.11	0.786
<b>Stage</b>												
I	6655	1	–	–	702	1	–	–	5953	1	–	–
II	2582	1.968	1.846–2.097	<0.001	91	3.74	2.54–5.50	<0.001	2491	1.92	1.80–2.04	<0.001
III	14,118	4.220	4.026–4.423	<0.001	441	9.95	7.69–12.88	<0.001	13,677	4.08	3.89–4.28	<0.001
IV	3493	4.868	4.596–5.157	<0.001	110	14.56	10.52–20.14	<0.001	3383	4.68	4.41–4.96	<0.001
Unknown	3581	4.924	4.655–5.208	<0.001	63	6.07	4.11–8.97	<0.001	3518	4.80	4.53–5.08	<0.001
<b>Grade</b>												
1	3001	1	–	–	448	1	–	–	2553	1	–	–
2	5203	1.503	1.408–1.604	<0.001	294	2.57	1.97–3.36	<0.001	4909	1.45	1.35–1.55	<0.001
3	10,704	1.446	1.358–1.539	<0.001	266	2.77	2.12–3.62	<0.001	10,438	1.40	1.31–1.49	<0.001
Unknown	11,521	2.035	1.914–2.165	<0.001	399	1.80	1.38–2.34	<0.001	11,122	2.01	1.88–2.14	<0.001
Incidence year	30,429	0.988	0.986–0.990	<0.001	1407	1.01	0.99–1.02	0.254	29,022	0.99	0.985–0.989	<0.001
<b>Age subgroup</b>												
> 40 years	1407	1	–	–		N/A				N/A		
≤ 40 years	29,022	0.495	0.456–0.537	<0.001		N/A				N/A		

Abbreviations: HR hazard ratio; 95%CI 95% confidence interval; NOS Not otherwise Specified; N/A Not applicable.

<sup>a</sup> The higher the hazard ratio, the lower survival.

98% and 92%, respectively). Poorest OS was observed in stage 3 poorly differentiated mucinous tumours and adenocarcinomas NOS (Table 3).

The largest subgroup of the women over 40 years, as shown in Table 4, had a stage III high-grade serous tumour (11.4%, n = 3316) with 5- and 10-year OS of 26% and 11%, respectively. The subgroup with the best prognosis (5- and 10-year OS of 89% and 77%, respectively) involved women with stage I well-differentiated endometrioid tumours (Table 4).

#### 4. Discussion

In this nationwide study we found that age ≤ 40 years at diagnosis is an independent favourable prognostic factor in EOC patients. Tumour characteristics and their impact on OS differ between age groups. Five- and 10-year OS for several subgroups, defined by combinations of histology, differentiation grade and stage, are reported for both women diagnosed ≤40 years and women older than 40 years. These results can be used to inform and individualise counselling on prognosis of young EOC patients.

Our findings regarding a better OS for women of 40 years and younger compared to women older than 40 years are in line with the study of Sardi et al. [9]. They showed that 10-year OS for women ≤40 years was significantly higher than for women >40 years old (81% and 35%, respectively;  $P < 0.001$ ). Stage of disease is known to be the most important prognostic factor in EOC, regardless of age, which is endorsed by the results of our study. Earlier studies also showed decreasing survival with higher tumour grade [7,8].

Several smaller studies on EOC in young women have previously been published. The previously mentioned study by Sardi et al. on young EOC patients, based on data of 40 patients diagnosed at 40 years or younger, showed similar findings on histology and tumour grade; young patients had more mucinous tumours (27%), well-differentiated tumours (67.5%), and were more often diagnosed at an early stage (70%) compared to women older than 40 years [9]. Serous histology was found to be the most frequently occurring histological subtype in three other studies including a total of 366 women of 45 years and younger [7,8,13]. Two of these studies failed to show that most young women had early stage disease and well-differentiated tumours [7,13].

Year of diagnosis appeared to be an independent prognostic factor. Earlier studies, of which two were performed in the Netherlands, have already suggested changes in treatment to be partly responsible for improved survival for women over the years [14–16]. After reorganisation of care in the late 1990's, an increased number of surgeries were performed by specialized gynaecologic oncologists, the number of interval debulkings increased, and the rate of optimal and complete (interval) debulkings increased. Altogether, reorganisation of care had a positive influence on survival [16,17]. Furthermore, OS increased after introduction of paclitaxel [18,19]. Moreover, changes in (histological) diagnostics may have improved staging and histological classification of tumours leading to the most appropriate therapy.

An important strength of our study is the nationwide coverage and inclusion of an extremely large population of young women with EOC. Use of the Dutch nationwide database gives a good overview of the tumour characteristics of Dutch EOC patients over a period of 25 years. Moreover, missing rare tumours is thereby obviated and the influence of regional differences or differences between hospitals is excluded. Data on vital status are highly accurate, because of the connection between the Netherlands Cancer Registry and the municipal personal records database.

The second important strength and new focus of this study is the demonstration of OS for specific combinations of tumour characteristics for both women ≤40 years old and older than 40 years at the time of diagnosis. Different prognostic models have been made for women with EOC [20,21], but these models included women of all ages. Since distinctive differences between women of ≤40 years old and older women are found, these prognostic models are not appropriate for young women with EOC. With our findings, a more personalized survival prediction can be communicated to women with EOC, based on their actual age, tumour histology, differentiation grade and stage of disease, even without knowing the response to chemotherapy or the completeness of cytoreductive surgery.

One of the limitations of this study is that not all possible prognostic factors are included in the analyses. Most important, the Netherlands Cancer Registry did not contain detailed information on surgery or chemotherapy: factors known to affect survival. However, the number of chemotherapy cycles and the response to

**Table 3**  
 Number of patients and 5- and 10-year OS for combinations of tumour characteristics of women ≤40 years old at diagnosis with EOC.

Stage	Grade	Histology																	
		Serous			Mucinous			Endometrioid			Clear cell			NOS			Other		
		N	5 yr (CI)	10 yr (CI)	N	5 yr (CI)	10 yr (CI)	N	5 yr (CI)	10 yr (CI)	N	5 yr (CI)	10 yr (CI)	N	5 yr (CI)	10 yr (CI)	N	5 yr (CI)	10 yr (CI)
1	1	43	98 (85–99)	92 (78–97)	207	95 (91–98)	94 (89–96)	38	95 (80–99)	90 (71–97)	<5	–	–	20	95 (69–99)	90 (66–97)	<5	–	–
	2	17	81 (53–94)	81 (53–94)	96	83 (73–89)	78 (68–86)	30	93 (75–98)	85 (66–94)	7	71 (26–92)	71 (26–92)	10	80 (41–95)	80 (41–95)	<5	–	–
	3	7	86 (33–98)	69 (21–91)	18	65 (38–82)	57 (30–77)	<5	–	–	6	80 (20–97)	0 (–)	5	40 (5–75)	20 (1–58)	<5	–	–
2	U	34	97 (81–99)	94 (78–98)	93	91 (83–95)	85 (75–91)	8	100 (–)	83 (27–97)	22	95 (71–99)	91 (67–98)	10	70 (33–89)	70 (33–89)	20	95 (69–99)	95 (69–99)
	1	17	94 (63–99)	94 (63–99)	5	80 (20–97)	53 (7–86)	6	100 (–)	100 (–)	<5	–	–	<5	–	–	<5	–	–
	2	<5	–	–	<5	–	–	<5	–	–	<5	–	–	<5	–	–	<5	–	–
3	3	6	67 (19–90)	0 (–)	<5	–	–	8	88 (39–98)	75 (31–93)	<5	–	–	5	50 (6–84)	0 (–)	<5	–	–
	U	7	86 (33–98)	86 (33–98)	<5	–	–	<5	–	–	6	63 (14–89)	31 (1–73)	6	67 (19–90)	67 (19–90)	<5	–	–
	1	76	78 (66–86)	63 (50–74)	8	25 (4–56)	25 (4–56)	<5	–	–	<5	–	–	<5	–	–	<5	–	–
4	2	54	37 (24–49)	17 (8–29)	16	13 (2–33)	6 (1–25)	10	57 (22–81)	29 (5–60)	<5	–	–	10	10 (1–36)	0 (–)	<5	–	–
	3	64	37 (25–50)	22 (12–34)	20	15 (4–37)	5 (1–22)	6	25 (1–65)	25 (1–65)	5	27 (1–69)	27 (1–69)	38	17 (1–35)	12 (4–27)	6	33 (5–68)	17 (1–52)
	U	61	36 (24–49)	25 (14–37)	17	29 (11–51)	22 (6–44)	<5	–	–	6	17 (1–52)	17 (1–52)	24	29 (13–48)	25 (10–43)	9	0 (–)	–
U	1	9	38 (9–68)	38 (9–68)	<5	–	–	<5	–	–	<5	–	–	<5	–	–	<5	–	–
	2	16	19 (5–40)	0 (–)	<5	–	–	<5	–	–	<5	–	–	<5	–	–	<5	–	–
	3	21	21 (7–41)	0 (–)	8	0 (–)	–	<5	–	–	<5	–	–	8	17 (1–52)	17 (1–52)	<5	–	–
U	U	22	34 (15–54)	17 (3–39)	<5	–	–	<5	–	–	<5	–	–	5	20 (1–58)	20 (1–58)	<5	–	–
	1	<5	–	–	<5	–	–	<5	–	–	<5	–	–	<5	–	–	<5	–	–
	2	<5	–	–	<5	–	–	<5	–	–	<5	–	–	<5	–	–	<5	–	–
U	3	6	50 (11–80)	17 (1–52)	<5	–	–	<5	–	–	<5	–	–	7	29 (4–61)	0 (–)	<5	–	–
	U	11	55 (23–78)	55 (23–78)	8	37 (5–71)	37 (5–71)	<5	–	–	<5	–	–	12	42 (17–71)	33 (11–63)	<5	–	–

Abbreviations: 5 yr 5-year observed survival in %; CI 95% confidence interval in %; 10 yr 10-year observed survival in %; NOS not otherwise specified; Other including neuroendocrine, small cell, squamous cell, mesonefric, undifferentiated, mixed subtypes and Brenner tumours; U unknown.

**Table 4**  
Number of patients and 5- and 10-year observed survival for combinations of tumour characteristics of women >40 years old at diagnosis with EOC.

Stage	Grade	Histology																	
		Serous			Mucinous			Endometrioid			Clear Cell			NOS			Other		
		N	5 yr (CI)	10 yr (CI)	N	5 yr (CI)	10 yr (CI)	N	5 yr (CI)	10 yr (CI)	N	5 yr (CI)	10 yr (CI)	N	5 yr (CI)	10 yr (CI)	N	5 yr (CI)	10 yr (CI)
1	1	340	83 (79–87)	70 (64–75)	664	85 (82–87)	74 (70–78)	401	89 (86–92)	77 (72–82)	38	82 (65–91)	71 (53–83)	120	82 (74–88)	70 (61–78)	20	88 (58–97)	77 (41–92)
	2	442	75 (70–78)	62 (57–66)	303	79 (73–83)	69 (63–74)	461	82 (78–85)	69 (64–73)	91	74 (63–82)	66 (55–75)	157	69 (61–75)	54 (46–61)	16	63 (32–83)	51 (19–76)
	3	513	69 (65–73)	50 (45–55)	83	61 (49–71)	48 (37–59)	219	73 (67–79)	55 (48–62)	132	79 (70–85)	62 (52–71)	251	62 (55–68)	47 (40–53)	44	54 (32–72)	24 (5–49)
2	U	358	73 (68–77)	57 (51–62)	356	79 (74–83)	67 (62–73)	151	85 (78–90)	72 (64–79)	432	75 (70–79)	66 (61–71)	264	44 (38–50)	34 (28–41)	97	84 (75–90)	66 (54–76)
	1	82	67 (55–76)	54 (41–64)	39	59 (42–73)	56 (38–70)	77	81 (69–89)	68 (52–80)	6	33 (5–68)	–	23	82 (59–93)	73 (50–87)	<5	–	–
	2	192	55 (48–62)	35 (28–43)	43	60 (43–73)	42 (26–57)	157	71 (62–77)	52 (43–61)	16	56 (30–76)	56 (30–76)	95	41 (31–51)	27 (19–37)	6	42 (6–77)	42 (6–77)
3	3	494	56 (51–61)	38 (33–44)	30	46 (27–62)	29 (13–47)	162	56 (48–63)	42 (33–50)	47	53 (37–67)	41 (25–56)	258	45 (38–51)	31 (25–37)	36	41 (17–64)	31 (9–56)
	U	221	51 (44–57)	37 (30–43)	52	47 (33–60)	37 (22–51)	60	67 (53–78)	50 (35–64)	128	54 (45–63)	50 (40–59)	253	14 (10–19)	8 (5–12)	12	58 (27–80)	47 (17–72)
	1	292	47 (41–53)	31 (26–38)	137	33 (16–30)	13 (8–20)	46	57 (41–71)	36 (21–52)	<5	–	–	80	13 (6–21)	7 (3–14)	<5	–	–
4	2	1243	25 (22–27)	11 (2–9)	179	11 (7–17)	5 (2–9)	217	36 (30–43)	26 (20–33)	35	31 (16–46)	18 (7–34)	563	14 (11–17)	6 (4–9)	8	50 (15–77)	50 (15–77)
	3	3316	26 (24–27)	11 (10–12)	183	16 (11–22)	8 (4–12)	414	33 (29–38)	17 (13–21)	97	17 (10–25)	14 (7–22)	1832	17 (15–18)	8 (7–9)	82	36 (19–53)	21 (7–39)
	U	2081	20 (18–21)	9 (8–11)	250	9 (6–13)	6 (3–10)	137	29 (21–37)	16 (10–24)	198	16 (11–22)	14 (9–20)	2233	7 (6–8)	3 (2–4)	49	25 (14–39)	16 (6–29)
U	1	51	28 (16–42)	19 (8–33)	22	11 (2–30)	–	8	0 (–)	–	<5	–	–	7	0 (–)	–	<5	–	–
	2	226	17 (12–22)	7 (4–11)	51	10 (4–20)	–	30	25 (11–42)	14 (5–30)	5	0 (–)	–	88	7 (3–14)	6 (2–13)	<5	–	–
	3	869	18 (15–21)	8 (6–11)	46	5 (1–14)	2 (0.2–10)	81	11 (5–20)	9 (3–17)	20	18 (5–38)	12 (2–31)	387	13 (10–16)	3 (1–6)	26	0 (–)	–
U	U	705	11 (8–14)	3 (1–5)	55	11 (4–21)	5 (1–15)	29	16 (5–33)	5 (0.4–21)	48	13 (5–25)	–	613	8 (6–11)	3 (2–6)	14	21 (5–45)	11 (8–35)
	1	43	42 (27–56)	19 (8–32)	16	69 (40–86)	69 (40–86)	5	60 (13–88)	60 (13–88)	<5	–	–	23	35 (17–54)	22 (8–40)	<5	–	–
	2	156	14 (9–20)	8 (4–13)	15	36 (13–59)	21 (5–45)	13	31 (10–55)	23 (6–47)	<5	–	–	99	11 (6–18)	8 (4–14)	<5	–	–
U	3	377	19 (15–23)	10 (7–14)	14	14 (2–37)	7 (0.5–28)	18	41 (19–63)	24 (7–45)	<5	–	–	396	19 (15–23)	13 (9–16)	9	33 (1–78)	–
	U	478	14 (11–18)	5 (3–8)	62	22 (12–33)	11 (4–21)	23	57 (34–74)	39 (20–58)	25	24 (10–42)	24 (10–42)	1722	5 (4–7)	2 (2–3)	16	56 (30–76)	38 (15–60)

Abbreviations: 5 yr 5-year observed survival in %; CI 95% confidence interval in %; 10 yr 10-year observed survival in %; NOS not otherwise specified; Other including neuroendocrine, small cell, squamous cell, mesonefric, undifferentiated, mixed subtypes and Brenner tumours; U unknown.

chemotherapy will be unclear at the time of counselling (shortly after diagnosis) in most cases, making it less relevant to take chemotherapy into account for counselling purposes. Furthermore, outcome of cytoreductive surgery might also be unknown at the time of counselling, since neoadjuvant chemotherapy and interval surgery has become the treatment of choice for an increasing proportion of EOC patients over time [22]. To account for the changes in treatment and diagnostics over time, the year of diagnosis is included as prognostic factor in the univariate and multivariate analyses. The inability to include therapy as prognostic factor might have resulted in an overestimation of the difference in OS between the younger and older age group in our study. Older patients, especially those who are over 70 years old at time of diagnosis, are known to receive (combination) therapy less often and, thereby, show worse overall and relative survival [22]. Nevertheless, significant differences in therapy within the younger age group are not expected, besides differences in therapy that are determined by factors we did adjust for: stage, grade or histology. In terms of other prognostic factors that might be of interest, data on *BRCA1/2* mutation status are lacking [23]. It is known that the minority of women who underwent DNA analysis because of EOC diagnosis under 40 years old appear to have a *BRCA* germline mutation [24].

Another limitation is the amount of missing data in our database. Data in the Netherlands Cancer Registry are retrieved from hospital records, which are not always complete. However, we observe a decrease in missing data over the years which is hopeful for future research.

In this study we set the cut-off point for early-onset EOC at 40 years of age. This is arbitrary, although the same cut-off has been used in other publications [8,9]. Other studies showed that very young women (under 30 years old) had even a better survival compared to women between 31 and 40 years old, and elderly (over 70 years old) had even worse survival rates compared to women under 70 years old [7,8]. This might be partially explained by differences in received therapy, as mentioned earlier in this section. The influence of age on elderly might disappear if they do receive optimal treatment [25]. Dividing our database into two age groups could have influenced the differences in survival and the impact of age on survival. The database was not divided in more age subgroups, because the number of patients per group would have significantly dropped and therefore would have made it more difficult to generate useful survival data.

In our study, we were not able to determine cause-specific survival because the Netherlands Cancer Registry does not contain data on recurrent disease or cause of death. Furthermore, relative survival ratios, i.e. correcting OS for age-dependent expected survival, were not calculated. Since expected survival in the general population would be expected higher in the older group, their relative survival might be lower. Differences in relative survival might thus be smaller between age groups than differences in OS. Nevertheless, we deliberately chose to calculate OS instead of relative survival, because our aim was to retrieve absolute survival risks in order to inform patients on their life expectancy. In our opinion, the exact cause of death would be less interesting to them.

In conclusion, women of 40 years and younger diagnosed with EOC showed better OS than women diagnosed at older age. In addition, distribution of tumour characteristics differs between age groups, and certain characteristics affect survival in a different manner when present in young women compared to older women. These findings emphasize the importance of counselling young women differently than women over 40 years old. Younger women should be counselled more favourable from the beginning about their chances to survive than older women, even without taking treatment and treatment outcomes into account.

## Authors' contributions

JE, MH and JdH were involved in the conception and design of the study. JE, MH, MvdA, AvA and JdH were involved in analysis and interpretation of the data. All aforementioned authors participated in drafting and/or revising the manuscript and all authors approved the final version that was submitted for publication.

## Declaration of competing interest

The authors declare that they have no conflicts of interests.

## References

- [1] Commissie Richtlijnen Gynaecologische Oncologie, Landelijke richtlijn Epitheliale Ovariumcarcinoom, 2012.
- [2] J.W. Carlson, et al., Serous tubal intraepithelial carcinoma: its potential role in primary peritoneal serous carcinoma and serous cancer prevention, *J. Clin. Oncol.* 26 (2008) 4160–4165.
- [3] S.H. George, R. Garcia, B.M. Slomovitz, Ovarian cancer: the fallopian tube as the site of origin and opportunities for prevention, *Front. Oncol.* 6 (2016) 108.
- [4] Cancer Research UK, Ovarian Cancer Statistics. <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/incidence>, 2012. (Accessed 13 June 2016).
- [5] National Cancer Institute, Cancer Stat Facts: Ovarian Cancer. <http://seer.cancer.gov/statfacts/html/ovary.html>, 2010–2012. (Accessed 13 June 2016).
- [6] Dutch cancer registration, Cijfers over kanker. <http://cijfersoverkanker.nl>, 1990–2015. (Accessed 12 June 2016).
- [7] D. Massi, et al., Epithelial ovarian tumors in the reproductive age group: age is not an independent prognostic factor, *Cancer* 77 (1996) 1131–1136.
- [8] L.R. Duska, et al., Epithelial ovarian carcinoma in the reproductive age group, *Cancer* 85 (1999) 2623–2629.
- [9] J.E. Sardi, P. Anchezar, A. Bermudez, Favorable clinical behavior in young ovarian carcinoma patients: a rationale for conservative surgery? *Int. J. Gynecol. Cancer* 15 (2005) 762–769.
- [10] Society of Gynecologic Oncology, FIGO Ovarian Cancer Staging Effective Jan. 1, 2014, 2014 (accessed 7 July 2016).
- [11] S.G. Silverberg, Histopathologic grading of ovarian carcinoma: a review and proposal, *Int. J. Gynecol. Pathol.* 19 (2000) 7–15.
- [12] F.A. Tavassoli, P. Devilee, Pathology and genetics of Tumours of the breast and female genital organs, in: WHO/IARC Classification of Tumours, third ed., 2003.
- [13] D. Pectasides, et al., Epithelial ovarian carcinoma in younger vs older women: is age an independent prognostic factor? The Hellenic Oncology Cooperative Group experience, *Int. J. Gynecol. Cancer* 17 (2007) 1003–1010.
- [14] A.M. van Altena, et al., Trends in therapy and survival of advanced stage epithelial ovarian cancer patients in the Netherlands, *Gynecol. Oncol.* 125 (2012) 649–654.
- [15] A.P. Heintz, et al., Carcinoma of the ovary. FIGO 26th annual report on the results of treatment in gynecological cancer, *Int. J. Gynaecol. Obstet.* 95 (2006) S161–S192.
- [16] F.A. Eggink, et al., Improved outcomes due to changes in organization of care for patients with ovarian cancer in the Netherlands, *Gynecol. Oncol.* 141 (2016) 524–530.
- [17] A.M. van Altena, et al., Efficacy of a regional network for ovarian cancer care, *Obstet. Gynecol.* 122 (2013) 668–675.
- [18] W.P. McGuire, et al., Cyclophosphamide and cisplatin versus paclitaxel and cisplatin: a phase III randomized trial in patients with suboptimal stage III/IV ovarian cancer (from the Gynecologic Oncology Group), *Semin. Oncol.* 23 (1996) 40–47.
- [19] A. Covens, et al., Systematic review of first-line chemotherapy for newly diagnosed postoperative patients with stage II, III, or IV epithelial ovarian cancer, *Gynecol. Oncol.* 85 (2002) 71–80.
- [20] T.G. Clark, et al., A prognostic model for ovarian cancer, *Br. J. Cancer* 85 (2001) 944–952.
- [21] H.J. Park, et al., A new prognostic index model using meta-analysis in early-stage epithelial ovarian cancer, *Gynecol. Oncol.* 126 (2012) 357–363.
- [22] M.S. Schuurman, et al., Treatment and outcome of elderly patients with advanced stage ovarian cancer: a nationwide analysis, *Gynecol. Oncol.* 149 (2018) 270–274.
- [23] K.L. Bolton, et al., Association between *BRCA1* and *BRCA2* mutations and survival in women with invasive epithelial ovarian cancer, *Jama* 307 (2012) 382–390.
- [24] M. Arts-de Jong, et al., Added value of family history in counseling about risk of *BRCA1/2* mutation in early-onset epithelial ovarian cancer, *Int. J. Gynecol. Cancer* 23 (2013) 1406–1410.
- [25] T.L. Jorgensen, et al., Significance of age and comorbidity on treatment modality, treatment adherence, and prognosis in elderly ovarian cancer patients, *Gynecol. Oncol.* 127 (2012) 367–374.