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Complete List of Authors:	Ørskov, Mette; Odense University Hospital, Department of Gynecology and Obstetrics; Institute of Clinical Research, University of Southern Denmark, Research Unit of Gynecology Iachina, Maria; Odense University Hospital, Centre for Clinical Epidemiology ; Institute of Clinical Research, University of Southern Denmark, Research Unit of Clinical Epidemiology Guldberg, Rikke; Odense University Hospital, Center for Clinical Epidemiology; Institute of Clinical Research, University of Southern Denmark, Research Unit of Clinical Epidemiology Mogensen, Ole; Odense University Hospital, , Department of Gynecology and Obstetrics; Institute of Clinical Research, University of Southern Denmark, Research Unit of Gynecology Nørgård, Bente; Odense University Hospital, Center for Clinical Epidemiology; Institute of Clinical Research, University of Southern Denmark, Research Unit of Clinical Epidemiology
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Predictors of mortality within one year after primary ovarian cancer surgery, a nationwide cohort study

Mette Ørskov, MD, PhD[1]

Maria Iachina, MSc, PhD[2]

Rikke Guldberg, MD, PhD[2]

Ole Mogensen, MD, DMSc[1]/Bente Mertz Nørgård, MD, PhD, DMSc[2]

1: Department of Gynecology and Obstetrics, Odense University Hospital, and Research Unit of Gynecology and Institute of Clinical Research, University of Southern Denmark.

2: Centre for Clinical Epidemiology and Research Unit of Clinical Epidemiology, Odense University Hospital and Institute of Clinical Research, University of Southern Denmark

Corresponding author: Mette Ørskov, email: oerskov@dadlnet.dk

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ABSTRACT

Objectives: To identify predictors of mortality within one year after primary ovarian cancer surgery.

Design: Prospective nationwide cohort study from 1 January 2005 to 31 December 2012.

Setting: The Danish Gynaecology Cancer Database and the Danish Civil Registration System.

Participants: 2,654 women with first-time ovarian cancer surgery.

Outcome measures: Overall one-year survival and predictors of mortality within 0-180 days and 181-360 days after ovarian cancer surgery. The examined predictors were age, preoperative American Society of Anesthesiologists (ASA) score, body mass index (BMI), International Federation of Gynaecology and Obstetrics (FIGO) stage, residual tumour tissue after surgery, perioperative blood transfusion, and calendar year of surgery.

Results: Overall one-year survival was 51%. Within 0-180 days after surgery, the three most important predictors of mortality were residual tumour tissue >2 cm (HR=4.58 (95% CI 3.19-6.56)), age above 61 years (HR=2.68 (95% CI 1.85-3.89)), and residual tumour tissue ≤ 2 cm (HR= 2.50 (95% CI 1.64-3.82)). Within 181-360 days after surgery FIGO-stage III-IV (HR=2.80 (95% CI 1.75-4.48)), BMI <18.5 kg/cm^2 (HR=2.09 (95% CI 1.18-3.67)), and residual tumour tissue >2 cm (HR=1.87 (95% CI 1.27-2.74)), were the three most important predictors. ASA score and perioperative blood transfusion were both found to be predictors of mortality, although no effect on calendar year of surgery was observed.

Conclusions: The most important predictors of mortality within one year after surgery were residual tumour tissue, advanced FIGO stage, and being underweight. We suggest that the surgeon should not only aim for radical surgery, but also pay special attention to comorbidity, nutritional state, and the need for perioperative blood transfusion.

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Strengths and limitations of this study

- A population-based study with prospective registered data

- In total of 2,654 women included

- High quality of data sources and no loss to follow-up

- Adjustment for several factors: age, preoperative health score, body mass index, FIGO stage, residual tumour tissue after surgery, perioperative blood transfusion

- Unable to perform analyses regarding neoadjuvant chemotherapy prior to surgery

- Missing data on smoking and alcohol

- No access to laboratory data

INTRODUCTION

The 5-year survival is a traditional measure of the survival of cancer patients. Women with ovarian cancer have a median survival of approximately two years [1] and we may overlook important factors for survival by primarily focusing on the long-term survival. Ovarian cancer has a high mortality [2], and we need to focus on additional areas of prognostic importance in order to improve the outcome. Previous studies of the survival of women with ovarian cancer have focused on mortality; either within the first 30-60 days after surgery or on long-term survival. These studies have identified commonplace predictors of mortality (i.e. complications to surgery, FIGO-stage and residual tumour tissue [3]). To the best of our knowledge, no former studies have focused on predictors on mortality within one year after primary ovarian cancer surgery. However, we hypothesised that analysing the intermediate survival of the women (up to one year after surgery) would provide valuable information on potentially significant factors for survival. If this hypothesis proves correct these factors should be considered in the perioperative settings and are useful in the counselling of the patient. Using data from the nationwide Danish Gynaecology Cancer Database (DGCD)

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obtained from 2005 until 2012, and the Danish Civil Registration System (CPR registry), the aims were to examine predictors of mortality within 0-180 days and 181-360 days after primary ovarian cancer surgery. The examined predictors of mortality were age, preoperative American Society of Anaesthesiologists (ASA) score [4], smoking, body mass index (BMI), International Federation of Gynaecology and Obstetrics (FIGO) stage, residual tumour tissue after surgery, perioperative blood transfusion, and calendar year of surgery.

MATERIALS AND METHODS

Study population

The study includes all Danish women who had undergone primary ovarian cancer surgery performed from January 1st 2005 to 31 December 2012, and identified in the DGCD. The DGCD is a national clinical database established on 1 January, 2005 [5], and since then every patient with a first-time diagnosis of ovarian cancer has been prospectively registered. This was due to mandatory reports from all Danish departments of gynaecology and histopathology. The DGCD contains details about preoperative patient characteristics (i.e. age, ASA score, smoking, and BMI), perioperative information (i.e. FIGO-stage, residual tumour tissue after surgery, blood transfusion, etc.), and postoperative details (i.e. histopathology, final tumour stage verification, complications, and adjuvant chemotherapy).

The ovarian cancer data in the DGCD has previously been validated, and the registry was concluded to be valuable for quality monitoring in gynaecological oncology [6]. Each patient is identified by a unique 10-digit number given to all Danish citizens by the CPR registry when residence permits are gained [7].

The DGCD included 2,831 women who had primary ovarian cancer surgery performed during the study period. The following were exclusion criteria: 1) a preoperative ASA score obtained more

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than six months before surgery (n=119), presuming six months to be the maximum time period to surgery if neoadjuvant chemotherapy prior to surgery has been administrated, and 2) a histopathology requisition completed later than two weeks after surgery (n=58), signifying that the specific pathology requisition most certainly originate from the current surgery. From the CPR registry we produced information on mortality.

Data on predictive variables

From the DGCD we specifically obtained data on age at the time of surgery, preoperative ASA score [4] (indicating comorbidity at the time of surgery), preoperative BMI [8], preoperative smoking habits, FIGO-stage [9], size of residual tumour tissue after surgery (visually evaluated by the surgeon at the end of surgery), perioperative blood transfusion, and calendar year of surgery. We also received data on alcohol consumption, but due to several missing pieces of data, this parameter was omitted from further analyses. All the above mentioned parameters, apart from alcohol, were evaluated as predictors of mortality.

Age: Women were divided in two groups according to the median age: 1) age ≤ 61 years (young) and 2) age > 61years (old) at the time of surgery.

ASA score: At the preoperative interview the anaesthetist reported the ASA score of each woman, who were divided in two groups: 1) ASA score = 1 (without comorbidity) and 2) ASA score > 1 (with comorbidity).

Smoking: At the preoperative interview, women were divided in two groups according to current smoking status: 1) non-smokers and 2) smokers.

BMI: At the preoperative interview women were assigned into three groups according to BMI: 1) BMI <18.5 kg/cm^2 (underweight), 2) BMI 18.5-25 kg/cm^2 (normal), and 3) BMI >25 kg/cm^2 (overweight).

FIGO-stage: FIGO-stage was evaluated by the surgeon at the end of surgery, and women were divided into two groups: 1) FIGO-stages I and II (localised disease), and 2) FIGO-stages III and IV (advanced disease).

Residual tumour: The size of residual tumour was evaluated by the surgeon at the end of surgery, and women were divided into three groups: 1) No residual tumour, 2) residual tumour ≤ 2 cm, and 3) residual tumour > 2 cm.

Blood transfusion: Women were grouped in two: 1) those who did not receive perioperative blood transfusion, and 2) those that did.

Statistical analysis

Overall survival was illustrated by Kaplan-Meier plot of each of the following variables: *age* (young, old), *ASA score* (1 and > 1), smoking (no, yes), *BMI* (underweight, normal, overweight), *FIGO-stage* (localised, advanced), residual tumour tissue after surgery (none, ≤ 2 cm, and > 2 cm), and *perioperative blood transfusion* (no, yes). Predictive variables of interests were assessed descriptively according to death within 0-180 days and 181-360 after surgery. To estimate the time-varying effect of the predictive variables on survival within the two time periods (0-180 days and 181-360 after surgery) we used an extended Cox model [10]. Included variables followed the abovementioned categorisation, and calendar year of surgery was included as a continuous variable. Since missing data concerning smoking was observed not to be random, the estimates obtained for this variable may be biased. Accordingly, if there is any interaction between this variable and other covariates, estimates of other covariates may also be biased. Omitting smoking from the model did not substantially change the estimates of the other variables, and thus the final model was reduced based on the results of the Wald tests. The final model included the following variables: *age*, *ASA score*, *BMI*, *FIGO-stage*, *residual tumour tissue after surgery*, *perioperative blood transfusion*, and

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calendar year. After applying the model, we tested whether there is a significant difference for each predictor variable between the two time periods by performing a Wald test. The results of the extended Cox model were reported by the Hazard Ratio (HR) and 95% confidence intervals (95% CI), and the Wald test with the p-values.

The present study was approved by the Danish Data Protection Agency (J. nr. 2012-41-0485). All analyses were conducted using Stata 12 software (StataCorp LP, College Station, TX, USA).

RESULTS

Our study included 2,654 women with primary ovarian cancer surgery from 1 January 2005 to 31 December 2012. At the time of surgery the majority of women were old (58%), with a preoperative ASA score >1 (61%), normal weighted (52%), had advanced FIGO-stage (63%), and radical surgery (68%), and did not receive perioperative blood transfusion (75%) (Table 1). Overall one-year survival was 51%. A total of 1,288 women (49%) died within the first postoperative year. Women who died after surgery (both within 0-180 days and 181-360 days) were all characterised by old age, ASA score >1, and advanced FIGO-stage. For further descriptive details, see Table 1.

<u>Survival</u>

The Kaplan-Meier figures show the separate effect of the included predictive variables on survival up to 360 days after surgery (Figure 1). The figures illustrate a worse rate of survival in old compared to young women, in women with ASA score >1 compared to ASA=1, in underweight women compared to over- and normal weight women, in women with advanced FIGO-stage compared to localised FIGO-stage, in women with >2cm residual tumour tissue left at surgery compared to ≤2cm, and no residual tumor tissue, respectively, and in women who received perioperative blood transfusion in comparison to no transfusion.

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Predictors on mortality

The results of the Cox regression analysis are shown in Table 2. Old age had a statistically significant negative impact on mortality both within 0-180 days and 181-360 days after surgery. ASA score ≥1 had a statistically significant negative impact on mortality only within 0-180 days after surgery. The magnitude of the effect of old age, as well as ASA score ≥1 decreased significantly during time, for age with HR=2.68 (95% CI 1.85-3.89) within 0-180 days after surgery, to HR=1.05 (95% CI 1.08-2.09) within 181-360 days, and for ASA score with HR=2.22 (95% CI 1.50-3.29) within 0-180 days after surgery to HR=1.30 (95% CI 0.92-1.83) within 181-360 days. Being underweight increased mortality in both time periods compared with normal weighted women with HR=2.01 (95% CI 1.30-3.10) and 2.09 (95% CI 1.18-3.67) within 0-180 days and 181-360 days after surgery, respectively. Advanced FIGO-stage only had a statistically significant effect within 181-360 days after surgery (HR=2.80 (95% CI 1.75-4.48)). Residual tumour ≤ 2 cm and > 2cm significantly decreased survival in both time periods after surgery, with the most pronounced effect for residual tumour > 2cm within 0-180 days after surgery (HR=4.58 (95% CI 3.19-6.56)). The impact of residual tumour > 2cm significantly decreased between the two time periods after surgery. Perioperative blood transfusion significantly increased mortality in the period 0-180 days after surgery (HR=1.61 (95% CI 1.21-2.15)). In the model, calendar year of surgery, did not affect mortality.

DISCUSSION

The present study examined predictors of mortality within 0-180 days and 181-360 days after primary ovarian cancer surgery. Within 0-180 days after surgery the most important predictors of mortality were residual tumor tissue > 2cm and ≤ 2cm, and old age, where residual tumour tissue of

more than 2cm was the most important predictor of death within the first six months after surgery. Within 181-360 days after surgery advanced FIGO-stage, being underweight, and residual tumour tissue > 2cm were the three most important predictors of mortality. It is worth noting that our study suggests that being underweight significantly increases mortality within the first postoperative year. Our study has several strengths; it is based on nationwide prospective registered data, it includes several important predictive variables for mortality, and no women were lost at follow-up due to complete information during the entire study period. The validity of data in the DGCD is essential for our results and the database has previously been validated on primary epithelial ovarian cancer by a comparison of the surgical and histopathological data in the registry with the corresponding medical file and the National Registry of Patients as reference. The DGCD was found to be valuable for quality monitoring in gynaecological oncology [6].

We observed that residual tumour tissue (both less and more than 2cm) left at surgery has a statistically significant negative effect on survival in both periods after surgery. This finding has been outlined in many other studies [11,12,13], but our results indicate that residual tumour of more than 2cm are the most important predictor of death within the first six months after surgery. The presents results and other studies unambiguously identify macroscopic tumour tissue resection as an important surgical issue in improving survival [14,15,16]

We also observed advanced FIGO-stage to be an important predictor of mortality, but mainly within 181-360 days after surgery. The negative impact of advanced FIGO-stage on mortality is well known, and has been described in other investigations [14,15,16], but the negative effect on mortality within the first year after surgery has not previously been reported.

We observed underweight to be a predictor of mortality both 0-180 days and 181-360 days after surgery. In contrast, Skírnisdóttir et al [17] concluded that BMI did not influence survival when evaluating women with low-stage ovarian cancer. As in our study, Skírnisdóttir et al used the BMI

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reported at the time of surgery, but although they did not evaluate its influence on survival until 19-214 months later. Therefore, for the first time we report the negative effect of being underweight on mortality within the first postoperative year. Malnutrition and ascites are well-known problems among ovarian cancer patients [18,19]. Due to the frequent concomitant presence of ascites, the real preoperative BMI may be lower than measured, and the negative influence exerted by underweight thereby underestimated in our analyses. In a recent study, Ataseven et al [20] observed low preoperative albumin to be an independent predictor for severe postoperative complications, and to be independently associated with reduced overall survival. We did not have information of serum albumin which could have qualified the measurement of nutritional status. Body composition CT may even be superior to serum albumin when nutritional status prior to surgery is evaluated due to the observation regarding low subcutaneous and muscular fat as an independent predictor of mortality [21], but we did not have such examinations.

In our study, old women demonstrated poorer survival in comparison to young women in the first year after surgery, with the most pronounced impact of old age on mortality observed 0-180 days after surgery and thereafter exceeded by more important factors. In several countries, the relative one- and five-year survival rates of women diagnosed with ovarian cancer have previously been reported to decrease with old age [22,23,24], however, to the best of our knowledge, the fact that the impact of old age occurs mainly in the first period after surgery it new information. Jørgensen et al [25], Trillsch et al [26], and Sabatier et al [27] noted that old women with ovarian cancer may demonstrate worse survival due to potentially inferior treatment, but our data does not include information to illuminate this aspect.

We found comorbidity (ASA >1) as a predictor of mortality, but only at 0-180 days after surgery, and with a decreasing importance over time. Grann et al [28], and Sperling et al [29] also observed comorbidity to be a predictor of mortality. However, in contrast to our results, they did not evaluate

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the effect on the immediate postoperative time period, but evaluated data after one (Grann and Sperling[28,29]), and five years (Grann [28]), respectively. Consequently, our data also offers new information in this field, and may indicate that reduction of any preexisting comorbidity might be important in increasing survival after primary ovarian cancer surgery.

Perioperative blood transfusion was observed to be a predictor of mortality 0-180 days after surgery. Within women with ovarian cancer this is a new finding, but a negative effect of blood transfusion on survival has been described in other diseases. As reported by Schiergens et al [30] perioperative blood transfusion was observed to be an independent predictor for reduced recurrence-free survival when evaluating patients undergoing curative intended liver resection for colorectal liver metastases, while preoperative anaemia, major intraoperative blood loss, and major postoperative complications were all independently associated with the need for transfusion. Hallet et al [31] also found perioperative blood transfusion to be an independent predictor for both reduced overall survival and reduced recurrence-free survival when evaluating patients with partial hepatectomy following colorectal liver metastasis. Among gynaecologic cancer patients who received perioperative blood transfusion(s), transfusion was also found to be associated with higher morbidity and increased mortality within the immediate 30 days after surgery, when controlling for parameters such as age, comorbidity, preexisting anaemia, type of surgery etc.[32]. Immune modulatory mechanisms have been suggested to induce the above-mentioned complications [33], but the total transfused blood units and the cancer stage should also be considered due to a possible negative effect relating to the more blood units transfused, and the more advanced cancer stage [32]. Since the DGCD does not contain information on haemoglobin levels, classified aneamia in general or total transfused blood units, we were unable to evaluate any possible influence of these parameters. This might indicate that perioperative blood transfusion should only be prescribed to a very restricted group of patients, although this aspect needs to be studied in more detail.

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Our study also contains limitations. Firstly, we have a considerable amount of missing data on certain variables, and we could therefore not examine the impact of smoking and alcohol. Secondly, we were unable to perform analyses regarding neoadjuvant chemotherapy prior to surgery simply due to absent information on this parameter throughout the entire study period, and thirdly, it would have been valuable with access to laboratory data (data, however, not being available nationwide).

Residual tumor tissue, advanced FIGO-stage, being underweight, old age, comorbidity, and perioperative blood transfusion were all found to be predictors of mortality within the first year after primary ovarian cancer surgery, although no effect on calendar year of surgery was observed. Our results suggest that that the surgeon should not only aim for radical surgery, but also pay special attention to comorbidity, nutritional state, old age, and the need for perioperative blood transfusion. These findings should be confirmed in other settings, and future studies are needed to assess the impact of smoking, alcohol, units of blood transfused, and neoadjuvant chemotherapy as predictors of mortality within the first postoperative year after primary ovarian cancer surgery.

ARTICLE SUMMARY

In the present study we aimed to examine predictors of mortality within 0-180 days and 181-360 days after ovarian cancer surgery. The examined predictors were age, ASA score, BMI, FIGO-stage, residual tumour tissue after surgery, perioperative blood transfusion, and calendar year of surgery. Overall one-year survival was 51 %. The most important predictors of mortality within one year after surgery were residual tumour tissue, advanced FIGO stage, and low BMI. Our results suggest that the surgeon should aim for radical surgery. However, comorbidity, being underweight, and blood transfusion were also significant predictors of mortality and need to be studied in more detail.

Table 1. Descriptive characteristics according to death up to 361 days after primary ovarian cancer surgery in Danish women performed from 2005-2012 (percentage distribution in brackets).

		Number of women	Women who died within 0-180 days after surgery	Women who died within 181-360 days after surgery	Women who survived at least 361 days after surgery
All women		2,654 (100)	226 (9)	1,062 (40)	1,366 (51)
Age	Young (%)	1,120 (42)	35 (15)	409 (39)	676 (49)
	Old (%)	1,534 (58)	191 (85)	653 (61)	690 (51)
ASA	Score 1 (%)	1,023 (39)	33 (14)	370 (35)	620 (45)
	Score > 1 (%)	1,622 (61)	192 (85)	687 (65)	743 (54)
	Missing (%)	9 (0)	1 (0)	5 (0)	3 (0)
Smoking	No (%)	1,306 (49)	95 (42)	520 (49)	691 (51)
	Yes (%)	1,046 (39)	89 (39)	399 (38)	558 (41)
	Missing (%)	303 (11)	42 (19)	143 (13)	117 (9)
BMI	Underweight (%)	117 (4)	24 (11)	42 (4)	51 (4)
	Normal (%)	1,369 (52)	122 (54)	553 (52)	694 (51)
	Overweight (%)	1,095 (41)	72 (32)	438 (41)	585 (43)
	Missing (%)	73 (3)	8 (4)	29 (3)	36 (3)
FIGO-stage	Localized (%)	965 (36)	34 (15)	186 (18)	745 (55)
	Advanced (%)	1,668 (63)	190 (84)	868 (82)	610 (45)
	Missing (%)	21 (1)	2 (1)	8 (1)	11 (1)
Residual tumour	None (%)	1,798 (68)	65 (29)	585 (55)	1,148 (84)
	≤ 2 cm (%)	328 (12)	45 (20)	193 (18)	90 (7)
	> 2 cm (%)	519 (20)	115 (51)	279 (26)	125 (9)
	Missing (%)	9 (0)	1 (0)	5 (0)	3 (0)
Blood transfusion	No (%)	2,000 (75)	143 (63)	756 (71)	1,101 (81)
	Yes (%)	648 (24)	83 (37)	304 (29)	261 (19)
	Missing (%)	6 (0)	0 (0)	2 (0)	4 (0)

Table 2. Results from Cox regression analyses estimating the impact of possible predictive variables on mortality after primary ovarian cancer surgery in Danish women from 2005-2012. Data are reported by Hazard Ratio (HR) and 95% confidence intervals (CI), and the results of the time-interval heterogeneity test are reported by p-values.

Variable	0 - 180 days after surgery, HR (95% CI)	181 – 360 days after surgery, HR (95% CI)	p-values for Wald tests
Age (Old vs. Young)	2.68 (1.85–3.89)	1.50 (1.08–2.09)	0.0221
ASA score (>1 vs. 1)	2.22 (1.50–3.29)	1.30 (0.92–1.83)	0.0435
BMI (Underweight vs. Normal)	2.01 (1.30-3.10)	2.09 (1.18-3.67)	0. 9203
BMI (Overweight vs. Normal)	0.80 (0.59-1.08)	1.07 (0.78-1.46)	0.1905
Residual tumour (≤ 2 cm vs. None)	2.50 (1.64–3.82)	1.69 (1.12–2.55)	0.1938
Residual tumour (> 2 cm vs. None**)**	4.58 (3.19–6.56)	1.87 (1.27–2.74)	0.0009
FIGO-stage (Advanced vs. Localized)	1.28 (0.83–1.95)	2.80 (1.75–4.48)	0.0153
Blood transfusion (Yes vs. No)	1.61 (1.21-2.15)	1.27 (0.92-1.77)	0.2843
Calendar year (Increasing)	0.87 (0.72-1.05)	1.00 (0.82-1.23)	0.3034

Contributors:

All authors have drafted the article, revised it critically for important intellectual content and approved the final version to be published. Maria Iachina (statistician) has performed the analysis. All the authors are responsible for the study concept and design and have participated in the interpretation of data.

Competing interests: None

Data Sharing Statement:

According to Danish law, we are not allowed to share data without seperat permission from the Danish Data Protection Agency.

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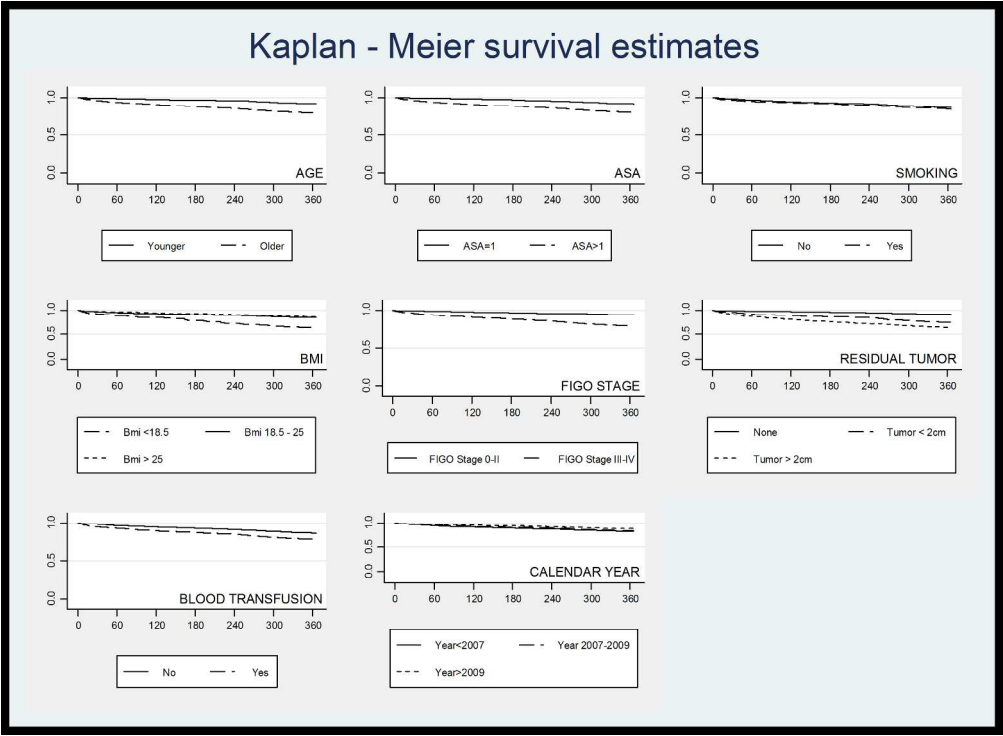
Figure 1.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	not relevant
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4,5,7
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4-7
		(b) Indicate number of participants with missing data for each variable of interest	13 (Table 1)
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8 14 (Table 2)
		(*b*) Report category boundaries when continuous variables were categorized	5-6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Reported in the submission system

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Predictors of mortality within one year after primary ovarian cancer surgery, a nationwide cohort study

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Predictors of mortality within one year after primary ovarian cancer surgery, a nationwide cohort study

Mette Ørskov, MD, PhD[1]

Maria Iachina, MSc, PhD[2]

Rikke Guldberg, MD, PhD[2]

Ole Mogensen, MD, DMSc[1]/Bente Mertz Nørgård, MD, PhD, DMSc[2]

1: Department of Gynecology and Obstetrics, Odense University Hospital, and Research Unit of Gynecology and Institute of Clinical Research, University of Southern Denmark

2: Centre for Clinical Epidemiology and Research Unit of Clinical Epidemiology, Odense University Hospital and Institute of Clinical Research, University of Southern Denmark

Corresponding author: Mette Ørskov, email: oerskov@dadlnet.dk

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ABSTRACT

Objectives: To identify predictors of mortality within one year after primary surgery of ovarian cancer.

Design: Prospective nationwide cohort study from January 1st, 2005 to December 31st, 2012.

Setting: Evaluation of data from the Danish Gynaecology Cancer Database and the Danish Civil Registration System.

Participants: 2,654 women with primary diagnosis of ovarian cancer surgery.

Outcome measures: Overall survival and predictors of mortality within 0-180 days and 181-360 days after the primary surgery. Examined predictors were age, preoperative American Society of Anesthesiologists (ASA) score, body mass index (BMI), International Federation of Gynaecology and Obstetrics (FIGO) stage, residual tumour tissue after surgery, perioperative blood transfusion, and calendar year of surgery.

Results: The overall one-year survival was 84%. Within 0-180 days after surgery, the three most important predictors of mortality from the multivariable model were residual tumour tissue >2 cm versus no residual tumour (HR=4.58 (95% CI 3.20-6.59)), residual tumour tissue ≤2 cm versus no residual tumour (HR=2.50 (95% CI 1.63-3.82)), and age >64 years versus age ≤64 years (HR=2.33 (95% CI 1.69-3.21)). Within 181-360 days after surgery FIGO-stage III-IV versus FIGO-stage I-II (HR=2.81(95% CI 1.75-4.50), BMI <18.5 kg/cm^2 versus BMI 18.5-25 kg/cm^2 (HR=2.08 (95% CI 1.18-3.66)), and residual tumour tissue >2 cm versus no residual tumour (HR=1.84 (95% CI 1.25-2.70)) were the three most important predictors.

Conclusions: The most important predictors of mortality within one year after surgery were residual tumour tissue (0-180 days after surgery) and advanced FIGO-stage (181-360 days after surgery). However, our results suggest that the surgeon should not only aim for radical surgery, but

also pay special attention to comorbidity, nutritional state, age >64, and the need for perioperative

blood transfusion.

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Strengths and limitations of this study

- A population-based study with prospective registered data

- A total of 2,654 women were included

- High quality of data sources and no loss to follow-up

- Adjustment for several factors: age, preoperative health score, body mass index, FIGO-stage, residual tumour tissue after surgery, perioperative blood transfusion

- Unable to perform analyses regarding neoadjuvant chemotherapy prior to surgery

- Missing data on smoking and alcohol

- No access to laboratory data

- Unknown cause of death

INTRODUCTION

The 5-year survival is a traditional measure of the survival of cancer patients. Women with ovarian cancer have a median survival of approximately two years [1] and we may overlook important factors for survival by primarily focusing on the long-term survival. Ovarian cancer has a high mortality [2], and we need to focus on additional areas of prognostic importance in order to improve the outcome. Previous studies of the survival of women with ovarian cancer have focused on mortality within the first 30-60 days after surgery or on long-term survival. These studies have identified commonplace predictors of mortality (i.e. complications to surgery, FIGO-stage and residual tumour tissue [3]). To the best of our knowledge, no former studies have focused on predictors on mortality within one year after primary ovarian cancer surgery. However, we hypothesised that analysing the intermediate survival of the women (up to one year after surgery) would provide valuable information on potentially significant factors for survival. If this hypothesis proves correct these factors should be considered in the perioperative settings and are useful in the counselling of the

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patient. Using data from the nationwide Danish Gynaecology Cancer Database (DGCD) obtained

from 2005 until 2012, and the Danish Civil Registration System (CPR registry), the aims were to

examine predictors of mortality within 0-180 days and 181-360 days after primary ovarian cancer

surgery. The examined predictors of mortality were age, preoperative American Society of

Anaesthesiologists (ASA) score [4], smoking, body mass index (BMI), International Federation of

Gynaecology and Obstetrics (FIGO) stage, residual tumour tissue after surgery, perioperative blood

transfusion, and calendar year of surgery.

MATERIALS AND METHODS

Study population

The study includes all Danish women who had undergone primary ovarian cancer surgery

performed from January 1st, 2005 to December 31st, 2012, and identified in the DGCD. The DGCD

is a national clinical database established on January 1st, 2005 [5], and since then all patients with a

first-time diagnosis of ovarian cancer have been prospectively registered. This was due to

mandatory reports from all Danish departments of gynaecology and histopathology. The DGCD

contains details about preoperative patient characteristics (i.e. age, ASA score, smoking, and BMI),

perioperative information (i.e. FIGO-stage, residual tumour tissue after surgery, blood transfusion,

etc.), and postoperative details (i.e. histopathology, final tumour stage verification, complications,

and adjuvant chemotherapy).

The ovarian cancer data in the DGCD has previously been validated and the registry was concluded

to be valuable for quality monitoring in gynaecological oncology [6]. Each patient is identified by a

unique 10-digit number given to all Danish citizens by the CPR registry when residence permits are

obtained [7].

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The DGCD included 2,831 women who had primary ovarian cancer surgery during the study period. The following were exclusion criteria: 1) a preoperative ASA score obtained more than six months before surgery (n=119), presuming six months to be the maximum time period to surgery if neoadjuvant chemotherapy had been administrated, and 2) a histopathology requisition completed later than two weeks after surgery (n=58), signifying that the specific pathology requisition most certainly originates from the current surgery. The CPR registry provided information on overall mortality.

Data on predictive variables

From the DGCD we specifically obtained data on age at the time of surgery, preoperative ASA score [4] (indicating comorbidity at the time of surgery), preoperative BMI [8], preoperative smoking habits, FIGO-stage [9], size of residual tumour tissue after surgery (visually evaluated by the surgeon at the end of surgery), perioperative blood transfusion, and calendar year of surgery. We also received data on alcohol consumption, but due to several missing pieces of data, this parameter was omitted from further analyses. All the above mentioned parameters, apart from alcohol, were evaluated as predictors of mortality.

Age: The women were divided in two groups according to the median age: 1) age ≤64 years and 2) age >64 years at the time of surgery.

ASA score: The anaesthetist reported the preoperative ASA score of each woman, who were divided in two groups: 1) ASA score = 1 (without comorbidity) and 2) ASA score >1 (with comorbidity).

Smoking: At the preoperative interview, women were divided in two groups according to the current smoking status: 1) non-smokers and 2) smokers.

BMI: Usually BMI is divided in the following groups: underweight, normal, overweight, and obese,

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but in our study population only a small group of women had BMI ≥30. Therefore, all women were assigned into three groups according to BMI: 1) BMI <18.5 kg/cm^2 (underweight), 2) BMI 18.5-25 kg/cm^2 (normal), and 3) BMI >25 kg/cm^2 (overweight).

FIGO-stage: The women were divided in two groups: 1) FIGO-stages I and II (localised disease), and 2) FIGO-stages III and IV (advanced disease).

Residual tumour: The size of the residual tumour was evaluated by the surgeon at the end of surgery thereby forming three groups: 1) No residual tumour, 2) residual tumour ≤2 cm, and 3) residual tumour >2 cm.

Blood transfusion: The women were grouped in two: 1) those who did not receive perioperative blood transfusion, and 2) those who did.

Statistical analysis

The overall survival was illustrated by Kaplan-Meier plots of each of the following variables: *age* (≤64 years and >64 years), *ASA score* (1 and >1), smoking (no, yes), *BMI* (underweight, normal, overweight), *FIGO-stage* (localised, advanced), residual tumour tissue after surgery (none, ≤2 cm, and >2 cm), and *perioperative blood transfusion* (no, yes). Predictive variables of interests were assessed descriptively according to death within 0-180 days and 181-360 after surgery. To estimate the time-varying effect of the predictive variables on survival within the two time periods (0-180 days and 181-360 after surgery) we used an extended Cox model [10]. Included variables followed the above mentioned categorisation, and the calendar year of surgery was included as a continuous variable. Since missing data concerning smoking was observed not to be random, the estimates obtained for this variable may be biased. Accordingly, if there is any interaction between this variable and other covariates, estimates of other covariates may also be biased. Omitting smoking from the model did not substantially change the estimates of the other variables, and thus the final

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model was reduced based on the results of the Wald tests. The final model included the following

variables: *age*, *ASA score*, *BMI*, *FIGO-stage*, *residual tumour tissue after surgery*, *perioperative*

blood transfusion, and *calendar year*. After applying the model, we tested whether there is a

significant difference for each predictor variable between the two time periods by performing a

Wald test. The results of the extended Cox model were reported by the Hazard Ratio (HR) and 95%

confidence intervals (95% CI), and the Wald test with the p-values.

All analyses were conducted using Stata 12 software (StataCorp LP, College Station, TX, USA).

The present study was approved by the Danish Data Protection Agency (J. nr. 2012-41-0485).

According to Danish law, ethical approval and patient consent is not required for purely registry-

based studies.

RESULTS

Our study included 2,654 women with primary ovarian cancer surgery from January 1st, 2005 to

December 31st, 2012. The majority of these women was characterized by age ≤64 years (52%),

preoperative ASA score >1 (61%), normal BMI (52%), advanced FIGO-stage (63%), radical

surgery (68%), and no perioperative blood transfusion (75%) (Table 1). The overall one-year

survival was 84%. A total of 412 women (16%) died within the first postoperative year. Women

who died after surgery (both within 0-180 days and 181-360 days) were predominantly

characterised by age >64 years, ASA score >1, and advanced FIGO-stage. For further descriptive

details, see Table 1.

<u>Survival</u>

The Kaplan-Meier figures show the separate effect of the included predictive variables on survival

up to 360 days after surgery (Figure 1). The figures illustrate a decreased survival in women >64

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years compared to women ≤64 years, in women with ASA score >1 compared to ASA=1, in underweight women compared to over- and normal weight women, in women with advanced FIGO-stage compared to localised FIGO-stage, in women with >2 cm residual tumour tissue left at surgery compared to ≤2 cm, and no residual tumour tissue, respectively, and in women who received perioperative blood transfusion in comparison to no transfusion.

<u>Predictors on mortality</u>

Table 2 shows the results of the multivariable Cox regression analysis and the included variables were thus mutually adjusted in the model. Age >64 years had a statistically significant negative impact on mortality both within 0-180 days and 181-360 days after surgery. ASA score ≥1 had a statistically significant negative impact on mortality only within 0-180 days after surgery. The magnitude of the effect of ASA score ≥1 decreased significantly during time with HR=2.17 (95% CI 1.46-3.23) within 0-180 days after surgery to HR=1.25 (95% CI 0.88-1.76) within 181-360 days. Being underweight increased mortality in both time periods compared with normal weighted women with HR=2.01 (95% CI 1.29-3.07) and HR=2.08 (95% CI 1.18-3.66) within 0-180 days and 181-360 days after surgery. Advanced FIGO-stage only had a statistically significant effect within 181-360 days after surgery (HR=2.81 (95% CI 1.75-4.50). Residual tumour ≤2 cm and >2 cm significantly decreased survival in both time periods after surgery, with the most pronounced effect for residual tumour >2 cm within 0-180 days after surgery (HR=4.58 (95% CI 3.20-6.59)). The impact of residual tumour >2 cm significantly decreased with time. Perioperative blood transfusion significantly increased mortality in the period 0-180 days after surgery (HR=1.62 (95% CI 1.21-2.16). In the model, calendar year of surgery did not affect mortality.

Some interaction exists between residual tumour and FIGO stage, but this did not change the overall conclusions.

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DISCUSSION

Predictors of the ovarian cancer mortality within the first year after surgery have not been intensively investigated. However, focusing only on the perioperative mortality and the 5-year survival may result in overlooking factors important for the survival of the patient. The present study examined predictors of mortality within 0-180 days and 181-360 days after primary ovarian cancer surgery. Within 0-180 days after surgery the three most important predictors of mortality were residual tumour >2cm followed by residual tumour ≤2 cm, and age >64 years. Within 181-360 days after surgery advanced FIGO-stage, underweight, and residual tumour tissue >2cm were the three most important predictors of mortality. Less important, but still statistically significant predictors of survival in the first six months after surgery, were ASA >1 and perioperative blood transfusion. Underweighted women had a significantly increased mortality within the first postoperative year.

Our study has several strengths; it is based on nationwide prospective registered data, it includes several important predictive variables for mortality, and no women were lost at follow-up due to complete information during the entire study period. The validity of data in the DGCD is essential for our results and the database has previously been successfully validated on primary epithelial ovarian cancer by a comparison of the surgical and histopathological data in the registry with the corresponding medical file and the National Registry of Patients as reference [6].

We observed that residual tumour tissue (both less and more than 2 cm) left at surgery has a statistically significant negative effect on survival in both periods after surgery. This finding has been outlined in many other studies [11,12,13], but our results indicate that residual tumour of more than 2 cm is the most important predictor of death within the first six months after surgery. The

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presents results and other studies unambiguously identify macroscopic tumour tissue resection as an important surgical issue in improving survival [14,15,16].

We were unable to identify women treated with neoadjuvant chemotherapy prior to surgery due to absent data throughout the entire study period. Since preoperative neoadjuvant chemotherapy is mainly administered to women with advanced FIGO-stages disease, in combination with the possible underestimation of residual tumour tissue at surgery following neoadjuvant chemotherapy [13], our results may be biased due to the possible blend of women with different characteristics. However, as neo-adjuvant chemotherapy is only administered to advanced FIGO-stages it is unlikely that our strongest predictor of mortality (residual tumour tissue) within one year after surgery is biased, and our main conclusion of this study remains unchanged.

We also observed advanced FIGO-stage to be an important predictor of mortality, but mainly within 181-360 days after surgery. The negative impact of advanced FIGO-stage on mortality is well known and has been described in other investigations [14,15,16], but the negative effect on mortality within the first year after surgery has not previously been reported. We observed underweight to be a predictor of mortality both 0-180 days and 181-360 days after surgery. In contrast, Skírnisdóttir et al [17] concluded that BMI did not influence survival when evaluating women with low-stage ovarian cancer. As in our study, Skírnisdóttir et al used the BMI reported at the time of surgery, but they did not evaluate its influence on survival until 19-214 months later. Therefore, for the first time, we report the negative effect of being underweight on mortality within the first postoperative year. Malnutrition and ascites are well-known problems among ovarian cancer patients [18,19]. Due to the frequent concomitant presence of ascites, the real preoperative BMI may be lower than measured and the negative influence exerted by underweight is thereby underestimated in our analyses. In a recent study, Ataseven et al [20] observed low preoperative albumin to be an independent predictor for severe postoperative complications, and to be independently associated with reduced overall

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survival. We did not have information of serum albumin which could have qualified the measurement of nutritional status. Body composition CT scan may even be superior to serum albumin when nutritional status prior to surgery is evaluated, due to the observation regarding low subcutaneous and muscular fat as an independent predictor of mortality [21], but we did not have such examinations.

In our study, women >64 years demonstrated poorer survival in comparison to women ≤64 years in the first year after surgery, with the most pronounced impact of older age on mortality observed 0-180 days after surgery and thereafter exceeded by more important factors. In several countries, the relative one and five-year survival of women diagnosed with ovarian cancer have previously been reported to decrease with old age [22,23,24]. However, to the best of our knowledge, the fact that the impact of old age occurs mainly in the first period after surgery is new information. Jørgensen et al [25], Trillsch et al [26], and Sabatier et al [27] noted that old women with ovarian cancer may demonstrate worse survival due to potentially inferior treatment, but our data does not include information to illuminate this aspect.

We found comorbidity (ASA >1) as a predictor of mortality, but only at 0-180 days after surgery, and with a decreasing importance over time. Grann et al [28], and Sperling et al [29] also observed comorbidity to be a predictor of mortality. However, in contrast to our results, they did not evaluate the effect on the immediate postoperative time period, but evaluated data after one (Grann and Sperling[28,29]), and five years (Grann [28]). Consequently, our data also offers new information in this field and may indicate that reduction of any pre-existing comorbidity could be important in the increasing survival after primary ovarian cancer surgery.

Perioperative blood transfusion was observed to be a predictor of mortality 0-180 days after surgery. This is a new finding in women with ovarian cancer, but a negative effect of blood transfusion on survival has been described in other diseases [30,31]. Among gynaecological cancer

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patients, transfusion has been described to be associated with higher morbidity and increased mortality within the immediate 30 days after surgery, when controlling for parameters such as age, comorbidity, pre-existing anaemia, type of surgery etc.[32]. Immune modulatory mechanisms are suggested to induce the above-mentioned complications [33]. Since the DGCD does not contain information on haemoglobin levels or total transfused blood units, we were unable to evaluate any possible influence of these parameters. Our findings might indicate that perioperative blood transfusion should only be prescribed to a very restricted group of patients, although this aspect needs to be studied in more detail.

Our study also has limitations. Missing information on smoking and alcohol prevented examining the impact on survival. As discussed previously, analyses regarding neoadjuvant chemotherapy prior to surgery were not available due to absent information of this parameter throughout the entire study period. In addition, information regarding laboratory data would have been valuable. Other causes of death than ovarian cancer increase with age and the use of overall survival may have caused confounding. However, information on the causes of death was not available.

Residual tumour tissue, advanced FIGO-stage, being underweight, age >64 years, comorbidity, and perioperative blood transfusion were all found to be predictors of mortality within the first year after primary ovarian cancer surgery. Our results suggest that the surgeon should not only aim for radical surgery, but also pay attention to comorbidity, nutritional state, age >64 years, and the use of perioperative blood transfusion. These findings should be confirmed in other settings, and future studies are needed to assess the impact of smoking, alcohol, units of blood transfused, and neoadjuvant chemotherapy as predictors of mortality within the first postoperative year after primary ovarian cancer surgery.

ARTICLE SUMMARY

In the present study, we aimed to examine predictors of mortality within 0-180 days and 181-360

days after ovarian cancer surgery. The examined predictors were age, ASA score, BMI, FIGO-

stage, residual tumour tissue after surgery, perioperative blood transfusion, and calendar year of

surgery. The overall one-year survival was 84%. The most important predictors of mortality within

one year after surgery were residual tumour tissue (0-180 days after surgery) and advanced FIGO-

stage (181-360 days after surgery). Our results suggest that the surgeon should aim for radical

surgery. However, comorbidity, being underweight, age >64 years, and blood transfusion were also

significant predictors of mortality and need to be studied in more detail.

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Table 1. Descriptive characteristics according to death up to 361 days after primary ovarian cancer surgery in Danish women performed from 2005-2012 (percentage distribution in brackets).

		Number of women	Women who died within 0-180 days after surgery	Women who died within 181-360 days after surgery	Women who survived at least 361 days after surgery
All women		2,654 (100)	226 (9)	186 (7)	2,242 (84)
Age*	≤64 years (%)	1,380 (52)	53 (4)	75 (5)	1252 (91)
	>64 years (%)	1,274 (48)	173 (14)	111 (9)	990 (78)
ASA	Score 1 (%)	1,023 (39)	33 (3)	52 (5)	938 (92)
	Score >1 (%)	1,622 (61)	192 (12)	133 (8)	1,297 (80)
	Missing (%)	9 (0)	1 (11)	1 (11)	7 (78)
Smoking	No (%)	1,306 (49)	95 (7)	86 (7)	1,125 (86)
	Yes (%)	1,046 (39)	89 (9)	74 (7)	883 (84)
	Missing (%)	302 (11)	42 (14)	26 (9)	234 (77)
BMI	Underweight (%)	117 (4)	24 (20)	17 (15)	76 (65)
	Normal (%)	1,369 (52)	122 (9)	91 (7)	1,156 (84)
	Overweight (%)	1,095 (41)	72 (6)	74 (7)	949 (87)
	Missing (%)	73 (3)	8 (11)	4 (5)	61 (84)
FIGO-stage	Localized (%)	965 (36)	34 (4)	24 (2)	907 (94)
	Advanced (%)	1,668 (63)	190 (11)	161 (10)	1,317 (79)
	Missing (%)	21 (1)	2 (10)	1 (5)	18 (85)
Residual tumour	None (%)	1,798 (68)	65 (4)	86 (5)	1,647 (91)
	≤2 cm (%)	328 (12)	45 (14)	36 (11)	247 (75)
	>2 cm (%)	519 (20)	115 (22)	63 (12)	341 (66)
	Missing (%)	9 (0)	1 (11)	1 (11)	7 (78)
Blood transfusion	No (%)	2,000 (75)	143 (7)	125 (6)	1,732 (87)
	Yes (%)	648 (24)	83 (13)	60 (9)	505 (78)
	Missing (%)	6 (0)	0 (0)	1 (17)	5 (83)
Calender year	2005-2007	764(29)	81 (11)	53 (7)	630 (82)
	2007-2009	1,073 (40)	99 (9)	79 (7)	895 (84)
	2009-2012	817 (31)	46 (6)	54 (6)	717 (88)

* Age was divided in two groups according to the median age

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Table 2. Results from the Cox multivariable regression analyses estimating the impact of possible predictive variables on mortality after primary ovarian cancer surgery in Danish women from 2005-2012. Data is reported by Hazard Ratio (HR), 95% confidence intervals (CI), and the results of the time-interval heterogeneity test are reported by p-values.
All HR were mutually adjusted for the other variables.

Variable	0 - 180 days after surgery, HR (95% CI)	181 – 360 days after surgery, HR (95% CI)	p-values for test for homogeneity between the two time periods
Age (>64 years vs. ≤64 years)	2.33 (1.69–3.21)	1.64 (1.19–2.25)	0.1240
ASA score (>1 vs. 1)	2.17 (1.46–3.23)	1.25 (0.88–1.76)	0.0383
BMI (Underweight vs. Normal)	2.01 (1.29-3.07)	2.08 (1.18-3.66)	0. 9046
BMI (Overweight vs. Normal)	0.82 (0.61-1.11)	1.08 (0.79-1.48)	0.2093
Residual tumour (≤2 cm vs. None)	2.50 (1.63–3.82)	1.68 (1.11–2.53)	0.1863
Residual tumour (>2 cm vs. None**)**	4.58 (3.20–6.59)	1.84 (1.25–2.70)	0.0007
FIGO-stage (Advanced vs. Localized)	1.28 (0.83–1.96)	2.81 (1.75–4.50)	0.0151
Blood transfusion (Yes vs. No)	1.62 (1.21-2.16)	1.28 (0.92-1.78)	0.2912
Calendar year (Increasing)	0.86 (0.72-1.04)	0.99 (0.81-1.21)	0.3076

* Age was divided in two groups according to the median age

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Contributors:

MØ, MI, RG, OM and BMN were involved in the conception or design of the study design, data

collection, interpretation of data, and involved in the drafting of the manuscript.

MI (statistician) performed the analyses. All authors have read and revised the manuscript critically

for important intellectual content, and approved the final version to be published.

Competing interests: No, there are no competing interests.

Data sharing

No additional data available.

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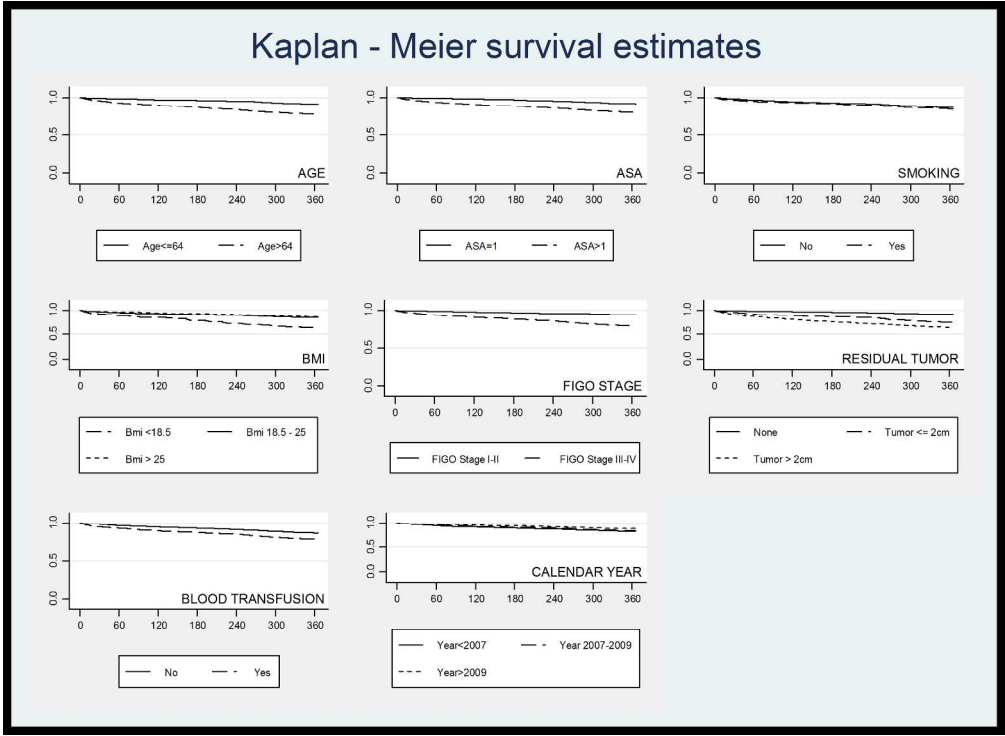
Figure 1

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5-6*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	not relevant
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4,5,7
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4-7
		(b) Indicate number of participants with missing data for each variable of interest	13 (Table 1)
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8 14 (Table 2)
		(*b*) Report category boundaries when continuous variables were categorized	5-6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Reported in the submission system

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Predictors of mortality within one year after primary ovarian cancer surgery: a nationwide cohort study

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Predictors of mortality within one year after primary ovarian cancer surgery, a nationwide cohort study

Mette Ørskov, MD, PhD[1]

Maria Iachina, MSc, PhD[2]

Rikke Guldberg, MD, PhD[2]

Ole Mogensen, MD, DMSc[1]/Bente Mertz Nørgård, MD, PhD, DMSc[2]

1: Department of Gynecology and Obstetrics, Odense University Hospital, and Research Unit of Gynecology and Institute of Clinical Research, University of Southern Denmark

2: Centre for Clinical Epidemiology and Research Unit of Clinical Epidemiology, Odense University Hospital and Institute of Clinical Research, University of Southern Denmark

Corresponding author: Mette Ørskov, email: oerskov@dadlnet.dk

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ABSTRACT

Objectives: To identify predictors of mortality within one year after primary surgery for ovarian cancer.

Design: Prospective nationwide cohort study from January 1st, 2005 to December 31st, 2012.

Setting: Evaluation of data from the Danish Gynaecology Cancer Database and the Danish Civil Registration System.

Participants: 2,654 women who underwent surgery due to a diagnosis of primary ovarian cancer.

Outcome measures: Overall survival and predictors of mortality within 0-180 days and 181-360 days after the primary surgery. Examined predictors were age, preoperative American Society of Anesthesiologists (ASA) score, body mass index (BMI), International Federation of Gynaecology and Obstetrics (FIGO) stage, residual tumour tissue after surgery, perioperative blood transfusion, and calendar year of surgery.

Results: The overall one-year survival was 84%. Within 0-180 days after surgery, the three most important predictors of mortality from the multivariable model were residual tumour tissue >2 cm versus no residual tumour (HR=4.58 (95% CI 3.20-6.59)), residual tumour tissue ≤2 cm versus no residual tumour (HR=2.50 (95% CI 1.63-3.82)), and age >64 years versus age ≤64 years (HR=2.33 (95% CI 1.69-3.21)). Within 181-360 days after surgery FIGO-stage III-IV versus FIGO-stage I-II (HR=2.81(95% CI 1.75-4.50), BMI <18.5 kg/cm^2 versus BMI 18.5-25 kg/cm^2 (HR=2.08 (95% CI 1.18-3.66)), and residual tumour tissue >2 cm versus no residual tumour (HR=1.84 (95% CI 1.25-2.70)) were the three most important predictors.

Conclusions: The most important predictors of mortality within one year after surgery were residual tumour tissue (0-180 days after surgery) and advanced FIGO-stage (181-360 days after surgery). However, our results suggest that the surgeon should not only aim for radical surgery, but

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also pay special attention to comorbidity, nutritional state, age >64, and the need for perioperative

blood transfusion.

Strengths and limitations of this study

- A population-based study with prospective registered data

- A total of 2,654 women were included

- High quality of data sources and no loss to follow-up

- Adjustment for several factors: age, preoperative health score, body mass index, FIGO-stage, residual tumour tissue after surgery, perioperative blood transfusion

- Unable to perform analyses regarding neoadjuvant chemotherapy prior to surgery

- Missing data on smoking and alcohol

- No access to laboratory data

- Unknown cause of death

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INTRODUCTION

The 5-year survival is a traditional measure of the survival of cancer patients. The majority (70-80%) of women with ovarian cancer are diagnosed in advanced stages [1,2], with a median survival of approximately two years [3] and we may therefore overlook important factors for survival by primarily focusing on the long-term survival. Ovarian cancer has a high mortality [4], and we need to focus on additional areas of prognostic importance in order to improve the outcome.

Previous studies of the survival of women with ovarian cancer have focused on mortality within the first 30-60 days after surgery or on long-term survival. These studies have identified commonplace predictors of mortality (i.e. complications to surgery, FIGO-stage and residual tumour tissue [5]). To the best of our knowledge, no former studies have focused on predictors on mortality within one year after primary ovarian cancer surgery. However, we hypothesised that analysing the intermediate survival of the women (up to one year after surgery) would provide valuable information on potentially significant factors for survival. If this hypothesis proves correct these factors should be considered in the perioperative settings and are useful in the counselling of the patient. Using data from the nationwide Danish Gynaecology Cancer Database (DGCD) obtained from 2005 until 2012, and the Danish Civil Registration System (CPR registry), the aims were to examine predictors of mortality within 0-180 days and 181-360 days after primary ovarian cancer surgery. The examined predictors of mortality were age, preoperative American Society of Anaesthesiologists (ASA) score [6], smoking, body mass index (BMI), International Federation of Gynaecology and Obstetrics (FIGO) stage, residual tumour tissue after surgery, perioperative blood transfusion, and calendar year of surgery.

MATERIALS AND METHODS

Study population

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The study includes all Danish women who had undergone primary ovarian cancer surgery performed from January 1st, 2005 to December 31st, 2012, and identified in the DGCD. The DGCD is a national clinical database established on January 1st, 2005 [7], and since then all patients with a first-time diagnosis of ovarian cancer have been prospectively registered. This was based on mandatory reports from all Danish departments of gynaecology and histopathology. The DGCD contains details about preoperative patient characteristics (i.e. age, ASA score, smoking, and BMI), perioperative information (i.e. FIGO-stage, residual tumour tissue after surgery, blood transfusion, etc.), and postoperative details (i.e. histopathology, final tumour stage verification, complications, and adjuvant chemotherapy).

The ovarian cancer data in the DGCD has previously been validated and the registry was concluded to be valuable for quality monitoring in gynaecological oncology [8]. Each patient is identified by a unique 10-digit number given to all Danish citizens by the CPR registry at birth or when residence permits are obtained [9].

The DGCD included 2,831 women who had primary ovarian cancer surgery during the study period. The following were exclusion criteria: 1) a preoperative ASA score obtained more than six months before surgery (n=119), presuming six months to be the maximum time period to surgery if neoadjuvant chemotherapy had been administrated, and 2) a histopathology requisition completed later than two weeks after surgery (n=58), signifying that the specific pathology requisition most certainly originates from the current surgery. The CPR registry provided information on overall survival.

Data on predictive variables

From the DGCD we specifically obtained data on age at the time of surgery, preoperative ASA score [6] (indicating comorbidity at the time of surgery), preoperative BMI [10], preoperative smoking

habits, FIGO-stage [11], size of residual tumour tissue after surgery (visually evaluated by the surgeon at the end of surgery), perioperative blood transfusion, and calendar year of surgery. We also received data on alcohol consumption, but due to several missing pieces of data, this parameter was omitted from further analyses. All the above mentioned parameters, apart from alcohol, were evaluated as predictors of mortality.

Age: The women were divided in two groups according to the median age: 1) age ≤64 years and 2) age >64 years at the time of surgery.

ASA score: The anaesthetist reported the preoperative ASA score of each woman, who were divided in two groups: 1) ASA score = 1 (without comorbidity) and 2) ASA score >1 (with comorbidity).

Smoking: At the preoperative interview, women were divided in two groups according to the current smoking status: 1) non-smokers and 2) smokers.

BMI: Usually BMI is divided in the following groups: underweight, normal, overweight, and obese, but in our study population only a small group of women had BMI≥30. Therefore, all women were assigned into three groups according to BMI: 1) BMI <18.5 kg/cm^2 (underweight), 2) BMI 18.5-25 kg/cm^2 (normal), and 3) BMI >25 kg/cm^2 (overweight).

FIGO-stage: The women were divided in two groups: 1) FIGO-stages I and II (localised disease), and 2) FIGO-stages III and IV (advanced disease).

Residual tumour: The size of the residual tumour was evaluated by the surgeon at the end of surgery thereby forming three groups: 1) No residual tumour, 2) residual tumour ≤2 cm, and 3) residual tumour >2 cm.

Blood transfusion: The women were grouped in two: 1) those who did not receive perioperative blood transfusion, and 2) those who did.

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Statistical analysis

The overall survival was illustrated by Kaplan-Meier plots of each of the following variables: *age* (≤64 years and >64 years), *ASA score* (1 and >1), smoking (no, yes), *BMI* (underweight, normal, overweight), *FIGO-stage* (localised, advanced), residual tumour tissue after surgery (none, ≤2 cm, and >2 cm), and *perioperative blood transfusion* (no, yes). Predictive variables of interests were assessed descriptively according to death within 0-180 days and 181-360 after surgery. To estimate the time-varying effect of the predictive variables on survival within the two time periods (0-180 days and 181-360 after surgery) we used an extended Cox model [12]. Included variables followed the above mentioned categorisation, and the calendar year of surgery was included as a continuous variable. Since missing data concerning smoking was observed not to be random, the estimates obtained for this variable may be biased. Accordingly, if there is any interaction between this variable and other covariates, estimates of other covariates may also be biased. Omitting smoking from the model did not substantially change the estimates of the other variables, and thus the final model was reduced based on the results of the Wald tests. The final model included the following variables: *age*, *ASA score*, *BMI*, *FIGO-stage*, *residual tumour tissue after surgery*, *perioperative blood transfusion*, and *calendar year*. After applying the model, we tested whether there is a significant difference for each predictor variable between the two time periods by performing a Wald test. The results of the extended Cox model were reported by the Hazard Ratio (HR) and 95% confidence intervals (95% CI), and the Wald test with the p-values.

All analyses were conducted using Stata 12 software (StataCorp LP, College Station, TX, USA).

The present study was approved by the Danish Data Protection Agency (J. nr. 2012-41-0485). According to Danish law, ethical approval and patient consent is not required for purely registry-based studies.

RESULTS

Our study included 2,654 women who underwent surgery after a diagnosis of primary ovarian cancer y from January 1st, 2005 to December 31st, 2012. The majority of these women was characterized by age ≤64 years (52%), preoperative ASA score >1 (61%), normal BMI (52%), advanced FIGO-stage (63%), radical surgery (68%), and no perioperative blood transfusion (75%) (Table 1). The overall one-year survival was 84%. A total of 412 women (16%) died within the first postoperative year. Women who died after surgery (both within 0-180 days and 181-360 days) were predominantly characterised by age >64 years, ASA score >1, and advanced FIGO-stage. For further descriptive details, see Table 1.

Survival

The Kaplan-Meier figures show the separate effect of the included predictive variables on survival up to 360 days after surgery (Figure 1). The Figures illustrate a decreased survival in women >64 years compared to women ≤64 years, in women with ASA score >1 compared to ASA=1, in underweight women compared to over- and normal weight women, in women with advanced FIGO-stage compared to localised FIGO-stage, in women with >2 cm residual tumour tissue left at surgery compared to ≤2 cm, and no residual tumour tissue, respectively, and in women who received perioperative blood transfusion in comparison to no transfusion.

Predictors on mortality

Table 2 shows the results of the multivariable Cox regression analysis and the included variables were thus mutually adjusted in the model. Age >64 years had a statistically significant negative impact on mortality both within 0-180 days and 181-360 days after surgery. ASA score ≥1 had a statistically significant negative impact on mortality only within 0-180 days after surgery. The

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magnitude of the effect of ASA score ≥1 decreased significantly during time with HR=2.17 (95% CI 1.46-3.23) within 0-180 days after surgery to HR=1.25 (95% CI 0.88-1.76) within 181-360 days. Being underweight increased mortality in both time periods compared with normal weighted women with HR=2.01 (95% CI 1.29-3.07) and HR=2.08 (95% CI 1.18-3.66) within 0-180 days and 181-360 days after surgery. Advanced FIGO-stage only had a statistically significant effect within 181-360 days after surgery (HR=2.81 (95% CI 1.75-4.50). Residual tumour ≤2 cm and >2 cm significantly decreased survival in both time periods after surgery, with the most pronounced effect for residual tumour >2 cm within 0-180 days after surgery (HR=4.58 (95% CI 3.20-6.59)). The impact of residual tumour >2 cm was still present after 6 months. Perioperative blood transfusion significantly increased mortality in the period 0-180 days after surgery (HR=1.62 (95% CI 1.21-2.16). In the model, calendar year of surgery did not affect mortality, but it was nearly significant within the first six months.

Some interaction exists between residual tumour and FIGO stage, but this did not change the overall conclusions.

DISCUSSION

Predictors of the ovarian cancer mortality within the first year after surgery have not been intensively investigated. However, focusing only on the perioperative mortality and the 5-year survival may result in overlooking factors important for the survival of the patient. The present study examined predictors of mortality within 0-180 days and 181-360 days after primary ovarian cancer surgery. Within 0-180 days after surgery the three most important predictors of mortality were residual tumour >2cm followed by residual tumour ≤2 cm, and age >64 years. Within 181-360 days after surgery advanced FIGO-stage, underweight, and residual tumour tissue >2cm were the three most important predictors of mortality. Less important, but still statistically significant

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predictors of survival in the first six months after surgery, were ASA >1 and perioperative blood transfusion. Underweighted women had a significantly increased mortality within the first postoperative year.

Our study has several strengths; it is based on nationwide prospective registered data, it includes several important predictive variables for mortality, and no women were lost at follow-up due to complete information during the entire study period. The validity of data in the DGCD is essential for our results and the database has previously been successfully validated on primary epithelial ovarian cancer by a comparison of the surgical and histopathological data in the registry with the corresponding medical file and the National Registry of Patients as reference [8].

We observed that residual tumour tissue (both less and more than 2 cm) left at surgery has a statistically significant negative effect on survival in both periods after surgery. This finding has been outlined in many other studies [13,14,15], but our results indicate that residual tumour of more than 2 cm is the most important predictor of death within the first six months after surgery. The present results and other studies unambiguously identify macroscopic tumour tissue resection as an important surgical issue in improving survival [16,17,18].

We were unable to identify women treated with neoadjuvant chemotherapy prior to surgery due to absent data throughout the entire study period. Since preoperative neoadjuvant chemotherapy is mainly administered to women with advanced FIGO-stages, in combination with the possible underestimation of residual tumour tissue at surgery following neoadjuvant chemotherapy [15], our results may be underestimated due to the possible blend of women with different characteristics. However, as neo-adjuvant chemotherapy is only administered to advanced FIGO-stages it is unlikely that our strongest predictor of mortality (residual tumour tissue) within one year after surgery is biased, and our main conclusion of this study remains unchanged.

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We also observed advanced FIGO-stage to be an important predictor of mortality, but mainly within 181-360 days after surgery. The negative impact of advanced FIGO-stage on mortality is well known and has been described in other investigations [16,17,18], but the negative effect on mortality within the first year after surgery has not previously been reported. We observed underweight to be a predictor of mortality both 0-180 days and 181-360 days after surgery. In contrast, Skírnisdóttir et al [19] concluded that BMI did not influence survival when evaluating women with low-stage ovarian cancer. As in our study, Skírnisdóttir et al used the BMI reported at the time of surgery, but they did not evaluate its influence on survival until 19-214 months later. Therefore, for the first time, we report the negative effect of being underweight on mortality within the first postoperative year. Malnutrition and ascites are well-known problems among ovarian cancer patients [20,21]. Due to the frequent concomitant presence of ascites, the real preoperative BMI may be lower than measured and the negative influence exerted by underweight is thereby underestimated in our analyses. In a recent study, Ataseven et al [22] observed low preoperative albumin to be an independent predictor for severe postoperative complications, and to be independently associated with reduced overall survival. We did not have information of serum albumin which could have qualified the measurement of nutritional status. Body composition CT scan may even be superior to serum albumin when nutritional status prior to surgery is evaluated, due to the observation regarding low subcutaneous and muscular fat as an independent predictor of mortality [23], but we did not have such examinations.

In our study, women >64 years demonstrated poorer survival in comparison to women ≤64 years in the first year after surgery, with the most pronounced impact of older age on mortality observed 0-180 days after surgery and thereafter exceeded by more important factors. In several countries, the relative one and five-year survival of women diagnosed with ovarian cancer have previously been reported to decrease with old age [24,25,26]. However, to the best of our knowledge, the fact that the

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impact of old age occurs mainly in the first period after surgery is new information. Jørgensen et al [27], Trillsch et al [28], and Sabatier et al [29] noted that old women with ovarian cancer may demonstrate worse survival due to potentially inferior treatment, but our data does not include information to illuminate this aspect.

We found comorbidity (ASA >1) as a predictor of mortality, but only at 0-180 days after surgery, and with a decreasing importance over time. Grann et al [30], and Sperling et al [31] also observed comorbidity to be a predictor of mortality. However, in contrast to our results, they did not evaluate the effect on the immediate postoperative time period, but evaluated data after one (Grann and Sperling[30,31]), and five years (Grann [30]). Consequently, our data also offers new information in this field and may indicate that reduction of any pre-existing comorbidity could be important in the increasing survival after primary ovarian cancer surgery.

Perioperative blood transfusion was observed to be a predictor of mortality 0-180 days after surgery. This is a new finding in women with ovarian cancer, but a negative effect of blood transfusion on survival has been described in other diseases [32,33]. Among gynaecological cancer patients, transfusion has been described to be associated with higher morbidity and increased mortality within the immediate 30 days after surgery, when controlling for parameters such as age, comorbidity, pre-existing anaemia, type of surgery etc.[34]. Immune modulatory mechanisms are suggested to induce the above-mentioned complications [35]. Since the DGCD does not contain information on haemoglobin levels or total transfused blood units, we were unable to evaluate any possible influence of these parameters. Our findings might indicate that perioperative blood transfusion should only be prescribed to a very restricted group of patients, although this aspect needs to be studied in more detail.

Our study also has limitations. According to the incident numbers of Danish ovarian cancer patients (2005-2012) [36], a total of 86-92% had primary ovarian cancer surgery performed [7], however, only

67 % of the operated patients were eligible for evaluation in our study. Missing information on smoking and alcohol prevented examining the impact on survival. As discussed previously, analyses regarding neoadjuvant chemotherapy prior to surgery were not available due to absent information of this parameter throughout the entire study period. In addition, information regarding laboratory data would have been valuable. Other causes of death than ovarian cancer increase with age and the use of overall survival may have caused confounding. However, information on the causes of death was not available.

Residual tumour tissue, advanced FIGO-stage, being underweight, comorbidity, and perioperative blood transfusion were all found to be predictors of mortality within the first year after primary ovarian cancer surgery. Our results suggest that the surgeon should not only aim for radical surgery, but also pay attention to comorbidity, nutritional state, and the use of perioperative blood transfusion. These findings should be confirmed in other settings, and future studies are needed to assess the impact of smoking, alcohol, units of blood transfused, and neoadjuvant chemotherapy as predictors of mortality within the first postoperative year after primary ovarian cancer surgery.

ARTICLE SUMMARY

In the present study, we aimed to examine predictors of mortality within 0-180 days and 181-360 days after ovarian cancer surgery. The examined predictors were age, ASA score, BMI, FIGO-stage, residual tumour tissue after surgery, perioperative blood transfusion, and calendar year of surgery. The overall one-year survival was 84%. The most important predictors of mortality within one year after surgery were residual tumour tissue (0-180 days after surgery) and advanced FIGO-stage (181-360 days after surgery). Our results suggest that the surgeon should aim for radical surgery. However, comorbidity, being underweight, age >64 years, and blood transfusion were also significant predictors of mortality and need to be studied in more detail.

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Table 1. Descriptive characteristics according to death up to 360 days after primary ovarian cancer surgery in Danish women performed from 2005-2012 (percentage distribution in brackets).

		Number of women	Women who died within 0-180 days after surgery	Women who died within 181-360 days after surgery	Women who survived at least 361 days after surgery
All women		2,654 (100)	226 (9)	186 (7)	2,242 (84)
Age*	≤64 years (%)	1,380 (52)	53 (4)	75 (5)	1252 (91)
	>64 years (%)	1,274 (48)	173 (14)	111 (9)	990 (78)
ASA	Score 1 (%)	1,023 (39)	33 (3)	52 (5)	938 (92)
	Score >1 (%)	1,622 (61)	192 (12)	133 (8)	1,297 (80)
	Missing (%)	9 (0)	1 (11)	1 (11)	7 (78)
Smoking	No (%)	1,306 (49)	95 (7)	86 (7)	1,125 (86)
	Yes (%)	1,046 (39)	89 (9)	74 (7)	883 (84)
	Missing (%)	302 (11)	42 (14)	26 (9)	234 (77)
BMI	Underweight (%)	117 (4)	24 (20)	17 (15)	76 (65)
	Normal (%)	1,369 (52)	122 (9)	91 (7)	1,156 (84)
	Overweight (%)	1,095 (41)	72 (6)	74 (7)	949 (87)
	Missing (%)	73 (3)	8 (11)	4 (5)	61 (84)
FIGO-stage	Localized (%)	965 (36)	34 (4)	24 (2)	907 (94)
	Advanced (%)	1,668 (63)	190 (11)	161 (10)	1,317 (79)
	Missing (%)	21 (1)	2 (10)	1 (5)	18 (85)
Residual tumour	None (%)	1,798 (68)	65 (4)	86 (5)	1,647 (91)
	≤2 cm (%)	328 (12)	45 (14)	36 (11)	247 (75)
	>2 cm (%)	519 (20)	115 (22)	63 (12)	341 (66)
	Missing (%)	9 (0)	1 (11)	1 (11)	7 (78)
Blood transfusion	No (%)	2,000 (75)	143 (7)	125 (6)	1,732 (87)
	Yes (%)	648 (24)	83 (13)	60 (9)	505 (78)
	Missing (%)	6 (0)	0 (0)	1 (17)	5 (83)
Calender year	2005-2006	764(29)	81 (11)	53 (7)	630 (82)
	2007-2009	1,073 (40)	99 (9)	79 (7)	895 (84)
	2010-2012	817 (31)	46 (6)	54 (6)	717 (88)

* Age was divided in two groups according to the median age

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Table 2. Results from the Cox multivariable regression analyses estimating the impact of possible predictive variables on mortality after primary ovarian cancer surgery in Danish women from 2005-2012. Data is reported by Hazard Ratio (HR), 95% confidence intervals (CI), and the results of the time-interval heterogeneity test are reported by p-values.
All HR were mutually adjusted for the other variables.

Variable	0 - 180 days after surgery, HR (95% CI)	181 – 360 days after surgery, HR (95% CI)	p-values for test for homogeneity between the two time periods
Age* (>64 years vs. ≤64 years)	2.33 (1.69–3.21)	1.64 (1.19–2.25)	0.1240
ASA score (>1 vs. 1)	2.17 (1.46–3.23)	1.25 (0.88–1.76)	0.0383
BMI (Underweight vs. Normal)	2.01 (1.29-3.07)	2.08 (1.18-3.66)	0.9046
(Overweight vs. Normal)	0.82 (0.61-1.11)	1.08 (0.79-1.48)	0.2093
Residual tumour (≤2 cm vs. None)	2.50 (1.63–3.82)	1.68 (1.11–2.53)	0.1863
(>2 cm vs. None)	4.58 (3.20–6.59)	1.84 (1.25–2.70)	0.0007
FIGO-stage (Advanced vs. Localized)	1.28 (0.83–1.96)	2.81 (1.75–4.50)	0.0151
Blood transfusion (Yes vs. No)	1.62 (1.21-2.16)	1.28 (0.92-1.78)	0.2912
Calendar year (Increasing)	0.86 (0.72-1.04)	0.99 (0.81-1.21)	0.3076

* Age was divided in two groups according to the median age

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Contributors:

MØ, MI, RG, OM and BMN were involved in the conception or design of the study design, data

collection, interpretation of data, and involved in the drafting of the manuscript.

MI (statistician) performed the analyses. All authors have read and revised the manuscript critically

for important intellectual content, and approved the final version to be published.

Competing interests: None

Data sharing: No additional data available.

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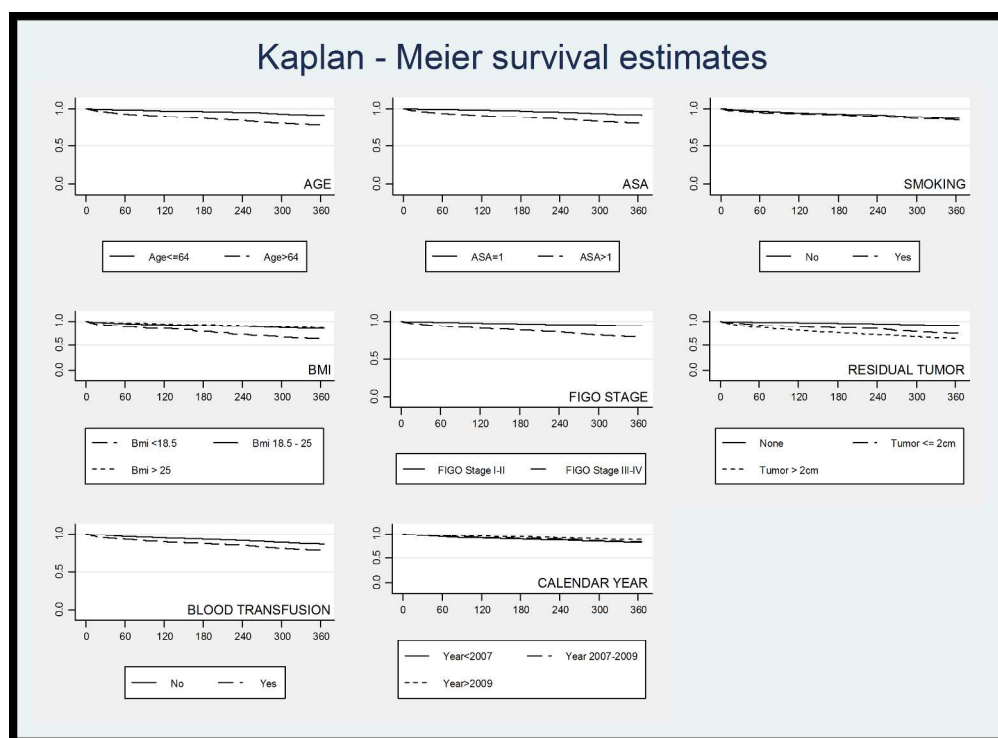
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Figure 1. Kaplan-Meier survival estimates on possible predictive variables in Danish women within the first year after primary ovarian cancer surgery (2005-2012), with the X-axis indicating days after surgery, and the Y-axis indicating the survival proportion in percentage.
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	not relevant
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6,9
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	15 (Table 1)
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10 16 (Table 2)
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11,14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	4,10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Reported in the submission system

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Predictors of mortality within one year after primary ovarian cancer surgery: a nationwide cohort study

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Predictors of mortality within one year after primary ovarian cancer surgery, a nationwide cohort study

Mette Ørskov, MD, PhD[1]

Maria Iachina, MSc, PhD[2]

Rikke Guldberg, MD, PhD[2]

Ole Mogensen, MD, DMSc[1]/Bente Mertz Nørgård, MD, PhD, DMSc[2]

1: Department of Gynecology and Obstetrics, Odense University Hospital, and Research Unit of Gynecology and Institute of Clinical Research, University of Southern Denmark

2: Centre for Clinical Epidemiology and Research Unit of Clinical Epidemiology, Odense University Hospital and Institute of Clinical Research, University of Southern Denmark

Corresponding author: Mette Ørskov, email: oerskov@dadlnet.dk

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ABSTRACT

Objectives: To identify predictors of mortality within one year after primary surgery for ovarian cancer.

Design: Prospective nationwide cohort study from January 1st, 2005 to December 31st, 2012.

Setting: Evaluation of data from the Danish Gynaecology Cancer Database and the Danish Civil Registration System.

Participants: 2,654 women who underwent surgery due to a diagnosis of primary ovarian cancer.

Outcome measures: Overall survival and predictors of mortality within 0-180 days and 181-360 days after the primary surgery. Examined predictors were age, preoperative American Society of Anesthesiologists (ASA) score, body mass index (BMI), International Federation of Gynaecology and Obstetrics (FIGO) stage, residual tumour tissue after surgery, perioperative blood transfusion, and calendar year of surgery.

Results: The overall one-year survival was 84%. Within 0-180 days after surgery, the three most important predictors of mortality from the multivariable model were residual tumour tissue >2 cm versus no residual tumour (HR=4.58 (95% CI 3.20-6.59)), residual tumour tissue ≤2 cm versus no residual tumour (HR=2.50 (95% CI 1.63-3.82)), and age >64 years versus age ≤64 years (HR=2.33 (95% CI 1.69-3.21)). Within 181-360 days after surgery FIGO-stage III-IV versus FIGO-stage I-II (HR=2.81(95% CI 1.75-4.50), BMI <18.5 kg/cm^2 versus BMI 18.5-25 kg/cm^2 (HR=2.08 (95% CI 1.18-3.66)), and residual tumour tissue >2 cm versus no residual tumour (HR=1.84 (95% CI 1.25-2.70)) were the three most important predictors.

Conclusions: The most important predictors of mortality within one year after surgery were residual tumour tissue (0-180 days after surgery) and advanced FIGO-stage (181-360 days after surgery). However, our results suggest that the surgeon should not only aim for radical surgery, but

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also pay special attention to comorbidity, nutritional state, age >64, and the need for perioperative

blood transfusion.

Strengths and limitations of this study

- This is a population-based study on 2,654 women with prospective registered data

- We used data sources of high quality and there were no loss to follow-up

- Adjustment for multiple factors were made: age, preoperative health score, body mass index, FIGO-stage, residual tumour tissue after surgery, perioperative blood transfusion

- We were unable to perform analyses regarding neoadjuvant chemotherapy prior to surgery

- There were missing data on smoking, alcohol, laboratory data and specific cause of death

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INTRODUCTION

The 5-year survival is a traditional measure of the survival of cancer patients. The majority (70-80%) of women with ovarian cancer are diagnosed in advanced stages [1,2], with a median survival of approximately two years [3] and we may therefore overlook important factors for survival by primarily focusing on the long-term survival. Ovarian cancer has a high mortality [4], and we need to focus on additional areas of prognostic importance in order to improve the outcome.

Previous studies of the survival of women with ovarian cancer have focused on mortality within the first 30-60 days after surgery or on long-term survival. These studies have identified commonplace predictors of mortality (i.e. complications to surgery, FIGO-stage and residual tumour tissue [5]). To the best of our knowledge, no former studies have focused on predictors on mortality within one year after primary ovarian cancer surgery. However, we hypothesised that analysing the intermediate survival of the women (up to one year after surgery) would provide valuable information on potentially significant factors for survival. If this hypothesis proves correct these factors should be considered in the perioperative settings and are useful in the counselling of the patient. Using data from the nationwide Danish Gynaecology Cancer Database (DGCD) obtained from 2005 until 2012, and the Danish Civil Registration System (CPR registry), the aims were to examine predictors of mortality within 0-180 days and 181-360 days after primary ovarian cancer surgery. The examined predictors of mortality were age, preoperative American Society of Anaesthesiologists (ASA) score [6], smoking, body mass index (BMI), International Federation of Gynaecology and Obstetrics (FIGO) stage, residual tumour tissue after surgery, perioperative blood transfusion, and calendar year of surgery.

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MATERIALS AND METHODS

Study population

The study includes all Danish women who had undergone primary ovarian cancer surgery performed from January 1st, 2005 to December 31st, 2012, and identified in the DGCD. The DGCD is a national clinical database established on January 1st, 2005 [7], and since then all patients with a first-time diagnosis of ovarian cancer have been prospectively registered. This was based on mandatory reports from all Danish departments of gynaecology and histopathology. The DGCD contains details about preoperative patient characteristics (i.e. age, ASA score, smoking, and BMI), perioperative information (i.e. FIGO-stage, residual tumour tissue after surgery, blood transfusion, etc.), and postoperative details (i.e. histopathology, final tumour stage verification, complications, and adjuvant chemotherapy).

The ovarian cancer data in the DGCD has previously been validated and the registry was concluded to be valuable for quality monitoring in gynaecological oncology [8]. Each patient is identified by a unique 10-digit number given to all Danish citizens by the CPR registry at birth or when residence permits are obtained [9].

The DGCD included 2,831 women who had primary ovarian cancer surgery during the study period. The following were exclusion criteria: 1) a preoperative ASA score obtained more than six months before surgery (n=119), presuming six months to be the maximum time period to surgery if neoadjuvant chemotherapy had been administrated, and 2) a histopathology requisition completed later than two weeks after surgery (n=58), signifying that the specific pathology requisition most certainly originates from the current surgery. The CPR registry provided information on overall survival.

Data on predictive variables

From the DGCD we specifically obtained data on age at the time of surgery, preoperative ASA score [6] (indicating comorbidity at the time of surgery), preoperative BMI [10], preoperative smoking habits, FIGO-stage [11], size of residual tumour tissue after surgery (visually evaluated by the surgeon at the end of surgery), perioperative blood transfusion, and calendar year of surgery. We also received data on alcohol consumption, but due to several missing pieces of data, this parameter was omitted from further analyses. All the above mentioned parameters, apart from alcohol, were evaluated as predictors of mortality.

Age: The women were divided in two groups according to the median age: 1) age ≤64 years and 2) age >64 years at the time of surgery.

ASA score: The anaesthetist reported the preoperative ASA score of each woman, who were divided in two groups: 1) ASA score = 1 (without comorbidity) and 2) ASA score >1 (with comorbidity).

Smoking: At the preoperative interview, women were divided in two groups according to the current smoking status: 1) non-smokers and 2) smokers.

BMI: Usually BMI is divided in the following groups: underweight, normal, overweight, and obese, but in our study population only a small group of women had BMI≥30. Therefore, all women were assigned into three groups according to BMI: 1) BMI <18.5 kg/cm^2 (underweight), 2) BMI 18.5-25 kg/cm^2 (normal), and 3) BMI >25 kg/cm^2 (overweight).

FIGO-stage: The women were divided in two groups: 1) FIGO-stages I and II (localised disease), and 2) FIGO-stages III and IV (advanced disease).

Residual tumour: The size of the residual tumour was evaluated by the surgeon at the end of surgery thereby forming three groups: 1) No residual tumour, 2) residual tumour ≤2 cm, and 3) residual tumour >2 cm.

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Blood transfusion: The women were grouped in two: 1) those who did not receive perioperative blood transfusion, and 2) those who did.

Statistical analysis

The overall survival was illustrated by Kaplan-Meier plots of each of the following variables: *age* (≤64 years and >64 years), *ASA score* (1 and >1), smoking (no, yes), *BMI* (underweight, normal, overweight), *FIGO-stage* (localised, advanced), residual tumour tissue after surgery (none, ≤2 cm, and >2 cm), and *perioperative blood transfusion* (no, yes). Predictive variables of interests were assessed descriptively according to death within 0-180 days and 181-360 after surgery. To estimate the time-varying effect of the predictive variables on survival within the two time periods (0-180 days and 181-360 after surgery) we used an extended Cox model [12]. Included variables followed the above mentioned categorisation, and the calendar year of surgery was included as a continuous variable. Since missing data concerning smoking was observed not to be random, the estimates obtained for this variable may be biased. Accordingly, if there is any interaction between this variable and other covariates, estimates of other covariates may also be biased. Omitting smoking from the model did not substantially change the estimates of the other variables, and thus the final model was reduced based on the results of the Wald tests. The final model included the following variables: *age*, *ASA score*, *BMI*, *FIGO-stage*, *residual tumour tissue after surgery*, *perioperative blood transfusion*, and *calendar year*. After applying the model, we tested whether there is a significant difference for each predictor variable between the two time periods by performing a Wald test. The results of the extended Cox model were reported by the Hazard Ratio (HR) and 95% confidence intervals (95% CI), and the Wald test with the p-values.

All analyses were conducted using Stata 12 software (StataCorp LP, College Station, TX, USA).

The present study was approved by the Danish Data Protection Agency (J. nr. 2012-41-0485). According to Danish law, ethical approval and patient consent is not required for purely registry-based studies.

RESULTS

Our study included 2,654 women who underwent surgery after a diagnosis of primary ovarian cancer y from January 1st, 2005 to December 31st, 2012. The majority of these women was characterized by age ≤64 years (52%), preoperative ASA score >1 (61%), normal BMI (52%), advanced FIGO-stage (63%), radical surgery (68%), and no perioperative blood transfusion (75%) (Table 1). The overall one-year survival was 84%. A total of 412 women (16%) died within the first postoperative year. Women who died after surgery (both within 0-180 days and 181-360 days) were predominantly characterised by age >64 years, ASA score >1, and advanced FIGO-stage. For further descriptive details, see Table 1.

<u>Survival</u>

The Kaplan-Meier figures show the separate effect of the included predictive variables on survival up to 360 days after surgery (Figure 1). The Figures illustrate a decreased survival in women >64 years compared to women ≤64 years, in women with ASA score >1 compared to ASA=1, in underweight women compared to over- and normal weight women, in women with advanced FIGO-stage compared to localised FIGO-stage, in women with >2 cm residual tumour tissue left at surgery compared to ≤2 cm, and no residual tumour tissue, respectively, and in women who received perioperative blood transfusion in comparison to no transfusion.

<u>Predictors on mortality</u>

Table 2 shows the results of the multivariable Cox regression analysis and the included variables were thus mutually adjusted in the model. Age >64 years had a statistically significant negative impact on mortality both within 0-180 days and 181-360 days after surgery. Using age as a continuously variable did not change the effect of the other variables. ASA score ≥1 had a

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statistically significant negative impact on mortality only within 0-180 days after surgery. The magnitude of the effect of ASA score ≥1 decreased significantly during time with HR=2.17 (95% CI 1.46-3.23) within 0-180 days after surgery to HR=1.25 (95% CI 0.88-1.76) within 181-360 days. Being underweight increased mortality in both time periods compared with normal weighted women with HR=2.01 (95% CI 1.29-3.07) and HR=2.08 (95% CI 1.18-3.66) within 0-180 days and 181-360 days after surgery. Advanced FIGO-stage only had a statistically significant effect within 181-360 days after surgery (HR=2.81 (95% CI 1.75-4.50). Residual tumour ≤2 cm and >2 cm significantly decreased survival in both time periods after surgery, with the most pronounced effect for residual tumour >2 cm within 0-180 days after surgery (HR=4.58 (95% CI 3.20-6.59)). The impact of residual tumour >2 cm was still present after 6 months. Perioperative blood transfusion significantly increased mortality in the period 0-180 days after surgery (HR=1.62 (95% CI 1.21-2.16). In the model, calendar year of surgery did not affect mortality, but it was nearly significant within the first six months.

Some interaction exists between residual tumour and FIGO stage, but this did not change the overall conclusions.

DISCUSSION

Predictors of the ovarian cancer mortality within the first year after surgery have not been intensively investigated. However, focusing only on the perioperative mortality and the 5-year survival may result in overlooking factors important for the survival of the patient. The present study examined predictors of mortality within 0-180 days and 181-360 days after primary ovarian cancer surgery. Within 0-180 days after surgery the three most important predictors of mortality were residual tumour >2cm followed by residual tumour ≤2 cm, and age >64 years. Within 181-360 days after surgery advanced FIGO-stage, underweight, and residual tumour tissue >2cm were the three most important predictors of mortality. Less important, but still statistically significant predictors of survival in the first six months after surgery, were ASA >1 and perioperative blood transfusion. Underweighted women had a significantly increased mortality within the first postoperative year.

Our study has several strengths; it is based on nationwide prospective registered data, it includes several important predictive variables for mortality, and no women were lost at follow-up due to complete information during the entire study period. The validity of data in the DGCD is essential for our results and the database has previously been successfully validated on primary epithelial ovarian cancer by a comparison of the surgical and histopathological data in the registry with the corresponding medical file and the National Registry of Patients as reference [8].

We observed that residual tumour tissue (both less and more than 2 cm) left at surgery has a statistically significant negative effect on survival in both periods after surgery. This finding has been outlined in many other studies [13,14,15], but our results indicate that residual tumour of more than 2 cm is the most important predictor of death within the first six months after surgery. The present results and other studies unambiguously identify macroscopic tumour tissue resection as an important surgical issue in improving survival [16,17,18].

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We were unable to identify women treated with neoadjuvant chemotherapy prior to surgery due to absent data throughout the entire study period. Since preoperative neoadjuvant chemotherapy is mainly administered to women with advanced FIGO-stages, in combination with the possible underestimation of residual tumour tissue at surgery following neoadjuvant chemotherapy [15], our results may be underestimated due to the possible blend of women with different characteristics. However, as neo-adjuvant chemotherapy is only administered to advanced FIGO-stages it is unlikely that our strongest predictor of mortality (residual tumour tissue) within one year after surgery is biased, and our main conclusion of this study remains unchanged.

We also observed advanced FIGO-stage to be an important predictor of mortality, but mainly within 181-360 days after surgery. The negative impact of advanced FIGO-stage on mortality is well known and has been described in other investigations [16,17,18], but the negative effect on mortality within the first year after surgery has not previously been reported. We observed underweight to be a predictor of mortality both 0-180 days and 181-360 days after surgery. In contrast, Skírnisdóttir et al [19] concluded that BMI did not influence survival when evaluating women with low-stage ovarian cancer. As in our study, Skírnisdóttir et al used the BMI reported at the time of surgery, but they did not evaluate its influence on survival until 19-214 months later. Therefore, for the first time, we report the negative effect of being underweight on mortality within the first postoperative year. Malnutrition and ascites are well-known problems among ovarian cancer patients [20,21]. Due to the frequent concomitant presence of ascites, the real preoperative BMI may be lower than measured and the negative influence exerted by underweight is thereby underestimated in our analyses. In a recent study, Ataseven et al [22] observed low preoperative albumin to be an independent predictor for severe postoperative complications, and to be independently associated with reduced overall survival. We did not have information of serum albumin which could have qualified the measurement of nutritional status. Body composition CT scan may even be superior to serum

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albumin when nutritional status prior to surgery is evaluated, due to the observation regarding low subcutaneous and muscular fat as an independent predictor of mortality [23], but we did not have such examinations.

In our study, women >64 years demonstrated poorer survival in comparison to women ≤64 years in the first year after surgery, with the most pronounced impact of older age on mortality observed 0-180 days after surgery and thereafter exceeded by more important factors. In several countries, the relative one and five-year survival of women diagnosed with ovarian cancer have previously been reported to decrease with old age [24,25,26]. However, to the best of our knowledge, the fact that the impact of old age occurs mainly in the first period after surgery is new information. Jørgensen et al [27], Trillsch et al [28], and Sabatier et al [29] noted that old women with ovarian cancer may demonstrate worse survival due to potentially inferior treatment, but our data does not include information to illuminate this aspect.

We found comorbidity (ASA >1) as a predictor of mortality, but only at 0-180 days after surgery, and with a decreasing importance over time. Grann et al [30], and Sperling et al [31] also observed comorbidity to be a predictor of mortality. However, in contrast to our results, they did not evaluate the effect on the immediate postoperative time period, but evaluated data after one (Grann and Sperling[30,31]), and five years (Grann [30]). Consequently, our data also offers new information in this field and may indicate that reduction of any pre-existing comorbidity could be important in the increasing survival after primary ovarian cancer surgery.

Perioperative blood transfusion was observed to be a predictor of mortality 0-180 days after surgery. This is a new finding in women with ovarian cancer, but a negative effect of blood transfusion on survival has been described in other diseases [32,33]. Among gynaecological cancer patients, transfusion has been described to be associated with higher morbidity and increased mortality within the immediate 30 days after surgery, when controlling for parameters such as age,

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comorbidity, pre-existing anaemia, type of surgery etc.[34]. Immune modulatory mechanisms are suggested to induce the above-mentioned complications [35]. Since the DGCD does not contain information on haemoglobin levels or total transfused blood units, we were unable to evaluate any possible influence of these parameters. Our findings might indicate that perioperative blood transfusion should only be prescribed to a very restricted group of patients, although this aspect needs to be studied in more detail.

Our study also has limitations. According to the incident numbers of Danish ovarian cancer patients (2005-2012) [36], a total of 86-92% had primary ovarian cancer surgery performed [7], however, only 67 % of the operated patients were eligible for evaluation in our study. Missing information on smoking and alcohol prevented examining the impact on survival. As discussed previously, analyses regarding neoadjuvant chemotherapy prior to surgery were not available due to absent information of this parameter throughout the entire study period. In addition, information regarding laboratory data would have been valuable. Other causes of death than ovarian cancer increase with age and the use of overall survival may have caused confounding. However, information on the causes of death was not available.

Residual tumour tissue, advanced FIGO-stage, being underweight, comorbidity, and perioperative blood transfusion were all found to be predictors of mortality within the first year after primary ovarian cancer surgery. Our results suggest that the surgeon should not only aim for radical surgery, but also pay attention to comorbidity, nutritional state, and the use of perioperative blood transfusion. These findings should be confirmed in other settings, and future studies are needed to assess the impact of smoking, alcohol, units of blood transfused, and neoadjuvant chemotherapy as predictors of mortality within the first postoperative year after primary ovarian cancer surgery.

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CONCLUSIONS

In the present study, we aimed to examine predictors of mortality within 0-180 days and 181-360 days after ovarian cancer surgery. The examined predictors were age, ASA score, BMI, FIGO-stage, residual tumour tissue after surgery, perioperative blood transfusion, and calendar year of surgery. The overall one-year survival was 84%. The most important predictors of mortality within one year after surgery were residual tumour tissue (0-180 days after surgery) and advanced FIGO-stage (181-360 days after surgery). Our results suggest that the surgeon should aim for radical surgery. However, comorbidity, being underweight, age >64 years, and blood transfusion were also significant predictors of mortality and need to be studied in more detail.

Table 1. Descriptive characteristics according to death up to 360 days after primary ovarian cancer surgery in Danish women performed from 2005-2012 (percentage distribution in brackets).

		Number of women	Women who died within 0-180 days after surgery	Women who died within 181-360 days after surgery	Women who survived at least 361 days after surgery
All women		2,654 (100)	226 (9)	186 (7)	2,242 (84)
Age*	≤64 years (%)	1,380 (52)	53 (4)	75 (5)	1252 (91)
	>64 years (%)	1,274 (48)	173 (14)	111 (9)	990 (78)
ASA	Score 1 (%)	1,023 (39)	33 (3)	52 (5)	938 (92)
	Score >1 (%)	1,622 (61)	192 (12)	133 (8)	1,297 (80)
	Missing (%)	9 (0)	1 (11)	1 (11)	7 (78)
Smoking	No (%)	1,306 (49)	95 (7)	86 (7)	1,125 (86)
	Yes (%)	1,046 (39)	89 (9)	74 (7)	883 (84)
	Missing (%)	302 (11)	42 (14)	26 (9)	234 (77)
BMI	Underweight (%)	117 (4)	24 (20)	17 (15)	76 (65)
	Normal (%)	1,369 (52)	122 (9)	91 (7)	1,156 (84)
	Overweight (%)	1,095 (41)	72 (6)	74 (7)	949 (87)
	Missing (%)	73 (3)	8 (11)	4 (5)	61 (84)
FIGO-stage	Localized (%)	965 (36)	34 (4)	24 (2)	907 (94)
	Advanced (%)	1,668 (63)	190 (11)	161 (10)	1,317 (79)
	Missing (%)	21 (1)	2 (10)	1 (5)	18 (85)
Residual tumour	None (%)	1,798 (68)	65 (4)	86 (5)	1,647 (91)
	≤2 cm (%)	328 (12)	45 (14)	36 (11)	247 (75)
	>2 cm (%)	519 (20)	115 (22)	63 (12)	341 (66)
	Missing (%)	9 (0)	1 (11)	1 (11)	7 (78)
Blood transfusion	No (%)	2,000 (75)	143 (7)	125 (6)	1,732 (87)
	Yes (%)	648 (24)	83 (13)	60 (9)	505 (78)
	Missing (%)	6 (0)	0 (0)	1 (17)	5 (83)
Calender year	2005-2006	764(29)	81 (11)	53 (7)	630 (82)
	2007-2009	1,073 (40)	99 (9)	79 (7)	895 (84)
	2010-2012	817 (31)	46 (6)	54 (6)	717 (88)

* Age was divided in two groups according to the median age

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Table 2. Results from the Cox multivariable regression analyses estimating the impact of possible predictive variables on mortality after primary ovarian cancer surgery in Danish women from 2005-2012. Data is reported by Hazard Ratio (HR), 95% confidence intervals (CI), and the results of the time-interval heterogeneity test are reported by p-values.

All HR were mutually adjusted for the other variables.

Variable	0 - 180 days after surgery, HR (95% CI)	181 – 360 days after surgery, HR (95% CI)	p-values for test for homogeneity between the two time periods
Age* (>64 years vs. ≤64 years)	2.33 (1.69–3.21)	1.64 (1.19–2.25)	0.1240
ASA score (>1 vs. 1)	2.17 (1.46–3.23)	1.25 (0.88–1.76)	0.0383
BMI (Underweight vs. Normal)	2.01 (1.29-3.07)	2.08 (1.18-3.66)	0.9046
(Overweight vs. Normal)	0.82 (0.61-1.11)	1.08 (0.79-1.48)	0.2093
Residual tumour (≤2 cm vs. None)	2.50 (1.63–3.82)	1.68 (1.11–2.53)	0.1863
(>2 cm vs. None)	4.58 (3.20–6.59)	1.84 (1.25–2.70)	0.0007
FIGO-stage (Advanced vs. Localized)	1.28 (0.83–1.96)	2.81 (1.75–4.50)	0.0151
Blood transfusion (Yes vs. No)	1.62 (1.21-2.16)	1.28 (0.92-1.78)	0.2912
Calendar year (Increasing)	0.86 (0.72-1.04)	0.99 (0.81-1.21)	0.3076

* Age was divided in two groups according to the median age

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Contributors:

MØ, MI, RG, OM and BMN were involved in the conception or design of the study design, data

collection, interpretation of data, and involved in the drafting of the manuscript.

MI (statistician) performed the analyses. All authors have read and revised the manuscript critically

for important intellectual content, and approved the final version to be published.

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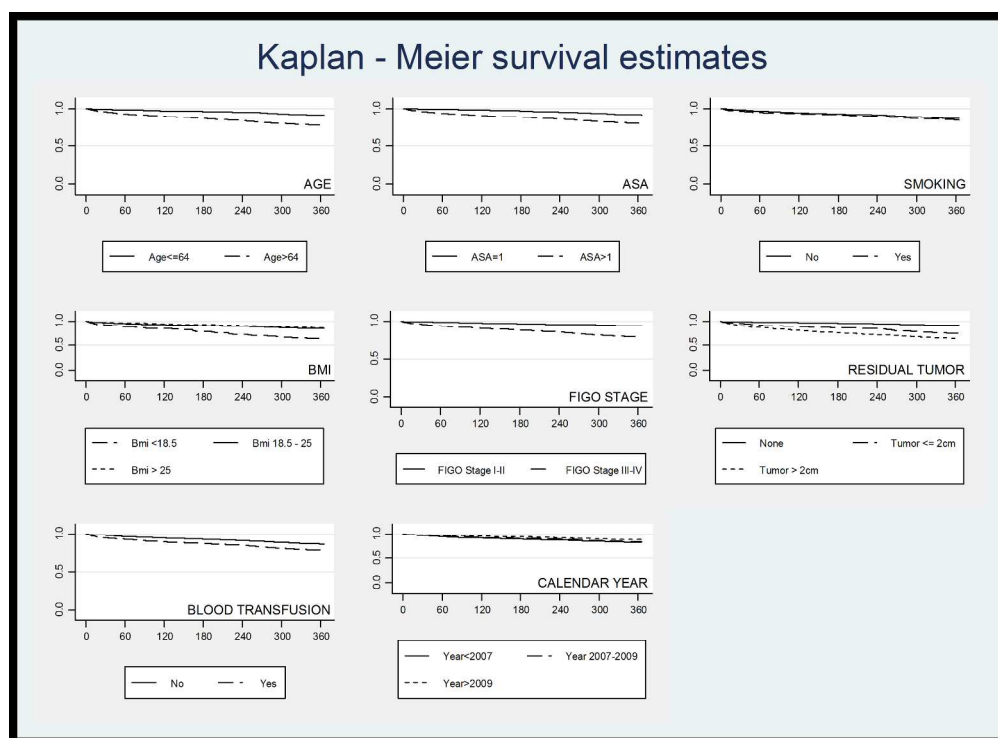
Figure 1. Kaplan-Meier survival estimates on possible predictive variables in Danish women within the first year after primary ovarian cancer surgery (2005-2012), with the X-axis indicating days after surgery, and the Y-axis indicating the survival proportion in percentage.
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, explain how loss to follow-up was addressed	not relevant
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6,9
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	15 (Table 1)
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10 16 (Table 2)
		(*b*) Report category boundaries when continuous variables were categorized	9-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11,14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	4,10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Reported in the submission system

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.