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ORIGINAL REPORT

Prognosis and Conditional Disease-Free Survival Among Patients With Ovarian Cancer

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ABSTRACT

Purpose
Traditional disease-free survival (DFS) does not reflect changes in prognosis over time. Conditional DFS accounts for elapsed time since achieving remission and may provide more relevant prognostic information for patients and clinicians. This study aimed to estimate conditional DFS among patients with ovarian cancer and to evaluate the impact of patient characteristics.

Patients and Methods
Patients were recruited as part of the Hormones and Ovarian Cancer Prediction case-control study and were included in the current study if they had achieved remission after a diagnosis of cancer of the ovary, fallopian tube, or peritoneum (N = 404). Demographic and lifestyle information was collected at enrollment; disease, treatment, and outcome information was abstracted from medical records. DFS was calculated using the Kaplan-Meier method. Conditional DFS estimates were computed using cumulative DFS estimates.

Results
Median DFS was 2.54 years (range, 0.03-9.96 years) and 3-year DFS was 48.2%. The probability of surviving an additional 3 years without recurrence, conditioned on having already survived 1, 2, 3, 4, and 5 years after remission, was 63.8%, 80.5%, 90.4%, 97.0%, and 97.7%, respectively. Initial differences in 3-year DFS at time of remission between age, stage, histology, and grade groups decreased over time.

Conclusion
DFS estimates for patients with ovarian cancer improved dramatically over time, in particular among those with poorer initial prognoses. Conditional DFS is a more relevant measure of prognosis for patients with ovarian cancer who have already achieved a period of remission, and time elapsed since remission should be taken into account when making follow-up care decisions.

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INTRODUCTION

There were approximately 22,240 incident cases of ovarian cancer (OC) and 14,030 deaths due to OC in the United States in 2013.[1] Patients diagnosed with localized OC have an estimated survival rate of 92%. Unfortunately, the majority of OC cases are diagnosed with regional or distant disease when survival rates are 72% and 27%, respectively.[2]

Survival estimates are traditionally reported from the time of diagnosis (overall survival [OS]) or remission (disease-free survival [DFS]). Although these estimates provide important information for patients and clinicians, they are not necessarily still applicable to patients who have already survived a period of time after their initial diagnosis and treatment. Conditional survival, which takes into account changes in risk over time, may offer more accurate estimates for these patients. Several previous studies assessed conditional OS among patients with OC; three used data from the SEER database,[3-5] and one used data from the European Network for Indicators on Cancer (EUNICE).[6] They reported that OS estimates improved as time elapsed since diagnosis and that the impact of prognostic factors such as age, stage, and histology diminished over time. These findings provide evidence that survival probabilities change significantly when accounting for time elapsed after diagnosis.

The majority of patients with OC achieve remission but, unfortunately, most will also eventually relapse. Follow-up care typically includes physical

exams, imaging tests, and the close monitoring of CA-125 levels. There is, however, controversy regarding the effectiveness of these efforts to meaningfully impact disease outcomes.[7-9] In addition, results from a recent clinical trial suggest that there is no survival benefit to initiating chemotherapy when CA-125 levels increase compared with delaying treatment until there is clinical evidence of disease.[10] Moreover, earlier deterioration in quality of life was observed among women who were treated based on rising CA-125 levels alone.[10] Therefore, there is a need to provide more accurate information regarding risk of recurrence, such as conditional DFS estimates, to patients so that they can make better informed decisions concerning their follow-up care.

To our knowledge, no prior studies have assessed conditional DFS among patients with OC. The objective of this study was to estimate conditional DFS among patients with OC and to evaluate the impact of patient characteristics.

PATIENTS AND METHODS

Study Population and Data Collection

Patients included in our analysis were enrolled as part of the Hormones and Ovarian Cancer Prediction (HOPE) case-control study, which has been described in detail previously.[11,12] Briefly, HOPE includes 902 ovarian, peritoneal, and fallopian tube cases from a contiguous region of Western Pennsylvania (PA), Eastern Ohio (OH), and Western New York (NY). Cases were diagnosed between February 2003 and December 2008, ≥ 25 years old, and within 9 months of initial diagnosis at the time of recruitment. All participants provided informed consent. The study was approved by the University of Pittsburgh institutional review board and by human subject committees at each hospital where cases were identified and enrolled.

Trained interviewers collected demographic, lifestyle, and medical history information via in-person interviews, using 9 months before enrollment as reference date. Follow-up data has been collected on an ongoing basis through annual requests for patients' medical records from their treating physicians. Information collected includes CA-125 laboratory results, chemotherapy flow sheets, pathology reports, surgical and hospitalization records, imaging results, and oncologist notes. The Social Security Death Index (SSDI) and the National Death Index (NDI) were also used to determine vital status. For the purposes of this study, the cutoff date for follow-up data collection was April 16, 2013.

Patients recruited from OH or PA were included in the current study if they had achieved remission. Cases with borderline or nonepithelial tumors were excluded. Of the 651 patients recruited from OH or PA, 404 fulfilled these criteria and were included.

Disease Characteristics, Treatment, and Outcome

Information on disease characteristics, treatment and outcome was abstracted from medical records. Tumors reported to be of mixed grade were assigned to the highest tumor grade category. Cases were considered to be optimally debulked if their residual disease was less than 1 cm. If residual tumor size was unavailable, they were classified as optimally debulked if their surgeon/oncologist declared them to be optimally debulked. The presence of ascites and pleural effusion was collected from imaging results. If scans were not available, the presence of ascites or pleural effusion was considered to be "could not be assessed." Chemotherapy agents were categorized into three groups: platinum-based (carboplatin, cisplatin, oxaliplatin, and abraxane), taxanes (taxol, taxotere, and xyotax), and other (all other chemotherapy agents, including: avastin, doxil, topotecan, gemzar, cytoxan, interferon, mytomycin, erbitux, ifosphomaide, catumaxomab, and ovarex). Total number of cycles received for each group was the sum of all neoadjuvant, adjuvant, maintenance, and persistent disease-related chemotherapy. Persistent disease was defined as the presence of measurable disease after primary treatment.

Date of diagnosis was the date of first positive cytology or, in cases with no available cytology before primary surgery, the date of primary surgery. Date of remission was the date an oncologist first declared the patient to have no evidence of disease (n = 278). For patients missing this information (n = 126), we used the following (listed in order of use): (1) date of the first negative surgical results (n = 17); (2) date of the first negative imaging results (n = 19); (3) date of first other event indicating no evidence of disease (eg, normalized CA-125 level; n = 3); and, if none of this was available, (4) a date of 4 weeks after completion of chemotherapy (n = 75) or, if no chemotherapy was received, the date of primary surgery (n = 12). Recurrence was defined as the return of disease after being in remission. A similar process as for date of remission was applied to determine date of recurrence. If available, the date an oncologist first diagnosed the patient with recurrence was used (n = 179); when this was not available, we used the following (listed in order of use): (1)

Table 1. Selected Demographic and Lifestyle Characteristics of the Study Population

Characteristic	Study Population (N = 404) No.	%
Age at remission, years		
< 45	42	10.4
45 to < 55	96	23.8
55 to < 65	126	31.2
≥ 65	140	34.6
Race		
White	391	96.8
African-American	9	2.2
Other	4	1.0
Education		
Non–high school graduate	36	8.9
High school graduate	131	32.4
Post–high school	237	58.7
Yearly income, $		
≥ 90,000	47	11.6
50,000 to < 90,000	117	29.0
25,000 to < 50,000	113	28.0
< 25,000	80	19.8
Could not be assessed	47	11.6
Body mass index, kg/m^2		
< 25	151	37.4
25 to < 30	121	29.9
≥ 30	132	32.7
Smoking status		
Never smoker	202	50.0
Former smoker	140	34.7
Current smoker	62	15.4
Alcohol use, drinks per week		
≤ 7	338	83.7
8 to ≤ 14	38	9.4
≥ 15	28	6.9
Family history*		
None	319	79.0
Breast only	63	15.6
Ovarian only	18	4.5
Breast and ovarian	4	1.0
Menopausal status†		
Premenopausal	97	24.0
Postmenopausal	307	76.0

*Family history was defined as having at least one reported diagnosis of the cancer(s) in a first-degree relative.
†Women were classified as postmenopausal if they were ≥ 55 years old, reported natural menopause, had used hormone replacement therapy, or reported no menstrual periods in the 6 months prior to the reference date.

Table 2. Distribution of Disease and Clinical Characteristics Across Years of Disease-Free Survival

Characteristic	Baseline (N = 404)		1 yr (n = 281)		2 yr (n = 219)		3 yr (n = 185)		4 yr (n = 148)		5 yr (n = 104)	
	No.	%	No.	%	No.	%	No.	%	No.	(%)	No.	(%)
Stage[a]												
I	124	30.8	118	42.1	112	51.4	108	58.7	89	60.5	64	61.8
II	44	10.9	37	13.2	31	14.2	28	15.2	25	17.0	19	18.6
III	205	50.9	113	40.4	69	31.7	44	23.9	30	20.4	17	16.7
IV	30	7.4	12	4.3	6	2.8	4	2.2	3	2.0	3	2.9
Primary site												
Ovarian	341	84.4	239	85.1	189	86.3	165	89.2	130	87.8	94	90.3
Peritoneal	30	7.4	18	6.4	11	5.0	4	2.2	3	2.0	2	1.9
Fallopian	28	6.9	22	7.8	17	7.8	15	8.1	14	9.5	7	6.8
Could not be assessed	5	1.2	2	0.7	2	0.9	1	0.5	1	0.7	1	1.0
Grade												
Well differentiated	42	10.4	39	13.9	34	15.5	32	17.3	28	18.9	16	15.4
Moderately differentiated	106	26.2	78	27.8	61	27.9	53	28.6	41	27.7	31	29.8
Poorly differentiated	221	54.7	139	49.5	102	46.6	83	44.9	63	42.6	47	45.2
Could not be assessed	35	8.7	25	8.9	22	10.0	17	9.2	16	10.8	10	9.6
Histology												
Serous	216	53.5	125	44.5	81	37.0	60	32.4	45	30.4	29	28.2
Endometrioid	68	16.8	60	21.4	52	23.7	51	27.6	38	25.7	32	31.1
Mucinous	21	5.2	20	7.1	20	9.1	18	9.7	16	10.8	10	8.7
Clear cell	29	7.2	28	10.0	24	11.0	22	11.9	20	13.5	14	13.6
Brenner	5	1.2	4	1.4	4	1.8	3	1.6	3	2.0	3	2.9
MMT	9	2.2	7	2.5	6	2.7	5	2.7	5	3.4	4	3.9
Mixed	40	9.9	29	10.3	25	11.4	21	11.4	17	11.5	11	10.7
Other[b]	3	0.7	2	0.7	1	0.5	1	0.5	0	0.0	0	0.0
Could not be assessed	13	3.2	6	2.1	6	2.7	4	2.2	4	2.7	1	1.0
Pretreatment CA-125												
≤ 35 U/mL	60	14.9	54	19.2	49	22.4	45	24.3	38	25.7	28	26.2
> 35 U/mL	274	67.8	178	63.4	136	62.1	112	60.5	94	63.5	68	66.0
Could not be assessed	70	17.3	49	17.4	34	15.5	28	15.1	16	10.8	8	7.8
Pretreatment pleural effusion												
No	58	14.4	36	12.8	29	13.2	29	15.7	27	18.2	19	18.5
Yes	44	10.9	23	8.2	15	6.9	10	5.4	7	4.7	6	5.8
Could not be assessed	302	74.8	222	79.0	175	79.9	146	78.9	114	77.0	79	75.7
Cytology of ascites/pelvic washings												
Negative	138	34.2	123	43.8	114	52.1	107	57.8	85	57.4	64	61.2
Positive	182	45.1	103	36.6	60	27.4	44	23.8	37	25.0	23	22.3
Atypical	16	4.0	11	3.9	9	4.1	7	3.8	7	4.7	4	3.9
Could not be assessed	68	16.8	44	15.7	36	16.4	27	14.6	19	12.8	13	12.6
Pretreatment ascites												
No	153	37.9	128	45.6	112	51.1	99	53.5	83	56.1	60	57.3
Yes	246	60.9	148	52.7	103	47.0	84	45.4	63	42.6	43	41.8
Could not be assessed	5	1.2	5	1.8	4	1.8	2	1.1	2	1.4	1	1.0
Lymph node involvement												
No palpable nodes, no biopsies	152	37.6	83	29.5	55	25.1	42	22.7	31	21.0	18	17.5
Palpable nodes, no biopsies	6	1.5	5	1.8	1	0.5	0	0.0	0	0.0	0	0.0
Biopsies negative	183	45.3	157	55.9	139	63.5	125	67.6	105	71.0	76	72.8
Biopsies positive	57	14.1	33	11.7	21	9.6	16	8.7	10	6.8	8	7.8
Could not be assessed	6	1.5	3	1.1	3	1.4	2	1.1	2	1.4	2	1.9
Synchronous primary tumor												
No	375	93.5	261	93.2	202	92.7	170	92.4	135	91.8	96	93.1
Yes, endometrial	20	5.0	15	5.4	14	6.4	13	7.1	11	7.5	7	6.9
Yes, other[c]	6	1.5	4	1.4	2	0.9	1	0.5	1	0.7	0	0.0
Residual disease after cytoreductive surgery[d]												
No	238	59.4	199	71.1	176	80.7	160	87.0	132	89.8	95	92.2
Yes	133	33.2	65	23.2	34	15.6	21	11.4	15	6.1	8	7.8
Could not be assessed	30	7.5	16	5.7	8	3.7	3	1.6	0	0.0	0	0.0

(continued on following page)

Table 2. Distribution of Disease and Clinical Characteristics Across Years of Disease-Free Survival (continued)

Characteristic	Baseline (N = 404)		1 yr (n = 281)		2 yr (n = 219)		3 yr (n = 185)		4 yr (n = 148)		5 yr (n = 104)	
	No.	%	No.	%	No.	%	No.	%	No.	(%)	No.	(%)
Residual disease after cytoreductive surgery, cm[d]												
No residual disease	238	59.4	201	71.8	178	81.7	161	87.5	132	89.8	95	92.2
0.1 to < 1.0	70	17.5	38	13.6	18	8.3	11	6.0	9	6.1	5	4.9
1.0 to < 2.0	24	6.0	10	3.6	5	2.3	1	0.5	1	0.7	1	1.0
≥ 2.0	17	4.2	3	1.1	3	1.4	3	1.6	2	1.4	0	0.0
Could not be assessed	52	13.0	28	10.0	14	6.4	8	4.4	3	2.0	2	2.0
Debulking at cytoreductive surgery[e]												
Optimal	307	76.0	244	86.8	196	89.5	171	92.5	138	93.2	97	93.2
Suboptimal	57	14.1	22	7.8	12	5.5	7	3.8	4	2.7	2	1.9
Received neoadjuvant chemotherapy	27	6.7	9	3.2	8	3.7	5	2.7	4	2.7	3	2.9
No primary surgery performed	3	0.7	1	0.4	1	0.5	1	0.5	1	0.7	1	1.0
Could not be assessed	10	2.5	5	1.8	2	0.9	1	0.5	1	0.7	1	1.0
Platinum chemotherapy, no. of cycles[f,g]												
No	31	7.7	28	10.0	28	12.8	25	13.5	21	14.2	13	11.7
0 to ≤ 3	21	5.2	20	7.1	18	8.2	16	8.7	13	8.8	11	10.7
3 to ≤ 6	247	61.1	173	61.6	130	59.4	115	62.2	91	61.5	64	62.1
> 6	102	25.3	57	20.3	41	18.7	27	14.6	21	14.2	16	15.5
Yes, number of cycles unknown	3	0.7	3	1.1	2	0.9	2	1.1	2	1.4	0	0.0
Taxane chemotherapy, no. of cycles[f,h]												
No	41	10.2	37	13.2	35	16.0	30	16.2	24	16.2	16	14.6
0 to ≤ 3	24	5.9	21	7.5	20	9.1	17	9.2	16	10.8	13	12.6
3 to ≤ 6	235	58.2	163	58.0	126	57.5	109	58.9	87	58.8	60	58.3
> 6	99	24.5	55	19.6	34	15.6	25	13.5	19	12.8	15	14.6
Yes, number of cycles unknown	5	1.2	5	1.8	4	1.8	4	2.2	2	1.4	0	0.0
Other chemotherapy, no. of cycles[f,i]												
No	355	89.0	253	90.0	201	91.8	175	94.6	142	96.0	100	96.1
0 to ≤ 3	3	0.8	5	1.8	3	1.4	2	1.1	1	0.7	1	1.0
3 to ≤ 6	16	4.0	11	3.9	7	3.2	4	2.2	4	2.7	3	2.9
> 6	21	5.3	10	3.6	8	3.7	4	2.2	1	0.7	0	0.0
Yes, number of cycles unknown	4	1.0	2	0.7	0	0.0	0	0.0	0	0.0	0	0.0
Maintenance chemotherapy												
No	366	90.6	252	89.7	204	93.2	174	94.1	142	96.0	101	97.1
Yes	38	9.4	29	10.3	15	6.9	11	5.9	6	4.0	3	2.9
Number of chemotherapy cycles before normalization of CA-125												
Normalized without/prior to chemotherapy	133	32.9	120	42.7	105	47.9	94	50.8	76	51.4	51	49.0
Normalized 1 to < 3	116	28.7	79	28.1	65	29.7	53	28.7	39	26.4	30	28.8
Normalized 3 to < 6	80	19.8	37	13.2	21	9.6	15	8.1	13	8.8	7	6.7
Normalized ≥ 6	37	9.2	19	6.8	9	4.1	7	3.8	7	4.7	5	4.8
Could not be assessed	38	9.4	26	9.3	19	8.7	16	8.7	13	8.8	11	10.6
Persistent disease after primary treatment												
No	391	96.8	277	98.6	216	98.6	183	98.9	146	98.7	103	99.0
Yes	13	3.2	4	1.4	3	1.4	2	1.1	2	1.3	1	1.0

Abbreviations: MMT, mixed Mullerian tumor; yr, year.
[a]One patient was missing stage information because she never had staging or cytoreductive surgeries and was never formally staged by oncologist.
[b]Includes one micropapillary serous, one adenosquamous, one papillary serous with multiple psammoma bodies.
[c]Includes one of each of the following synchronous cancers: fallopian tube, granulosa cell tumor of the ovary, recurrent breast, GI stromal, skin, and appendiceal.
[d]Excludes three patients that did not have cytoreductive surgery.
[e]Patients were considered to be optimally debulked if their disease was <1 cm or their surgeon/oncologist declared them to be optimally debulked at the conclusion of their cytreductive surgery.
[f]Includes neoadjuvant, adjuvant, and maintenance chemotherapies received as well as any chemotherapy received for persistent disease.
[g]Includes carboplatin, cisplatin, oxaliplatin, and abraxane.
[h]Includes taxol, taxotere, and xyotax.
[i]Includes avastin, doxil, topotecan, gemzar, cytoxan, interferon, mytomycin, erbitux, ifosphomaide, catumaxomab, and ovarex. Many of these other chemotherapies were given as part of a clinical trial and in some cases it was unclear whether participants received placebo or the active agent; cases that were reported to have gotten the placebo were considered to have received no chemotherapy.

date of the first positive surgical results (n = 16); (2) date of the first positive imaging results (n = 11); (3) date of chemotherapy/radiation initiation (n = 14); and (4) date of first other event indicating return of disease (eg, elevated CA-125 level; n = 2) after being disease-free. OS was defined as the time elapsed between date of diagnosis and date of death or last contact. DFS was defined as the interval between date of remission and date of recurrence or last contact. Patients who were not diagnosed with recurrent OC during the follow-up period were censored at the date of last contact.

Statistical Analysis

Traditional OS and DFS estimates were calculated using the Kaplan-Meier approach. Conditional DFS, an extension of the concept of conditional OS, is the probability of staying disease-free an additional *y* years given that the patient has already been in remission for *x* years.[13-15] Conditional DFS estimates were computed using cumulative DFS estimates.[14] For example, to compute the 3-year conditional DFS estimate for patients who had already been in remission for 2 years, the 5-year cumulative DFS was divided by the 2-year cumulative DFS. Changes in DFS over time were assessed by comparing 3-year conditional DFS estimates at 1, 2, 3, 4, and 5 years after achieving remission with baseline (date of remission) 3-year DFS estimates. In addition to overall conditional DFS, to evaluate the effect of patient characteristics, we also computed 3-year conditional DFS estimates within strata defined by age, stage, histology, and grade. Impact of patient characteristics on DFS at baseline and at 1 and 2 years after achieving remission was also evaluated using age-adjusted Cox proportional hazards models to calculate hazard ratios and corresponding 95% CIs for recurrence. We used the landmark analysis approach to assess impact at years 1 and 2 of remission.[16,17] The size of some of the subgroups and the number of events was too small to yield meaningful results for later years. Women who had recurred or whose date of last contact was within 1 year of remission were excluded from the 1-year time point analysis. Similarly, women who had this happen within 2 years of remission were excluded from the 2-year time point analysis. DFS was measured from the time point of interest and age used in the models was current age (that is, age at baseline plus 1 year for the 1-year time point, plus 2 years for the 2-year time point). All significance tests were two-sided; *P* values less than 0.05 were considered statistically significant. All analyses were conducted using Stata version 12.1 (StataCorp LP, College Station, TX).

RESULTS

Selected demographic and lifestyle characteristics of the study population are shown in Table 1. The majority of patients were white and postmenopausal. Median age at diagnosis was 58.6 years (not in table), and 5.5% had a family history of ovarian-only or breast and ovarian cancer.

Table 2 presents the distribution of disease and clinical characteristics among patients across years of disease-free survival (ie, at baseline and 1, 2, 3, 4, and 5 years after achieving remission, given that they remained in remission at these time points). Only 30.8% of the study participants had been diagnosed with stage I disease, however, 61.8% of the women who survived 5 years without recurrence had stage I disease. Similar relationships were observed for histologic subtypes, cytology of ascites/pelvic washings, pretreatment ascites, lymph node involvement, presence and size of residual disease, debulking status, and number of chemotherapy cycles before normalization of CA-125.

Among all 404 patients included in this study, median OS was 4.50 years (range, 0.82-9.89 years). At the cutoff date for follow-up, 235 (58.2%) study participants were still alive. Median time elapsed between date of diagnosis and remission was 6.45 months (range, 0-26.20 months; this includes 12 women whose date of diagnosis was the date of their cytoreductive surgery after which there was no residual disease and no further treatment necessary). Traditional DFS curves, stratified by age at remission and stage, are depicted in Appendix Figure A1 (online only). Within our study, 222 (55.0%) women were diagnosed with recurrent OC and median DFS was 2.54 years (range, 0.03-9.36 years).

At baseline, 3-year DFS was 48.2%. The probability of surviving an additional 3 years without recurrence, conditioned on having already survived 1, 2, 3, 4, and 5 years after remission, improved to 63.8%, 80.5%, 90.4%, 97.0%, and 97.7%, respectively (see Fig 1).

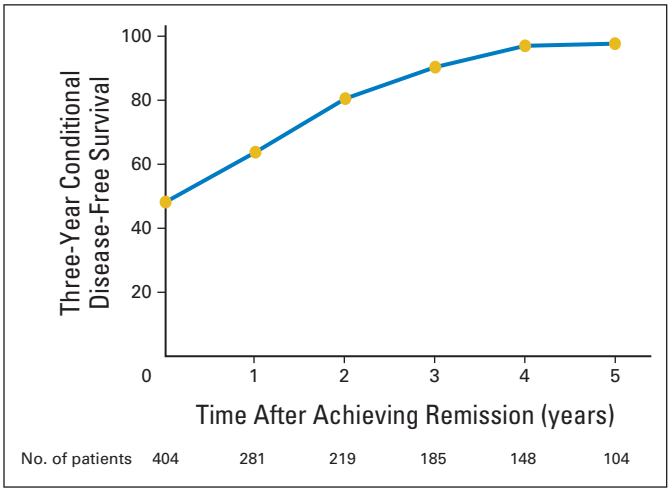

Fig 1. Three–year conditional disease-free survival estimates. Number of patients still in remission at particular time point.

Presented differently, the probability that a patient will still be disease-free 5 years after achieving remission increases from 44.6% at baseline to 63.3%, 80.5%, 92.4%, and 99.2% after being already disease-free for, respectively, 1, 2, 3, and 4 years.

Figure 2 shows 3-year conditional DFS estimates stratified by age, stage, histology, and grade. Generally, 3-year DFS estimates increased for all age, stage, histology, and grade groups evaluated and the disparity in estimates decreased with longer time in remission. For instance, 3-year DFS estimates for histology groups ranged from 28.8% to 95.2% at baseline but this range became tighter over time and at year 5 was 90.9% to 100% (see Fig 2). The largest improvements in 3-year DFS estimates were observed for older women and those diagnosed with stage III/IV disease, serous tumors, and poorly differentiated tumors (see Fig 2).

Cox proportional hazards models adjusted for current age were used to evaluate the effect of patient characteristics on subsequent DFS at baseline and at years 1 and 2 of remission; results are reported in Table 3. For the 1- and 2-year time points, DFS was measured from the specified time point and only women who were still disease-free at that time point were included in the analysis. At baseline, characteristics significantly associated with higher risk of recurrence (compared with reference group, see Table 3) included family history of breast and OC, later stage, peritoneal cancer, higher grade, pretreatment CA-125 greater than 35 U/mL, pretreatment pleural effusion, positive cytology of ascites/pelvic washings, pretreatment ascites, presence and larger size of residual disease, nonoptimal debulking, higher number of platinum, taxane, and other chemotherapy cycles, receiving maintenance chemotherapy, higher number of chemotherapy cycles before CA-125 normalization, and having persistent disease after primary treatment. Decreased risk of recurrence was significantly associated with negative lymph node biopsies and endometrioid, mucinous, clear cell, and mixed tumors. All these characteristics except pretreatment CA-125 level and persistent disease after primary treatment remained predictive of subsequent DFS at the 1- and 2-year time points. We were unable to assess the impact of several characteristics at the 2-year time point due to limitations of subgroup size.

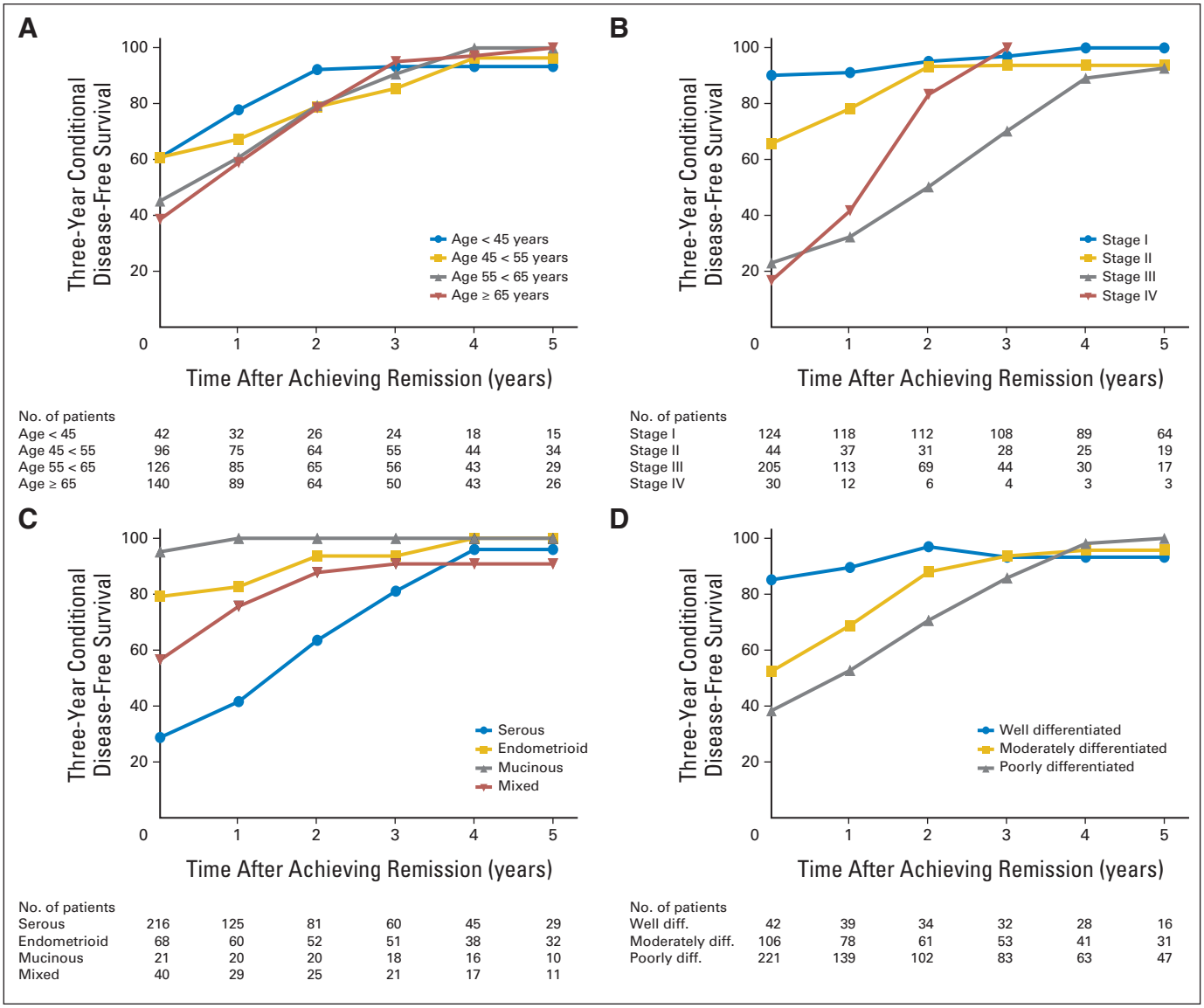

Fig 2. Three-year conditional disease-free estimates stratified by age at remission (A), stage (B), histology (C), and grade (D). Number of patients still in remission at particular time point. diff., differentiated.

DISCUSSION

To our knowledge, this is the first study to assess conditional DFS among patients with OC. Our findings demonstrate that DFS estimates improve dramatically for patients with OC who have already achieved a period of remission and that conditional DFS is a more relevant measure of prognosis for these women. Generally, we observed that DFS improved most for patients who initially had the poorest prognosis. Consistent with results from studies examining conditional OS among patients with OC,[3-6] we found that the initial differences in DFS at time of remission between age, stage, histology, and grade groups diminished over time. This suggests that the prognostic importance of these factors decreases as time in remission increases.

At baseline, we observed significant associations between a large number of the evaluated patient characteristics and risk of recurrence. Our results are in line with previous studies that established these factors as predictors of overall or disease-free survival. The significant characteristics included: family history,[18] stage,[19,20] primary site,[21] grade,[19,22,23] histology,[20,21-24] pretreatment CA-125,[25,26] pretreatment pleural effusion,[27,28] cytology of ascites/pelvic washings,[29,30] pretreatment ascites,[20] lymph node involvement,[23,31-33] residual disease and debulking status after cytoreductive surgery,[20,22,24,34] number of chemotherapy cycles before normalization of CA-125,[35-37] and total number of platinum, taxane, and other chemotherapy cycles received.[20,23,38,39] While previous studies have provided conflicting results regarding the role of maintenance chemotherapy in improving overall survival,[40,41] risk of recurrence was significantly increased for patients receiving maintenance chemotherapy in our population. It is important to note that maintenance chemotherapy is not considered standard of care for patients with OC and it is possible that in particular women who were at high risk of recurrence were more likely to be

Table 3. HRs and Corresponding 95% CIs for Recurrence at Baseline and at Years 1 and 2 of Remission[a]

Characteristic	Baseline (N = 404)		Year 1 (n = 281)		Year 2 (n = 219)	
	HR[b]	95% CI	HR[b]	95% CI	HR[b]	95% CI
Race						
White	1.0	ref	1.0	ref	1.0	ref
African-American	0.56	0.21 to 1.50	0.76	0.24 to 2.41	1.21	0.29 to 5.11
Other	0.51	0.07 to 3.68	1.06	0.14 to 7.87	—	—
Education						
Non–high school graduate	1.0	ref	1.0	ref	1.0	ref
High school graduate	1.45	0.87 to 2.43	1.72	0.76 to 3.90	5.46	0.72 to 41.48
Post–high school	1.24	0.74 to 2.05	1.53	0.68 to 3.42	4.78	0.63 to 36.19
Yearly Income, $						
≥ 90,000	1.0	ref	1.0	ref	1.0	ref
50,000 to < 90,000	1.55	0.94 to 2.56	0.88	0.49 to 1.57	1.16	0.45 to 3.01
25,000 to < 50,000	1.71	1.03 to 2.84	0.70	0.37 to 1.32	0.71	0.24 to 2.12
< 25,000	1.52	0.89 to 2.60	0.88	0.46 to 1.69	1.35	0.48 to 3.78
Could not be assessed	1.65	0.92 to 2.95	0.83	0.39 to 1.76	1.08	0.33 to 3.56
Body mass index, in kg/m^2						
< 25	1.0	ref	1.0	ref	1.0	ref
25 to < 30	1.14	0.83 to 1.57	0.84	0.53 to 1.34	0.86	0.42 to 1.78
≥ 30	0.95	0.69 to 1.30	0.68	0.42 to 1.08	0.67	0.32 to 1.38
Smoking status						
Never smoker	1.0	ref	1.0	ref	1.0	ref
Former smoker	0.88	0.66 to 1.18	1.06	0.69 to 1.63	0.98	0.51 to 1.89
Current smoker	0.93	0.63 to 1.38	1.26	0.73 to 2.18	0.95	0.38 to 2.35
Alcohol use, drinks per week						
≤ 7	1.0	ref	1.0	ref	1.0	ref
8 to ≤ 14	0.97	0.61 to 1.55	0.90	0.45 to 1.79	1.37	0.57 to 3.24
≥ 15	0.89	0.52 to 1.54	0.78	0.34 to 1.78	0.33	0.04 to 2.39
Family history						
None	1.0	ref	1.0	ref	1.0	ref
Breast only	0.84	0.58 to 1.22	0.89	0.53 to 1.51	1.15	0.55 to 2.40
Ovarian only	0.69	0.34 to 1.40	0.73	0.27 to 1.98	0.47	0.06 to 3.40
Breast and ovarian	3.24	1.19 to 8.78	4.22	1.02 to 17.41	13.87	1.81 to 105.96
Menopausal status						
Premenopausal	1.0	ref	1.0	ref	1.0	ref
Postmenopausal	1.15	0.75 to 1.78	1.12	0.60 to 2.08	1.10	0.44 to 2.78
Stage[c]						
I	1.0	ref	1.0	ref	1.0	ref
II	3.45	1.70 to 7.0	3.09	1.25 to 7.63	2.15	0.51 to 9.07
III	12.59	7.38 to 21.50	12.27	6.31 to 23.87	14.77	5.74 to 38.02
IV	16.10	8.41 to 30.82	11.00	4.14 to 29.21	4.21	0.49 to 36.47
Primary site						
Ovarian	1.0	ref	1.0	ref	1.0	ref
Peritoneal	1.70	1.11 to 2.61	2.72	1.53 to 4.85	5.32	2.32 to 12.19
Fallopian	0.78	0.45 to 1.38	0.94	0.44 to 2.05	0.65	0.15 to 2.69
Could not be assessed	1.64	0.60 to 4.47	1.06	0.15 to 7.73	3.00	0.39 to 23.04
Grade						
Well differentiated	1.0	ref	1.0	ref	1.0	ref
Moderately differentiated	3.37	1.52 to 7.44	2.52	0.96 to 6.61	2.23	0.47 to 10.60
Poorly differentiated	5.06	2.36 to 10.85	3.92	1.57 to 9.79	4.98	1.17 to 21.15
Could not be assessed	3.41	1.41 to 8.24	2.12	0.67 to 6.70	3.31	0.60 to 18.10
Histology						
Serous	1.0	ref	1.0	ref	1.0	ref
Endometrioid	0.22	0.13 to 0.37	0.23	0.12 to 0.44	0.13	0.04 to 0.42
Mucinous	0.04	0.01 to 0.28	—	—	—	—
Clear cell	0.21	0.10 to 0.44	0.30	0.13 to 0.70	0.19	0.05 to 0.80
Brenner	0.36	0.09 to 1.47	0.32	0.04 to 2.31	0.59	0.08 to 4.36
MMT	0.44	0.16 to 1.20	0.40	0.10 to 1.62	0.39	0.05 to 2.86
Mixed	0.46	0.28 to 0.75	0.37	0.18 to 0.77	0.38	0.13 to 1.08
Other[d]	1.17	0.28 to 4.86	1.48	0.19 to 11.27	—	—
Could not be assessed	0.87	0.44 to 1.70	0.39	0.10 to 1.60	0.87	0.21 to 3.66

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Table 3. HRs and Corresponding 95% CIs for Recurrence at Baseline and at Years 1 and 2 of Remission[a] (cotinued)

Characteristic	Baseline (N = 404)		Year 1 (n = 281)		Year 2 (n = 219)	
	HR[b]	95% CI	HR[b]	95% CI	HR[b]	95% CI
Pretreatment CA-125						
≤ 35 U/mL	1.0	ref	1.0	ref	1.0	ref
> 35 U/mL	2.92	1.75 to 4.89	2.35	1.21 to 4.58	2.27	0.88 to 5.87
Could not be assessed	2.93	1.64 to 5.22	2.96	1.40 to 6.26	2.24	0.71 to 7.07
Pretreatment pleural effusion						
No	1.0	ref	1.0	ref	1.0	ref
Yes	1.98	1.22 to 3.24	3.66	1.53 to 8.75	17.02	2.04 to 141.74
Could not be assessed	0.97	0.66 to 1.44	1.91	0.92 to 3.96	7.64	1.04 to 55.97
Cytology of ascites/pelvic washings						
Negative	1.0	ref	1.0	ref	1.0	ref
Positive	5.49	3.72 to 8.09	5.58	3.33 to 9.36	4.67	2.20 to 9.91
Atypical	3.20	1.52 to 6.70	2.91	0.99 to 8.56	3.09	0.67 to 14.15
Could not be assessed	3.52	2.21 to 5.59	3.02	1.59 to 5.77	3.68	1.53 to 8.84
Pretreatment ascites						
No	1.0	ref	1.0	ref	1.0	ref
Yes	2.85	2.08 to 3.89	2.77	1.79 to 4.29	2.97	1.52 to 5.81
Could not be assessed	1.10	0.27 to 4.50	2.00	0.48 to 8.41	2.54	0.33 to 19.73
Lymph node involvement						
No palpable nodes, no biopsies	1.0	ref	1.0	ref	1.0	ref
Palpable nodes, no biopsies	1.48	0.64 to 3.38	5.39	2.10 to 13.82	6.53	0.84 to 50.92
Biopsies negative	0.30	0.22 to 0.42	0.36	0.23 to 0.58	0.43	0.21 to 0.88
Biopsies positive	1.16	0.82 to 1.64	1.41	0.84 to 2.37	2.06	0.93 to 4.56
Could not be assessed	0.59	0.19 to 1.87	—	—	—	—
Synchronous primary tumor						
No	1.0	ref	1.0	ref	1.0	ref
Yes, endometrial	0.42	0.17 to 1.01	0.16	0.02 to 1.18	0.36	0.05 to 2.61
Yes, other[e]	1.20	0.44 to 3.25	1.61	0.39 to 6.66	—	—
Residual disease after cytoreductive surgery[f]						
No	1.0	ref	1.0	ref	1.0	ref
Yes	4.82	3.59 to 6.48	5.02	3.29 to 7.66	4.54	2.34 to 8.78
Could not be assessed	5.31	3.39 to 8.32	6.99	3.73 to 13.10	9.71	3.61 to 26.09
Size of residual disease after cytoreductive surgery, cm[f]						
No residual disease	1.0	ref	1.0	ref	1.0	ref
0.1 to < 1.0	4.41	3.12 to 6.22	5.23	3.21 to 8.5	4.43	1.96 to 10.04
1.0 to < 2.0	5.62	3.50 to 9.02	6.86	3.32 to 14.19	11.12	3.77 to 32.84
≥ 2.0	6.72	3.85 to 11.75	1.40	0.19 to 10.18	2.76	0.37 to 20.51
Could Not Be Assessed	4.89	3.37 to 7.11	5.87	3.47 to 9.92	5.54	2.36 to 12.99
Debulking at cytoreductive surgery[g]						
Optimal	1.0	ref	1.0	ref	1.0	ref
Suboptimal	3.77	2.72 to 5.22	3.40	2.01 to 5.77	4.60	2.02 to 10.48
Received neoadjuvant chemotherapy	2.99	1.89 to 4.72	1.31	0.48 to 3.58	2.50	0.76 to 8.20
No primary surgery performed	1.70	0.42 to 6.95	—	—	—	—
Unknown	3.76	1.91 to 7.40	4.27	1.56 to 11.70	3.60	0.49 to 26.39
Platinum chemotherapy, no. of cycles[h,i]						
No	1.0	ref	1.0	ref	1.0	ref
0 to ≤ 3	2.21	0.63 to 7.85	3.80	0.74 to 19.59	2.33	0.39 to 13.93
3 to ≤ 6	5.66	2.09 to 15.31	6.29	1.54 to 25.70	2.38	0.56 to 10.11
> 6	9.96	3.64 to 27.24	10.72	2.57 to 44.76	6.59	1.51 to 28.67
Yes, number of cycles unknown	2.46	0.27 to 22.02	5.14	0.46 to 56.88	—	—
Taxane chemotherapy, no. of cycles)[h,j]						
No	1.0	ref	1.0	ref	1.0	ref
0 to ≤ 3	1.50	0.54 to 4.14	1.34	0.36 to 4.99	1.66	0.33 to 8.23
3 to ≤ 6	3.52	1.72 to 7.19	2.96	1.19 to 7.36	2.15	0.65 to 7.14
> 6	6.82	3.29 to 14.14	6.03	2.35 to 15.47	4.49	1.27 to 15.92
Yes, number of cycles unknown	1.84	0.39 to 8.66	2.95	0.57 to 15.23	2.54	0.26 to 24.67

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Table 3. HRs and Corresponding 95% CIs for Recurrence at Baseline and at Years 1 and 2 of Remission[a] (continued)

Characteristic	Baseline (N = 404)		Year 1 (n = 281)		Year 2 (n = 219)	
	HR[b]	95% CI	HR[b]	95% CI	HR[b]	95% CI
Other chemotherapy, no. of cycles[h,k]						
No	1.0	ref	1.0	ref	1.0	ref
0 to ≤ 3	1.01	0.32 to 3.16	1.53	0.38 to 6.24	—	—
3 to ≤ 6	1.75	1.03 to 2.98	2.59	1.25 to 5.36	3.90	1.38 to 11.00
> 6	2.29	1.39 to 3.78	2.13	0.93 to 4.88	4.34	1.53 to 12.31
Yes, number of cycles unknown	4.66	1.72 to 12.64	18.13	4.28 to 76.72	—	—
Maintenance chemotherapy						
No	1.0	ref	1.0	ref	1.0	ref
Yes	1.79	1.21 to 2.64	3.51	2.15 to 5.71	3.43	1.51 to 7.78
Number of chemotherapy cycles before normalization of CA-125						
Normalized without/prior to chemotherapy	1.0	ref	1.0	ref	1.0	ref
1 to < 3	2.56	1.71 to 3.84	1.80	1.06 to 3.05	2.29	1.08 to 4.85
3 to < 6	5.59	3.72 to 8.39	4.33	2.50 to 7.52	4.23	1.78 to 10.08
≥ 6	5.19	3.19 to 8.43	4.51	2.27 to 8.96	2.17	0.48 to 9.72
Could not be assessed	2.94	1.75 to 4.95	2.26	1.12 to 4.58	1.91	0.61 to 5.91
Persistent disease after primary treatment						
No	1.0	ref	1.0	ref	1.0	ref
Yes	2.96	1.57 to 5.60	0.84	0.12 to 6.0	—	—

Abbreviations: HR, hazard ratio; MMT, mixed Mullerian tumor; ref, reference.
[a]Landmark method was used for years 1 and 2. Please see Tables 1and 2 for number of participants in the different categories.
[b]HRs were calculated using Cox regression models adjusted for current age (continuous) and disease-free survival was measured from the specified time point.
[c]One patient was missing stage information because she never had staging or cytoreductive surgeries and was never formally staged by oncologist.
[d]Includes one micropapillary serous, one adenosquamous, one papillary serous with multiple psammoma bodies.
[e]Includes one of each of the following synchronous cancers: fallopian tube, granulosa cell tumor of the ovary, recurrent breast, GI stromal, skin, and appendiceal.
[f]Excludes three patients that did not have cytoreductive surgery.
[g]Patients were considered to be optimally debulked if their disease was <1 cm or their surgeon/oncologist declared them to be optimally debulked at the conclusion of their cytreductive surgery.
[h]Includes neoadjuvant, adjuvant and maintenance chemotherapies received as well as any chemotherapy received for persistent disease.
[i]Includes carboplatin, cisplatin, oxaliplatin, and abraxane.
[j]Includes taxol, taxotere, and xyotax.
[k]Includes avastin, doxil, topotecan, gemzar, cytoxan, interferon, mytomycin, erbitux, ifosphomaide, catumaxomab, and ovarex. Many of these other chemotherapies were given as part of a clinical trial and in some cases it was unclear whether participants received placebo or the active agent; cases that were reported to have gotten the placebo were considered to have received no chemotherapy.

prescribed maintenance chemotherapy. Risk of recurrence was also significantly increased among those with persistent disease after primary treatment. However, the number of women with persistent disease after primary treatment was small; most HOPE patients with persistent disease after completion of primary therapy never achieved remission and were therefore excluded from this study. We also evaluated the effect of patient characteristics on subsequent DFS among women who had already been in remission for 1 or 2 years. In these analyses, all factors that were predictive of prognosis at baseline with the exception of pretreatment CA-125 and persistent disease after primary treatment remained significant. This is consistent with the results presented in Figure 2 where the difference in 3-year conditional DFS estimates between the various stage, histology. and grade groups was still large in the first 2 years and suggests that at least in the first 2 years after achieving remission these factors are still of prognostic value.

Follow-up care after treatment for OC is a controversial topic with disagreement over whether increased surveillance for recurrent disease effectively improves OS.[18-20,42] Although monitoring of CA-125 levels for the early detection of recurrent disease has not resulted in meaningful improvements in OS,[21] a study by Oskay-Oezcelik et al[43] found that the majority of patients believe routine CA-125 testing was the most important factor in determining their cancer outcomes. This suggests that physician-patient communication regarding the goals and efficacy of follow-up care may be insufficient. Improved measures of recurrence risk, such as conditional DFS estimates, may help clinicians provide more accurate prognostic information to patients. Risk assessment tools that take into account time already in remission should be developed to help inform personalized follow-up treatment plans.

The extensive follow-up information collected from our participants allowed us to estimate 3-year conditional DFS estimates up to 5 years after achieving remission and to examine the impact of many different patient characteristics. Use of the landmark approach[16,17] enabled us to explore whether patient characteristics were predictive of subsequent DFS at years 1 and 2 of remission. Our study was further strengthened by a short recruitment period, which limits the possibility that OC outcomes were influenced by changes in standard of care. Although our study included 404 participants in total, the small size of certain subgroups resulted in large CIs and some associations with risk of recurrence may not have been detected due to insufficient power. In addition, as more time elapsed from the date of remission, the number of women in the study, and thus in the subgroups, decreased because they developed a recurrence, died, or became lost to further follow-up, and it is possible that some of the trends observed were due to small

patient numbers. Demographic and lifestyle characteristics were collected at time of enrollment and, therefore, do not necessarily reflect the status of the participants throughout treatment and follow-up. In addition, women included in this study were predominantly white and the majority had completed at least some post–high school education and a yearly income of at least $25,000, which does not reflect the general US population and hence may limit the generalizability of our results.

To conclude, DFS estimates for patients with OC improved dramatically over time, in particular among patients with poorer initial prognoses. If confirmed by other studies, future research should focus on the development and validation of prognostic tools that take time in remission into account. More accurate information about risk of recurrence will allow patients and clinicians to make better informed decisions regarding follow-up care after cancer treatment and may also improve quality of life by ameliorating patients' fear of recurrence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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Appendix

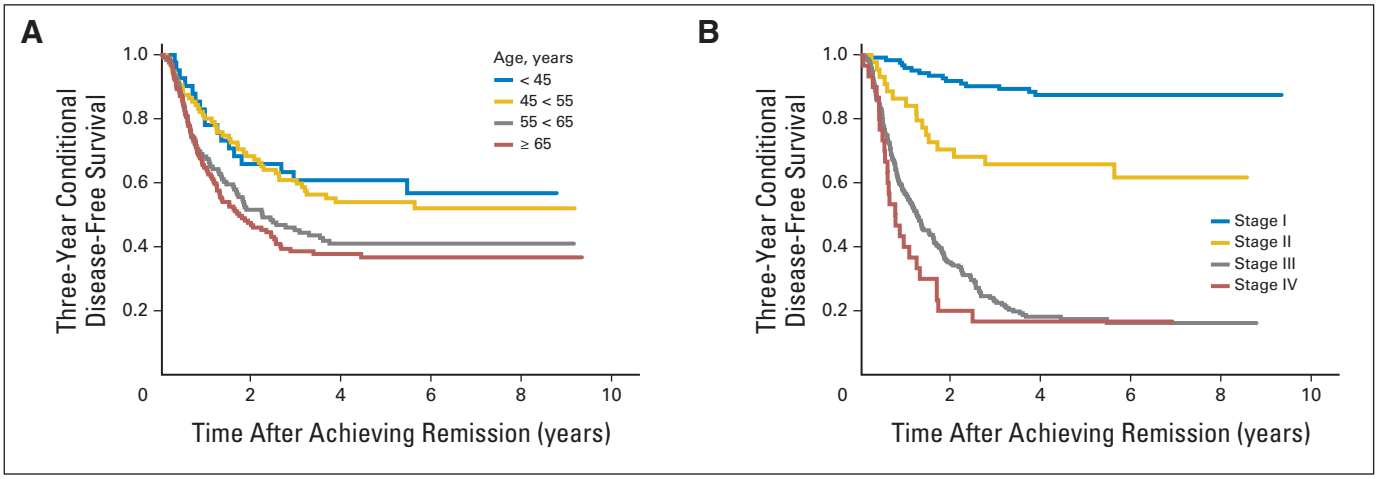

Fig A1. Traditional disease-free survival curves (Kaplan-Meier curves), stratified by age at remission (A; log-rank test, $P = .01$) and stage (B; log-rank test, $P < .01$).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prognosis and Conditional Disease-Free Survival Among Patients With Ovarian Cancer

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