The N-Terminally Truncated p53 Isoform Δ40p53 Influences Prognosis in Mucinous Ovarian Cancer

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Objective: The tumor suppressor p53 generates the N-terminally truncated isoforms Δ40p53 and Δ133p53 that possess the ability to modulate p53 function in vitro. The aim of the present study was to evaluate the clinical relevance of p53 isoforms in the main histological subtypes of ovarian cancer.

Methods: *Δ40p53*, *Δ133p53*, and *full-length p53* (*FLp53*) expression was determined in 45 mucinous, 30 endometrioid, and 91 serous ovarian cancer specimens as well as 42 normal ovarian tissues using reverse transcriptase–quantitative polymerase chain reaction. In a subgroup of mucinous ovarian cancer cases, Δ40p53 expression was examined using Western blot analysis. A functional yeast-based assay and subsequent sequencing were performed to analyze the *p53* mutational status.

Results: In endometrioid cancer specimens, *Δ133p53* expression was significantly lower than in mucinous and serous cases ($P = 0.016$) or in normal tissues ($P = 0.004$). Mucinous cancer samples showed elevated *Δ40p53* expression as compared with normal ovarian tissues ($P = 0.003$). In addition, high *Δ40p53* expression constituted an independent prognostic marker for recurrence-free but not for overall survival in patients with mucinous ovarian cancer (hazard ratio, 0.267; 95% confidence interval, 0.094–0.756 [$P = 0.013$]; hazard ratio, 0.453, 95% confidence interval, 0.193–1.064 [$P = 0.069$]). Western blot analysis confirmed the presence of p53β and Δ40p53α in a subset of patients with mucinous ovarian cancer. Expression of *p53* isoforms was not associated with *p53* mutational status or clinicopathologic parameters.

Conclusions: We show that expression of *p53* isoforms differs in histological subtypes, thus supporting the hypothesis that histological subtypes represent distinct disease entities. In addition, we provide first evidence for a favorable role of Δ40p53 in patients with mucinous ovarian cancer.

Key Words: p53 Isoforms, Δ40p53, Ovarian cancer, Mucinous ovarian cancer

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Emerging evidence suggests that ovarian cancer constitutes a heterogeneous disease.[1] A recent study showed that risk factors such as age, duration of breast-feeding, age at menopause, duration of estrogen use, and smoking vary by histological subtype.[2] Also, tumor stages differ in histological subtypes. Whereas nonserous carcinomas are usually diagnosed at early stages, serous carcinomas preferentially present at advanced stages.[3] In addition, histological subtypes respond differently to chemotherapy.[4,5] The dismal response rate of clear cell carcinomas (15%) contrasts sharply with that of high-grade serous carcinomas (80%).[6] These different clinical characteristics are accompanied by distinct biomarker expression profiles.[7] For instance, serous carcinomas show WT1, mesothelin, estrogen receptor, and CA-125 expression in greater than 75%, whereas the mucinous subtype displays frequent expression of matriptase, and endometrioid carcinomas express high rates of estrogen and progesterone receptor and CA-125.[8]

Recently, the N-terminally truncated p53 isoforms Δ40p53 and Δ133p53 were added to the complex p53 regulatory network (Fig. 1). Δ40p53 is generated by alternative splicing of intron 2 or altered initiation of translation in exon 4, whereas Δ133p53 is derived from an alternative promoter located in intron 4. Δ40p53 lacks the first 40 amino acids but retains the second transactivation domain. By contrast, Δ133p53 is devoid of both transactivation domains and part of the DNA-binding domain. The N-terminally truncated p53 isoforms retain the C-terminal tetramerization domain and can thus be incorporated into p53 tetrameres. As the exact function of Δ40p53 and Δ133p53 has not yet been fully characterized, the present consensus is that their ratio to FLp53 determines functional outcome. Low Δ40p53 and Δ133p53 levels have been reported to act as potent dominant-negative inhibitors of FLp53, suppressing transcription of genes under the control of a p53-binding element as well as p53-induced apoptosis.

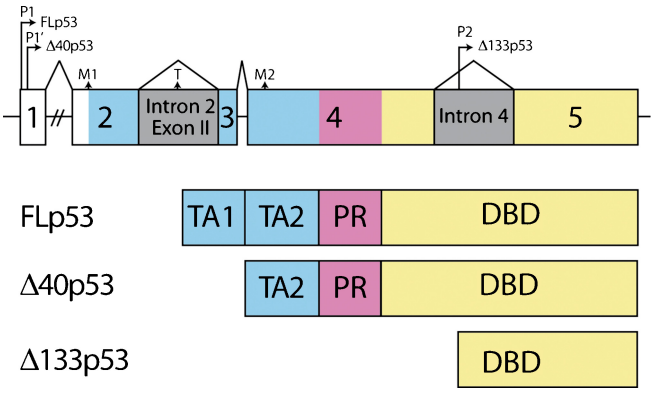

FIGURE 1. Gene architecture of the N-terminus of the *p53* gene, indicating the mode of generation for the various *p53* isoforms, as well as their resulting protein structure (TA, transactivation domain [blue]; PR, prolin-rich domain [red]; DBD, DNA-binding domain [yellow]; untranscribed regions [white]; introns [gray]).

Contrarily, high Δ40p53 and Δ133p53 levels have resulted in enhanced transcription of FLp53 target genes.[9]

The aim of the present study was to evaluate the clinical relevance of the N-terminally truncated p53 isoforms Δ40p53 and Δ133p53 in the main histological subtypes of ovarian cancer.

MATERIALS AND METHODS

Patients and Tissue Samples

Forty-five mucinous, 30 endometrioid, and 91 serous ovarian cancer specimens were derived from the Departments of Gynecology and Obstetrics of Medical University Innsbruck (n = 117), Berlin Charité University-Hospital (n = 27), and Medical University of Vienna (n = 22). The number of available clear-cell cancer specimens was too small for analysis. Mixed epithelial ovarian tumors were not included. Moreover, 42 normal ovarian tissue samples had been collected during surgery for other than inflammatory or malignant conditions. The specimens were obtained between July 1994 and February 2004 during primary surgery after informed consent was obtained. One experienced gynecologic pathologist reviewed all slides to confirm the histological diagnosis, which was made according to the World Health Organization criteria.[10] Tissue specimens were immediately pulverized under cooling with liquid nitrogen and stored at −70°C. Institutional review board approval was obtained from the local ethics committees.

Clinicopathologic parameters and follow-up data were obtained by retrospective chart review. Patients with a secondary malignancy were not included in the present study. All patients underwent primary surgery. This involved total abdominal hysterectomy and bilateral salpingo-oophorectomy in all patients unless done previously for benign conditions; 142 (86%) of 166 patients underwent additional omentectomy, and partial bowel resection was necessary in 32 patients (19%). Lymphadenectomy was performed in 67 (40%) of 166 patients. In 41 (61%) of 67 patients, lymph nodes were positive.

All patients received adjuvant platinum-based chemotherapy. This involved platinum monotherapy (carboplatinum [n = 27], cisplatin [n = 2]), a combination of platinum and cyclophosphamide (cisplatin and cyclophosphamide [n = 66], carboplatinum and cyclophosphamide [n = 4]), or a combination of platinum and taxane (carboplatinum and paclitaxel [n = 65], carboplatinum and docetaxel [n = 2]). All patients received a median of 6 chemotherapy cycles. Median follow-up was 48.5 months (range, 2–252 months).

RNA Isolation and Real-Time Reverse Transcriptase–Quantitative Polymerase Chain Reaction

RNA extraction and reverse transcription were performed as described previously.[11] In addition, DNase treatment was done according to the manufacturer's protocol (Roche, Basel, Switzerland). Primer pairs and probes for all *p53* isoforms and the internal control TATA box-binding protein were designed using the Primer Express software

TABLE 1. Prognostic relevance of clinicopathologic variables in univariate and multivariate survival analyses in 166 patients with primary ovarian cancer

	Recurrence-Free Survival			Overall Survival		
	Univariate	Multivariate		Univariate	Multivariate	
	P	HR (95% CI)	*P*	*P*	HR (95% CI)	*P*
Age (y) ≤59 vs >59*	0.006	1.023 (1.006–1.040)	0.007	<0.001	1.040 (1.023–1.057)	<0.001
Tumor stage I/II vs III/IV	<0.001	4.527 (1.773–11.558)	0.002	<0.001	2.280 (1.086–4.785)	0.029
Tumor grade I/II vs III	0.001	1.683 (1.139–2.485)	0.009	<0.001	2.028 (1.372–2.998)	<0.001
Residual disease 0 vs >0 cm	<0.001	1.903 (1.226–2.953)	0.004	<0.001	1.818 (1.165–2.837)	0.009

*Median age at diagnosis was 59 years.
CI, confidence interval; HR, hazard ratio.

(Applied Biosystems, Foster City, CA; Supplementary Table 1, http://links.lww.com/IGC/A81). Real-time TaqMan reverse transcriptase–polymerase chain reaction was performed using the ABI Prism 7900 Detection System (Applied Biosystems) according to the manufacturer's protocol. Reactions were performed in duplicates. To determine absolute copy numbers for all *p53* isoforms, standard curves were generated as reported previously.[12]

Western Blot Analysis

Twelve mucinous ovarian cancer specimens were analyzed by Western blot. Tissue was lysed using CelLytic-buffer (Sigma, St Louis, MO) containing HALT protease inhibitor cocktail (Pierce, Rockford, IL) and HALT phosphatase inhibitor cocktail (Pierce). For quantification, the Bradford assay (BioChain-Protein-Assay, Hayward, CA) was performed according to the manufacturer's protocol. The protein lysates were separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis gels (NuSep, Lane Cove, New South Wales, Australia). The Fermentas PageRuler Prestained Protein Ladder Plus (Fermentas International Inc, Burlington, Ontario, Canada) was used. After transfer, membranes were incubated with Odyssey blocking buffer (OBB; LI-COR Biotechnology, Bad Homburg, Germany). Thereafter, they were treated with the p53 antibodies (DO-1 [Santa Cruz Biotechnology, Santa Cruz, CA] and 1801 [Abcam, Cambridge, UK]) and the IR dye-tagged secondary antibody (Alexa Fluor 680; Invitrogen, Carlsbad, CA). Images were obtained using the Odyssey infrared imaging system. GAPDH served as loading control (Biomol, Hamburg, Germany). In vitro translated p53 isoforms (FLp53α, FLp53β, and Δ40p53α) were used as positive controls.

In Vitro Transcription Translation of p53 Proteins

Vectors containing FLp53α, FLp53β, and Δ40p53α (courtesy of J.-C. Bourdon) were used for in vitro translation of proteins using the TNT Quick Coupled Transcription/Translation Systems (Promega, Madison, WI) according to the manufacturer's instructions.

Evaluation of *p53* Mutational Status

To detect inactivating mutations in the *p53* gene, a functional yeast-based assay and subsequent sequencing were performed as described previously.[12]

Statistical Analysis

The Shapiro-Wilk test was performed to assess the normality assumption. As the distribution of *p53* isoforms was non-Gaussian, the Kruskal-Wallis test was used to compare *p53* isoform expression between histological subtypes. The Mann-Whitney *U* test was performed to compare *p53* isoform expression with tissue type and *p53* mutational status. For correlations among *p53* isoforms, Spearman correlation coefficients were calculated. Cases were divided at the 50th percentile of *p53* isoform expression levels into 2 groups for high (above the 50th percentile) versus low (below the 50th percentile) expression. The χ^2 test was used to examine the relationships between *p53* isoform expression and clinicopathologic parameters as well as between the type of *p53* alteration and histological subtype. Survival probabilities were calculated with the product-limit method of Kaplan and Meier. The Cox proportional hazards model was used for

TABLE 2. Clinicopathologic parameters in histological subtypes of ovarian cancer

		Mucinous	Endometrioid	Serous	*P*
Median age, y		56	62.5	60	0.476
FIGO stage	I/II	14	8	7	0.001
	III/IV	31	22	84	
Tumor grade	I/II	36	16	42	0.001
	III	9	14	49	
Residual disease, cm	None	23	17	30	0.041
	≤2	14	4	32	
	>2	8	8	29	

multivariate analysis to assess the independence of different prognostic factors. Statistical Package for the Social Sciences for Windows 18.0 software (SPSS, Inc, Chicago, IL) was used for all analyses. $P < 0.05$ was considered statistically significant. For multiple testing, the Bonferroni correction was applied. In the case of 6 post hoc comparisons (between histological subtypes as well as between histological subtypes and normal), $P < 0.0084$ was considered statistically significant. Although several subgroup analyses were performed with regard to the clinical effect of the examined *p53* isoforms, no corrections for multiple comparisons were made because of the explorative character of these analyses.

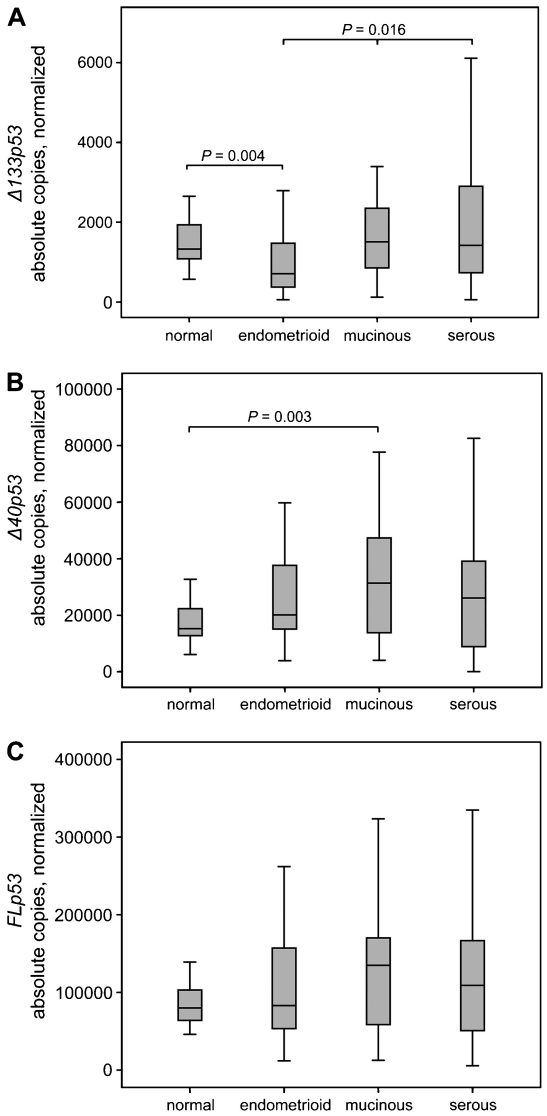

FIGURE 2. Box plot diagrams showing the expression levels of (A) *Δ133p53*, (B) *Δ40p53*, and (C) *FLp53* in endometrioid, mucinous, and serous ovarian cancer specimens as well as 42 normal ovarian tissues. The line within the boxes indicates the median expression level. The top edge of the boxes represents the 75th percentile; the bottom edge, the 25th percentile. The range is shown as a vertical line. Whiskers demarcate the minimum and maximum, excluding outliers.

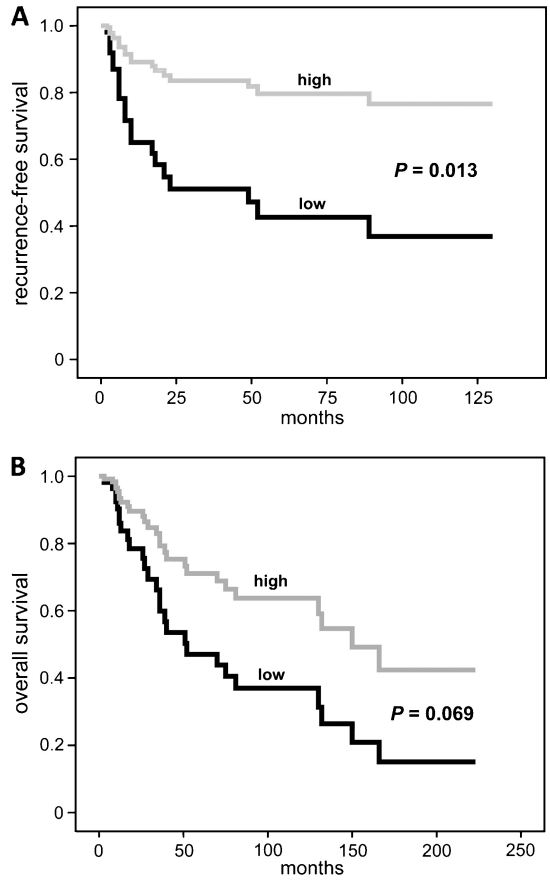

FIGURE 3. In multivariate analysis considering FIGO stage, tumor grading, residual tumor, and age, *Δ40p53* expression constituted an independent prognostic marker for (A) recurrence-free but not (B) overall survival in mucinous ovarian cancer cases.

RESULTS

The influence of clinicopathologic parameters on prognosis is provided in Table 1. Age at diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor grading, and residual disease constituted significant independent prognostic factors. These data substantially validate the reliability of our collective of patients with primary ovarian cancer. Clinicopathologic parameters, but not age, significantly varied by histological subtype in the examined ovarian cancer cases (Table 2).

Comparison of *p53* isoform expression for the 3 histological subtypes showed endometrioid cases to have the lowest *Δ133p53* expression (median copy number, 709 for endometrioid vs 1508 for mucinous vs 1420 for serous [$P = 0.016$]; Fig. 2A). In contrast, *Δ40p53* and *FLp53* expression did not differ between histological subtypes (Figs. 2B, C).

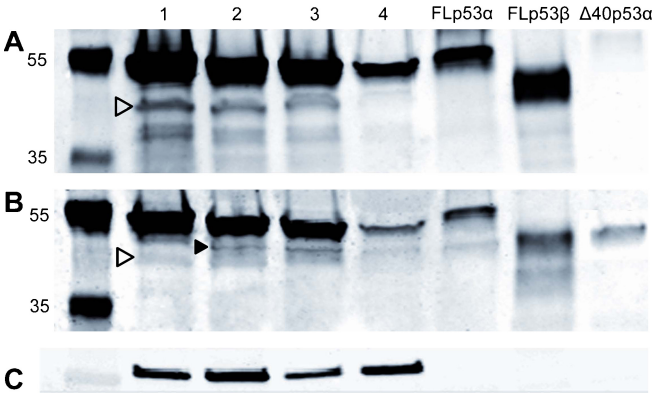

FIGURE 4. Representative Western blot analysis in 4 mucinous ovarian cancer samples. Endogenous expression of FLp53α, FLp53β, and Δ40p53α was analyzed using a combination of 2 antibodies. The in vitro translated p53 isoforms served as positive controls (courtesy of J.-C. Bourdon). A, The DO-1 antibody recognizes an epitope at the far N-terminus of the p53 protein (amino acids 11-25) and thus detects FLp53α, FLp53β, but not Δ40p53α. B, The 1801 antibody is directed against an epitope located at amino acids 45-55 and consequently recognizes FLp53α, FLp53β, and Δ40p53α. The white arrowhead indicates a small-molecular-weight form of p53 in samples 2 and 3, which is detected with the DO-1 and the 1801 antibody, suggesting that it is indeed FLp53β. The black arrowhead indicates another small-molecular-weight form of p53 that is recognized only with the 1801 antibody, but not with DO-1, suggesting that this band represents Δ40p53α. C, Expression of GAPDH was used as a loading control.

Compared with normal ovarian tissues, *Δ133p53* levels were down-regulated in endometrioid cancer samples (median, 1326 vs 709 copies [$P = 0.004$]; Fig. 2A). In mucinous cancer cases, *Δ133p53* expression showed no difference (median, 1508 vs 1326 copies [$P = 0.631$]), whereas *Δ40p53* levels were elevated as compared with normal tissues (median, 31339 vs 15238 [$P = 0.003$]; Figs. 2B, C). In serous ovarian cancer specimens, expression of *p53* isoforms did not differ from that of normal tissues. In the entire group of ovarian cancer specimens, *Δ40p53* levels were higher than in normal tissues (median, 26472 vs 15238 copies [$P = 0.005$]).

In all 3 histological subgroups as well as in the entire group of ovarian cancer specimens, significant correlations between all *p53* isoforms levels were observed. On the contrary, in normal ovarian tissues, only *FLp53* was associated with *Δ40p53* expression (Spearman correlation coefficient $r_s = 0.852$; $P < 0.001$).

In patients with mucinous ovarian cancer, high *Δ40p53* expression was associated with improved recurrence-free and overall survival as compared with low *Δ40p53* expression (149.2 vs 88.2 months [$P = 0.046$], 128.7 vs 96.5 months [$P = 0.261$]). However, *Δ40p53* expression did not reach statistical significance for overall survival. In multivariate analyses considering FIGO stage, tumor grading, residual tumor, and age *Δ40p53* expression constituted an independent prognostic marker for recurrence-free but not overall survival (hazard ratio, 0.267; 95% confidence interval [CI] 0.094–0.756 [$P = 0.013$]; hazard ratio, 0.453; 95% CI, 0.193–1.064 [$P = 0.069$]; Fig. 3). In endometrioid and serous cases as well as in the entire group of ovarian cancer specimens, *p53* isoform expression lacked prognostic significance.

Western blot analysis was performed in a subgroup of mucinous ovarian cancer specimens to determine whether *Δ40p53* transcript levels are translated into the respective protein. We used a combination of 2 antibodies. The DO-1 antibody is directed against an epitope located at amino acids 11-25 and therefore recognizes FLp53 but not Δ40p53. The 1801 antibody recognizes an epitope located within residues 46-55 and consequently detects Δ40p53 and FLp53 proteins. We detected a small-molecular-weight form of p53 using the DO-1 antibody (Fig. 4A). This p53 isoform was also found

TABLE 3. Survival data for *p53* mutational status stratified by histological subtype, univariate analyses

		RFS				OS			
		Recurrence†				Survival Status			
Histological Subtype	*p53* Status*	No (n = 59)	Yes (n = 105)	Mean RFS (95% CI), mo	*P*	Alive (n = 57)	Dead (n = 109)	Mean OS (95% CI), mo	*P*
Mucinous	Wt 21	14	7	157.8 (117.5–198.1)	0.024	13	8	158.2 (232.0–295.3)	0.002
	Mut 24	9	15	83.8 (42.5–125.0)		4	20	76.3 (43.7–108.9)	
Endometrioid	Wt 11	5	4	100.3 (47.2–54.2)	0.685	6	5	100.2 (53.6–146.6)	0.832
	Mut 19	8	11	93.5 (54.2–132.8)		8	11	104.1 (67.1–141.1)	
Serous	Wt 21	9	12	92.7 (52.2–133.2)	0.066	11	10	125.7 (88.9–162.5)	0.006
	Mut 70	14	56	53.9 (31.9–73.9)		15	55	70.4 (51.8–88.9)	

*p53 mutational status: Wt and Mut.
†Two patients with endometrioid ovarian cancer could not be followed up for recurrence, but were known to be alive.
CI, confidence interval; Mut, mutant; OS, overall survival; RFS, recurrence-free survival; Wt, wild type.

TABLE 4. Type of *p53* alteration stratified by histological subtype

p53 Alteration	Endometrioid, n (%)	Mucinous, n (%)	Serous, n (%)
Missense	14 (73.7)	23 (95.8)	46 (66.7)
Frameshift	4 (21.0)	1 (4.2)	16 (23.2)
Nonsense	1 (5.3)	0	7 (10.1)

with the 1801 antibody, although with much lower affinity, thus providing further evidence that it is indeed the β isoform of p53. Another small-molecular-weight form of p53 was detected with the 1801 antibody, but not with the DO-1 antibody, suggesting that it is the Δ40p53α isoform (Fig. 4B).

Univariate survival data for the *p53* mutational status stratified by histological subtype are shown in Table 3. In patients with mucinous ovarian cancer, *p53* mutational status remained significant for overall survival in multivariate analyses (hazard ratio, 3.25; 95% CI, 1.305–8.093 [P = 0.011]). In patients with serous ovarian cancer, *p53* mutational status lost its significance for overall survival in multivariate analyses.

Of 24 mucinous carcinomas, 23 (95.8%) harbored *p53* missense mutations as compared with 46 (66.7%) of 69 endometrioid and 14 (73.7%) of 19 mucinous cases (Table 4). Type of *p53* alteration in each histological subtypes did not significantly differ (P = 0.084).

None of the 3 histological subgroups or the entire group of ovarian cancer specimens showed a difference in *Δ40p53*, *Δ133p53*, and *FLp53* expression levels with regard to clinicopathologic parameters (age at diagnosis, FIGO stage, tumor grade, histological subtype, and residual disease after primary surgery) or *p53* mutational status. In particular, *Δ40p53* expression and tumor grading (I/II vs III) did not correlate in mucinous ovarian cancer cases (median copies, 28232 vs 21466 [P = 0.267]).

DISCUSSION

Prompted by the recent discovery of N-terminally truncated p53 isoforms that possess the ability to modulate p53 function in vitro, this study evaluates the clinical relevance of p53 isoforms in the main histological subtypes of ovarian cancer.

p53 isoform expression significantly varied by histological subtype. To the best of our knowledge, only one previous study examined *p53* isoform expression in ovarian cancer.[13] The authors, however, did not differentiate between histological subtypes and did not include normal ovarian tissue. They reported significantly higher *FLp53* expression in stage I than in stage III ovarian cancer specimens. In the present study, *p53* isoform expression did not differ by tumor stage. Studies analyzing the expression patterns of N-terminally truncated p53 isoforms in human carcinomas and corresponding normal tissues are rare. In accordance with the up-regulation of *Δ40p53* expression in mucinous ovarian cancer specimens observed in the present study, *Δ40p53* has also been up-regulated in melanomas.[14] *Δ133p53* was expressed at lower levels in endometrioid ovarian cancer specimens than in other histological subtypes or normal tissues. Previous studies have reported differential *Δ133p53* expression in distinct types of cancers. While *Δ133p53* has been up-regulated in breast carcinomas and melanomas, its expression did not differ between tumors of the head and neck and renal and colon carcinomas in comparison to corresponding normal tissue.[15–18] Finally, the different expression of N-terminally truncated *p53* isoforms in histological subtypes supports the hypothesis that histological subtypes represent distinct disease entities with different tumor biology.

In accordance with Marabese et al,[13] expression of *p53* isoforms did not correlate with *p53* mutational status in the examined ovarian cancer specimens. In colon carcinomas, significantly elevated *Δ133p53* levels were previously found in p53 wild-type cases.[18] In accordance with this finding, wild-type but not mutant FLp53 was recently reported to activate the P2 promoter of the *p53* gene, which generates Δ133p53.[19] Thus, the absent correlation between *Δ133p53* expression and *p53* mutational status in ovarian cancer raises the possibility of alternative regulators of *Δ133p53* transcription.

We provide the first clinical evidence for a favorable role of *Δ40p53* in patients with mucinous ovarian cancer. Existing in vitro studies support a possible beneficial role of Δ40p53 by an enhancement of wild-type p53 function. FLp53 and Δ40p53 have been reported to readily form heterocomplexes. As Δ40p53 lacks the MDM2-binding site, these heterocomplexes escape MDM2-mediated degradation and therefore accumulate.[20] In addition, Δ40p53 supports a conformation of FLp53 that is associated with a more active state. Δ40p53 has also been found to alter the posttranslational modification profile of FLp53.[21] Posttranslational modifications at the N-terminus of FLp53, for instance, might increase the recruitment of transcriptional coactivators such as p300 and PCAF and thus be responsible for increased promoter-binding capacity of the heterocomplexes. Interestingly, however, Δ40p53 expression was not associated with the p53 mutational status in the present study. This suggests that the function of *Δ40p53* might not be confined to wild-type *p53*. Δ40p53 alone has been reported to induce apoptosis through the transcriptional activation of many apoptosis-related genes that are not induced by FLp53, such as TP53BP2 (tumor protein p53 binding protein 2) and TIAL1 (TIA1 cytotoxic granule-associated RNA-binding protein–like 1).[22] Thus, further studies evaluating the exact function of Δ40p53 also in the presence of p53 missense mutations are clearly warranted.

As Δ40p53 mRNA possessed clinical relevance in mucinous ovarian cancer, we aimed to detect the Δ40p53 protein. It is not possible to produce specific antibodies against Δ40p53. Thus, Δ40p53 can be determined only indirectly with a combination of p53 antibodies in Western blot analyses.[23] The matter is further complicated by the fact that Δ40p53α and FLp53β have very similar molecular weights.[15] Only 5 previous studies performed p53 isoform-specific

Western blot analyses.[14,16,17,24,25] One of these showed a band representing the Δ40p53α protein in a melanoma cell line.[14] To the best of our knowledge, the present study has now detected the Δ40p53α protein in cancer tissue for the first time.

The present study also found a relatively high rate of *p53* mutations as compared with previous studies. In a recent meta-analysis, mutant p53 was observed in 65% (range, 49%–75%) of serous ovarian carcinomas, whereas it occurs less frequently in endometrioid and mucinous subtypes.[26] Schuijer and Berns[27] reported mutant p53 in 37% of endometrioid and 21% of mucinous tumors using immunohistochemistry. We hypothesize that the relatively high rate of *p53* mutations observed in the present study is the result of the method used to determine *p53* mutational status. The yeast-based assay tests the critical biochemical function of p53, its transcriptional activity. The direct comparison of methods for p53 mutational analysis confirmed the superiority of the yeast-based assay as compared with single-strand conformation polymorphism analysis and immunohistochemistry.[28] The second reason for the high rate of *p53* mutations might be the high percentage of FIGO III and IV in the present study. It is well known that the prevalence of p53 mutations is significantly greater in advanced than in early stages of ovarian cancer.[27]

A limitation of the study lies in the small case numbers in the mucinous and especially endometrioid subgroups. Thus, we cannot exclude that some of the currently insignificant findings for *p53* isoform expression and prognosis might turn out to be positive correlations in larger groups. Prospective studies in distinct histological subgroups comprising larger case numbers are clearly warranted.

In conclusion, we show that the expression of *p53* isoforms differs in histological subtypes, supporting the hypothesis that histological subtypes represent distinct disease entities. In addition, we provide the first evidence for a favorable role of Δ40p53 in patients with mucinous ovarian cancer.

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