Prevalence of Allelic Loss at *TP53* in Endometrial Carcinomas

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Key Words

TP53 · Endometrial carcinoma · Loss of heterozygosity · Metastasis · p53

Abstract

Alterations within the *TP53* tumor suppressor belong to the most common genetic features reported in various human neoplasms, including endometrial cancer. In this article, the prevalence of allelic loss at the *TP53* locus in primary human endometrial carcinomas (ECs) is discussed. Furthermore, we reviewed the role of allelic imbalance at 17p13.1 in metastatic human ECs on the basis of a literature review and on recently published data ascertained by our laboratory staff.

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Alterations within oncogenes, tumor suppressor genes (TSGs), and mismatch-repair genes have been found to play a pivotal role in the development and progression of various human neoplasias [1–3]. *TP53*, the ‘guardian of the genome’, is spanned on the short arm of chromosome 17 in region 17p13.1 and consists of 11 exons. It encodes a 53-kDa phosphoprotein, the activity of which gives rise to a number of intracellular activities, including cell cycle arrest and apoptosis [4, 5]. *TP53* is one of the most frequently mutated genes found in a wide spectrum of sporadically occurring human tumors, including the prima-

ry origin of endometrial carcinomas (ECs) [6–12]. Mutations of both alleles of *TP53*, usually caused by a point mutation or gross deletion, and the others by allelic imbalance, constitute an important step in malignant transformation. Furthermore, it has also been reported that tumor tissues obtained from patients with germ line *TP53* mutations retain the allele with the germ line mutation and somatically lose the remaining wild-type allele [13]. This phenomenon, explained by the Knutson ‘two-hit’ theory [14], is considered to predispose constitutional *TP53* mutation carriers to develop neoplasia. However, it has also been suggested that some germline *TP53* mutants may exhibit dominant effects on wild-type p53 function [11]. Moreover, Sakuragi et al. [11] showed that dominant-negative *TP53* point mutations are often found in advanced-stage uterine tumors and represent a predictor of unfavorable outcome for women affected by ECs. Therefore, the loss of tumor suppressor functions of wild-type protein caused by these effects of mutant *TP53* in germ line is not inconceivable. Possibly, inactivation mutations and allelic loss at *TP53* are the most common genetic events in human ECs (particularly in uterine papillary serous carcinoma, UPSC), apart from *PTEN* alterations and defects in DNA mismatch repair machinery [13, 15–18].

Allelic imbalance is implicated in the development and progression of various human malignancies, and is observed either at an early or advanced stage of neoplasms [13, 19]. Allelic loss at *TP53* locus has been report-

Table 1. Frequency of LOH *TP53* in subtype I and II human ECs

Reference	Study group	
	cases/subtype II neoplasms total n/n	LOH-positive/informative n/n
Okamoto et al. [27]	24/0	2/7 (29%)
Imamura et al. [28]	42/n.a.	5/33 (15%)
Enomoto et al. [29]	37/0	6/19 (32%)
Fujino et al. [30]	79/n.a.	3/28 (11%)
Jones et al. [31]	35/n.a.	2/13 (15%)
Kihana et al. [32]	92/4	23/72 (32%)
Peiffer et al. [33]	39/7	4/14 (29%)
Saegusa and Okayasu [34]	92/0	18/80 (22.5%)
Tashiro et al. [35]	21/21	18/18 (100%)
Tritz et al. [36]	31/13	14/30 (47%)
Koul et al. [37]	50/5	6/36 (17%)
Niederacher et al. [38]	113/8	18/67 (26.9%)
Tong et al. [39]	30/8	9/24 (26.9%)
Sirchia et al. [40]	37/7	n.a./n.a. (25.7%)
Semczuk et al. [41]	20/0	1/19 (5.3%)
Liang et al. [42]	19/19	10/16 (62.5%)
Semczuk et al. [43]	46/0	8/42 (19%)
Graesslin et al. [44]	43/5	13/43 (30.2%)

n.a. = Data not available. Only 3 *TP53*-mutated cases were analyzed for the allelic loss by Risinger et al. [6], which is why this study was not included in the table.

ed in tumors originating from genital tract organs, including ovarian [20–23], cervical [24–26] and endometrial [6, 27–44] carcinomas. Table 1 summarizes data presenting the prevalence of allelic loss at the *TP53* locus in primary human ECs (divided into two subtypes). Representative examples of loss of heterozygosity (LOH) at the *TP53* locus are shown at figure 1A.

A high frequency of *TP53* alterations has been described in UPSCs, subtype II uterine malignancies [45–47], where approximately 90% of tumors revealed point mutations and an accumulation of p53 protein immunohistochemically [35, 42, 47–54]. Moreover, the unfavorable outcome of USPC patients has been attributed to *TP53* mutations/p53 overexpression [55–60], suggesting that *TP53* alterations may play an essential role in the development and progression of this EC subtype. Data presented by Ito et al. [61] revealed significantly poorer prognosis of EC patients with *TP53* mutations than in those without mutations ($p = 0.033$); however, the Cox proportional hazards regression model showed that only the clinical stage was an independent significant predictor

of postoperative mortality. Interestingly, Koul et al. [62] reported that *TP53* mutations were twice as frequent in tumors without hyperplasia than in neoplasms with hyperplasia. Finally they suggested that *TP53* alterations represent an alternative route in subtype 2 EC development [62].

A higher frequency of LOH at the *TP53* locus was reported by Liang et al. [42]. In that study, 62.5% of informative UPSCs revealed allelic imbalance. It is obvious that LOH at chromosome 17p has previously been identified in all informative UPSCs ($n = 18$) and in 3 of 7 (43%) informative endometrial intraepithelial carcinomas as a precursor lesion of UPSC [35].

LOH *TP53* and Clinicopathological Features of EC

In the study conducted by Kihana et al. [32], the prevalence of LOH was significantly higher in poorly differentiated than in well and moderately differentiated uterine neoplasms ($p = 0.049$), whereas none of other clinico-

Fig. 1. **A** *TP53* allelic loss present at intron 1/variable number of tandem repeats (VNTR) in primary human EC but not in the corresponding metastasis. **B** *TP53* allelic loss present at intron 4/VNTR in EC metastasis but not in the primary human EC. Arrows indicate the allelic loss. S = Molecular weight marker; N = normal DNA; T = tumor DNA; M = metastatic DNA.

pathological variables of cancer was related to allelic loss. Altogether, 10 of 72 (14%) tumors displayed *TP53* point mutations and LOH, whereas a total of 33 (36%) EC women showed point mutations, LOH, or both genetic alterations simultaneously [32]. The overall number of allelic losses appears to increase with advanced tumor stage, thereby indicating the significant association between LOH accumulation and the progression of the disease [28]. Analysis of Southern blot hybridization using probes YNZ22 (D17S5) and MCT35.1 (D17S31) revealed allelic loss in 5 tumors: 2 clear-cell carcinomas (stages IA and IB due to the International Federation of Gynecology and Obstetrics, FIGO), 1 endometrioid-type uterine adenocarcinoma (stage IIB), and 2 advanced-stage (both at IVB stages of the disease) endometrioid-type ECs [28]. In another report, LOH was related to histological grading ($p = 0.03$), advanced clinical stage of the disease ($p = 0.01$), and the presence of lymph node metastasis ($p = 0.025$) [34]. Myometrial invasion was not related to the frequency of LOH at *TP53* locus only. LOH, encompassing the highly polymorphic (CA)₂₅ di-nucleotide repeat at *TP53*, was studied in 65 primary human ECs by Koul et al. [37]. Allelic loss, detected in 17% (6/36) of the informative cases, was significantly associated with *TP53* point mutations ($p = 0.024$). In the study conducted by Tritz et al. [36], the prevalence of allelic loss at chromosome 17 was much higher in type II tumors compared to type I ECs (87 vs. 22%, respectively). It is worth pointing out that none of the atrophic or hyperplastic endometrial tissues were LOH-positive. Moreover, endometrioid-type tumors revealed a higher frequency of LOH on the short arm of chromosome 17p (where the *TP53* TSG is spanned) than on the long arm – 17q (87 and 62%, respectively). As a conclusion, they suggested that alterations at 17p13 may preferentially be involved in human endometrial tumorigenesis. German scientists [38] have reported that the frequency of LOH at the *TP53* locus correlates significantly with patient age (<50 vs. >50 years old; $p = 0.04$), histological grading (G3 vs. G2. vs. G1; $p = 0.015$), positive progesterone receptor status ($p = 0.047$), and no application of hormone replacement therapy ($p = 0.04$). In another study, *BRCA1*, *BRCA2*, and *TP53* allelic imbalances were assessed in a series of various human malignant tumors, including 30 sporadic ECs [39]. LOH at *TP53* was significantly associated with allelic imbalance at *BRCA2*, but not at *BRCA1*. These data were surprising for the authors because *TP53* and *BRCA2* genes are located on different human chromosomes, on 17p13.1 and 13q12–13, respectively. In a recent study published by Graesslin et al. [44], 13 of 43 (30.2%) primary human ECs revealed

LOH at the *TP53* locus. The frequency of LOH was significantly higher in papillary serous/clear cell (80%) neoplasms than in endometrioid (25%; $p = 0.03$) and tamoxifen-induced (16%; $p = 0.01$) uterine tumors. There was also statistically higher allelic loss between well and poorly differentiated neoplasms (6 and 60%, respectively; $p = 0.004$), whereas the prevalence of LOH was not related to the clinical stage of the disease, depth of myometrial invasion, lymph node metastases, lymphovascular space invasion, recurrence, or death of the disease. Finally, ploidy status was not related to *TP53* allelic imbalance [44].

Allelic loss at codon 72 has been shown in 32% (6 of 19) of informative uterine tumors, but there was no significant link between allelic imbalance and the clinicopathological variables of cancer, including FIGO stage, histological grade, myoinvasion, or the existence of distant metastases [29].

In our previous study [41], 1 of 19 (5%) informative ECs displayed allelic loss at *TP53* locus, but none of the cases showed *TP53* and *Rb* alterations simultaneously. These data suggest that LOH at *TP53* and *Rb* occur independently of each other in primary ECs. In another report, there was no significant relationship between LOH *TP53* and the clinical and pathologic features of cancer [43]. However, none of the 7 tumors associated with hyperplasia revealed allelic loss, whereas 30% (8 of 27) tumors without hyperplasia exhibited LOH ($p = 0.312$). Finally, allelic imbalance was not related to MIB-1 proliferative index values in primary human ECs [43].

LOH and point mutations at *TP53* have been reported in 35% (when the homozygous cases were excluded) and in 45% of uterine leiomyosarcomas, respectively, whereas both alterations have been reported in only 3 tumors [63]. There was no significant difference in patient survival between those cases with and those cases without LOH. As a final conclusion, the authors cannot exclude the possibility that *TP53* alterations may be implicated in the progression of human uterine leiomyosarcomas [63].

LOH *TP53* and p53 Overexpression

Human p53 protein comprises 393 amino acids and contains 3 domains: an N-terminal transactivation domain, a central DNA-binding domain, and a C-terminal homo-oligomerization domain [4, 5]. All three domains are necessary for efficient p53 activity, although the vast majority of genetic alterations within *TP53* occur within the DNA-binding domain (amino acids 97–292) [4, 5, 64–66]. It is worth pointing out that neither the acquisition

Fig. 2. Various mechanisms causing p53 overexpression.

of the oncogenic function by the mutant p53 protein nor loss of normal p53 activity contribute to carcinogenesis. Overexpression of p53 may be caused by several different ways, including point mutations, gross deletions, allelic imbalance, or by interaction between p53 and cellular/viral oncoproteins [5, 67] (fig. 2). In the literature, several p53 variants have been described; the human *TP53* TSG can encode at least 9 different p53 isoforms: p53, p53 β , p53 γ , Δ 133p53, Δ 133p53 β and Δ 133p53 γ due to alternative splicing of the intron 9 and alternative initiation of translation or alternative splicing of the intron 2 [68–70]. Interestingly, the tissue-specific expression of these isoforms could explain the regulation of p53 transcriptional activity in normal and pathological human conditions. p53 isoform variants are expressed in several normal tissues and tumor samples; however, novel specific p53 isoform antibodies are still being generated [70]. Most of the p53 isoforms showed increased stability compared to wild-type protein [5, 70].

Overexpression of p53, detected by immunohistochemistry, is common in malignant tumors, although the frequency rate is different in various human neoplasms [67]. In our previous report [50], p53 overexpression correlates significantly with the advanced clinical stage of human ECs (I/II vs. III/IV, $p = 0.02$). A population-based study performed by Salvesen et al. [71] revealed that p53 overexpression (staining index >4), apart from patient age, FIGO stage, MVD, and Ki-67, showed an unfavorable prognostic impact for EC patients. The results of their study were in line with several data indicating an independent prognostic significance of p53 overexpression in primary human ECs [72–79]. By contrast, however, Inoue et al. [80] reported that p53 overexpression itself does not appear to be an independent prognostic factor in primary human ECs. Interestingly, Coronado et

al. [81] previously demonstrated that p53 overexpression was an independent predictor of recurrent disease in ECs, even better than HER-2/neu overexpression. In another report, overexpression of p53 was significantly predictive for recurrent EC; however, protein immunoreactivity was mostly not correlated with *TP53* point mutations [82]. From the clinical point of view, determination of p53 status could identify high-risk patients who may develop recurrence even after aggressive surgical management. It is worth citing the gentle study conducted by Ohkouchi et al. [83], who reported a statistically significant difference in the 5-year survival rate of women with stage III/IV disease without and with p53 overexpression (75 and 40%, respectively). These authors recommended an aggressive strategy for advanced-stage EC women affected by tumors overexpressing p53. Previously, Mariani et al. [84] suggested an evaluation of the ploidy status, MIB-1, and p53 overexpression in preoperative EC samples to stratify patients into low- and high-risk groups before the inclusion of a definitive anticancer therapy.

Only a few reports have evaluated the relationship between *TP53* alterations (including LOH study) with p53 overexpression in primary human ECs. Increased p53 level has been reported in all mdm2-positive ECs without detectable *TP53* alterations, suggesting that p53 may be stabilized and inactivated by complex formation with mdm2 [8]. Mdm2 is an E3 ligase, promoting p53 degradation through a ubiquitin-dependent pathway on nuclear and cytoplasmic proteasomes [85, 86]. In general, mdm2 inhibits p53 cellular activity by different ways including binding to the transactivation domain of p53, by targeting p53 for ubiquitination, by inhibiting acetylation of p53 and by shutting p53 to the cytoplasm [5]. Moreover, mdm2 plays an important role in regulating the subcellular localization of p53 [87, 88]. Its ligase activity contrib-

utes to the efficient nuclear export of p53, possibly by driving p53 into a monomeric variant [89].

Another study found no significant association between p53 immunopositivity and the presence of allelic loss at *TP53* [34]. Data from our laboratory also revealed the lack of a relationship between overexpression of p53 and the allelic imbalance at *TP53* locus [43]. Similar to the all above-mentioned data, Graesslin et al. [44] recently failed to reveal a relationship between LOH *TP53* and quantitative p53 overexpression. Altogether, overexpression of p53 does not seem to be related to allelic imbalance at *TP53* in primary human ECs. As an explanation, allelic imbalance at 17p may be connected with whole chromosome loss [22], with a subsequent lack of p53 immunoreactivity. On the other hand, mdm2 binds to the transcription activation domain in the N-terminus of p53 and also promotes the degradation of this protein by the ubiquitin-proteasome system [85, 86]. By contrast, phosphorylation that could inhibit mdm2 binding to p53 may be involved in the regulation of p53 cellular localization, probably by enhancing the nuclear accumulation of this protein [89–91] (fig. 2). Other proteins, for example Mot2, bcl-2 or calcium-dependent protein kinase C, may also be involved in the regulation of p53 [65]. Finally, the application of commercially available different anti-p53 antibodies, various methods of detection, antigen retrieval techniques, and immunostaining criteria complicate the comparison between the different studies [64].

Prognostic Relevance of Allelic Loss at *TP53*

The prognostic relevance of the immunoreactivity of various receptors, cell-cycle proliferation markers, oncogenes, and TSGs in endometrial neoplasia was reviewed previously by Sivridis and Giatromanolaki [91] and Prat [92]. They reported that p53 overexpression was associated with an unfavorable outcome of patients affected by primary EC. However, a limited number of studies have provided data addressing the prognostic relevance of allelic loss at *TP53* in primary human ECs [32, 38, 43]. The first study dealing with this topic was published by Kihana et al. [32] where 85 of 92 (93%) cases were of endometrioid-type ECs. LOH *TP53* was an indicator of a unfavorable outcome that was independent of tumor stage, histologic grade or muscular invasion by Cox regression analysis ($p = 0.015$; OD 1.681; RR 5.07). Kaplan-Meier analysis also revealed that EC patients with LOH *TP53* had a significantly shorter survival compared to patients lacking allelic loss either in stages I–IV ($p = 0.002$) or in

stage I alone ($p = 0.009$). They finally suggested that LOH *TP53* may accumulate through the various steps of EC development. By contrast, LOH at *TP53* did not correlate significantly with disease-free survival or overall survival in 113 patients affected by endometrial cancer (93% of the tumors were of endometrioid type) [38]. However, the main bias of their study was the application of only one genetic marker (AFM051). A previous study conducted at our laboratory revealed a tendency towards a poorer outcome of women affected by uterine corpus cancer displaying LOH ($p = 0.093$). Most of our cases (96%) were of endometrioid-type ECs, but no multivariate analysis was performed therewithal. We finally suggest that the evaluation of LOH at *TP53* may affect a subgroup of ECs characterized by an unfavorable prognosis, and allelic positive group should undergo careful treatment modalities.

LOH at *TP53* Locus in Metastatic ECs

Development of metastasis is the most dangerous manifestation of tumor progression and is the main cause of death for oncological patients. Metastatic cells form a complex of several unfavorable signs associated with the acquisition of neoangiogenesis and the dysregulation of the whole genetic machinery [93–96]. Although EC is the most common malignancy of the female genital tract, with 4,196 new incidences in Poland in 2005, only 2.3–5% of the cases are widespread at the time of primary diagnosis [97]. The prognosis of EC patients with disseminated uterine cancer is in general poor, with overall survival of <20% after 5 years [97]. ECs spread primarily to the pelvic and para-aortic lymph nodes, and to the adnexa and omentum [98, 99]. Distant metastases, for example to the brain [100, 101], lungs [102–104], or bones [105, 106], have also been described. Moreover, this cancer type can incidentally metastasize to the scalp [107], iris [108], mandible [109], pleura [110], or to the pancreas [111].

The exact genetic mechanisms implicated in the development process of EC metastases (either in animal models or in humans) are not fully recognized [112–116]. Based on the data published in the literature, there are several reports dealing with allelic loss at the *TP53* locus in primary human ECs, whereas data assessing the prevalence of allelic imbalance in metastatic ECs are scarce (a representative image of LOH *TP53* in metastatic EC is shown in fig. 1B). Previously, Jones et al. [31] found no significant relationship between lymph node metastases and the incidence of LOH at any particular locus, includ-

ing LOH on chromosome 17p. Similarly, the LOH *TP53* pattern did not correlate with the presence of metastases to the lymph nodes [32, 43] or to other organs [38]. By contrast, there was a significant linkage between *TP53* LOH and lymph node metastases in a Japanese study [34]. The data from our laboratory [117] recently showed differences in the frequency of allelic imbalance at *TP53* between primary ECs and corresponding metastases. The coexistence of allelic loss at *TP53* in primary ECs and corresponding metastatic lesions at introns 1 and 4 was detected in only 9%. We finally stated that allelic imbalance at *TP53* may be associated not only with primary uterine tumors but also with corresponding metastases, although this phenomenon was not shown in all cases [117]. Evaluation of LOH at *TP53* should be performed in a large group of type II ECs to precisely evaluate the prognostic value of this alteration in aggressive endometrial neoplasms.

Perspectives

Although the molecular findings reported herein may be of limited clinical value, the unique molecular phenotype among cancer subtypes is important to better understand the pathogenesis and to develop new target ther-

apeutic modalities for future applications [118]. It is well known that acquisition of the *TP53* alterations leads to the development of virulent, subtype II EC (estrogen 'independent'), which is not transited through a hyperplastic endometrium and is associated with a rapid and uncontrolled growth. Allelic loss should be investigated in these cancer subtypes to verify the exact role of *TP53* allelic imbalance during the formation of metastases. In addition, as suggested by Velasco et al. [13], analysis of allelic loss is a very good tool to identify new TSGs and to find out which inactivation may be implicated, apart from *TP53*, in wide-spreading uterine cancers. Finally, LOH analysis (including allelic loss at *TP53*) has been widely used to distinguish synchronous primary ovarian and endometrial cancers and metastatic lesions [119, 120]. In such cases, however, molecular genetic data should be interpreted with great caution, and in coexistence with the clinical and pathological variables available [121].

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