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p53 REVIEW ARTICLE

TP53 and Ovarian Cancer

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For the p53 Special Issue

Ovarian cancer represents the fourth most frequent type of cancer among females and is the leading cause of death from gynecological cancer in the western world. This review describes gene alterations in ovarian cancer. Specific emphasis is placed on genetic alterations and the prevalence of TP53 (p53) gene alterations in the distinct biological ovarian tumors (benign, borderline, and malignant) and histological subtypes (serous, mucinous, endometrioid, clear cell), as well as in BRCA1-associated hereditary ovarian cancer. Although multi-modality treatment regimens, including cytoreductive surgery and cisplatin-containing combination chemotherapy, have usefully prolonged survival, the overall cure rate of the disease has not changed dramatically. Ovarian cancer is difficult to eradicate completely by surgery and many patients have only a partial response to postoperative chemotherapy and/or many will develop chemotherapy resistance. All these important factors contribute to the poor prognosis of ovarian cancer patients. In this review, the putative prognostic or predictive value of TP53 in ovarian cancer is addressed. Hum Mutat 21:285–291, 2003. © 2003 Wiley-Liss, Inc.

KEY WORDS: cancer; ovarian cancer; TP53; histology; prognosis; BRCA1; DPH2L1; OVCA1; OVCA2; tumor suppressor

DATABASES:
TP53 – OMIM: 191170; GenBank: NM_000546 (mRNA)
http://p53.curie.fr/ (p53 Web Site at Institut Curie)
ww.iarc.fr/p53 (IARC p53 Mutation Database)

INTRODUCTION: OVARIAN CANCER

Ovarian cancer represents the fourth most frequent type of cancer among females and is the leading cause of death from gynecological cancer in the western world. The risk of developing ovarian cancer in a woman's lifetime is estimated to be 1 in 70. The incidence increases with age, reaching its peak in the eighth decade. Ovarian cancer has a high frequency of metastasis, yet generally remains localized within the peritoneal cavity. Because of the absence of early symptoms, approximately two-thirds of the patients will have disease that has already spread beyond the ovaries at the time of diagnosis. Extensive intra-abdominal disease is difficult to eradicate completely by surgery. Moreover, many patients have only a partial response to postoperative chemotherapy and/or many will develop chemotherapy resistance. All these important factors contribute to the poor prognosis of ovarian cancer patients.

The cause of ovarian cancer is unknown. One of the strongest risk factors found in epidemiologic studies is a positive family history of breast cancer [Amos and Struewing, 1993]. Environmental factors may play an important role in ovarian carcinogenesis, although clear associations with industrial exposure to carcinogens or to diagnostic and therapeutic radiation have not been established. Endocrine factors are thought to play an important role in the development of ovarian cancer [Rao and Slotman, 1991]. For example, the risk of ovarian cancer has been related to high levels of gonadotropins in women in early postmenopause [Rao and Slotman, 1991; Risch, 1998], to factors associated with excess androgenic stimulation of ovarian epithelial cells [Risch, 1998] and, although inconsistent, to exposure to fertility drugs or hormone replacement therapy [Venn et al., 1995; Risch, 1996; Weber, 1997; Garg et al., 1998; Burmeister and Healy, 1998; Venn et al., 1999; Rossing and Daling, 1999; Coughlin et al., 2000]. On the other hand, epidemiological studies have demonstrated that reproductive factors, i.e., (multi)-parity and oral contraceptive use, are associated with

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a decreased risk of ovarian cancer [Negri et al., 1991; Franceschi et al., 1991a, b]. These observations have led to the incessant ovulation hypothesis, where each ovulation causes a minor trauma to the ovarian surface epithelium by the formation of inclusion cysts [Fathalla, 1971, 1972]. Aberrations in the repair mechanism, in which wild-type TP53 (MIM# 191170) as the "guardian of the genome" [Lane, 1992] contributes directly and indirectly, might lead to unrestrained proliferation and neoplasia.

Cancer of the ovary is a collection of diverse pathologic entities that can be broadly characterized as epithelial, germ cell, or stromal in origin. The common malignant epithelial tumors account for more than 90% of all ovarian cancers and are thought to arise from the surface epithelium of the ovary and its inclusion cysts [Woodruff, 1976; Scully, 1977]. These epithelial neoplasms can be divided into three biological subtypes: benign, low malignant potential (borderline), and malignant tumors and in becoming malignant, the ovarian surface epithelium can exhibit a variety of mullerian-type differentiations, i.e., (in order of decreasing frequency): serous, mucinous, endometrioid, and clear-cell tumors [Ozols et al., 1992].

GENETIC ALTERATIONS IN OVARIAN CANCER

It is widely accepted that the pathway leading to formation of a tumor is a multistep process involving the accumulation of genetic alterations and many oncogenes and tumor suppressor genes (TSG) have been discovered. Only few of these have been studied in (some) detail in ovarian cancer, but most studies have been small and inconclusive and often no mutations have been found in candidate TSGs. A summary of some of the most intensively studied or the most promising oncogenes and TSGs that may be involved in ovarian cancer is listed in Table 1. In general, TSG-studies have received far more attention than oncogene studies in ovarian cancer and much of the work has focused on identifying possible locations where TSG may reside in the genome rather than the actual study of known TSGs.

As shown in Table 1, loss of heterozygosity (LOH) studies have indicated that chromosome 17 plays the most significant role in ovarian tumor development. On the short arm, LOH at 17p13.1 [Saretzki et al., 1997; Eccles et al., 1992; Foulkes et al., 1993; Godwin et al., 1994] as well as LOH at a more distal locus, 17p13.3 [Godwin et al., 1994; Phillips et al., 1993, 1996], has been observed in a high percentages of these tumors. Mutation of the p53 gene *TP53,* which maps to 17p13.1, is the most common genetic alteration thus far in ovarian cancer, with mutations being present in approximately 50% of advanced stage ovarian carcinomas (see next paragraph). With respect to chromosome 17p13.3, two candidate tumor suppressor genes have been reported: *OVCA1* (MIM# and *OVCA2* (see DPH2L1); MIM# 603527) [Schultz et al., 1996]. Expression of OVCA1

TABLE 1. **Putative Oncogenes and Tumor Suppressor Genes Investigated in Ovarian Cancer**

Gene	Chromosome location	Function	% altered	Spectrum of mutations
Oncogenes				
c-FMS	5q33.3–q34	Receptor-like tyrosine kinase	57–100%	Overexpression
CMYC	8q24	Transcription factor	30%	Amplification, overexpression
K-RAS	12p12	Signal transduction	4–30%	Simple (codon 12,13 and codon 61)
HER-2/neu	17q21–q22	Receptor-like tyrosine kinase	8–40%	Amplification, overexpression
AKT2	19q13.1–q13.2	Serine-threonine protein kinase	10–15%	Amplification, overexpression
Tumor suppressor genes				
FHIT	3p14.2	Unknown	4–8%	Altered transcripts
APC	5q21	Binds α- and β-catenin: involved in adhesion	Rare	Multiple mutations
CDKN2/MTS1	9p21	Cyclin-dependent kinase inhibitor	Rare	Multiple mutations
PTEN	10q23.3	Phosphatase	Rare	Multiple mutations
WT1	11p13	Transcription factor	None	Mutations
ATM	11q22–q23	Protein kinase	None	Mutations
$p27^{KIP1}$	12p13	Cyclin-dependent kinase inhibitor	30–50%	Loss of expression
			None	Mutations
TEL	12p13	Transcription factor	None	Mutations
RB1	13q14	Cell cycle regulator	Rare	Multiple mutations and loss of expression
TP53	17p13.1	Cell cycle regulator; DNA repair and apoptosis	50%	Multiple mutations and overexpression
OVCA1&2	17p13.3	Unknown	?	Loss of expression
NF1	17q11.2	Downregulates the active form of RAS	None	Mutation
NM23	17q21.3	Nucleoside diphosphate kinase	Rare	Mutation
			70%	Enhanced expression
BRCA1	17q21	Transcription factor	Rare	Multiple mutations

was shown to be reduced in ovarian tumor cell lines and in ovarian tumor tissues compared to normal ovarian tissues [Bruening et al., 1999]. Moreover, overexpression of OVCA1 in the ovarian cancer cell line A2780 was shown to suppress clonal outgrowth in a colony formation assay [Bruening et al., 1999]. Interestingly, hypermethylation at chromosome 17p13.3 has also been reported in approximately one-third of ovarian tumors and it was suggested that hypermethylation precedes chromosome 17 loss [Pieretti et al., 1995b].

On the long arm of chromosome 17, loss of 17q12-q21 has frequently been observed [Foulkes et al., 1993; Godwin et al., 1994; Cornelis et al., 1995; Miki et al., 1994]. The breast and ovarian cancer susceptibility gene *BRCA1* (MIM# 113705) localizes to this region (17q21). Germ-line mutations in *BRCA1* are responsible for approximately 50% of families that have a predisposition to breast cancer and up to 80% of those in which multiple cases of both breast and ovarian cancer occur [Easton et al., 1995]. However, mutations have proven to be infrequent in sporadic forms of ovarian cancer [Merajver et al., 1995; Takahashi et al., 1995; Berchuck et al., 1998; Tong et al., 1999]. In addition to the *BRCA1* locus, two other regions of common loss have been identified on chromosome 17, one at chromosome band 17q11.2 (*NF1* locus) and the other at 17q23-24 (*NM23/NME1*; MIM# 156490 and *PHB/prohibitin*; MIM# 176705) [Godwin et al., 1994; Jacobs et al., 1993; Wertheim et al., 1996; Tangir et al., 1996]. Interestingly, an increased sensitivity to cisplatin has been observed in NM23-transfected breast (MDA-MB-435) and ovarian carcinoma (OVCAR-3) cell lines [Ferguson et al., 1996], but expression of NM23 could not predict response to platinum-containing therapy [Baekelandt et al., 1999]. Finally, many studies have suggested that loss of the entire chromosome 17 may be a relatively frequent event in ovarian tumors, thus deleting *TP53*, *BRCA1*, and other potential tumor suppressor genes in a single event [Tavassoli et al., 1993; Pieretti et al., 1995a; Papp et al., 1996; Quezado et al., 1999].

TP53 ALTERATIONS IN OVARIAN CANCER IN RELATION TO DEGREE OF BIOLOGICAL MALIGNANCY AND HISTOLOGIC CLASSIFICATION

Benign epithelial ovarian tumors most frequently develop in women between the ages of 20 and 60. They are frequently large in size and are typically cystic, hence the term cystadenoma. Benign tumors almost always have a serous or mucinous histology. Furthermore, benign serous tumors are more commonly bilateral than the other epithelial benign tumors. Neither TP53 gene mutations nor its overexpression have been described in these tumors [reviewed by Shelling et al., 1995; Skilling et al., 1996].

Ovarian borderline tumors, a distinct category with the interchangeable terms cystadenomas of borderline malignancy and carcinomas of low malignant potential [Serov et al., 1973; FIGO, 1973], constitute approximately 15% of ovarian tumors. Patients with borderline tumors are usually older than patients with benign neoplasms but younger than women with frank malignancies. The survival of patients with borderline tumors is superior to patients with epithelial ovarian cancer. The 5-year survival rate is about 95% and 20-year survival is 80%. Most borderline tumors are of the serous (60%) or mucinous (34%) histological subtype, with endometrioid, clear cell, Brenner, and mixed epithelial types making up the remaining 6%. With respect to *TP53* alterations, we and others have shown that mutation of the *TP53* gene is infrequent (<5%) [Shelling et al., 1995; Skilling et al., 1996; Schuyer et al., 1999; Teneriello et al., 1993; Wertheim et al., 1994; Kupryjanczyk et al., 1995; Lee et al., 1995]. TP53 immunostaining with at least one monoclonal antibody (DO1 or DO7) was observed in 10 of 28 (36%) tumor specimens analyzed by us. Only 4 out of 27 (15%) tumor specimens, however, showed immunopositivity with both monoclonal antibodies. Surprisingly, the percentages of stained tumor cells are much smaller than usually observed in ovarian adenocarcinomas [Schuyer et al., 2001]. Several other studies have also shown that TP53 overexpression is rather uncommon in borderline tumors and depending on cut-off levels and methods used, the reported percentages varied from 4 to 24% (mean between 10 and 15%) [Caduff et al., 1999; Berchuck et al., 1994; Kupryjanczyk et al., 1994; Eltabbakh et al., 1997; Skomedal et al., 1997]. Interestingly, the *K-RAS* gene, that has been implicated as the most commonly mutated oncogene associated with human tumors, is more commonly mutated in borderline tumors and these mutations are strongly associated (63%) with the mucinous cell type [Schuyer et al., 1999; Caduff et al., 1994; Enomotoet al., 1991; Mok et al., 1993; Ichikawa et al., 1994].

Seven borderline components were studied by us from tumors that included a carcinoma component. An increased incidence of *TP53* mutation and accumulation was observed in these borderline components compared to pure borderline tumors, suggesting that these tumors indeed progress to the malignant invasive phenotype through an accumulation of genetic alterations (Schuyer, unpublished data). However, the number is small. It would be interesting, especially in these tumors, to study both the borderline and the invasive component. Microdissection techniques, however, are a prerequisite.

In conclusion, although *TP53* is the most commonly mutated tumor suppressor gene in human

TABLE 2. *TP53* Mutations and/or Protein Accumulation in *BRCA1*-Associated Ovarian Tumors

Reference[a]	TP53 mutation[b]	%	TP53 accumulation[c]	%	TP53 mutation and accumulation combined	%	Remarks
Crook et al. [1997]	1/1		N.D.		N.A.		Type of *BRCA1* mutations not described
Schlichtholz et al. [1998]	0/3		1/2		1/2		*TP53* exons 4–9 analyzed
Rhei et al. [1998]	24/29	83	21/29	72	28/29	97	*TP53* exons 2–11 analyzed; 93% Ashkenazi Jewish *BRCA1* founder mutations: 185delAG (76%), 5382insC (17%)[d]
Ramus [2000]	18/30	60	21/30	70	N.A.		–
Schuijer [2000]	7/7	100	N.D.		N.A.		*TP53* exons 4–10 analyzed; Dutch *BRCA1* founder mutations
Ravid et al. [2000]	N.D.	80	17/27	63	N.A.		Only *BRCA1* founder mutation 185delAG tested
Buller [2001]	16/20		N.D		N.A		*TP53* has different mutation spectrum

[a] Only those papers are listed that clearly define *BRCA1* mutations.

[b] A direct but rather tedious approach to examine TP53 dysfunction is mutation analysis of the gene. The majority of *TP53* mutations localize to the sequence-specific DNA-binding region comprising exons 5–8, which often leads investigators to study only this part of the gene. A detailed database of *TP53* mutations in all human cancers including sporadic breast and ovarian cancers can be found on the website http://perso.curie.fr/Thierry.soussi [Beroud and Soussi, 2003].

[c] A rapid and simple approach to study the *TP53* gene is to examine TP53 protein expression. In its wild-type form, TP53 has a very short half-life. The majority of *TP53* mutations (approximately 80%) result in stabilization of the protein, which allows for immunological detection.

[d] Also referred to as 187delAG and 5385insC. A database of *BRCA1* mutations can be found on www.nhgri.nih.gov/Intramural_research/Lab_transfer/bic/index.html; N.D., not determined; N.A., not applicable.

cancer, *TP53* gene alteration is infrequent in borderline ovarian tumors.

Malignant tumors are characterized by infiltrative destructive growth. They often present as solid masses with areas of necrosis. These tumors are uncommon in younger women under age 35. Symptoms often present late, when the tumor has already spread beyond the ovary and seeded the peritoneum. The most important determinant of clinical outcome is the surgicopathologic stage at the initial time of diagnosis. The staging system defined by the International Federation of Gynecologic Oncologists [FIGO, 1971; Cannistra, 1993]. For patients with stage I disease survival rates have been reported over 90% [Young et al., 1990]. Patients with stage III disease, in which the disease has spread outside the pelvis into the abdominal cavities, have a 5-year survival rate of approximately 20% whereas patients with stage IV disease have a survival rate of $<5\%$ [Ozols et al., 1992; Makar et al., 1995]. The prevalence of TP53 gene alterations appears to raise with increasing stage. TP53 gene mutations occur more often in stage III and IV ovarian cancers when compared to stage I and II, i.e., in 58% versus 37% in stage III/IV and in stage I/II, respectively [as reviewed by Shelling et al., 1995; on 900 cases]. Moreover, as reviewed by Skilling et al. [1996] on 850 primary ovarian tumors, *TP53* gene mutations or overexpression are more prevalent in serous primary ovarian cancers, i.e., in 58% and 59% of the cases, respectively. The percentage of *TP53* gene mutations was reported to be lower for endometrioid, mucinous, and clear-cell ovarian tumors, i.e., 28%, 16%, and 10%, respectively, but slightly higher when using immunohistochemical techniques, i.e., 37% in the endometrioid and 31% in mucinous tumor types (the number for clear-cell tumors is too low).

Hereditary ovarian cancer, which comprises approximately 10% of epithelial ovarian cancers, has been described in association with three autosomal dominant syndromes: hereditary breast and ovarian cancer (HBOC), hereditary site-specific ovarian cancer (HOC), and hereditary nonpolyposis colon cancer syndrome (HNPCC, MIM# 114500). In 80% of families with inherited breast and ovarian cancer and in nearly half of familial breast cancers, linkage to the *BRCA1* gene exists. Data have shown that BRCA1 and TP53 physically associate and that BRCA1 enhances TP53-dependent gene expression by acting as a co-activator, whereas mutant forms of BRCA1 lacking the second BRCA1 C-terminal (BRCT) domain show reduced TP53-mediated transcriptional activation [Ouchi et al., 1998; Zhang et al., 1998]. The cooperative action of BRCA1 and TP53 is further strengthened by the observation that early embryonic lethality of *brca1*-deficient mice could be partially rescued by *tp53* or *p21* null mutations [Hakem et al., 1996]. Although there are few data available on *TP53* in hereditary ovarian cancers, *TP53* alterations indisputably occur more often in *BRCA1*-associated ovarian tumors than in sporadic ovarian tumors, as summarized in Table 2.

Several studies have shown that TP53 is also more frequently inactivated in *BRCA1*-associated breast tumors than in sporadic breast cancers [reviewed in Schuijer et al., 1999; and Gasco et al., this issue]. This implies that loss of *TP53* function is a critical event in the molecular pathogenesis of *BRCA1*-associated breast and ovarian tumors. Although the incidence of *TP53* abnormalities in *BRCA1*-associated tumors is high (70–80%, Table 2), not all *BRCA1*-associated ovarian tumors seem to harbor a *TP53* aberration. TP53 function may be eliminated through other mechanisms, such as hypermethylation or mutation of the *TP53* promoter region or large chromosomal deletions involving the *TP53* locus. Besides, we speculate that other genes, most likely involving the *TP53* checkpoint mechanism, might be involved. Based on the hypothesis by Kinzler and Vogelstein [1997], we would like to propose a role for *BRCA1* as a caretaker whereas *TP53* appears to fit the gatekeeper class more explicitly in *BRCA1*-associated ovarian cancer.

TP53 ALTERATIONS IN OVARIAN CANCER IN RELATION TO PROGNOSIS

Although multimodality treatment regimens, including cytoreductive surgery and cisplatin-containing combination chemotherapy have usefully prolonged survival, the overall cure rate of the disease has not changed dramatically. The 5-year survival for patients with localized disease is approximately 80%, whereas only 20% of the patients diagnosed with disease that has spread outside the pelvis are alive after 5 years [Cannistra, 1993; Friedlander, 1998; Makar et al., 1995]. Interval debulking surgery has resulted in a slight improvement in survival rates for patients with advanced ovarian cancer [van der Burg et al., 1995] but survival rates are still poor. Current routinely used prognostic factors are mainly based on clinicopathological criteria, which are subject of inter- and intra-observer differences. Therefore, more quantitative approaches to identify new biologic factors associated with clinical prognostic significance may decrease the subjectivity frequently associated with prognostic factors. Numerous molecular genetic lesions have been identified, which may be useful for prognostic characterization of ovarian cancer patients. Although several genes involved in ovarian cancer have been identified, many more genes remain to be discovered and the clinical significance of the cancer genes already known is still in its infancy.

TP53 is one of the most studied genes in relation to prognosis and prediction of response to (adjuvant) chemotherapy of ovarian cancer, with about 150 papers so far written (PubMed update 2002, keywords: TP53/p53; prognosis; ovarian cancer). These reports, on the relation between TP53 status and disease progression or survival, have appeared in the last 10 years, however, conflicting conclusions were reached on the prognostic value of TP53 in ovarian cancer. Although there seems to be a trend that TP53 status, as determined by immunohistochemical analysis and mainly in univariate analyses, might be of prognostic value, these data have to be interpreted with caution. The lack of unanimity between authors may be explained by: 1) differences in the techniques used for the analysis of TP53 status (for example, immunohistochemical analysis with different antibodies on frozen or paraffin-embedded tissues using different cutoff levels, ELISA, PCR-single-strand conformational polymorphism/constant denaturing gel electrophoresis analysis of primarily exons 5–8, or cDNA sequencing of the entire gene); 2) patient sample size; 3) biological and/or histological ovarian tumor subset analyses; 4) retrospective nature of the studies; 5) different treatments of the patient population; 6) different (modern) prognostic covariates used in the multivariate analyses; 7) the subjectivity inherent to some approaches; and 8) publication bias. Despite these uncertainties, a phase I trial of intraperitoneal delivery of ONYX-015, which allows selective replication in and lysis of p53-deficient tumor cells, in patients with recurrent epithelial ovarian cancer is ongoing [Vasey et al., 2002].

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