TP53 Mutations in Breast and Ovarian Cancer

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Breast and ovarian cancers are the second and fifth leading causes of cancer deaths among women. Both breast and ovarian cancers are highly heterogeneous and are presented with diverse morphology, natural history, and response to therapy. In recent years, international efforts have led to extensive molecular characterization of both breast and ovarian tumors and identified biologically and clinically relevant subtypes of the diseases based on these molecular features. The role of TP53 in tumor initiation and progression is context dependent, and abrogation of the TP53 pathway seems to be essential for the development of basal-like breast cancers and high-grade serous ovarian cancers. These subtypes of breast and ovarian cancer show several genomic similarities including high frequency of *TP53* mutation, which seems to be an early, initiating, and driving alteration in these cancer subtypes.

Genomic and epigenomic alterations are major factors affecting normal activity of genes and contributing to a disturbed cellular homeostasis in a malignant cell. International efforts in recent years performing large-scale molecular studies through the Cancer Genome Atlas (TCGA) (cancergenome.nih.gov) and the International Cancer Genome Consortium (ICGC) (2010) have resulted in comprehensive characterization of alterations in cancer genomes across various cancer types originated in different organs, including breast and ovary. In addition, following advances in array and sequencing technologies, several independent studies are continuously producing high-throughput molecular data on different cancer types. The coordinated analysis of the genomic and epigenomic abnormalities in cancer genomes integrated with data on multiple molecular levels (mRNA, miRNA, and protein level)

has profoundly improved our understanding of cancer as a genetic disease. To date, mutations in the *TP53* gene are still by far the most frequent genomic event in cancer genomes, as was suggested >25 years ago. The rich source of data has also provided unique opportunity to dissect the functional consequences of *TP53* mutations in cancer initiation and progression in the light of other abnormalities present in the genome. In this article, we will provide perspectives on *TP53* mutations incorporated with new insights gained in breast and ovarian cancer, with a special focus on basal-like subtype of breast cancer and high-grade serous ovarian cancer—subtypes in which TP53 seems to have a driver role.

The TP53 protein is best characterized as a DNA-binding transcription factor with potential to bind to several hundred different promoter elements in the genome, hence regulating expression of hundreds of genes. More than

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three decades of research on TP53 have documented its fundamental role in regulating key cellular processes involved in controlling proliferation and in maintaining the integrity and stability of the genome (Lane and Levine 2010). The importance of TP53 in tumor suppression is unambiguous, evidenced by *Trp53*-null mice being highly predisposed to tumor development (Donehower et al. 1992) individuals with Li–Fraumeni syndrome carrying hereditary *TP53* mutations having high risk of developing early-onset cancers (Malkin et al. 1990), and inactivation of the gene occurring in half of all sporadic cancers (Hollstein et al. 1991; Olivier et al. 2010).

The TP53 protein gets activated in response to a variety of stress signals such as DNA damage, hyperproliferative signals, hypoxia, oxidative stress, and ribonucleotide depletion and suppresses cellular transformation and proliferation mainly by triggering cell-cycle arrest, DNA repair, and apoptosis. Over the years, the role of TP53 in other cellular processes such as metabolism, angiogenesis, immune responses, stem cell maintenance, and tumor-stromal cell cross talk have emerged (Bieganski et al. 2014). TP53 has thus earned a position as an “all-rounder” in cancer biology by being involved in orchestration of the basic events that must be overcome for cancer initiation and progression, summarized as “the hallmarks of cancer” (Solomon et al. 2011; Langerød et al. 2013).

TP53 MUTATION PATTERNS AND FUNCTIONAL CONSEQUENCE

Point mutations are the most common somatic aberrations in the *TP53* gene reported in cancer, followed by small insertions and deletions, and with more complex rearrangements being less frequent. The mutation spectrum, across all cancers, including breast and ovarian, is dominated by missense mutations predominantly located in exons 5–8, spanning the DNA-binding domain of the protein, with mutational hotspots at particular codons (e.g., 175, 245, 273, 285, 220, 306). Frameshift mutations are scattered all over the coding region and show an even distribution over the gene (Ahmed et al. 2010; Oliv-

ier et al. 2010; Leroy et al. 2014; Silwal-Pandit et al. 2014). Interestingly, alterations in the *TP53* gene have been reported in all but five residues of the 393 amino acids in human cancer, making it unique among all the cancer genes (Leroy et al. 2014).

TP53 mutations may exert a loss-of-function (LOF) effect and deprive the cells of anti-cancer protection, a dominant-negative effect, in which the mutant allele masks the function of the wild-type allele (Ko and Prives 1996; Willis et al. 2004), or a gain-of-function (GOF) effect and equip cells with novel tumor-promoting abilities (Brosh and Rotter 2009; Oren and Rotter 2010). In tumors, a *TP53* mutation in one allele is often accompanied by the loss of the other allele to fully inactivate the gene, fulfilling Knudson’s two hit hypothesis (Knudson 1971). Loss of heterozygosity (LOH) at the *TP53* locus has been shown to be a frequent event in ovarian cancer (Godwin et al. 1994; Saretzki et al. 1997). In breast cancer, LOH has been observed in up to 80% of the *TP53*-mutated tumors (Silwal-Pandit et al. 2014). This suggests that LOF is the most significant functional outcome associated with a *TP53* mutation in both ovarian and breast cancer.

Existence of *TP53* mutations with GOF effect has been systematically confirmed in both in vitro and in vivo studies using various mouse models (Oren and Rotter 2010; Solomon et al. 2011; Freed-Pastor and Prives 2012). Regulation of oncogenic Ras circuit (Solomon et al. 2012), regulation of steroid metabolism through transcription factor SREBP (Freed-Pastor et al. 2012), and inhibition of AMP-activated protein kinase (AMPK) signaling (Zhou et al. 2014) are some of the biological consequences linked to GOF effect of *TP53* mutations in human cancer. Recently, GOF mutant TP53 protein was shown to be involved in histone modification, subsequently affecting chromatin modeling and gene expression (Zhu et al. 2015). However, it should be kept in mind that in the presence of a wild-type allele, a GOF effect is difficult to distinguish from a dominant-negative effect. Despite compelling evidences for selected *TP53* mutations showing novel oncogenic properties in human cancer, clinical relevance of GOF mutations

remains uncertain because of a lack of systematic methods to distinguish GOF effects from dominant-negative effects of *TP53* mutations.

ASSOCIATIONS OF *TP53* MUTATIONS TO CLINICOPATHOLOGICAL VARIABLES

Breast and ovarian cancers are among the most common cancers affecting women, ranking, respectively, as the second and fifth leading causes of death in females. Cause of death by ovarian cancer can be largely attributed to a highly aggressive clinical course of high-grade serous ovarian cancer (HGS-OvCa), which represents the most prevalent ovarian cancer type. *TP53*-mutated tumors in general have an aggressive phenotype and are characterized by poor differentiation, increased invasiveness, and high metastatic potential (Olivier et al. 2010; Silwal-Pandit et al. 2014). A considerably high mutation frequency of 50%–100% is reported across all ovarian cancers (Schuijjer and Berns 2003; Berns and Bowtell 2012). This variation in frequency stems from the fact that studies estimating *TP53* mutation frequency have had different composition of histological types of ovarian cancer, which show a significant difference in prevalence of *TP53* mutations. Mutations in *TP53* are infrequent in low-grade serous carcinomas or serous borderline tumors, whereas they are ubiquitous in HGS-OvCa, in which *TP53* mutations are reported in up to 100% of the cases (Ahmed et al. 2010; Cancer Genome Atlas Network 2011). In breast cancer, *TP53* mutations are present in 25%–30% of all cases (Børresen-Dale 2003; Olivier et al. 2006; Silwal-Pandit et al. 2014). Breast tumors with characteristics associated with proliferative and aggressive behavior and poor clinical outcome, such as large tumor size, axillary lymph node metastasis, high histological grade, and estrogen receptor (ER) negativity, are frequently mutated for *TP53* (Langerød et al. 2007; Silwal-Pandit et al. 2014).

TP53 Mutations in Molecular Subtypes of Breast and Ovarian Cancer

Analysis of human tumors through a pan-cancer approach has revealed that various can-

cers at the molecular level are so different, yet so similar—with substantial intracancer heterogeneity, but also considerable cross-cancer similarities (Ciriello et al. 2013; Prat et al. 2013; Hoadley et al. 2014). Both breast and ovarian cancers are highly heterogeneous with distinct morphological and biological features, clinical behavior, and therapy responses, hence the need for tailored therapy. Although the choice of treatment in the clinic today is largely dependent on morphological and histopathological characteristics for both breast and ovarian cancer, information on the molecular background is increasingly being incorporated to improve disease management. With advances in technologies for extensive molecular profiling of tumors, classification of the diseases at a resolution beyond morphological and histopathological characteristics has been possible. The PAM50 subtypes of breast cancer (luminal A, luminal B, HER2-enriched, basal-like, and normal-like), based on differential gene-expression profiles (Perou et al. 2000; Sørlie et al. 2001; Parker et al. 2009), are well acknowledged as a robust classification for breast tumors, reliably reproduced in many independent studies (Sørlie et al. 2003; Cancer Genome Atlas Network 2012), and are recommended by the expert panel of St. Gallen for diagnostic purposes (Goldhirsch et al. 2011). Importantly, the basal-like subtype has been established as a unique molecular entity within breast cancer (Prat et al. 2013; Hoadley et al. 2014). With profiles as distinct as any other cancer type, basal-like subtype shows significant dissimilarity from other breast tumors in genetic and epigenetic alterations and genome-wide mRNA, copy number, miRNA, and protein profiles.

Not surprisingly, breast tumors show a subtype-specific *TP53* mutation spectrum, suggesting a diverse role for *TP53* in different subtypes (Langerød et al. 2007; Holstege et al. 2009; Silwal-Pandit et al. 2014). The frequency of *TP53* mutation in luminal A subtype, which is the most prevalent breast cancer subtype, is lowest. *TP53* mutations are most frequent in the basal-like subtype; with the mutation frequency as high as 85% in the TCGA data set and reported to be the only recurrently mutated gene in

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the basal-like subtype (Cancer Genome Atlas Network 2012). Both basal-like and HER2-enriched subtypes show enrichment for truncating mutations, whereas the luminal B subtype is enriched for missense mutations, of which the majority affects the DNA-binding domain (Langerød et al. 2007; Silwal-Pandit et al. 2014).

Recently, based on gene-expression patterns, the Cancer Genome Atlas Network study has delineated immunoreactive, differentiated, proliferative, and mesenchymal subtypes of HGS-OvCa, supporting an earlier finding by the Australian Ovarian Cancer Study (Tothill et al. 2008; Cancer Genome Atlas Network 2011). The subtypes have been shown to carry prognostic information (Konecny et al. 2014), but a robust subtyping algorithm as PAM50 for subtyping breast tumors (Parker et al. 2009) is not yet available, and the subtypes are yet to be validated across independent cohorts (Waldron et al. 2014). Nevertheless, it would be interesting to investigate *TP53* mutations with a subtype perspective to gain insight into associations between the genetic architecture of these subtypes of ovarian cancer and the presence of *TP53* mutations.

***TP53* Mutations in Basal-Like Subtype and HGS-OvCa**

The pattern of high mutation frequency in *TP53* and the absence of other frequently mutated genes observed for basal-like cancers is similar to what has been reported for HGS-OvCa, with *TP53* mutations present in almost 100% of the samples (Cancer Genome Atlas Network 2011, 2012). As described by the Cancer Genome Atlas (TCGA) Network study and suggested by earlier studies, these particular subtypes of breast and ovarian cancer possess highly unstable genomes with extensive copy number aberrations and defects in the DNA-repair pathways. High genomic instability in human cancer is distinctly associated with *TP53* mutations (Hanel and Moll 2012). Whether *TP53* mutation is a cause or consequence of an unstable cancer genome is not fully clarified and may depend on the background genetic architecture of the tumor.

In tumors with high genomic instability, an inverse relationship between copy number alterations and somatic mutations is observed and termed “the cancer genome hyperbola,” in which the samples either have a large number of somatic mutations or copy number changes, but never both. Both breast and HGS-OvCa segregate to the copy number–driven category. Interestingly, *TP53* mutations are an exception to the cancer genome hyperbola concept and are enriched in the copy number–driven tumor population (Ciriello et al. 2013). In addition to inactivation of *TP53*, basal-like breast cancers and HGS-OvCa share several hallmark features of “BRCAness” (Turner et al. 2004). High rates of chromosomal gains and losses presumably are a consequence of a dysfunctional DNA-repair system in these tumors. Molecular studies have shown that mutations in the *BRCA1* and *BRCA2* genes are rare events in sporadic breast and ovarian cancers, but loss of genomic regions where genes involved in double-stranded break repair, such as where *RAD51*, *RAD17*, *RAD70*, *RAP80*, and *PTEN* are located, occur frequently in both basal-like subtype and HGS-OvCa (Weigman et al. 2012; De Summa et al. 2013). Deletion of *BRCA1/BRCA2* locus and hypermethylation of *BRCA1/BRCA2*-promoter regions may also eliminate *BRCA1/BRCA2* functions (Lips et al. 2013). High frequency of deletions and insertions in the *TP53* gene observed in these tumors may thus reflect the global effect of the deficient DNA-repair pathway, which makes the tumor more susceptible to DNA breaks (De Summa et al. 2013). Cell-cycle arrest and apoptosis are the main effects of activated wild-type *TP53* and are the expected biological consequences in tumors with deficient DNA damage repair. To bypass the *TP53*-induced growth arrest and continue proliferation, *TP53* LOF would be required. In fact, *BRCA1*-deficient embryonic cells, which also lack a properly functioning DNA-repair system, have been experimentally shown to exert selective pressure against wild-type *TP53* to continue cellular proliferation after growth arrest induced by DNA damage (Brugarolas and Jacks 1997). This impaired DNA-repair-system-driven selection for *TP53* mutation potentially

may be more important in highly proliferating tumor cell population as in the basal-like subtype. Furthermore, higher prevalence of *TP53* mutations in BRCA1-associated breast and ovarian tumors compared with sporadic cancers (Greenblatt et al. 1994) implies that loss of *TP53* function is a required event in the pathogenesis of both basal-like breast cancer and HGS-OvCa showing BRCAness. Although *TP53* mutations are not detected in all basal-like cancers, the *TP53* function is suggested to be compromised in most cases, through alterations in other genes in the *TP53* pathway (Cancer Genome Atlas Network 2012). Alternative mechanisms such as hypermethylation or large deletions involving the *TP53* locus may also eliminate *TP53* function.

Next-generation sequencing data have uncovered new patterns of mutational processes in cancer genomes; chromothripsis—massive chromosomal rearrangements (Stephens et al. 2011) thought to occur in a single catastrophic genome-shattering event; kataegis—clusters of localized hypermutated regions presumably occurring in a single event (Nik-Zainal et al. 2012a); and chromoplexy-structural derangement consisting of 4–12 distinct breakpoint junctions leading to formation of a closed chain of chromosomes (Baca et al. 2013). Some recent studies have reported chromothripsis to be modest events (Stephens et al. 2011; Cai et al. 2014; Goncalves et al. 2014) and kataegis to occur frequently in breast cancer (Nik-Zainal et al. 2012a,b; Alexandrov et al. 2013). In case of ovarian cancer, both chromothripsis and kataegis are reported to be infrequent (Chien et al. 2015; Patch et al. 2015). However, a comprehensive study is required to reliably ascertain these observations and gain insight into how these patterns of genomic instability may be associated to subtypes of breast and ovarian cancers. Enzymatic activity of APOBEC cytidine deaminases has been recently implicated in mutational processes in cancer, with a possible link to kataegis (Nik-Zainal et al. 2012a). Interestingly, tumors with high levels of expression of *APOBEC-3B* seem to be more likely to harbor *TP53* mutations (Burns et al. 2013). This association between expression levels of *APOBEC3B*

and *TP53* mutation status was also observed in our study in which the association was strongest in the basal-like subtype (Silwal-Pandit et al. 2014).

Given the striking association shown by Rausch et al. (2012), between chromothripsis and *TP53* mutations in cases with medulloblastoma of the sonic hedgehog subtype and in acute myeloid leukemia and high expression of the APOBEC gene family observed in *TP53*-mutated tumors (Burns et al. 2013; Silwal-Pandit et al. 2014), it would be interesting to systematically explore these newly emerged concepts of mutational processes in relation to *TP53* mutations in breast and ovarian cancers.

PROGNOSTIC AND PREDICTIVE RELEVANCE OF *TP53* MUTATIONS IN BREAST AND OVARIAN CANCERS

The key role played by the *TP53* protein in the pathogenesis of human cancer and high prevalence of *TP53* mutations across all human cancers has led researchers to explore the possibility of using *TP53* mutations as a prognostic and predictive tool. The studies unfortunately show large interstudy variability. In breast cancer, there is now strong evidence for *TP53* mutation status being associated to worse overall and disease-free survival (Børresen-Dale 2003; Olivier et al. 2006; Silwal-Pandit et al. 2014), whereas its predictive value is still debated. By performing analyses on *TP53* mutations in a large cohort of 1420 samples with extensive clinical and molecular annotation, we clearly showed that prognostic impact of *TP53* is subtype-specific (Silwal-Pandit et al. 2014). In that study, mutations in *TP53* were associated with increased mortality in patients with luminal B, HER2-enriched, and normal-like tumors but not in patients with luminal A and basal-like tumors. Low frequency of *TP53* mutation in luminal A subtype combined with the observation that *TP53* mutations did not impact survival suggests a less important role of *TP53* mutation in this ER-positive, hormone-driven subtype. Recent whole-genome analyses of breast tumors performed in a subtype-specific manner has revealed that luminal A subtype is enriched

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for mutations in known drivers like *PIK3CA*, *GATA3*, *MAP3K1*, and *MAP2K4* (Stephens et al. 2012), supporting the notion that genes other than *TP53* might have a central role in tumorigenesis of luminal A tumors. In luminal B and HER2-enriched tumors, ER overexpression and HER2 amplification, respectively, are credited as the driving force. Understanding the relationship between ER/HER2 and *TP53*, therefore, may provide additional insight into the selection process and the unfavorable prognosis conferred by *TP53* mutations in these subgroups. As mentioned earlier, *TP53* function is suggested to be compromised through alternative mechanisms in basal-like tumors in which *TP53* mutations are not detected (Cancer Genome Atlas Network 2012). This implies that the *TP53* pathway is likely inactivated also in tumors with wild-type *TP53* of the basal-like subtype, which may explain the lack of prognostic value of *TP53* mutation status in this subtype.

Functional effects of *TP53* mutations in tumors may also depend on whether the mutations arise early or late in the process of tumorigenesis. A study by Zhou et al. (2009) explored and found *TP53* mutations in pure ductal carcinoma in situ (DCIS), which is an earlier pathological stage in breast cancer development. In the same study, identical *TP53* mutations were detected in both the DCIS and the invasive components of mixed lesions (invasive cancer with an in situ component), indicating that *TP53* mutations arise early in the developmental process of breast cancer. In a recent study by Shah et al. (2012), in which they investigated mutational processes through an evolutionary perspective in triple-negative breast cancers (ER, PR, and HER2-negative cancers overlapping considerably with basal-like cancers), they found that *TP53* mutations tended to occur in the highest clonal frequency group supporting that *TP53* mutation is an early event in majority of the basal-like tumors. *TP53* mutations are proposed to be acquired early also in HGS-OvCa, supported by detection of *TP53* mutations in almost all cases of low-stage HGS-OvCa (Kindelberger et al. 2007; Chien et al. 2015) as well as in high-stage HGS-OvCa (Ahmed et al. 2010; Cancer Genome Atlas Network 2011;

Chien et al. 2015). These observations strongly suggest that inactivation of the *TP53* pathway is an early, initiating, and required event in both basal-like tumors and HGS-OvCa.

Based on the hypothesis that the different types of *TP53* mutations have a distinct functional effect, which in turn may affect survival differently, several studies have investigated clinical impact of different types of *TP53* mutations in breast cancer (Børresen-Dale 2003; Olivier et al. 2006; Silwal-Pandit et al. 2014), with conflicting results. In our recent study, we could not detect a significant difference in survival between the patients harboring different mutation types in breast cancer. Neither the hotspot mutations nor the mutations residing in the DNA-binding region impacted survival differently than other mutations. Preliminary investigations of gene-expression profiles of different *TP53* mutation types in our study (L Silwal-Pandit, A Langerød, and A-L Børresen-Dale, unpubl.) did not show a significant difference in gene expression between different *TP53* mutation types, also suggesting that different *TP53* mutation types do not behave significantly differently in the context of breast cancer. However, larger studies stratifying for *TP53* mutation types, also within the five PAM50 groups, are needed to optimally investigate such effects. By systematic analyses of *TP53* mutations in relation to copy number defects at the *TP53* locus in the same study, we observed that the frequency of LOH showed no clear association to mutation type (Silwal-Pandit et al. 2014). In addition, the LOH events in the mutated tumors were often accompanied by duplication of the retained allele (copy-neutral LOH). Importantly, this phenomenon occurred equally in tumors with mutations predicted to have LOF (truncating mutations) and GOF (selected hotspot mutations) effects. This observation suggests that additional copies of GOF mutant allele do not confer selection advantages beyond LOF mutations in human breast tumors.

Prognostic relevance of *TP53* mutations and *TP53* mutation types is controversial in ovarian cancer as well (Shahin et al. 2000; de Graeff et al. 2008; Ahmed et al. 2010; Köbel et al. 2010). A meta-analysis performed by de

Graeff et al. clearly shows a wide range of heterogeneity in methods used to assess *TP53* mutation status (mostly IHC staining) and categorization of *TP53* mutations into functionally relevant groups. Kang et al. (2013) observed that patients with GOF *TP53* mutations in the TCGA cohort were more likely to develop distant metastasis, supporting the proposed role of GOF in promoting metastasis. However, no significant association between GOF *TP53* mutations and clinical outcome was observed, consistent with a study by Ahmed et al. (2010).

Predictive value of *TP53* in human cancers including breast and ovarian cancer remains inconclusive. Anthracyclines (e.g., doxorubicin, epirubicin) in combination with alkylating agents (e.g., cyclophosphamide), antimetabolites (e.g., 5-fluorouracil gemcitabine), or mitotic inhibitors/taxanes (e.g., paclitaxel, docetaxel) is the most common form of chemotherapy used to treat breast cancer patients. There are contradictory reports on a link between *TP53* deficiency and chemotherapy response, which has further been found to be dependent on type and dose of chemotherapeutic drug administered (Lønning and Knappskog 2013). There are, for instance, studies relating mutations in *TP53* to resistance with anthracycline containing treatment, but not with taxanes (Aas et al. 1996; Geisler et al. 2003; Chrisanthar et al. 2011; Lønning and Knappskog 2013). High doses of cyclophosphamide administered is proposed to be the underlying cause of the association of *TP53* mutations with improved response in a study by Lehmann-Che et al. (2010; Song et al. 2012). Drug-dose intensification has further been shown to be beneficial only for ER-negative subsets (surrogate for basal-like subtype) of breast tumors (Lehmann-Che et al. 2010).

To completely understand the effect of *TP53* mutations on treatment response, it is equally important to understand how different drugs exert their cytotoxic effect in breast tumors, which is not fully understood. Whether response to chemotoxic drugs is *TP53*-mediated growth arrest, senescence, or apoptosis is also unclear (Biegging et al. 2014). Previously, it was thought that DNA damage induced by cytotoxic agents led to *TP53*-mediated apoptosis in cells,

but recent studies suggest that growth arrest and senescence, not apoptosis, is induced in *TP53* wild-type cells in response to chemotherapy (Varna et al. 2009; Jackson et al. 2012). Bailey et al. (2012) have further found that ER represses *TP53*-mediated apoptotic response on induction of DNA damage, which may partly explain chemotherapy resistance observed in an ER-positive subset (low prevalence of *TP53* mutations) of breast cancer, in which tumor cell senescence would trigger resistance to cytotoxic agents. In ER-negative subset of tumors, with a high prevalence of *TP53* mutations, the lack of arrest may lead to a mitotic catastrophe and cell death and potentially explain the higher rates of pathological complete response achieved in ER-negative tumors (Bertheau et al. 2013).

Standard treatment of choice today for ovarian cancer in advanced stages is platinum-based therapy including cisplatin or carboplatin in combination with taxanes (Lavarino et al. 2000). Previously, *TP53* mutations have been associated with improved response in platinum-based therapy combined with chemotherapy but not to platinum monotherapy in ovarian cancer (Righetti et al. 1996; Lavarino et al. 2000). Analysis of standard platinum- and taxane-based chemotherapy treated HGS-OvCa in the TCGA study with respect to *TP53* mutation types indicated higher rates of platinum resistance in tumors with oncomorphic mutations—mutations with predicted GOF effects in the absence of a wild-type *TP53* allele (Brachova et al. 2013), as compared with other mutations (Brachova et al. 2015). This indicates that different *TP53* mutations have different biological consequences in the context of HGS-OvCa and was further supported by the observation that oncomorphic mutations were associated with unique protein profiles (Brachova et al. 2015).

CONCLUDING REMARKS

Taken together, *TP53* mutations show subtype-specific roles in breast and ovarian cancer. The prognostic and predictive capacity of *TP53* remains inconclusive with discrepant indications reported by studies in the past. The discrepan-

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cies observed between studies can largely be attributed to inadequate methods for mutation screening, including immunohistochemical (IHC) staining of TP53 protein and sequencing of exons 5–8 spanning the DNA-binding domain, in which mutations tend to cluster. Twenty to thirty percent of the mutations remain undetected by these surrogate methods used to assess *TP53* mutations leading to a large number of misclassified cases and erroneous conclusions on the clinical significance of *TP53* mutation (Langerød et al. 2013; Silwal-Pandit et al. 2014). To take advantage of *TP53* mutations as a prognostic and predictive marker, correct evaluation of the functional status of TP53 is necessary. Lønning and Knappskog (2013) recently showed that inactivation of either TP53 or its key activators CHK2 and ATM superiorly predicted resistance to DNA-damaging drugs in breast cancer (Knappskog et al. 2012). They also recently showed concomitant inactivation of the TP53 and RB1 pathways in resistant breast tumor cells (Knappskog et al. 2015). Sequencing of all coding exons of TP53 (exons 2–11) is now established as the gold standard of assessing *TP53* mutation status, but findings from Lønning and colleagues suggest that functionality of TP53 may be better assessed by evaluating key genes in the TP53 pathway as well as its redundant pathways that compensate for TP53 loss, in addition to assessing *TP53* mutation status (Lønning and Knappskog 2013).

High prevalence of *TP53* mutations in human cancer has also motivated development of targeted therapeutics exploiting TP53 pathways (Lane et al. 2010). But regardless of whether the therapy involves delivery of wild-type TP53 by adenovirus vectors, TP53-based vaccines to attract T-cells, usage of siRNAs to knock down the negative regulators of TP53, or usage of small molecules (e.g., PRIMA-1, RITA) to restore the activity of TP53, the road to realization of TP53-based therapy relies on complete understanding of the biological consequence of a *TP53* mutation in individual patients. Investigation of highly heterogeneous breast and ovarian cancer as a bulk without stratifying for subtypes, which show considerable variation in *TP53* mutation frequency and subsequent functional conse-

quences, has been a major pitfall of earlier studies. The fact that subtypes of breast and ovarian tumors show varying clinical outcome and sensitivity to drugs further necessitates evaluation of prognostic and predictive capacity of TP53 in a subtype-specific manner, also beyond the subtypes identified to date. It is of utmost important to take into account tumor heterogeneity and perform analyses in tumor groups as homogenous as possible to be able to optimally assess clinical significance of types of *TP53* mutations and to be able to correctly relate the observations to biological mechanisms in cancer. Molecular data at multiple levels (mRNA, miRNA, protein, methylation, etc.) and integrative approaches of data analysis may provide proper insight into how a *TP53* mutation contributes to tumor progression and influences prognosis and drug sensitivity in the background of a myriad of other genetic aberrations that potentially drive tumorigenesis.

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TP53 Mutations in Breast and Ovarian Cancer

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