BRCA2 Mutations in Prostate Cancer: A Literature Review

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Abstract: *Background:* Prostate cancer is one of the most frequently diagnosed neoplastic disease and the second leading cause of cancer mortality in men of the Western world. Despite improved methods for early detection, a large proportion of patients succumb to metastatic prostate cancer that is resistant to conventional therapies. The development of novel effective strategies to prevent and treat prostate cancer relies considerably upon increasing our knowledge of the interplay among various molecular and genetic alterations that lead to onset and progression of prostate cancer. To date, germline mutations in the cancer susceptibility gene *BRCA2* represent one of the strongest risk factor to develop prostate cancer.

Objective: Goal of this review is to summarize current reports investigating the presence of *BRCA2* mutations in prostate cancer.

Design: A comprehensive analysis of the literature on *BRCA2* mutations in prostate cancer. Data source: Pubmed. Terms included in the search: "BRCA2 mutations", "prostate cancer".

Results: A total of 18 studies were included in the review. The studies focused on the clinical implications of *BRCA2* mutations in prostate cancer. The findings indicate that inherited pathogenic mutations in *BRCA2* predispose to highly aggressive prostate cancers and poor survival. Very recent reports also suggest that metastatic castration-resistant prostate cancers are "enriched" of *BRCA2* mutations compared to the primary tumors.

Conclusion: Because *BRCA2*-mutated tumors are very sensitive to PARP-inhibitors'-based chemotherapy, *BRCA2* genomic testing of patients with advanced metastatic prostate disease may enable an effective, personalized, therapeutic strategy.

Keywords: Prostate cancer, BRCA2, Genetic predisposition.

INTRODUCTION

Prostate cancer is a leading cause of morbidity and mortality among men in the Western world. The American Cancer Society estimates that in the United States about 220,800 new cases of prostate cancer will be diagnosed in 2015 and about 27,500 deaths from prostate cancer will occur in the same year. Approximately 1 man in 7 will be diagnosed with prostate cancer during his life. Despite improved methods for early detection, a large proportion of patients succumb to disseminated metastatic prostate cancer that is resistant to conventional therapies [1]. Therapeutic approaches involve androgen ablation, which prevents androgen-dependent cancer cell growth by predisposing cancer cells to enter an apoptotic pathway [2]. However, tumor clones that evade apoptotic death and thrive in absence of androgens (castration-resistant prostate cancer) normally arise after a few years [1]. Furthermore, the biological events resulting in castration-resistant prostate cancer also reduce the effectiveness of conventional chemotherapeutic agents, at least partly explained by the fact that apoptosis, the predominant form of cell death triggered by many chemotherapeutic agents, is impaired in the advanced disease [1, 2].

Age, lifestyle and genetic factors have been implicated in the development of prostate cancer. In addition, the inherited genetic background may confer an increased risk to develop prostate carcinoma. Several studies have identified recurrent somatic mutations or copy number alterations in oncogenes and/or in tumor suppressor genes in primary prostate cancer specimens [3]. Among these, point mutations in TP53, SPOP, FOXA1 and MED12 have been detected in a high proportion of primary prostate cancer [4]. Mutations in TP53 and androgen receptor (AR) are further enriched in metastatic, castration-resistant prostate cancer compared to primary prostate cancer [3]. New genomic alterations have been recently identified in PIK3CA/B, BRAF/RAF1, APC, and β-catenin [3]. Among the inherited genetic factors, there is strong evidence that mutations in the Breast Cancer Susceptibility gene 2 (*BRCA2*) confer the highest risk to develop prostate cancer (8.6-fold in men below the age of 65 years) [5]. The risk of *BRCA2*-mutation carriers to develop prostate cancer at an early age (< 56 years) is even higher (about 23-fold compared to non-carrier) [6].

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Together with *BRCA1*, the tumor suppressor gene *BRCA2* is among the best-known cancer-susceptibility genes. Germline presence of a single mutated copy of *BRCA2* is associated with increased susceptibility to breast and ovarian cancer in women and prostate cancer in men [7]. Although several different genes have been implicated in the development of prostate cancer, very few confer a risk as high as mutations in *BRCA2* [8]. Somatic inactivation of the wild-type copy of the *BRCA2* gene is always required to support tumorigenesis in *BRCA2* mutant carriers [9]. The tumor suppressor BRCA2 is a caretaker protein that plays an important role in repairing DNA double-strand breaks (DSBs) through the homologous recombination (HR) process by regulating the activity of the recombinase Rad51 [10]. Thus, cells deficient of functional BRCA2 would use alternative, error-prone mechanisms to repair DSBs, potentially resulting in genomic instability that may underlie the increased susceptibility to develop cancer in *BRCA2* mutation carriers [11]. In addition, BRCA2 has been implicated in the regulation of transcription, proliferation, cell cycle control and cell invasion [12, 13]. These studies suggest that BRCA2 may control a diverse range of cellular processes, besides its well-recognized role in DNA recombination and repair processes, and that its loss may contribute to prostate cancer development and progression through multiple mechanisms, including increased genome instability, cell proliferation and metastatic potential. In agreement with these findings, Francis *et al.* [14] have found that specific deletion of *Brca2* in murine prostate epithelial cells causes hyperplasia and low-grade prostatic intra-epithelial neoplasia (PIN). In addition, simultaneous deletion of *Brca2* and *Trp53* in these cells lead to high-grade PIN, further confirming that *BRCA2* acts as a tumor suppressor in prostate epithelial cells.

Aim of this study is to summarize current literature reporting mutations of *BRCA2* in primary and in metastatic, castration-resistant prostate cancer as well as their correlation with patients' clinical outcome.

METHODS

A comprehensive search of Pubmed was performed. The keywords: "prostate cancer" and "BRCA2 mutations" were used to identify the relevant literature from 2003 to 2015. A total of 177 potentially relevant manuscripts were retrieved. After removal of single case-report studies and articles citing the term "prostate" but not effectively including prostate cancer specimens, 18 manuscripts were included in this literature review (Figure **1**; Table **1**).

RESULTS AND DISCUSSION

One of the first large-scale study investigating the potential relation between occurrence of *BRCA2* mutations and prostate cancer development is dated 2003. Edwards *et al.* [6] sequenced the *BRCA2* coding region for germline mutations in the lymphocytes of 263 men diagnosed with prostate cancer at an early age (≤ 55 years old). Deleterious protein-truncating mutations were detected in 2.3% men (6 patients), and 22 BRCA2 variants of uncertain significance were also found. Overall, the relative risk of early-onset prostate cancer in *BRCA2*-mutation carriers was 23-fold.

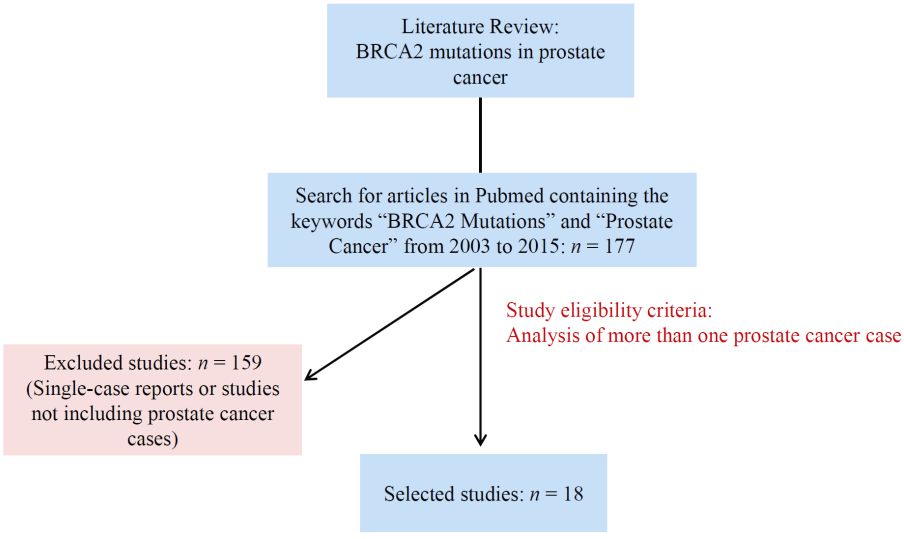

Figure 1: Flow diagram of the criteria used for the studies selected in this review.

Table 1: Characteristics of the Included Studies

Study	# Samples	Study Design	Results
Edwards *et al.* 2003 [6]	263 men diagnosed with prostate cancer at an early age (≤ 55 years old)	The complete *BRCA2* coding region was sequenced in lymphocytes collected from patients	2.3% men displayed deleterious protein-truncating *BRCA2* mutations; 22 *BRCA2* variants of uncertain significance were identified. The relative risk of early-onset prostate cancer in *BRCA2*-mutation carriers was 23-fold.
Tryggvadottir *et al.* 2007 [15]	527 prostate cancer patients	Prevalence of the *BRCA2* 999del 5 founder mutation was assessed in prostate cancer patients belonging to the Icelandic population	5.7% of the patients carried the *BRCA2* 999del 5 mutation. The mutation conferred lower mean age at diagnosis, higher tumor grade, more advanced tumor stage and reduced median survival.
Mitra *et al.* 2008 [16]	16 *BRCA2* mutation carriers and 20 controls affected by prostate cancer	Archived histopathological tissue sections of *BRCA2* mutation carriers were collected, reviewed and compared to age-matched controls	*BRCA2* mutations conferred higher Gleason grade (8-10).
Agalliu *et al.* 2009 [17]	979 prostate cancer cases and 1.251controls among Ashkenazi Jewish men	Biological samples were screened for the *BRCA1* 185delAG, *BRCA1* 5382insC and the *BRCA2* 6174delT founder mutations	Prostate cancer risk was increased (odd ratios: 1.9) for *BRCA2* mutation carriers but not for *BRCA1* mutation carriers. *BRCA2* founder mutation conferred a 3-fold elevated risk of high-grade prostate cancer.
Gallagher *et al.* 2010 [18]	832 prostate cancer cases in the Ashkenazi Jewish population	Prevalence of the *BRCA2* 6174delT mutation was assessed in prostate cancer patients from the Ashkenazi Jewish population. Clinical outcome was compared	26/832 patients were *BRCA2* 6174delT mutation carriers. *BRCA2* mutation was associated with a 3-fold risk of prostate cancer and higher histological grade.
Narod *et al.* 2008 [19]	182 prostate cancer patients with a *BRCA2* mutation and 119 prostate cancer patients with a *BRCA1* mutation	Survival between *BRCA2* and *BRCA1* mutation carriers was compared	The median survival from diagnosis was 4 years for patients with a *BRCA2* mutation and 8 years for patients with a *BRCA1* mutation.
Edwards *et al.* 2010 [20]	21 prostate cancer patients with a *BRCA2* mutation and 1587 controls	Clinical outcome was compared	The median survival from diagnosis was 4.8 years for patients with a *BRCA2* mutation and 8.5 years for control patients. Loss of heterozygosity was found in most of the tumors from *BRCA2* mutation carriers.
Willems *et al.* 2008 [21]	14 prostate cancer patients with a *BRCA2* mutation	Loss of heterozigosity at the *BRCA2* gene was examined	10/14 tumors exhibited loss of heterozigosity at the *BRCA2* gene.
Thorne *et al.* 2011 [22]	148 men with prostate cancer from 1.423 families with a history of breast cancer were analyzed from the kConFab consortium	Presence of *BRCA2* mutations and pathological/clinical outcome were analyzed	40/148 men showed *BRCA2* mutations. 77.5% of *BRCA2* mutation carriers and 58.7% of noncarriers had high-risk disease: *BRCA2* mutation carriers had higher Gleason grade and more locally advanced disease than the noncarriers.
Mitra *et al.* 2011 [23]	300 prostate cancer cases: 205 *BRCA1* (89) or *BRCA2* (116) mutation carriers, 95 controls	PSA levels were monitored	The positive predictive value of PSA screening was 47.6% for potentially aggressive prostate cancer in *BRCA2* mutation carriers.
Akbari *et al.* 2014 [24]	4.187 prostate cancer men	*BRCA2* gene was sequenced in its entirety and clinical outcome was assessed	12-year prostate-cancer specific survival rate was 94.3% for non-carriers and 61.8% for *BRCA2*-mutation carriers.
Maier *et al.* 2014 [25]	382 familial and 92 sporadic prostate cancer cases with early-onset (≤ 60 years old)	All *BRCA2* exons were sequenced	5 *BRCA2* pathogenic mutations were detected in familial cases of prostate cancer. 10 *BRCA2* variants of uncertain significance were detected in *BRCA2* carriers and noncarriers groups. Carriers of the 5 *BRCA2* pathogenic mutations had increased PSA levels at diagnosis, aggressive disease and reduced survival compared to noncarriers.

(Table 1). Contd …..

Study	# Samples	Study Design	Results
Kote-Jarai *et al.* 2011 [5]	1.864 prostate cancer patients	*BRCA2* gene was sequenced	19 protein-truncating mutations, 3 in-frame deletions and 69 missense variants of uncertain significance were identified. The 19 protein-truncating mutations were all present in younger onset cases with age at diagnosis $\leq$ 65 years
Castro *et al.* 2013 [26]	2.019 prostate cancer cases: 61 *BRCA2* mutation carriers, 18 *BRCA1* mutation carriers, and 1940 noncarriers	Tumor features and clinical outcomes were analyzed	*BRCA2* mutations predisposed to an aggressive prostate cancer phenotype. Nodal involvement and distant metastasis were more common in *BRCA2* mutation carriers than in noncarriers.
Castro *et al.* 2015 [27]	1.302 cases of local/locally advanced prostate cancer (67 *BRCA2* carriers and 1.235 noncarriers)	Tumor features and clinical outcomes were analyzed	At 10 years after treatment, 84% of noncarriers and 50% of carriers were free of metastasis. Multivariate analysis confirmed that *BRCA2* mutation status was an independent prognostic factor for metastasis-free survival.
Arbini *et al.* 2011 [28]	80 cases of sporadic prostate cancer	BRCA2 protein levels were analyzed by immunohistochemistry in prostate cancer and adjacent normal prostate tissue	Significant reduction of BRCA2 protein in about 70% of sporadic prostate cancer cases.
Beltran *et al.* 2013 [30]	45 cases of sporadic prostate cancer: 16 localized, 4 metastatic hormone-naive, and 25 metastatic castration-resistant prostate cancers	DNA alterations in several genes were analyzed by sequencing	Homozygous *BRCA2* deletions were detected in 1 out of 4 metastatic hormone-naive cancers and 3 out of 25 metastatic castration-resistant prostate carcinomas. Clinically localized prostate cancers did not show *BRCA2* alterations, besides one primary tumor from a patient known to have later developed metastatic castration-resistant disease.
Robinson *et al.* 2015 [3]	150 metastatic castration-resistant sporadic prostate cancers	Whole-exome and transcriptome sequencing of bone or soft tissue tumor biopsies from prostate cancer patients	Aberrations of *BRCA2* detected at substantially higher frequency in the metastatic lesions (13%) compared to primary prostate cancers (5%).

More recent studies have associated the presence of deleterious germline mutations in *BRCA2* with a more aggressive phenotype, nodal involvement and poor survival in prostate cancer patients. Tryggvadottir *et al*. [15] analyzed occurrence of the *BRCA2* 999del5 mutation in prostate cancer patients. This mutation, which occurs in exon 9 of the *BRCA2* gene, is present in 6-7% of breast cancer patients in the Icelandic population. The authors assessed the potential association between *BRCA2* 999del5 mutation and progression of prostate carcinoma in 527 patients diagnosed with prostate cancer. The mutation, which was carried by 5.7% of the patients (30/527), conferred a lower mean age at diagnosis (69 years compared to 74 years of non-carriers), higher tumor grade (84% of carriers with Gleason grade 3-4 compared to 52.7% of non-carriers), more advanced tumor stage (T3 or T4 in carriers: 79.3% compared to 38.6% of non-carriers), and reduced median survival (2.1 ÷ 3.6 years in carriers and 12.4 ÷ 19.7 years in non-carriers), indicating that the Icelandic *BRCA2* 999del5 founder mutation is strongly correlated with a rapidly progressing lethal disease. The results of this study were consistent with a subsequent study performed in UK on 16 *BRCA2* mutation carriers and a control group [16] showing higher Gleason grade in *BRCA2* mutation carriers. Similar results were obtained by Agalliu *et al.* [17] on Ashkenazi Jewish men which carry the *BRCA2* 6174delT founder mutation. The study was conducted on 979 prostate cancer cases and 1.251 controls. Overall, *BRCA2* mutation carriers had an increased risk to develop high-grade prostate cancer with a poorly differentiated phenotype. Gallagher *et al*. [18] confirmed the clinical impact of the same *BRCA2* founder mutation, 6174delT, in Ashkenazi Jewish men: out of 832 men diagnosed with prostate cancer, 26 displayed the mutation which was associated with a poorly differentiated phenotype.

Narod *et al.* [19] compared survival of 182 prostate cancer patients with a *BRCA2* mutation with that of 119 prostate cancer patients with a mutation in the tumor suppressor gene *BRCA1* and found that the median survival from diagnosis was significantly reduced in the *BRCA2* mutation carriers (4 years *versus* 8 years of *BRCA1* mutation carriers). Poorer survival of prostate

cancer patients with a *BRCA2* germline mutation was also observed by other two subsequent studies. Edwards *et al.* [20] performed an analysis on 21 *BRCA2*-mutation carriers and matched controls, and found that median survival of BRCA2 mutation carriers was 4.8 years *versus* 8.5 years of the control. In addition, out of 5 prostate tissue specimens available from *BRCA2*-mutation carriers, 33 exhibited loss of heterozigosity (LOH) of the wild-type *BRCA2* allele, consistent with a tumor suppressor model for BRCA2. LOH at the *BRCA2* locus was also previously reported in 10 out of 14 prostate tissue specimens from *BRCA2*-mutation carriers [21]. Thorne *et al.* [22] confirmed significantly elevated risk of high-grade cancer in prostate cancer patients which carried a *BRCA2* mutations. In this study, a total of 148 men from 1.423 families with a history of breast cancer were analyzed from the kConFab consortium (Australia). Each participant had a verified case of prostate cancer and was confirmed as carrier or non carrier of a *BRCA2* pathogenic mutation. The results of this study show that 77.5% of *BRCA2* mutation carriers and 58.7% of non carriers control displayed high-risk disease.

In 2011, the first multicentre prostate cancer large screening study targeted at men with mutations to *BRCA1* or *BRCA2* (IMPACT project) was published [23]. In total, 300 subjects from 20 different medical centers were recruited over a period of 33 months: 205 were carriers of either *BRCA1* or *BRCA2* mutations (89 *BRCA1* and 116 *BRCA2*) and 95 were controls (no *BRCA* mutations). In this first screening, prostate-specific antigen (PSA) levels were reported as a more accurate predictor of potentially aggressive prostate cancer in *BRCA*-mutation carriers than in the general population. This study has been followed by other large-scale studies. In a 2014's report from Narod's group and collaborators [24], 4187 men who underwent prostate cancer biopsy between 1998 and 2010 were screened for mutations of the *BRCA2* gene in its entirety and the patients were followed for survival from prostate cancer until December 2012: the 12-year prostate-cancer specific survival rate 94.3% for non-carriers and 61.8% for BRCA2-mutation carriers. All exons of *BRCA2* were also sequenced by Maier *et al.* [25] in a German set of 382 familial prostate cancer cases and 92 sporadic cancer cases with early onset of the neoplastic disease ($\leq$ 60 years). Five *BRCA2* pathogenic mutations and ten *BRCA2* variants of uncertain significance were detected. While the first were specifically detected in patients with a familial history of prostate cancer, the 10 variants were present in both groups of patients. Carriers of the five pathogenic mutations had increased PSA levels at diagnosis, aggressive disease and reduced survival compared to noncarriers.

Three recent studies from Dr. Eeles' group [5, 26, 27] have provided more insights into the clinical implications of deleterious mutations in the *BRCA2* gene. In the first study [5], 1.864 patients with prostate cancer recruited from the UK Genetic Prostate Cancer Study were screened, and 19 protein-truncating mutations (16 frameshift and 3 nonsense mutations) all present in younger onset cases with age at diagnosis $\leq$ 65 years were identified, further confirming that deleterious *BRCA2* mutations predispose to young-onset prostate cancer (8.6-fold increased risk of prostate cancer by age 65). In the next study, the prostate tumor features and outcomes of 2.019 patients with prostate cancer, of which 61 *BRCA2* carriers, 18 *BRCA1* carriers, and 1.940 noncarriers, were analyzed. The analysis confirmed that *BRCA2* mutations predispose to an aggressive prostate cancer phenotype, with nodal involvement and distant metastasis more common in *BRCA2* mutation carriers than in noncarriers. In addition, the study confirmed that mutation carriers diagnosed with local prostate carcinoma developed metastasis earlier than noncarriers and had worse survival outcome [26]. Finally, in a study published in 2015, tumor features and outcomes of 1.302 patients (67 *BRCA2* carriers and 1.235 noncarriers) with locally advanced prostate cancer were analyzed [27]. At 10 years after treatment, 84% of noncarriers and 50% of carriers were free of metastasis. Multivariate analysis confirmed that *BRCA2* mutation status was an independent prognostic factor for metastasis-free survival. All these studies demonstrate that inherited *BRCA2* pathogenic mutations predispose to highly aggressive, metastatic prostate cancer. The molecular basis for the aggressive behavior of the *BRCA2*-associated prostate carcinomas is still not clear, but it may be related to the increased migratory and invasive properties that exhibit prostate cancer cells after suppression of BRCA2 protein levels [13].

All the above described studies have been performed in *BRCA2*-mutation carriers, and clinical histopathological features of the tumors as well as studies of LOH at the *BRCA2* locus have been reported by analyzing primary prostate tumors. The potential role of BRCA2 in sporadic prostate cancers, which represent the vast majority of prostate carcinomas, is still under investigation. Indeed, though deleterious

BRCA2 mutations are rare in sporadic prostate cancer patients (*BRCA* noncarrier patients), a recent study, which included 80 sporadic prostate cancer specimens and the adjacent normal tissue, reported that a significant percentage of prostate cancer tissues (about 70%) had decreased BRCA2 protein levels [28], suggesting that at least a group of sporadic prostate cancers may develop "BRCAness" clinical characteristics. This latter study included analysis of BRCA2 protein levels but not a *BRCA2*-mutational analysis of the patients. However, despite the fact that *BRCA2* mutations are rare in sporadic cancers, it should be noted that reduction of BRCA2 protein in prostate cancer tissues may be ascribed to mechanisms different than mutations, including post-translational regulation [28, 29]. In addition, a recent study has shown that about 12% of advanced, highly aggressive sporadic prostate carcinomas display genomic alterations leading to genetic deletion of *BRCA2* [30]. This study analyzed the DNA alterations in 45 prostate tumors representing the various stages of progression of the disease: 16 localized prostate cancers, 4 metastatic hormone-naive prostate cancers, 25 metastatic castration-resistant prostate carcinomas. Interestingly, homozygous *BRCA2* deletions were detected in 1 out of 4 metastatic hormone-naive cancers and 3 out of 25 metastatic castration-resistant prostate carcinomas. Clinically localized prostate cancers did not show *BRCA2* alterations, besides one primary tumor from a patient known to have later developed metastatic castration-resistant disease. These results suggest that *BRCA2* gene deletions, though not present in primary tumors, may be acquired during cancer progression, and further support a role of BRCA2 loss in conferring an aggressive phenotype to prostate cancer cells. Intriguingly, a multi-institutional study published a few months ago conducted whole-exome and transcriptome sequencing of bone or soft tissue tumor biopsies from 150 metastatic castration-resistant prostate cancers and found aberrations of *BRCA2* at substantially higher frequency in the metastatic lesions (13%) compared to primary prostate cancers (5%) (3]. This finding has significant clinical implications because tumors with loss of BRCA2 have been reported to be very sensitive to PARP inhibitors, a new class of anticancer drugs [31].

CONCLUSIONS

The development of newly effective strategies for prevention and therapy of prostate carcinoma relies heavily upon increasing our knowledge of the interplay among various molecular alterations that lead to onset and progression of prostate cancer. Germline mutations in *BRCA2* not only increase the risk of developing prostate cancer but also predispose to a highly aggressive disease with poor outcome. A genomic analysis on prospective biopsies from sporadic, metastatic castration-resistant cancers may enable personalized therapies, which could include the PARP inhibitor olaparib, a recently FDA-approved anti-cancer drug which acts against cancers in patients with hereditary *BRCA* mutations.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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