[Frontiers in Bioscience 18, 1445-1459, June 1, 2013]

The role of BRCA1 and BRCA2 in prostate cancer

Dan Li[1,3], Easwari Kumaraswamy[1,3], Lisa M. Harlan-Williams[2,3], Roy A. Jensen[1,2,3]

[1]Department of Pathology & Laboratory Medicine, [2]Department of Anatomy & Cell Biology and [3]The University of Kansas Cancer Center, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160

TABLE OF CONTENTS

1. ABSTRACT

The familial aggregation of prostate cancer and breast cancer has been observed for almost half a century and about 85% of the inherited breast cancer can be linked to germ-line mutations of *BRCA1* (breast cancer 1, early onset) and *BRCA2*. In this review, we are mainly focusing on the contribution of *BRCA1/2* sequence variations to prostate cancer risk and disease progression. We will discuss the biological functions of BRCA1/2 and BRCA1/2-related signaling pathways in prostate cancer biology. The majority of studies supporting the link between *BRCA1/2* mutations and prostate cancer are from populations with a high frequency of mutations, such as Ashkenazi Jewish, Icelandic, and U.K. population. BRCA1 can directly interact with the androgen receptor (AR) and Janus kinase (JAK), and can differentially regulate insulin-like growth factor 1 receptor (IGF-IR) expression in an AR-dependent manner. BRCA2 homeostasis in prostate cancer cells has been found to be critical in determining cell fates during prostate cancer progression. This review may be helpful for medical professionals and prostate cancer patients when discussing prostate cancer risks, treatment and prognosis.

2. INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer in males worldwide, and the most frequent cancer in economically developed countries. It accounted for 14% (903,500) of the total new cancer cases and 6% (258,400) of the total cancer deaths in males world-wide in 2008 (1). In the United States, prostate cancer accounts for 29% (241,470) of expected new cancer cases and 9% (28,170) of cancer deaths in males in 2012 (2). Among the well-established risk factors for prostate cancer are age, ethnic background, and family history (3, 4). About 60% of men diagnosed with prostate cancer are >70 years old. Males of African descent in the Caribbean region have the highest prostate cancer mortality rates in the world (3, 5-7). A positive family history of prostate cancer is one of the strongest risk factors. In first-degree relatives of affected men, the relative risk of prostate cancer is about 2-fold higher, and the risk is much higher when they are diagnosed at younger ages (8-10).

The familial clustering (aggregation) of prostate cancer and breast cancer has been observed for almost half a century. A family history of breast cancer significantly

increases the risk of the prostate cancer in men (11-14). In 1993, an Icelandic study found a higher risk of prostate cancer in families with multiple breast cancer cases, and haplotype analysis proved its association with the breast cancer susceptibility gene *BRCA1* (breast cancer 1, early onset) (15). Germ-line mutations of *BRCA1* and *BRCA2* (breast cancer 2, early onset) have been found to account for 85% of hereditary (inherited) breast cancer (5-10% of total breast cancer) (16-20). Among the sporadic breast cancers, 30-40% of cases have lower BRCA1/2 expression (20-24), frequently due to the loss of heterozygosity (LOH) and hypermethylation-mediated silencing of these two genes (25-27). Other studies have examined germ-line mutations of *BRCA1/2* in prostate cancer patients. It has been reported that the relative risk of prostate cancer in male *BRCA1* mutation carriers is 2–3 fold increased, with a lifetime risk up to 30% (28, 29), and male *BRCA2* mutation carriers have a 5–23-fold increase of prostate cancer ≤ 55 years age (30) and the lifetime risk is 19%–34% (31-33). The contribution of *BRCA2* germ-line mutations to prostate cancer risk is relatively clear, whereas the association of *BRCA1* mutations and prostate cancer has been controversial in various ethnic groups (28, 32, 34). *BRCA1* (Chr17q21.31) and *BRCA2* (Chr13q12.3) are tumor suppressor genes, mainly involved in the DNA repair process. Recently, BRCA1 and BRCA2 have been shown to act as prostate cancer suppressors, interacting with the AR, JAK, IGFR, Skp2, MMP-9 and PI3-kinase/AKT and MAPK/ERK signaling pathways. Mice with a conditional knock-out of the *Brca2* gene in prostate epithelia demonstrate focal hyperplasia and low-grade prostate intraepithelial neoplasia (PIN) (35). Loss of BRCA1 induces GADD153-mediated doxorubicin resistance in prostate cancer (36). Here we review the recent advances about the role of BRCA1 and BRCA2 in prostate cancer, discussing both clinical relevance and basic research. This information might be helpful for genetic counselors, medical professionals, and prostate cancer patients and their family, when discussing prostate cancer risks, treatment options and prognosis for men in these susceptible families.

3. *BRCA1* AND *BRCA2* SEQUENCE VARIANTS AND PROSTATE CANCER

We used the HUGO Genome Nomenclature Committee (HGNC) nomenclature for *BRCA1* (Genbank: U14680, RefSeq: NM_007294) and *BRCA2* (U43746, NM_000059) variants in this review, as recommended by the Human Genome Variation Society (HGVC) (Table 1). The Breast cancer Information Core (BIC) nomenclature, which represents the largest repository of cases were referenced in parallel (Table 2). The *BRCA1* gene has 24 exons encoding a protein of 1,863 amino acids, and the *BRCA2* gene has 27 exons encoding a protein of 3,418 amino acids. The name of *BRCA1/2* variants begins with c. (see below) in the HGNC nomenclature, which stands for a coding DNA sequence (transcript).

3.1. *BRCA1/2* founder variants in the Ashkenazi Jewish population

Three common founder allelic variants have been found in the Ashkenazi Jewish population, *BRCA1* gene c.66_67delAG (185delAG) and c.5263_5264insC (5382insC), and *BRCA2* gene c.5946delT (6174delT) (37-39). *BRCA1* c.66_67delAG was first found in Ashkenazi Jewish breast cancer patients, and the frequency distribution in the general Ashkenazi Jewish population is ~ 1% (40). This variant has also been found in the non-Ashkenazi Jewish, Spanish and United Kingdom (Yorkshire) populations (41, 42).

For prostate cancer, *BRCA2* c.5946delT was found to be significantly associated with an increased risk of prostate cancer in Ashkenazi Jews. In a large-scale case control study, 251 unselected Ashkenazi prostate cancer patients and 1472 male healthy controls were enrolled (43). The above three founder mutations of *BRCA1/2* genes were detected. Thirteen (5.2%) cases had a deleterious mutation in *BRCA1/2* compared with that of 28 (1.9%) in controls. After adjusting for age, the presence of a *BRCA1* or *BRCA2* mutation was significantly associated with the development of prostate cancer (odds ratio (OR): 3.41, 95% confidence interval (CI): 1.64–7.06). When results were stratified by gene, *BRCA2* mutation carriers demonstrated an increased risk of prostate cancer (OR: 4.78, 95% CI: 1.87–12.25), whereas the risk in *BRCA1* mutation carriers was not significantly increased (OR: 2.20, 95% CI: 0.72–6.70). In another Israeli study, 87 prostate cancer patients were compared with 87 healthy controls. The frequency distribution of Ashkenazi Jewish founder variant carriers was found to be the same in the two groups. However, prostate cancer patients carrying *BRCA1/2* mutations were found to have a much higher Gleason score (average above 8), than that for non-carrier prostate cancer patients (average 5.9) (44).

Thus, it was indicated that *BRCA2* mutations may contribute more to prostate cancer risk whereas *BRCA1/2* mutations may be related to the severity and the prognosis of the disease. This was confirmed by another Ashkenazi Jewish study. In a case-control study of 979 prostate cancer cases and 1,251 controls among men, the prostate cancer risk for *BRCA2* mutation carriers was elevated (OR=1.9, 95% CI: 0.9–4.1), but not for *BRCA1* mutation carriers compared to non-carriers. If stratified by Gleason score, *BRCA2* founder mutation confers a 3-fold elevated risk (OR = 3.2, 95% CI: 1. 4–7.3) of high-grade prostate cancer (Gleason score of 7 to 10). At the same time, the *BRCA1*- c.66_67delAG variant was observed to be associated with high Gleason score tumors (45).

However, no significant association of these Ashkenazi founder variants of *BRCA1/2* genes with the prostate cancer risks was observed in other studies (44, 46-49). Twenty-nine carriers of Ashkenazi Jewish founder *BRCA1/2* mutations who developed prostate cancer were compared with non-carrier prostate cancer patients. No difference was seen in Gleason pattern, incidence of PIN or atypical adenomatous hyperplasia (50). A meta-analysis on published research of six Ashkenazi-Jewish prostate cancer studies (3005 cases and 6834 controls) showed a non-statistically significant odds ratio 1.8 (95% CI: 0.91–3.57) for the c.66_67delAG variant (51). The inconsistent results observed in different studies may be due to the variations of sample size, mutation screening techniques, or patient selection criteria.

Table 1. Summary of *BRCA1/2* sequence variants and prostate cancer risk and prognosis in literatures[1]

Genes	Mutation	Ethnicity	No. of subjects[2]	Statistics[3]	Study Center[4]	References
BRCA1						
	c.66_67delAG c.5263_5264insC	Ashkenazi Jews	251 patients 1472 controls	(–)	Memorial Sloan-Kettering Cancer Center	(43)
	c.66_67delAG c.212+1G>T c.1952_1953insA c.2475delC	Not mentioned	913 patients	(+) RR ~ 3.75 (95% CI: 1.02–9.6)	United Kingdom GPCS	(3)
	c.181T>G c.4035delA	Polish	1793 patients 4570 controls	(+) OR =3.6 (95% CI: 1.1–11.3)	13 centers in Poland	(57)
	c.211A>G	Galician	905 patients 936 controls	(–)	Clinical University Hospital of Santiago de Compostela	(51)
	c.1067A>G[5]	African-American	128 patients 342 controls	(+) OR = 4.17 (95% CI: 1.27–13.72)	Flint Men's Health Study	(75, 77)
	c.1067A>G[5]	non-Hispanic White	817 men (323 families)	(+) OR = 2.25 (95% CI: 1.21–4.20)	Univ. of Michigan PCGP	(75)
BRCA2						
	c.5946delT	Ashkenazi Jews	251 patients 1472 controls	(+) OR = 4.78 (95%CI: 1.87–12.25)	Memorial Sloan-Kettering Cancer Center	(43)
	c.5946delT	Ashkenazi Jews	979 patients 1251 controls	(+) OR = 3.2 (95% CI: 1. 4–7.3)	Albert Einstein College of Medicine	(45)
	c.771_775del5[6]	Icelandic	527 patients	(+) HR = 2.35 (95% CI: 1.08–5.11)	Icelandic Cancer Registry	(55)
	18 variants	~81% Whites	1865 patients	(+) HR = 2.14 (95% CI: 1.28–3.56)	United Kingdom GPCS	(70)
	26 variants	Not mentioned	148 men (130 families)	(+) HR = 4.5 (95% CI: 2.12–9.52)	kConFab	(72)
	6 variants	96% Whites	263 patients	(+) RR ~23 (95% CI: 9–57)	CRC/BPG	(30)
	19 variants	Not mentioned	1832 patients	(+) RR ~8.6 (95% CI: 5.1–12.6)	United Kingdom GPCS	(64)
	61 variants	Not mentioned	266 men (194 families)	(–)	Seattle-based PCGRS	(118)
BRCA1 & BRCA2						
	7 *BRCA2* mutations 11 *BRCA1* mutations	Finnish	548 patients (BRCA2) 46 patients (BRCA1)	(–)	Finland Tampere University Hospital	(119)
	BRCA1 c.66_67delAG, c.5263_5264insC *BRCA2* c.5946delT	55% Ashkenazi Jews	174 patients	(–)	Israel Rabin, Sheba and Wolfson Medical Centers	(49)
	BRCA1 c.66_67delAG, c.5263_5264insC *BRCA2* c.5946delT	Ashkenazi Jews	146 patients	(–)	McGill University affiliated hospitals	(120)
	BRCA1 c.66_67delAG *BRCA2* c.5946delT	Ashkenazi Jews	60 patients	(–)	Mount Sinai School of Medicine	(46)
	BRCA1 c.66_67delAG *BRCA2* c.5946delT	Ashkenazi Jews	83 patients	(–)	NYU & Columbia Presbyterian medical centers	(47)
	BRCA1 c.66_67delAG *BRCA2* c.5946delT	Not mentioned	87 patients 87 controls	(–)	Sharett Institute, Hadassah Hebrew University Hospital	(44)

[1]: studies in which >50 individuals were enrolled, [2]: controls: healthy controls in a case-control study, [3]: (+): The association is statistically significant ($P < 0.05$), RR: relative risk; OR: odds ratio; HR: hazard ratio, 95% CI: 95% confidence interval, (–): The association is not statistically significant ($P \geq 0.05$), [4]: United Kingdom GPCS: United Kingdom Genetic Prostate Cancer Study; Univ. of Michigan PCGP: University of Michigan Prostate Cancer Genetics Project; kConFab: Kathleen Cuningham Consortium for Research; CRC/BPG: Cancer Research UK/British Prostate Group; Seattle-based PCGRS: Seattle-based Prostate Cancer Genetic Research Study; NYU: New York University, [5]: The same variant as Gln356Arg (protein level) in reference (75) (77), [6]: The same variant as 999del5 (Breast Cancer Information Core nomenclature) in reference (55)

Table 2. *BRCA1* and *BRCA2* sequence variants both in the BIC[1] nomenclature and in the HGNC[2] nomenclature

Gene	BIC[1, 3] name	HGNC[2, 3] name	Location	RefSNP[3]	References
BRCA1					
	185delAG	c.66_67delAG	Exon 2	rs77944974, rs80357713 [4]	(39)
	300T>G	c.181T>G	Exon 5	rs28897672	(56) [5]
	330A>G	c.211A>G	Exon 5	rs80357382	(58) [6]
	IVS5+1G>T	c.212+1G>T	Splice site	rs80358042	(3)
	1186A>G	c.1067A>G	Exon 11	rs1799950	(75) [7]
	2080insA	c.1952_1953insA	Exon 11	rs80357885	(3) [8]
	2594delC	c.2475delC	Exon 11	rs80357970	(3)
	4153delA	c.4035delA	Exon 11	rs80357711	(121)
	5382insC	c.5263_5264insC	Exon 20	rs76171189, rs80357906	(39)
BRCA2					
	999del5	c.771_775delTCAAA	Exon 9	rs80359675	(122)
	2558insA	c.2330_2331insA	Exon 11	rs80359328	(30)
	N/A	c.4691A>T	Exon 11	N/A	(69)
	5369delATTT	N/A	Exon 11	N/A	(68)
	5531delTT	N/A	Exon 11	N/A	(66)
	6051delA	N/A	Exon 11	N/A	(67)
	6174delT	c.5946delT	Exon 11	rs80359550	(42)
	6710del4	c.6486_6489delACAA	Exon 11	rs80359598	(30) [9]
	7084del5	N/A	Exon 12	N/A	(30)
	7772insA	N/A	Exon 15	N/A	(30) [10]
	IVS17-1g>c	c.7977-1g>c	Splice site	rs81002874	(30)
	8525delC	c.8297delC	Exon 18	rs80359705	(30)
	9078G>T	c.8850G>T	Exon 22	rs28897754	(66) [11]

[1]: BIC nomenclature: Breast cancer Information Core database, [2]: HGNC nomenclature: HUGO Genome Nomenclature Committee, [3]: N/A: no information available, [4]: The same variant with two refSNP I.D.s from two complement strands, respectively, [5]: The same variant named as C61G in the reference (56) and (57), [6]: The same variant named as R71G in the reference (58), [7]: The same variant named as Gln356Arg in the reference (75), [8]: The same variant named as c.1954dupA in the reference (3), [9]: The same variant named as 6714del4 in the reference (70), [10]: The same variant named as 7771insA in the reference (70), [11]: The same variant named as K2950N in the reference (66)

3.2. *BRCA2* founder variant in the Icelandic population

A five base-pair deletion, c.771_775delTCAAA (999del5) was detected in the Icelandic population and accounts for 40% of Icelandic male breast cancer patients (52). In some of these affected families, multiple prostate cancer cases were also found. To evaluate the prostate cancer risk, a case control study shows that 2.7% of Icelandic prostate cancer patients below 65 years of age carry the c.771_775del5 mutation, compared with 0.5% in the healthy controls (53). In breast cancer families carrying the c.771_775del5 variant, the relative risk of prostate cancer was 4.6 (95% CI: 1.9–8.8) in male first-degree relatives (54). This association was also confirmed by a large-scale family study from the Breast Cancer Linkage Consortium (BCLC) in Europe and North America. In this study of 173 breast or ovarian cancer families, 3047 individuals including 681 patients were enrolled. The relative risk for prostate cancer in male *BRCA2* variant carriers was 4.65 (95% CI: 3.48–6.22), and this risk increased to 7.33 (95% CI: 4.66–11.52) in patients below 65 years of age (32). These results suggest that *BRCA2* mutation screening in men may help detect prostate cancer at an earlier clinical stage.

Additionally, the *BRCA2* c.771_775del5 variant appears to be a marker for poor prognosis of prostate cancer in the Icelandic population (53), which was confirmed by a large-scale study (55). In this study, 527 Icelandic prostate cancer patients with a family history of unselected breast cancer probands were enrolled. *BRCA*2 c.771_775del5 founder mutation carriers were detected in 30 of 527 (5.7%) patients. The prostate cancer-specific survival was evaluated by multivariable regression model with the adjustment for cancer stage and grade. Compared with non-carriers, *BRCA2* c.771_775del5 carriers had a lower mean age at diagnosis (69.0 years versus 74.0 years), more advanced tumor stage (stages 3 or 4, 79.3% versus 38.6%), higher tumor grade (grades G3 – 4, 84.0% versus 52.7%), and shorter median survival time (2.1 years versus 12.4 years). In addition, there was an increased risk of dying from prostate cancer (adjusting for year of diagnosis and birth, hazard ratio (HR): 3.42, 95% CI: 2.12–5.51), and the association remained significant after adjustment for stage and grade (HR: 2.35, 95% CI: 1.08–5.11).

3.3. *BRCA1* founder variants in the Polish population

Poland has relative genetic homogeneity of its population. *BRCA1* gene c.181T>G (300T>G, C61G), c.4035delA (4153delA) and c.5263_5264insC (5382insC) are three common founder variants in the Polish population. The frequency distribution of these three founder alleles in Polish breast cancer and breast-ovarian cancer patients was 34% (c.181T>G), 15.5% (c.4035delA) and 6% (c.5263_5264insC) (56). The three allelic variants in total can account for 90% of all *BRCA1* variants in the Polish population (56, 57).

To evaluate the prostate cancer risk, one case control study genotyped 1793 cases of prostate cancer and 4570 healthy controls in Poland. These results suggested that the presence of either c.181T>G or c.4035delA mutations was associated with an increased risk for prostate

cancer (OR=3.6, 95% CI: 1.1–11.3) and the association was more significant for familial prostate cancer (OR=12, 95% CI: 2.9–51). The c.5263_5264insC variant is unlikely to contribute to prostate cancer risk in the Polish population (57). Therefore, *BRCA1* founder variants in the Polish population may be helpful to evaluate the prostate cancer risk of individuals in the affected families. These results may not be applied to other ethnic groups until specific studies in different populations are conducted.

3.4. *BRCA1* founder variant in the Galician population

In the Galician (Northwest Iberia) population, one splicing founder variant of c.211A>G (330A>G, R71G) is present in more than 50% of the breast and/or ovarian cancer families (58, 59). This variant localized at position - 2 of exon 5 donor splice site in the *BRCA1* gene, which changes the alternative transcript ratios, decreasing the full-length transcript (*BRCA1*-ex5FL) and increasing the transcript with a deletion of the last 22nt of exon 5 (*BRCA1*-Δ22ntex5) (60). For prostate cancer risk, no significant contribution of this variant was found in a large-scale case control study (51). In this study of 905 unselected prostate cancer patients and 936 healthy controls, four carriers of c.211A>G variants were found including one patient and three controls. No significant association of prostate cancer risk (OR = 0.27, 95% CI: 0.01–2.36) was observed with this variant. The low frequency distribution of variant carriers in patients (0.1%, 1 out of 905) and in controls (0.3%, 3 out of 936) might be one of the confounding factors. Thus a larger sample size may be needed to confirm the result.

3.5. *BRCA1/2* variants in ethnically mixed population

3.5.1. United Kingdom (U.K.) population

BRCA1 mutation carriers were found to have an increased risk of prostate cancer in men. In a large-scale study of 913 prostate cancer patients in U.K., four deleterious *BRCA1* germ-line mutations were detected, including c.66_67delAG (one of the founder variants in Ashkenazi Jews), c.212+1G>T (IVS5+1G>T), c.1952_1953insA (c.1954dupA, 2080insA) and c.2475delC (2594delC). The estimated frequency of *BRCA1* mutation carriers was 0.45% of the U.K. prostate cancer patients. These *BRCA1* germ-line mutations confer a relative risk of ~3.75 fold (95% CI: 1.02–9.6) for prostate cancer and an 8.6% cumulative risk by the age of 65 years (3). In addition, the c.1952_1953insA mutation (truncated protein at codon 672) has been reported as a Pakistani founder mutation in breast and ovarian cancer patients (61). The c.2475delC mutation (truncated protein at codon 845) appears to be a Scandinavian/Northern European founder mutation in breast and ovarian cancer patients (62, 63). Further studies evaluating prostate cancer patients in Pakistani or Scandinavian/Northern European population, may be needed to further confirm the contribution of these variants to prostate cancer risk.

BRCA2 gene variants also contribute to the prostate cancer risk in the U.K. population. In a study of 1832 prostate cancer patients in the United Kingdom, *BRCA2* gene variants were detected by a high-throughput multiplex fluorescence heteroduplex detection system. Nineteen protein-truncating mutations were detected. The prostate cancer risk of *BRCA2* variant carriers was ~ 8.6-fold (95% CI: 5.1–12.6) higher than non-carriers, corresponding to 15% of risk by age 65 (64). These results suggest that in this relatively ethnically mixed population, the high-throughput screening of *BRCA2* mutations may be needed to evaluate the contribution of this gene to prostate cancer risks.

BRCA1/2 mutations are associated with more aggressive prostate cancer. In a study of U.K. prostate cancer patients, the contribution of *BRCA1* and *BRCA2* mutation carriers to histopathology outcome was evaluated. In 20 prostate cancer patients carrying *BRCA1/2* mutations, 15 *BRCA2* mutations and 3 *BRCA1* mutations were observed. Gleason scores of prostate cancer in the *BRCA1/2* mutation carriers (8, 9 or 10) were significantly higher than those in the control group (P=0.012). It was indicated that the evaluation of *BRCA1/2* mutation status may be a helpful prognostic factor for prostate cancer in the U.K. population. (65).

3.5.2. Other populations

Three novel germ-line mutations in *BRCA2* were found in a study of 38 non-Ashkenazi prostate cancer families (66), including 6710delACAA (c.6486_6489delACAA), 5531delTT, and 9078G>T (c.8850G>T, K2950N). In one prostate and breast cancer non-Ashkenazi family, a *BRCA2* variant of 6051delA was also found (67). In a Spanish family of breast, ovarian and prostate cancers, a *BRCA2* germ-line variant of 5396delATTT was detected in a 45-year-old woman with bilateral breast cancer. This 4-nucleic acid deletion was also detected in her father with prostate cancer and her sister with breast cancer (68). In a study of the Turkish population, 50 prostate cancer patients and 50 healthy controls were enrolled. One truncating mutation in *BRCA2* c.4691A>T was detected in a high-risk prostate cancer patient diagnosed at 45 years of age (69).

BRCA2 germ-line mutations were found to contribute to the prostate cancer risk in a non-Ashkenazi (96% whites) study (30). In this study, 263 men with diagnoses of early-onset prostate cancer (<=55 years of age) were enrolled. After screening of the complete coding sequence of *BRCA2* for germ-line mutations, six protein-truncating mutations (2558insA, 6710del4, 7084del5, 7772insA, 8525delC, IVS17-1g>c) were found in six patients (2.3%), respectively. The relative risk of developing prostate cancer by age 56 years was 23-fold (95% CI: 9–57) higher for germ-line *BRCA2* mutation carriers compared with the non-carriers (30). The same research group further investigated loss of heterozygosity (LOH) at *BRCA2* in tumors of patients carrying *BRCA2* mutations. LOH was found in 5 of the 6 tumors (70).

BRCA2 mutations are associated with the prostate cancer survival rates. In a study of non-Ashkenazi (~81% whites) prostate cancer patients, the survival rates were assessed in 21 patients carrying *BRCA2* variants and 1844 non-carrier patients. Eighteen *BRCA2* variants were detected. It was shown that median survival of the prostate

cancer patients carrying *BRCA2* variations was 4.8 years, which is much shorter than that of 8.5 years in non-carrier controls (HR: 2.14, 95% CI: 1.28–3.56). Multivariate analysis confirmed that the poorer survival of prostate cancer in *BRCA2* mutation carriers is associated with germline *BRCA2* variants (70). This result was confirmed by another prostate cancer study from 33 centers in 5 countries, which indicated that *BRCA2* mutations are more likely to contribute to poor prostate cancer survival compared to *BRCA1* mutations. In this study, the survival was compared between 182 patients carrying *BRCA2* familial mutations and 119 patients carrying *BRCA1* familial mutations. The median survival from diagnosis was 4.0 years for *BRCA2* mutation carriers, compared with 8.0 years for *BRCA1* mutation carriers (71). In another study of 148 prostate cancer patients from 130 families in Australia and New Zealand, *BRCA2* mutation carriers have an increased risk of death and prostate cancer-related death (HR=4.5, 95% CI: 2.12–9.52), compared with non-carriers (72).

3.6. *BRCA1* c.1067A>G (Gln356Arg) variant

Several studies provide evidence that *BRCA1* c.1067A>G (Gln356Arg) partially accounts for prostate cancer susceptibility and contributes to prostate cancer linkage to chromosome 17q21. The results from two small-scale family studies of Caucasians have been inconsistent. One study found only 1 of 22 prostate cancer families with the Arg356 variant (73) and the other study found all 14 prostate cancer families having the Arg356 variant (74). In a large-scale study of 323 prostate cancer families, there is a significant association of this variant with prostate cancer susceptibility (75), and the prostate cancer linkage to the *BRCA1* region on chromosome 17q21 was confirmed (76). This result was also confirmed by studies in other populations. A case control study suggests that Arg356 allele carriers are more likely to develop prostate cancer than non-carriers in the African-American population (77). Furthermore, the Arg356 allele distribution varies in different ethnic groups. The frequency of this variant is higher in Caucasians (prostate cancer patients 8% and healthy controls 6%) than that in African-Americans (5.5% and 1.5%) (75).

3.7. IMPACT prospective study

A large prospective international multicenter prostate cancer screening research study is called IMPACT (Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in *BRCA1/2* mutation carriers and controls; http://www.impact-study.co.uk). The IMPACT study is the first prospective multicenter study of targeted prostate cancer screening in men with *BRCA1* and *BRCA2* mutations. A preliminary analysis of 300 individuals from the IMPACT study demonstrated that targeted prostate cancer screening in men with mutations in *BRCA1* and *BRCA2* is associated with more aggressive prostate cancer. Results showed that the positive predictive value of PSA screening in *BRCA1/2* mutation carriers is higher than that in non-carriers. Screening with *BRCA1/2* mutations can detect clinically significant prostate cancer (34). IMPACT plans to enroll 1700 subjects in the study, and the number is anticipated to complete enrollment by the end of 2012. All men enrolled will be screened for prostate cancer risk, progression and prognosis for at least 5 years. The IMPACT results will explore how *BRCA1/2* mutations may contribute to prostate cancer management in the future.

3.8. Summary

Here we summarize the association studies of the *BRCA1/2* sequence variants with prostate cancer in different ethnic groups. The absence of studies in other populations may limit the practical implications of these results to specific ethnic groups. Some studies summarized here are the familial prostate cancer studies or early-onset prostate cancer studies, which may not generalize to sporadic and/or late-onset prostate cancer cases. In addition, different mutation *loci* within the gene may produce differential effects on BRCA1 or BRCA2 function, thus the contribution of *BRCA1/2* genes to prostate cancer may be mutation-specific. The contribution of *BRCA1* mutations to prostate cancer is relatively weak, compared with much stronger evidence of the involvement of *BRCA2* mutations in prostate cancer risk and prognosis. The most supportive studies of the link between *BRCA1/2* mutations and prostate cancer come from populations with a high frequency of mutations, such as Ashkenazi Jews, Icelandic men, and the U.K. population. Prostate cancer is a polygenic disease, determined by multiple genes and the interaction between genetics and environment. It is important to integrate the information from the clinical manifestation, family history and genomic background for clinicians and patients to make a wise decision in medical counseling.

4. BRCA1 AND BRCA2 IN PROSTATE CANCER BIOLOGY

BRCA1 as a multifunctional tumor suppressor gene, likely plays multiple roles in different stages of prostate cancer pathophysiology. Overexpression of wild-type *BRCA1* in a prostate cancer cell line was found to decrease the cell proliferation rate and increase sensitivity to chemotherapy drugs (78). Furthermore, a naturally occurring *BRCA1* splice variant *BRCA1a* (deletion of the major exon 11, amino acids 263-1365) was shown to significantly inhibit tumor mass in triple-negative prostate cancer xenografts (79). In addition, more BRCA1 loss was found in lymph node metastasis (27%, 62 of 196) in prostate cancer patients than in primary prostate cancer tumors (14%, 18 of 133), which might be due to the role of BRCA1 in the epithelial mesenchymal transition (EMT) (80).

On the other hand, BRCA1 can interact with multiple (even opposing) cellular signaling pathways in various cellular and animal models of prostate cancer. It was reported that *BRCA1* was expressed at a high level in human prostate cancer compared to a very low level in normal prostate epithelium (81). BRCA1-positive prostate tumors have much higher tumor proliferation index (47.0) than that of BRCA1-negative tumors (10.3) through regulating cell cycles to allow for DNA repair (23). More patients carrying BRCA1-positive prostate tumors died of

prostate cancer (26.7%, 16 of 60), compared with BRCA1-negative prostate tumors patients (7.2%, 24 out of 332) (23). In transgenic tumor mouse models, *Brca1* was overexpressed in aggressive prostate, breast, and lung cancers, in conjunction with a network of genes related to Brca1 function (82).

Compared to *BRCA1*, less basic science studies have been conducted on the *BRCA2* gene. In one immuno-histochemistry study, BRCA2 protein was virtually absent in normal human prostate (19), whereas another study reported that nuclear BRCA2 protein is significantly reduced in premalignant PIN compared with normal prostate tissue. (83). The different techniques used to detect BRCA2 expression under different physiological/pathological conditions may contribute to the inconsistent results. Different antibodies used in immunostaining might also influence the results of a particular study. In the animal model, it was proved that Brca2 can act as a tumor suppressor in prostate cancer tumorigenesis and there is a synergistic effect between Brca2 and the tumor suppressor Trp53. *Brca2* conditional knock-outs in mouse prostate epithelia, develop focal hyperplasia and low-grade PIN over 12 months of age. Simultaneous deletion of *Brca2* and *Trp53* in prostate epithelia gave rise to focal hyperplasia and atypical cells at 6 months, leading to high-grade PIN in animals at 12 months of age (35). Below we summarize the BRCA1 and BRCA2 regulators in the prostate cancer biology.

4.1. BRCA1 co-regulators

4.1.1. Direct binding of BRCA1 with androgen receptor (AR)

Prostate cancer and breast cancer are two hormone-related tumors. Estrogen receptor (ER)-α is thought to play a major role in breast cancer tumorigenesis (84). BRCA1 suppresses estrogen-dependent transcriptional pathways in mammary epithelial cell proliferation, by binding with the estrogen-responsive enhancer element to block the transcriptional activation function (AF)-2 of ER-α (85). Similarly, the androgen receptor (AR) signaling pathway plays an important role in prostate cancer tumorigenesis (86). Transient transfection assays proved that BRCA1 physically interacts with the NH_2-terminal activation function (AF)-1 of AR (87) and enhances AR-dependent transcriptional pathways, resulting in the increase of androgen-induced cell death in prostate cancer cells (88).

AR can play both stimulatory and inhibitory roles in prostate cancer cell proliferation and apoptosis, depending on the cofactor environment, somatic mutations and post-translational modifications of AR (87). BRCA1 may serve as a signal 'directing' differential biological activities of AR towards the pathway of growth inhibition and apoptosis (89). Furthermore, the role of BRCA1 may be regarded as a potentiation of AR transactivation in prostate cancer cells. It was reported that BRCA1-enhanced AR transactivation can act synergistically with AR-associated co-regulators (ARAs), such as CBP, ARA55, and ARA70. AR transactivation can be increased from 5- to 90-fold by simultaneous addition of BRCA1 and ARAs (88).

4.1.2. Direct binding of BRCA1 with Janus kinase (JAK)

BRCA1 can interact with the JAK-STAT signaling cascade in prostate cancer cells. BRCA1 physically interacts with JAK1 and JAK2, as shown by immunoprecipitation, leading to constitutive activation of STAT3, which promotes cell proliferation and suppresses apoptosis. This constitutive activation of STAT3 by BRCA1 provides a survival signal for escaping the tumor suppressing activity of BRCA1 and benefiting the growth of prostate cancer (90).

4.1.3. Transcriptional complex of BRCA1/E2F-1/Rb and BRCA1/E2F-1/CtIP

BRCA1 can act as a transcriptional co-regulator and repress its own transcription through E2F-1/Rb protein interaction in an autoregulatory loop (91). Tandem chromatin immunoprecipitation studies show that BRCA1 assembles with the E2F1/Rb complex to form a dynamic repressive complex at the *BRCA1* promoter and inhibits *BRCA1* transcription. This multicomponent transcriptional complex can be disrupted by DNA-damaging agents, resulting in the displacement of BRCA1 from the *BRCA1* promoter and the activation of *BRCA1* transcription. This autoregulatory mechanism can maintain BRCA1 homeostasis by selectively adjusting its level to protect genome integrity in response to genotoxic stress.

BRCA1 can also regulate the transcription of the *ATM* (ataxia telangiectasia mutated) gene in prostate cancer cell lines, through binding with E2F-1/CtIP proteins (92). ATM belongs to the PI3-kinase family and is a component of the DNA damage repair system (93). The multicomponent transcriptional complex of BRCA1/E2F1/CtIP proteins can be recruited to the E2F1 binding site on the *ATM* promoter and activate *ATM* transcription. After topoisomerase II poison doxorubicin exposure, BRCA1/CtIP are released from the complex and *ATM* transcription is repressed (92).

4.1.4. BRCA1 regulates insulin-like growth factor 1 receptor (IGF-IR)

The insulin-like growth factor (IGF) system plays an important role in prostate cancer tumorigenesis. Clinical data suggests that men with higher serum levels of IGF-I and certain androgens are more likely to develop prostate cancer in the subsequent 6-9 years following assessment (94-97). The insulin-like growth factor-I receptor (IGF-IR), mediating the effects of IGF-I and IGF-II on cell proliferation and differentiation, contributes to prostate cancer initiation and progression (95). In addition, IGF-IR can interact with AR during prostate cancer tumorigenesis (95) and the alteration of the IGF signaling pathway may confer androgen independence in a human prostate cancer xenograft study (98).

BRCA1 can regulate IGF-IR activity during prostate cancer tumorgenesis, depending on AR status. Coexpression experiments in prostate cancer cells revealed that BRCA1 can differentially regulate *IGF-IR* gene in an AR-dependent manner (81). In AR-negative prostate cancer cell lines, BRCA1 suppressed *IGF-IR* promoter

activity (~50% reduction) and endogenous IGF-IR levels. In prostate cell lines expressing endogenous AR, BRCA1 enhanced the IGF-IR levels. The reduction of *IGF-IR* promoter activity by BRCA1 may be through physical interaction between BRCA1 and transcription factor Sp1, interfering the binding of Sp1 and cis-elements in the *IGF-IR* promoter (99). On the other hand, the effect of BRCA1 on enhancing *IGF-IR* gene expression in prostate epithelial cells that express an active AR, is mediated through increasing AR transcription and subsequent AR-mediated IGF-IR expression (81). That may be one of the reasons that BRCA1 reduction was observed more frequently in AR-negative prostate cancer.

On the other hand, it was shown that IGF-II, whose levels are largely increased in prostate carcinoma, is a potent stimulator of BRCA1 expression (94) (99). An integrated network and cross-talk of hormone signaling pathway (such as AR and IGF) and regulators (such as BRCA1) should be considered as a whole to appreciate its complex role in prostate cancer biology.

4.2. BRCA2 co-regulators

4.2.1. Prostate neoplastic transformation

The E3 ubiquitin ligase S-phase kinase-associated protein (Skp) 2, an oncogenic protein, is highly expressed in PIN and prostate cancer (100-102). Skp2 was found to be an important regulator determining the abundance of BRCA2 in prostate cells, regulating BRCA2 protein levels through ubiquitin-mediated proteolysis (83, 103, 104). In the prostate cancer cells, Skp2 regulation of BRCA2 expression behaves differently in the nucleus and the cytoplasm. In the studies of sporadic prostate cancer specimens, nuclear BRCA2 expression was significantly reduced, whereas cytoplasmic BRCA2 level was retained, although Skp2 expressed both in the nucleus and cytoplasm (83, 105). Furthermore, the decrease of nuclear BRCA2 expression is more consistent in premalignant lesions than that in high-grade PIN, indicating that loss of BRCA2 by Skp2 more likely contributes to an early stage of prostate neoplastic transformation. Functional studies revealed that elevated Skp2 protein can down-regulate BRCA2 protein levels, resulting in increased migratory and proliferative capabilities in preneoplastic prostate cells. Thus, it was indicated that the BRCA2-Skp2 oncogenic pathway may serve as a target for the prevention of prostate cancer (83).

4.2.2. Prostate cancer progression

The abnormal interaction of cancer cells with extracellular matrix (ECM) and basement membrane (BM) proteins plays an important role during the cancer metastatic cascade, from carcinoma *in situ* to invasive carcinoma and metastasis (106-109). It was reported that the adhesion of prostate cancer cells to the ECM protein collagen type I (COL1) can activate the COL1-β1 integrin signaling pathway, followed by activation of phosphatidylinositol (PI)3-kinase/AKT, and upregulation of the Skp2 expression. Skp2 directly led to the degradation of BRCA2 and sustained BRCA2 depletion. Loss of BRCA2 can switch on cell proliferation and produce an abnormal proliferative response (103, 110). Unlike cancer cells, in which adhesive stimuli activated PI3-kinase/AKT signaling resulting in BRCA2 degradation and cancer cell proliferation and metastasis (103), in normal prostate cells, adhesive stimuli triggered the MAPK/ERK signaling pathway, resulting in upregulation of *BRCA2* mRNA and protein.

Both PI3-kinase/AKT signaling and MAPK/ERK signaling pathways are important to maintain BRCA2 homeostasis in prostate cells and altered BRCA2 levels may determine prostate cell fates. Defective MAPK/ERK signaling was found in prostate cancer cells and was associated with unresponsiveness to ECM adhesion, whereas PI3-kinase/AKT signaling was triggered by adhesion stimuli leading to BRCA2 protein depletion and cell proliferation (111). Reconstitution of MAPK/ERK effectively increased BRCA2 expression upon interaction with ECM proteins and reversed the neoplastic proliferation. Thus, restoring MAPK/ERK activity in prostate cells may be a candidate target for preventive interventions in prostate cancer tumorigenesis (111). Furthermore, the inhibition of PI3-kinase/AKT and activation of the MAPK/ERK pathway leads to BRCA2 depletion, reduces BRCA2-mediated matrix metalloproteinase (MMP)-9 proteolysis and up-regulates MMP-9 protein levels, contributing to cancer cell migration and invasion (112). Moreover, it was also shown that BRCA2 itself may inhibit the PI3-kinase/AKT signaling pathway and act as a regulatory element in an autocrine loop with PI3-kinase/AKT, which influences cancer cell proliferation and stromal invasion (112).

4.3. Chemical regulators of BRCA1/2 expression

DNA-damaging agents such as adriamycin and camptothecin inhibit *BRCA1/2* mRNA and protein expression in prostate cancer cell lines, which may serve as a cytoprotective effect in prostate cancer cells (113). 1α, 25-dihydroxy (OH)2 vitamin D3 , a ligand for the vitamin D3 receptor (VDR) can induce *BRCA1* mRNA/protein expression and its transcriptional activation in prostate cancer and breast cancer cell lines, and partly contributes to the anti-proliferative effects of 1α, 25(OH)2 D3 in prostate cancer and breast cancer tumorgenesis (114).

Phytochemicals indole-3-carbinol (I3C) and genistein are natural chemicals derived from cruciferous vegetables and soy, respectively, with potential cancer prevention activity for hormone-responsive breast and prostate cancers. Both I3C and genistein induce the expression of BRCA1/2 in prostate cancer and breast cancer cells in a time- and dose- dependent manner, through endoplasmic reticulum stress response signaling. BRCA1/2 may contribute to cancer prevention effects by I3C and genistein in breast and prostate cancer cells, partly due to modulating ER and/or AR activity (115).

4.4. Summary

BRCA1 and *BRCA2* are multifunctional tumor suppressor genes, which can act pleiotropically in different stages of prostate cancer pathophysiology. The difficulties of detecting BRCA1/2 expression under various physiological/pathological conditions may limit the use of BRCA1/2 as a diagnostic or prognostic tool in the clinical

practice. Multiple (even opposing) cellular signaling pathways are involved in BRCA1/2 related prostate cancer tumorigenesis, invasion and metastasis. BRCA2 homeostasis, maintained by the PI3-kinase/AKT and MAPK/ERK signaling pathways, was found to be critical in determining cell fate during prostate cancer progression. Further understanding of the molecular pathways in prostate cancer may identify molecular markers that enhance cancer risk and prognostic evaluation of the disease, beyond prostate-specific antigen (PSA), Gleason score, and clinical stage. It also may help identify potential targets for new preventive or therapeutic interventions modifying the natural history of prostate cancer.

5. PERSPECTIVE

Prostate cancer is the most common non-cutaneous malignancy in men in developed countries. The majority of large-scale disease association studies indicate that *BRCA1* and/or *BRCA2* mutations contribute to clinical and/or pathological features of prostate cancer, such as an earlier diagnostic age, poorly-differentiated tumors and a relatively poor prognosis (44, 54, 67). It will be important to replicate these studies in specific populations and evaluate clinical significance and economic benefit at the same time. Currently, clinicians and researchers recommend that males carrying *BRCA1/2* mutations are screened for prostate cancer at an earlier age than the general population (32, 116). On the other hand, translation of BRCA1/2 basic knowledge from the bench to the bedside is equally important to identify novel molecular targets for the prevention, diagnosis and therapy of prostate cancer.

Prostate cancer is a polygenic disease that can be influenced by various gene-gene interactions. A risk prediction model based on family history and multiple genetic variants has been applied to prostate cancer and has potential clinical utility (117). The accuracy of the predictions in different independent populations and their potential role in prostate cancer screening needs to be further evaluated especially in prospective studies (117).

6. ACKNOWLEGEMENTS

We would like to thank Dr. Jeremy Chien for his valuable suggestions regarding the preparation of the sequence variants data in Table 2. The authors would also like to acknowledge support from the University of Kansas Cancer Center.

7. REFERENCES

1. A. Jemal, F. Bray, M. M. Center, J. Ferlay, E. Ward and D. Forman: Global cancer statistics. *CA Cancer J Clin*, 61(2), 69-90 (2011)

2. R. Siegel, D. Naishadham and A. Jemal: Cancer statistics, 2012. *CA Cancer J Clin*, 62(1), 10-29 (2012)

3. D. Leongamornlert, N. Mahmud, M. Tymrakiewicz, E. Saunders, T. Dadaev, E. Castro, C. Goh, K. Govindasami, M. Guy, L. O'Brien, E. Sawyer, A. Hall, R. Wilkinson, D. Easton, D. Goldgar, R. Eeles and Z. Kote-Jarai: Germline BRCA1 mutations increase prostate cancer risk. *Br J Cancer*, 106(10), 1697-701 (2012)

4. M. P. Zeegers, A. Jellema and H. Ostrer: Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis. *Cancer*, 97(8), 1894-903 (2003)

5. C. H. Bock, A. G. Schwartz, J. J. Ruterbusch, A. M. Levin, C. Neslund-Dudas, S. J. Land, A. S. Wenzlaff, D. Reich, P. McKeigue, W. Chen, E. I. Heath, I. J. Powell, R. A. Kittles and B. A. Rybicki: Results from a prostate cancer admixture mapping study in African-American men. *Hum Genet*, 126(5), 637-42 (2009)

6. D. C. Miller, S. L. Zheng, R. L. Dunn, A. V. Sarma, J. E. Montie, E. M. Lange, D. A. Meyers, J. Xu and K. A. Cooney: Germ-line mutations of the macrophage scavenger receptor 1 gene: association with prostate cancer risk in African-American men. *Cancer Res*, 63(13), 3486-9 (2003)

7. C. L. Goh, F. R. Schumacher, D. Easton, K. Muir, B. Henderson, Z. Kote-Jarai and R. A. Eeles: Genetic variants associated with predisposition to prostate cancer and potential clinical implications. *J Intern Med*, 271(4), 353-65 (2012)

8. S. M. Edwards and R. A. Eeles: Unravelling the genetics of prostate cancer. *Am J Med Genet C Semin Med Genet*, 129C(1), 65-73 (2004)

9. D. J. Schaid: The complex genetic epidemiology of prostate cancer. *Hum Mol Genet*, 13 Spec No 1, R103-21 (2004)

10. R. A. Eeles, Z. Kote-Jarai, G. G. Giles, A. A. Olama, M. Guy, S. K. Jugurnauth, S. Mulholland, D. A. Leongamornlert, S. M. Edwards, J. Morrison, H. I. Field, M. C. Southey, G. Severi, J. L. Donovan, F. C. Hamdy, D. P. Dearnaley, K. R. Muir, C. Smith, M. Bagnato, A. T. Ardern-Jones, A. L. Hall, L. T. O'Brien, B. N. Gehr-Swain, R. A. Wilkinson, A. Cox, S. Lewis, P. M. Brown, S. G. Jhavar, M. Tymrakiewicz, A. Lophatananon, S. L. Bryant, A. Horwich, R. A. Huddart, V. S. Khoo, C. C. Parker, C. J. Woodhouse, A. Thompson, T. Christmas, C. Ogden, C. Fisher, C. Jamieson, C. S. Cooper, D. R. English, J. L. Hopper, D. E. Neal and D. F. Easton: Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet*, 40(3), 316-21 (2008)

11. E. U. Thiessen: Concerning a familial association between breast cancer and both prostatic and uterine malignancies. *Cancer*, 34(4), 1102-7 (1974)

12. H. Tulinius, V. Egilsson, G. H. Olafsdottir and H. Sigvaldason: Risk of prostate, ovarian, and endometrial cancer among relatives of women with breast cancer. *BMJ*, 305(6858), 855-7 (1992)

13. D. E. Anderson and M. D. Badzioch: Familial breast cancer risks. Effects of prostate and other cancers. *Cancer*, 72(1), 114-9 (1993)

14. T. A. Sellers, J. D. Potter, S. S. Rich, C. R. Drinkard, R. M. Bostick, L. H. Kushi, W. Zheng and A. R. Folsom: Familial clustering of breast and prostate cancers and risk of postmenopausal breast cancer. *J Natl Cancer Inst*, 86(24), 1860-5 (1994)

15. A. Arason, R. B. Barkardottir and V. Egilsson: Linkage analysis of chromosome 17q markers and breast-ovarian cancer in Icelandic families, and possible relationship to prostatic cancer. *Am J Hum Genet*, 52(4), 711-7 (1993)

16. Y. Miki, J. Swensen, D. Shattuck-Eidens, P. A. Futreal, K. Harshman, S. Tavtigian, Q. Liu, C. Cochran, L. M. Bennett, W. Ding and *et al.*: A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science*, 266(5182), 66-71 (1994)

17. D. F. Easton, D. T. Bishop, D. Ford and G. P. Crockford: Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*, 52(4), 678-701 (1993)

18. J. M. Hall, M. K. Lee, B. Newman, J. E. Morrow, L. A. Anderson, B. Huey and M. C. King: Linkage of early-onset familial breast cancer to chromosome 17q21. *Science*, 250(4988), 1684-9 (1990)

19. S. M. Edwards, W. D. Dunsmuir, C. E. Gillett, S. R. Lakhani, C. Corbishley, M. Young, R. S. Kirby, D. P. Dearnaley, A. Dowe, A. Ardern-Jones, J. Kelly, N. Spurr, D. M. Barnes and R. A. Eeles: Immunohistochemical expression of BRCA2 protein and allelic loss at the BRCA2 locus in prostate cancer. CRC/BPG UK Familial Prostate Cancer Study Collaborators. *Int J Cancer*, 78(1), 1-7 (1998)

20. R. Wooster, S. L. Neuhausen, J. Mangion, Y. Quirk, D. Ford, N. Collins, K. Nguyen, S. Seal, T. Tran, D. Averill and *et al.*: Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science*, 265(5181), 2088-90 (1994)

21. C. R. Mueller and C. D. Roskelley: Regulation of BRCA1 expression and its relationship to sporadic breast cancer. *Breast Cancer Res*, 5(1), 45-52 (2003)

22. K. Cheeseman, E. Rouleau, A. Vannier, A. Thomas, A. Briaux, C. Lefol, P. Walrafen, A. Bensimon, R. Lidereau, E. Conseiller and M. Ceppi: A diagnostic genetic test for the physical mapping of germline rearrangements in the susceptibility breast cancer genes BRCA1 and BRCA2. *Hum Mutat*, 33(6), 998-1009 (2012)

23. M. Fiorentino, G. Judson, K. Penney, R. Flavin, J. Stark, C. Fiore, K. Fall, N. Martin, J. Ma, J. Sinnott, E. Giovannucci, M. Stampfer, H. D. Sesso, P. W. Kantoff, S. Finn, M. Loda and L. Mucci: Immunohistochemical expression of BRCA1 and lethal prostate cancer. *Cancer Res*, 70(8), 3136-9 (2010)

24. H. Ozcelik, M. D. To, J. Couture, S. B. Bull and I. L. Andrulis: Preferential allelic expression can lead to reduced expression of BRCA1 in sporadic breast cancers. *Int J Cancer*, 77(1), 1-6 (1998)

25. M. W. Beckmann, F. Picard, H. X. An, C. R. van Roeyen, S. I. Dominik, D. S. Mosny, H. G. Schnurch, H. G. Bender and D. Niederacher: Clinical impact of detection of loss of heterozygosity of BRCA1 and BRCA2 markers in sporadic breast cancer. *Br J Cancer*, 73(10), 1220-6 (1996)

26. F. Magdinier, S. Ribieras, G. M. Lenoir, L. Frappart and R. Dante: Down-regulation of BRCA1 in human sporadic breast cancer; analysis of DNA methylation patterns of the putative promoter region. *Oncogene*, 17(24), 3169-76 (1998)

27. A. Catteau, W. H. Harris, C. F. Xu and E. Solomon: Methylation of the BRCA1 promoter region in sporadic breast and ovarian cancer: correlation with disease characteristics. *Oncogene*, 18(11), 1957-65 (1999) 28. D. Thompson and D. F. Easton: Cancer Incidence in BRCA1 mutation carriers. *J Natl Cancer Inst*, 94(18), 1358-65 (2002)

29. D. Ford, D. F. Easton, D. T. Bishop, S. A. Narod and D. E. Goldgar: Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. *Lancet*, 343(8899), 692-5 (1994)

30. S. M. Edwards, Z. Kote-Jarai, J. Meitz, R. Hamoudi, Q. Hope, P. Osin, R. Jackson, C. Southgate, R. Singh, A. Falconer, D. P. Dearnaley, A. Ardern-Jones, A. Murkin, A. Dowe, J. Kelly, S. Williams, R. Oram, M. Stevens, D. M. Teare, B. A. Ponder, S. A. Gayther, D. F. Easton and R. A. Eeles: Two percent of men with early-onset prostate cancer harbor germline mutations in the BRCA2 gene. *Am J Hum Genet*, 72(1), 1-12 (2003)

31. D. Thompson and D. Easton: Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. *Am J Hum Genet*, 68(2), 410-9 (2001)

32. Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. *J Natl Cancer Inst*, 91(15), 1310-6 (1999)

33. D. F. Easton, L. Steele, P. Fields, W. Ormiston, D. Averill, P. A. Daly, R. McManus, S. L. Neuhausen, D. Ford, R. Wooster, L. A. Cannon-Albright, M. R. Stratton and D. E. Goldgar: Cancer risks in two large breast cancer families linked to BRCA2 on chromosome 13q12-13. *Am J Hum Genet*, 61(1), 120-8 (1997)

34. A. V. Mitra, E. K. Bancroft, Y. Barbachano, E. C. Page, C. S. Foster, C. Jameson, G. Mitchell, G. J. Lindeman, A. Stapleton, G. Suthers, D. G. Evans, D. Cruger, I. Blanco, C. Mercer, J. Kirk, L. Maehle, S. Hodgson, L. Walker, L. Izatt, F. Douglas, K. Tucker, H. Dorkins, V. Clowes, A.

Male, A. Donaldson, C. Brewer, R. Doherty, B. Bulman, P. J. Osther, M. Salinas, D. Eccles, K. Axcrona, I. Jobson, B. Newcombe, C. Cybulski, W. S. Rubinstein, S. Buys, S. Townshend, E. Friedman, S. Domchek, Y. C. T. Ramon, A. Spigelman, S. H. Teo, N. Nicolai, N. Aaronson, A. Ardern-Jones, C. Bangma, D. Dearnaley, J. Eyfjord, A. Falconer, H. Gronberg, F. Hamdy, O. Johannsson, V. Khoo, Z. Kote-Jarai, H. Lilja, J. Lubinski, J. Melia, C. Moynihan, S. Peock, G. Rennert, F. Schroder, P. Sibley, M. Suri, P. Wilson, Y. J. Bignon, S. Strom, M. Tischkowitz, A. Liljegren, D. Ilencikova, A. Abele, K. Kyriacou, C. van Asperen, L. Kiemeney, D. F. Easton and R. A. Eeles: Targeted prostate cancer screening in men with mutations in BRCA1 and BRCA2 detects aggressive prostate cancer: preliminary analysis of the results of the IMPACT study. *BJU Int*, 107(1), 28-39 (2011)

35. J. C. Francis, A. McCarthy, M. K. Thomsen, A. Ashworth and A. Swain: Brca2 and Trp53 deficiency cooperate in the progression of mouse prostate tumourigenesis. *PLoS Genet*, 6(6), e1000995 (2010)

36. P. De Luca, E. S. Vazquez, C. P. Moiola, F. Zalazar, J. Cotignola, G. Gueron, K. Gardner and A. De Siervi: BRCA1 loss induces GADD153-mediated doxorubicin resistance in prostate cancer. *Mol Cancer Res*, 9(8), 1078-90 (2011)

37. P. Tonin, O. Serova, G. Lenoir, H. Lynch, F. Durocher, J. Simard, K. Morgan and S. Narod: BRCA1 mutations in Ashkenazi Jewish women. *Am J Hum Genet*, 57(1), 189 (1995)

38. S. A. Narod and W. D. Foulkes: BRCA1 and BRCA2: 1994 and beyond. *Nat Rev Cancer*, 4(9), 665-76 (2004)

39. J. Simard, P. Tonin, F. Durocher, K. Morgan, J. Rommens, S. Gingras, C. Samson, J. F. Leblanc, C. Belanger, F. Dion and *et al.*: Common origins of BRCA1 mutations in Canadian breast and ovarian cancer families. *Nat Genet*, 8(4), 392-8 (1994)

40. S. L. Neuhausen, M. H. Skolnick and L. Cannon-Albright: Familial prostate cancer studies in Utah. *Br J Urol*, 79 Suppl 1, 15-20 (1997)

41. S. L. Neuhausen, S. Mazoyer, L. Friedman, M. Stratton, K. Offit, A. Caligo, G. Tomlinson, L. Cannon-Albright, T. Bishop, D. Kelsell, E. Solomon, B. Weber, F. Couch, J. Struewing, P. Tonin, F. Durocher, S. Narod, M. H. Skolnick, G. Lenoir, O. Serova, B. Ponder, D. Stoppa-Lyonnet, D. Easton, M. C. King and D. E. Goldgar: Haplotype and phenotype analysis of six recurrent BRCA1 mutations in 61 families: results of an international study. *Am J Hum Genet*, 58(2), 271-80 (1996)

42. J. D. Fackenthal and O. I. Olopade: Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. *Nat Rev Cancer*, 7(12), 937-48 (2007)

43. T. Kirchhoff, N. D. Kauff, N. Mitra, K. Nafa, H. Huang, C. Palmer, T. Gulati, E. Wadsworth, S. Donat, M. E. Robson, N. A. Ellis and K. Offit: BRCA mutations and risk of prostate cancer in Ashkenazi Jews. *Clin Cancer Res*, 10(9), 2918-21 (2004)

44. A. Hubert, T. Peretz, O. Manor, L. Kaduri, N. Wienberg, I. Lerer, M. Sagi and D. Abeliovich: The Jewish Ashkenazi founder mutations in the BRCA1/BRCA2 genes are not found at an increased frequency in Ashkenazi patients with prostate cancer. *Am J Hum Genet*, 65(3), 921-4 (1999)

45. I. Agalliu, R. Gern, S. Leanza and R. D. Burk: Associations of high-grade prostate cancer with BRCA1 and BRCA2 founder mutations. *Clin Cancer Res*, 15(3), 1112-20 (2009)

46. S. Lehrer, F. Fodor, R. G. Stock, N. N. Stone, C. Eng, H. K. Song and M. McGovern: Absence of 185delAG mutation of the BRCA1 gene and 6174delT mutation of the BRCA2 gene in Ashkenazi Jewish men with prostate cancer. *Br J Cancer*, 78(6), 771-3 (1998)

47. K. L. Nastiuk, M. Mansukhani, M. B. Terry, P. Kularatne, M. A. Rubin, J. Melamed, M. D. Gammon, M. Ittmann and J. J. Krolewski: Common mutations in BRCA1 and BRCA2 do not contribute to early prostate cancer in Jewish men. *Prostate*, 40(3), 172-7 (1999)

48. E. P. Wilkens, D. Freije, J. Xu, D. R. Nusskern, H. Suzuki, S. D. Isaacs, K. Wiley, P. Bujnovsky, D. A. Meyers, P. C. Walsh and W. B. Isaacs: No evidence for a role of BRCA1 or BRCA2 mutations in Ashkenazi Jewish families with hereditary prostate cancer. *Prostate*, 39(4), 280-4 (1999)

49. A. Vazina, J. Baniel, Y. Yaacobi, A. Shtriker, D. Engelstein, I. Leibovitz, M. Zehavi, A. A. Sidi, Y. Ramon, T. Tischler, P. M. Livne and E. Friedman: The rate of the founder Jewish mutations in BRCA1 and BRCA2 in prostate cancer patients in Israel. *Br J Cancer*, 83(4), 463-6 (2000)

50. R. M. Giusti, J. L. Rutter, P. H. Duray, L. S. Freedman, M. Konichezky, J. Fisher-Fischbein, M. H. Greene, B. Maslansky, A. Fischbein, S. B. Gruber, G. Rennert, R. D. Ronchetti, S. M. Hewitt, J. P. Struewing and J. Iscovich: A twofold increase in BRCA mutation related prostate cancer among Ashkenazi Israelis is not associated with distinctive histopathology. *J Med Genet*, 40(10), 787-92 (2003)

51. L. Fachal, A. Gomez-Caamano, C. Celeiro-Munoz, P. Peleteiro, A. Blanco, A. Carballo, J. Forteza, A. Carracedo and A. Vega: BRCA1 mutations do not increase prostate cancer risk: results from a meta-analysis including new data. *Prostate*, 71(16), 1768-79 (2011)

52. S. Thorlacius, G. Olafsdottir, L. Tryggvadottir, S. Neuhausen, J. G. Jonasson, S. V. Tavtigian, H. Tulinius, H. M. Ogmundsdottir and J. E. Eyfjord: A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes. *Nat Genet*, 13(1), 117-9 (1996)

53. G. Johannesdottir, J. Gudmundsson, J. T. Bergthorsson, A. Arason, B. A. Agnarsson, G. Eiriksdottir, O. T. Johannsson, A. Borg, S. Ingvarsson, D. F. Easton, V. Egilsson and R. B. Barkardottir: High prevalence of the 999del5 mutation in icelandic breast and ovarian cancer patients. *Cancer Res*, 56(16), 3663-5 (1996)

54. S. Sigurdsson, S. Thorlacius, J. Tomasson, L. Tryggvadottir, K. Benediktsdottir, J. E. Eyfjord and E. Jonsson: BRCA2 mutation in Icelandic prostate cancer patients. *J Mol Med (Berl)*, 75(10), 758-61 (1997)

55. L. Tryggvadottir, L. Vidarsdottir, T. Thorgeirsson, J. G. Jonasson, E. J. Olafsdottir, G. H. Olafsdottir, T. Rafnar, S. Thorlacius, E. Jonsson, J. E. Eyfjord and H. Tulinius: Prostate cancer progression and survival in BRCA2 mutation carriers. *J Natl Cancer Inst*, 99(12), 929-35 (2007)

56. B. Gorski, A. Jakubowska, T. Huzarski, T. Byrski, J. Gronwald, E. Grzybowska, A. Mackiewicz, M. Stawicka, M. Bebenek, D. Sorokin, L. Fiszer-Maliszewska, O. Haus, H. Janiszewska, S. Niepsuj, S. Gozdz, L. Zaremba, M. Posmyk, M. Pluzanska, E. Kilar, D. Czudowska, B. Wasko, R. Miturski, J. R. Kowalczyk, K. Urbanski, M. Szwiec, J. Koc, B. Debniak, A. Rozmiarek, T. Debniak, C. Cybulski, E. Kowalska, A. Toloczko-Grabarek, S. Zajaczek, J. Menkiszak, K. Medrek, B. Masojc, M. Mierzejewski, S. A. Narod and J. Lubinski: A high proportion of founder BRCA1 mutations in Polish breast cancer families. *Int J Cancer*, 110(5), 683-6 (2004)

57. C. Cybulski, B. Gorski, J. Gronwald, T. Huzarski, T. Byrski, T. Debniak, A. Jakubowska, D. Wokolorczyk, B. Gliniewicz, A. Sikorski, M. Stawicka, D. Godlewski, Z. Kwias, A. Antczak, K. Krajka, W. Lauer, M. Sosnowski, P. Sikorska-Radek, K. Bar, R. Klijer, Z. Romuald, B. Malkiewicz, A. Borkowski, T. Borkowski, M. Szwiec, M. Posmyk, S. A. Narod and J. Lubinski: BRCA1 mutations and prostate cancer in Poland. *Eur J Cancer Prev*, 17(1), 62-6 (2008)

58. A. Vega, B. Campos, B. Bressac-De-Paillerets, P. M. Bond, N. Janin, F. S. Douglas, M. Domenech, M. Baena, C. Pericay, C. Alonso, A. Carracedo, M. Baiget and O. Diez: The R71G BRCA1 is a founder Spanish mutation and leads to aberrant splicing of the transcript. *Hum Mutat*, 17(6), 520-1 (2001)

59. A. Vega, M. Torres, J. I. Martinez, C. Ruiz-Ponte, F. Barros and A. Carracedo: Analysis of BRCA1 and BRCA2 in breast and breast/ovarian cancer families shows population substructure in the Iberian peninsula. *Ann Hum Genet*, 66(Pt 1), 29-36 (2002)

60. C. Santos, A. Peixoto, P. Rocha, A. Vega, M. J. Soares, N. Cerveira, S. Bizarro, M. Pinheiro, D. Pereira, H. Rodrigues, F. Castro, R. Henrique and M. R. Teixeira: Haplotype and quantitative transcript analyses of Portuguese breast/ovarian cancer families with the BRCA1 R71G founder mutation of Galician origin. *Fam Cancer*, 8(3), 203-8 (2009)

61. A. Liede, I. A. Malik, Z. Aziz, L. Rios Pd Pde, E. Kwan and S. A. Narod: Contribution of BRCA1 and BRCA2 mutations to breast and ovarian cancer in Pakistan. *Am J Hum Genet*, 71(3), 595-606 (2002)

62. O. Johannsson, E. A. Ostermeyer, S. Hakansson, L. S. Friedman, U. Johansson, G. Sellberg, K. Brondum-Nielsen, V. Sele, H. Olsson, M. C. King and A. Borg: Founding BRCA1 mutations in hereditary breast and ovarian cancer in southern Sweden. *Am J Hum Genet*, 58(3), 441-50 (1996)

63. M. Thomassen, T. V. Hansen, A. Borg, H. T. Lianee, F. Wikman, I. S. Pedersen, M. L. Bisgaard, F. C. Nielsen, T. A. Kruse and A. M. Gerdes: BRCA1 and BRCA2 mutations in Danish families with hereditary breast and/or ovarian cancer. *Acta Oncol*, 47(4), 772-7 (2008)

64. Z. Kote-Jarai, D. Leongamornlert, E. Saunders, M. Tymrakiewicz, E. Castro, N. Mahmud, M. Guy, S. Edwards, L. O'Brien, E. Sawyer, A. Hall, R. Wilkinson, T. Dadaev, C. Goh, D. Easton, D. Goldgar and R. Eeles: BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. *Br J Cancer*, 105(8), 1230-4 (2011)

65. A. Mitra, C. Fisher, C. S. Foster, C. Jameson, Y. Barbachanno, J. Bartlett, E. Bancroft, R. Doherty, Z. Kote-Jarai, S. Peock, D. Easton and R. Eeles: Prostate cancer in male BRCA1 and BRCA2 mutation carriers has a more aggressive phenotype. *Br J Cancer*, 98(2), 502-7 (2008)

66. S. A. Gayther, K. A. de Foy, P. Harrington, P. Pharoah, W. D. Dunsmuir, S. M. Edwards, C. Gillett, A. Ardern-Jones, D. P. Dearnaley, D. F. Easton, D. Ford, R. J. Shearer, R. S. Kirby, A. L. Dowe, J. Kelly, M. R. Stratton, B. A. Ponder, D. Barnes and R. A. Eeles: The frequency of germ-line mutations in the breast cancer predisposition genes BRCA1 and BRCA2 in familial prostate cancer. The Cancer Research Campaign/British Prostate Group United Kingdom Familial Prostate Cancer Study Collaborators. *Cancer Res*, 60(16), 4513-8 (2000)

67. H. Gronberg, A. K. Ahman, M. Emanuelsson, A. Bergh, J. E. Damber and A. Borg: BRCA2 mutation in a family with hereditary prostate cancer. *Genes Chromosomes Cancer*, 30(3), 299-301 (2001)

68. J. Salgado, J. M. Aramendia, C. Gutierrez, C. Gil, M. Robles and J. Garcia-Foncillas: A novel BRCA2 mutation that segregates with breast and prostate cancer in a Spanish family. *Breast Cancer Res Treat*, 121(1), 219-20 (2010)

69. E. Manguoglu, S. Guran, D. Yamac, T. Colak, M. Simsek, M. Baykara, M. Akaydin and G. Luleci: Germline mutations of BRCA1 and BRCA2 genes in Turkish breast, ovarian, and prostate cancer patients. *Cancer Genet Cytogenet*, 203(2), 230-7 (2010)

70. S. M. Edwards, D. G. Evans, Q. Hope, A. R. Norman, Y. Barbachano, S. Bullock, Z. Kote-Jarai, J. Meitz, A.

Falconer, P. Osin, C. Fisher, M. Guy, S. G. Jhavar, A. L. Hall, L. T. O'Brien, B. N. Gehr-Swain, R. A. Wilkinson, M. S. Forrest, D. P. Dearnaley, A. T. Ardern-Jones, E. C. Page, D. F. Easton and R. A. Eeles: Prostate cancer in BRCA2 germline mutation carriers is associated with poorer prognosis. *Br J Cancer*, 103(6), 918-24 (2010)

71. S. A. Narod, S. Neuhausen, G. Vichodez, S. Armel, H. T. Lynch, P. Ghadirian, S. Cummings, O. Olopade, D. Stoppa-Lyonnet, F. Couch, T. Wagner, E. Warner, W. D. Foulkes, H. Saal, J. Weitzel, A. Tulman, A. Poll, R. Nam, P. Sun, J. Danquah, S. Domchek, N. Tung, P. Ainsworth, D. Horsman, C. Kim-Sing, C. Maugard, A. Eisen, M. Daly, W. McKinnon, M. Wood, C. Isaacs, D. Gilchrist, B. Karlan, R. Nedelcu, W. Meschino, J. Garber, B. Pasini, S. Manoukian and C. Bellati: Rapid progression of prostate cancer in men with a BRCA2 mutation. *Br J Cancer*, 99(2), 371-4 (2008)

72. H. Thorne, A. J. Willems, E. Niedermayr, I. M. Hoh, J. Li, D. Clouston, G. Mitchell, S. Fox, J. L. Hopper and D. Bolton: Decreased prostate cancer-specific survival of men with BRCA2 mutations from multiple breast cancer families. *Cancer Prev Res (Phila)*, 4(7), 1002-10 (2011)

73. C. S. Sinclair, R. Berry, D. Schaid, S. N. Thibodeau and F. J. Couch: BRCA1 and BRCA2 have a limited role in familial prostate cancer. *Cancer Res*, 60(5), 1371-5 (2000)

74. K. A. Zuhlke, J. J. Madeoy, J. Beebe-Dimmer, K. A. White, A. Griffin, E. M. Lange, S. B. Gruber, E. A. Ostrander and K. A. Cooney: Truncating BRCA1 mutations are uncommon in a cohort of hereditary prostate cancer families with evidence of linkage to 17q markers. *Clin Cancer Res*, 10(18 Pt 1), 5975-80 (2004)

75. J. A. Douglas, A. M. Levin, K. A. Zuhlke, A. M. Ray, G. R. Johnson, E. M. Lange, D. P. Wood and K. A. Cooney: Common variation in the BRCA1 gene and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev*, 16(7), 1510-6 (2007)

76. E. M. Lange, E. M. Gillanders, C. C. Davis, W. M. Brown, J. K. Campbell, M. Jones, D. Gildea, E. Riedesel, J. Albertus, D. Freas-Lutz, C. Markey, V. Giri, J. B. Dimmer, J. E. Montie, J. M. Trent and K. A. Cooney: Genome-wide scan for prostate cancer susceptibility genes using families from the University of Michigan prostate cancer genetics project finds evidence for linkage on chromosome 17 near BRCA1. *Prostate*, 57(4), 326-34 (2003)

77. K. A. Cooney, M. S. Strawderman, K. J. Wojno, K. M. Doerr, A. Taylor, K. H. Alcser, S. G. Heeringa, J. M. Taylor, J. T. Wei, J. E. Montie and D. Schottenfeld: Age-specific distribution of serum prostate-specific antigen in a community-based study of African-American men. *Urology*, 57(1), 91-6 (2001)

78. S. Fan, J. A. Wang, R. Q. Yuan, Y. X. Ma, Q. Meng, M. R. Erdos, L. C. Brody, I. D. Goldberg and E. M. Rosen: BRCA1 as a potential human prostate tumor suppressor: modulation of proliferation, damage responses and expression of cell regulatory proteins. *Oncogene*, 16(23), 3069-82 (1998)

79. C. Yuli, N. Shao, R. Rao, P. Aysola, V. Reddy, G. Oprea-llies, L. Lee, J. Okoli, E. Partridge, E. S. Reddy and V. N. Rao: BRCA1a has antitumor activity in TN breast, ovarian and prostate cancers. *Oncogene*, 26(41), 6031-7 (2007)

80. N. Bednarz, E. Eltze, A. Semjonow, M. Rink, A. Andreas, L. Mulder, J. Hannemann, M. Fisch, K. Pantel, H. U. Weier, K. P. Bielawski and B. Brandt: BRCA1 loss preexisting in small subpopulations of prostate cancer is associated with advanced disease and metastatic spread to lymph nodes and peripheral blood. *Clin Cancer Res*, 16(13), 3340-8 (2010)

81. H. Schayek, K. Haugk, S. Sun, L. D. True, S. R. Plymate and H. Werner: Tumor suppressor BRCA1 is expressed in prostate cancer and controls insulin-like growth factor I receptor (IGF-IR) gene transcription in an androgen receptor-dependent manner. *Clin Cancer Res*, 15(5), 1558-65 (2009)

82. K. K. Deeb, A. M. Michalowska, C. Y. Yoon, S. M. Krummey, M. J. Hoenerhoff, C. Kavanaugh, M. C. Li, F. J. Demayo, I. Linnoila, C. X. Deng, E. Y. Lee, D. Medina, J. H. Shih and J. E. Green: Identification of an integrated SV40 T/t-antigen cancer signature in aggressive human breast, prostate, and lung carcinomas with poor prognosis. *Cancer Res*, 67(17), 8065-80 (2007)

83. A. A. Arbini, M. Greco, J. L. Yao, P. Bourne, E. Marra, J. T. Hsieh, P. A. di Sant'agnese and L. Moro: Skp2 overexpression is associated with loss of BRCA2 protein in human prostate cancer. *Am J Pathol*, 178(5), 2367-76 (2011)

84. R. B. Dickson and G. M. Stancel: Estrogen receptor-mediated processes in normal and cancer cells. *J Natl Cancer Inst Monogr*(27), 135-45 (2000)

85. S. Fan, J. Wang, R. Yuan, Y. Ma, Q. Meng, M. R. Erdos, R. G. Pestell, F. Yuan, K. J. Auborn, I. D. Goldberg and E. M. Rosen: BRCA1 inhibition of estrogen receptor signaling in transfected cells. *Science*, 284(5418), 1354-6 (1999)

86. S. P. Balk: Androgen receptor as a target in androgen-independent prostate cancer. *Urology*, 60(3 Suppl 1), 132-8; discussion 138-9 (2002)

87. J. J. Park, R. A. Irvine, G. Buchanan, S. S. Koh, J. M. Park, W. D. Tilley, M. R. Stallcup, M. F. Press and G. A. Coetzee: Breast cancer susceptibility gene 1 (BRCAI) is a coactivator of the androgen receptor. *Cancer Res*, 60(21), 5946-9 (2000)

88. S. Yeh, Y. C. Hu, M. Rahman, H. K. Lin, C. L. Hsu, H. J. Ting, H. Y. Kang and C. Chang: Increase of androgen-induced cell death and androgen receptor transactivation by BRCA1 in prostate cancer cells. *Proc Natl Acad Sci U S A*, 97(21), 11256-61 (2000)

89. E. M. Rosen, S. Fan, R. G. Pestell and I. D. Goldberg: BRCA1 in hormone-responsive cancers. *Trends Endocrinol Metab*, 14(8), 378-85 (2003)

90. B. Gao, X. Shen, G. Kunos, Q. Meng, I. D. Goldberg, E. M. Rosen and S. Fan: Constitutive activation of JAK-STAT3 signaling by BRCA1 in human prostate cancer cells. *FEBS Lett*, 488(3), 179-84 (2001)

91. A. De Siervi, P. De Luca, J. S. Byun, L. J. Di, T. Fufa, C. M. Haggerty, E. Vazquez, C. Moiola, D. L. Longo and K. Gardner: Transcriptional autoregulation by BRCA1. *Cancer Res*, 70(2), 532-42 (2010)

92. C. Moiola, P. De Luca, J. Cotignola, K. Gardner, E. Vazquez and A. De Siervi: Dynamic coregulatory complex containing BRCA1, E2F1 and CtIP controls ATM transcription. *Cell Physiol Biochem*, 30(3), 596-608 (2012)

93. J. P. Truman, S. A. Rotenberg, J. H. Kang, G. Lerman, Z. Fuks, R. Kolesnick, V. E. Marquez and A. Haimovitz-Friedman: PKCalpha activation downregulates ATM and radio-sensitizes androgen-sensitive human prostate cancer cells *in vitro* and *in vivo*. *Cancer Biol Ther*, 8(1), 54-63 (2009)

94. M. K. Tennant, J. B. Thrasher, P. A. Twomey, R. H. Drivdahl, R. S. Birnbaum and S. R. Plymate: Protein and messenger ribonucleic acid (mRNA) for the type 1 insulin-like growth factor (IGF) receptor is decreased and IGF-II mRNA is increased in human prostate carcinoma compared to benign prostate epithelium. *J Clin Endocrinol Metab*, 81(10), 3774-82 (1996)

95. J. D. Wu, K. Haugk, L. Woodke, P. Nelson, I. Coleman and S. R. Plymate: Interaction of IGF signaling and the androgen receptor in prostate cancer progression. *J Cell Biochem*, 99(2), 392-401 (2006)

96. M. A. Rowlands, D. Gunnell, R. Harris, L. J. Vatten, J. M. Holly and R. M. Martin: Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis. *Int J Cancer*, 124(10), 2416-29 (2009)

97. J. M. Chan, M. J. Stampfer, E. Giovannucci, P. H. Gann, J. Ma, P. Wilkinson, C. H. Hennekens and M. Pollak: Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science*, 279(5350), 563-6 (1998)

98. T. Nickerson, F. Chang, D. Lorimer, S. P. Smeekens, C. L. Sawyers and M. Pollak: *In vivo* progression of LAPC-9 and LNCaP prostate cancer models to androgen independence is associated with increased expression of insulin-like growth factor I (IGF-I) and IGF-I receptor (IGF-IR). *Cancer Res*, 61(16), 6276-80 (2001)

99. S. B. Maor, S. Abramovitch, M. R. Erdos, L. C. Brody and H. Werner: BRCA1 suppresses insulin-like growth factor-I receptor promoter activity: potential interaction between BRCA1 and Sp1. *Mol Genet Metab*, 69(2), 130-6 (2000)

100. G. Yang, G. Ayala, A. De Marzo, W. Tian, A. Frolov, T. M. Wheeler, T. C. Thompson and J. W. Harper: Elevated Skp2 protein expression in human prostate cancer: association with loss of the cyclin-dependent kinase inhibitor p27 and PTEN and with reduced recurrence-free survival. *Clin Cancer Res*, 8(11), 3419-26 (2002)

101. M. Drobnjak, J. Melamed, S. Taneja, K. Melzer, R. Wieczorek, B. Levinson, A. Zeleniuch-Jacquotte, D. Polsky, J. Ferrara, R. Perez-Soler, C. Cordon-Cardo, M. Pagano and I. Osman: Altered expression of p27 and Skp2 proteins in prostate cancer of African-American patients. *Clin Cancer Res*, 9(7), 2613-9 (2003)

102. P. L. Nguyen, D. I. Lin, J. Lei, M. Fiorentino, E. Mueller, M. H. Weinstein, M. Pagano and M. Loda: The impact of Skp2 overexpression on recurrence-free survival following radical prostatectomy. *Urol Oncol*, 29(3), 302-8 (2011)

103. L. Moro, A. A. Arbini, E. Marra and M. Greco: Up-regulation of Skp2 after prostate cancer cell adhesion to basement membranes results in BRCA2 degradation and cell proliferation. J Biol Chem, 281(31), 22100-7 (2006)

104. A. R. Schoenfeld, S. Apgar, G. Dolios, R. Wang and S. A. Aaronson: BRCA2 is ubiquitinated in vivo and interacts with USP11, a deubiquitinating enzyme that exhibits prosurvival function in the cellular response to DNA damage. Mol Cell Biol, 24(17), 7444-55 (2004)

105. D. W. Abbott, M. L. Freeman and J. T. Holt: Double-strand break repair deficiency and radiation sensitivity in BRCA2 mutant cancer cells. *J Natl Cancer Inst*, 90(13), 978-85 (1998)

106. S. H. Barsky, G. P. Siegal, F. Jannotta and L. A. Liotta: Loss of basement membrane components by invasive tumors but not by their benign counterparts. *Lab Invest*, 49(2), 140-7 (1983)

107. W. Guo and F. G. Giancotti: Integrin signalling during tumour progression. *Nat Rev Mol Cell Biol*, 5(10), 816-26 (2004)

108. P. J. Kostenuik, O. Sanchez-Sweatman, F. W. Orr and G. Singh: Bone cell matrix promotes the adhesion of human prostatic carcinoma cells via the alpha 2 beta 1 integrin. *Clin Exp Metastasis*, 14(1), 19-26 (1996)

109. B. R. Zetter: The cellular basis of site-specific tumor metastasis. *N Engl J Med*, 322(9), 605-12 (1990)

110. L. Moro, A. A. Arbini, E. Marra and M. Greco: Down-regulation of BRCA2 expression by collagen type I promotes prostate cancer cell proliferation. *J Biol Chem*, 280(23), 22482-91 (2005)

111. L. Moro, A. A. Arbini, E. Marra and M. Greco: Constitutive activation of MAPK/ERK inhibits prostate cancer cell proliferation through upregulation of BRCA2. *Int J Oncol*, 30(1), 217-24 (2007)

112. L. Moro, A. A. Arbini, J. L. Yao, P. A. di Sant'Agnese, E. Marra and M. Greco: Loss of BRCA2 promotes prostate cancer cell invasion through up-regulation of matrix metalloproteinase-9. *Cancer Sci*, 99(3), 553-63 (2008)

113. R. Yuan, S. Fan, J. A. Wang, Q. Meng, Y. Ma, D. Schreiber, I. D. Goldberg and E. M. Rosen: Coordinate alterations in the expression of BRCA1, BRCA2, p300, and Rad51 in response to genotoxic and other stresses in human prostate cancer cells. *Prostate*, 40(1), 37-49 (1999)

114. M. J. Campbell, A. F. Gombart, S. H. Kwok, S. Park and H. P. Koeffler: The anti-proliferative effects of 1alpha,25(OH)2D3 on breast and prostate cancer cells are associated with induction of BRCA1 gene expression. *Oncogene*, 19(44), 5091-7 (2000)

115. S. Fan, Q. Meng, K. Auborn, T. Carter and E. M. Rosen: BRCA1 and BRCA2 as molecular targets for phytochemicals indole-3-carbinol and genistein in breast and prostate cancer cells. *Br J Cancer*, 94(3), 407-26 (2006) doi:10.1038/sj.bjc.6602935

116. A. Liede, B. Y. Karlan and S. A. Narod: Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. *J Clin Oncol*, 22(4), 735-42 (2004)

117. R. J. Macinnis, A. C. Antoniou, R. A. Eeles, G. Severi, A. A. Al Olama, L. McGuffog, Z. Kote-Jarai, M. Guy, L. T. O'Brien, A. L. Hall, R. A. Wilkinson, E. Sawyer, A. T. Ardern-Jones, D. P. Dearnaley, A. Horwich, V. S. Khoo, C. C. Parker, R. A. Huddart, N. Van As, M. R. McCredie, D. R. English, G. G. Giles, J. L. Hopper and D. F. Easton: A risk prediction algorithm based on family history and common genetic variants: application to prostate cancer with potential clinical impact. *Genet Epidemiol*, 35(6), 549-56 (2011)

118. I. Agalliu, E. M. Kwon, D. Zadory, L. McIntosh, J. Thompson, J. L. Stanford and E. A. Ostrander: Germline mutations in the BRCA2 gene and susceptibility to hereditary prostate cancer. *Clin Cancer Res*, 13(3), 839-43 (2007)

119. T. Ikonen, M. P. Matikainen, K. Syrjakoski, N. Mononen, P. A. Koivisto, A. Rokman, E. H. Seppala, O. P. Kallioniemi, T. L. Tammela and J. Schleutker: BRCA1 and BRCA2 mutations have no major role in predisposition to prostate cancer in Finland. *J Med Genet*, 40(8), e98 (2003)

120. N. Hamel, K. Kotar and W. D. Foulkes: Founder mutations in BRCA1/2 are not frequent in Canadian Ashkenazi Jewish men with prostate cancer. *BMC Med Genet*, 4, 7 (2003)

121. B. Gorski, T. Byrski, T. Huzarski, A. Jakubowska, J. Menkiszak, J. Gronwald, A. Pluzanska, M. Bebenek, L. Fischer-Maliszewska, E. Grzybowska, S. A. Narod and J. Lubinski: Founder mutations in the BRCA1 gene in Polish families with breast-ovarian cancer. *Am J Hum Genet*, 66(6), 1963-8 (2000)

122. S. V. Tavtigian, J. Simard, J. Rommens, F. Couch, D. ShattuckEidens, S. Neuhausen, S. Merajver, S. Thorlacius, K. Offit, D. StoppaLyonnet, C. Belanger, R. Bell, S. Berry, R. Bogden, Q. Chen, T. Davis, M. Dumont, C. Frye, T. Hattier, S. Jammulapati, T. Janecki, P. Jiang, R. Kehrer, J. F. Leblanc, J. T. Mitchell, J. McArthurMorrison, K. Nguyen, Y. Peng, C. Samson, M. Schroeder, S. C. Snyder, L. Steele, M. Stringfellow, C. Stroup, B. Swedlund, J. Swensen, D. Teng, A. Thomas, T. Tran, T. Tran, M. Tranchant, J. WeaverFeldhaus, A. K. C. Wong, H. Shizuya, J. E. Eyfjord, L. CannonAlbright, F. Labrie, M. H. Skolnick, B. Weber, A. Kamb and D. E. Goldgar: The complete BRCA2 gene and mutations in chromosome 13q-linked kindreds. *Nat Genet*, 12(3), 333-337 (1996)

Abbreviations: BRCA1: breast cancer 1, early onset; BRCA2: breast cancer 2, early onset; AR: androgen receptor; JAK: Janus kinase; IGF-IR: insulin-like growth factor 1 receptor; LOH: loss of heterozygosity; PIN: prostate intraepithelial neoplasia

Key Words: BRCA1, BRCA2, Prostate cancer, Sequence variants, Signaling pathways, Tumor suppressor, Review

Send correspondence to: Roy A. Jensen, 3901 Rainbow Boulevard, MS 1027, Kansas City, KS, 66160, Tel: 913-588-2568, Fax: 913-588-4701, E-mail: rjensen@kumc.edu