Venyo AKG. (April 2017). A review on genetic testing in carcinoma of the prostate gland: An update. Jour of Med Sc & Tech; 6(2); Page No: 101 – 118.

Journal of Medical Science & Technology

Review article Open Access

A Review on genetic testing in carcinoma of the prostate gland: An update

Anthony Kodzo-Grey Venyo[1]

[1]North Manchester General Hospital, Department of Urology, Delaunay's Road, Crumpsall, Manchester, United Kingdom

Abstract

Genetic testing has not been widely undertaken previously in order to provide a means by which men who have a high risk for the development of prostate cancer can be identified at an early age. Recently a number of genetic studies have been reported relating to carcinoma of the prostate. Literature review on the predisposition to the development of prostate cancer and genetic testing relating to the disease has been summarized as follows: Carcinoma of the prostate gland is the second most common malignancy which affects men in the world. Carcinoma of the prostate gland tends to be rare in men who are aged less than 40 years. Men who are said to have an increased risk for the development of prostate cancer include: a person diagnosed with carcinoma of prostate at an age less than 55 years; a person with 3 first-degree relatives including a brother, son who are diagnosed with carcinoma of prostate; diagnosis of carcinoma of prostate in 3 successive generations of a man; Ashkenazi Jewish ancestry as well as carcinomas of breast, ovary, and prostate; several relatives being diagnosed with carcinoma of breast at an age less than 50 years, family histories of carcinoma of male breast, carcinoma of ovary, bilateral breast carcinomas, carcinoma of bowel or womb diagnosed at less than 50 years, several relatives being diagnosed with carcinoma of the colon or womb at an early age. Genome-wide associated studies had identified alleles which are associated with an increased susceptibility for the development of carcinoma of the prostate gland and these studies rely on presence of genetic variations that are known as single nucleotide polymorphisms (SNPs). Multiple foci had been identified in the 8q24 and in the 17q region as well as in other chromosomes. Mutations had been found in a number of genes in men with carcinomas of the prostate diagnosed at an early age or at risk for the development of the disease including BRCA2, ATM, CHEK2, BRCA1, and in other DNA-repair genes. It is therefore possible to undertake genetic testing at an early age in men who fit the criteria of being at risk for the development of prostate cancer in order to screen them at an early age to detect their prostate cancers at earlier stages of the disease so that treatment of curative intent can be provided early. However, genetic testing should not be undertaken on all adult men because the cost-benefits would be low. Results of more studies on genetic testing in prostate cancer would be needed for a consensus opinion to emanate relating to the cost benefits of genetic testing in men to detect prostate cancer early.

Key Words: Carcinoma of prostate; genetic testing; BRCA2; ATM; CHEK2; BRCA1; HOXB13; MLH1; MSH2; MSH6; PMS2; EPCAM.

*Corresponding Author: Dr. Anthony Kodzo-Grey Venyo, MB, ChB, FRCS(Ed), FRCSI, FGCS, Urol. LLM. Department of Urology, North Manchester General Hospital, Delaunay's Road, Crumpsall, Manchester, United Kingdom. Email: akodzogrey@yahoo.co.uk

Received: December 20, 2016 Accepted: March 1, 2017. Published: April 20, 2017.

Introduction

It has been documented that in the United Kingdom carcinoma of the prostate gland is the most common carcinoma in men and that 1 out of 8 men would be diagnosed with carcinoma of the prostate and 75% of men diagnosed with prostate cancer would be more than 65 years old. [1] It has also been stated that men would tend to have a 12.5% lifetime risk of developing carcinoma of the prostate gland and that most of the cases of carcinoma of the prostate gland develop by chance; nevertheless it has been estimated that between 5% and 9% of cases of carcinoma of the prostate gland would be hereditary

and that 25% of carcinomas of the prostate gland are hereditary. It would be asked whether or not there are ways of determining beforehand those who would subsequently develop hereditary or familial carcinomas of the prostate gland. The ensuing paper on genetics of carcinoma of the prostate gland is divided into two parts (A) overview and (B) miscellaneous narrations and discussions from some genetics related cases and case series on prostate cancer.

Aim

To update knowledge relating to the role of genetic testing in carcinoma of the prostate gland

Methods

Various internet data bases were searched including: Google, Google Scholar, Educus, and PUB MED. The search words used included genetic testing in prostate cancer, genetic testing in carcinoma of the prostate, cancer of the prostate gland and genetic testing. In all 67 references were used for the review of the literature.

Literature Review

(A) Overview

General Comments

Carcinoma of the prostate gland is said to be the second most common carcinoma in men globally, and it has been estimated that 1,100,000 cases of carcinoma of the prostate gland and 300,000 deaths related to prostate cancer were documented in 2012. [2] The current lifetime risk for the development of carcinoma of the prostate gland in the United States of America has been estimated to be about one in six. [3]

Risk factors

It has been stated that the important risk factors for the development of carcinoma of the prostate include: age, ethnicity, genetic factors, and possibly dietary factors. [4]

Age

It has been stated that clinically diagnosed carcinoma of the prostate rarely occurs prior to 40 years, but the incidence of prostate cancer tends to rise rapidly there after [4] [5] [6].

With regard to possible signs or ways that would help predict the possibility for the development of hereditary carcinoma of the prostate gland it has been stated that men who meet the following criteria would tend to have an increased risk for the development of carcinoma of the prostate gland: [1]

- A person diagnosed with early onset carcinoma of the prostate gland at an age less than 55 years.
- A person who has 3 first degree relatives including a brother, son, and diagnosed with carcinoma of the prostate gland
- Cases in which relatives are diagnosed with carcinoma of the prostate gland in 3 successive generations.
- Ashkenazi Jewish ancestry as well as carcinoma of breast, carcinoma of ovary, and carcinoma of the prostate.
- A history of several relatives having been diagnosed with carcinoma of the breast, especially in cases of the diagnosis having been made at an age earlier than 50 years.
- Family history of carcinoma of male breast, carcinoma of the ovary, or of bilateral carcinomas of the breast.
- Family history of early onset carcinoma of bowel or womb and in which the carcinomas were diagnosed at ages earlier than 50 years.
- A family history of several relatives diagnosed with colon-carcinoma or carcinoma of the womb at an early age.

Genetic factors

It has been stated that even though evidence does exist that carcinoma of the prostate gland has a strong genetic component, the identification of specific genes which underlie the disease process have been challenging but research has indicated that various genes are involved; nevertheless, the results have tended to be inconsistent. [4] It has also been stated that evidence that supports the role of genetic factors in relation to the development of carcinoma of the prostate gland emanates from studies of relatives of patients who have been diagnosed as having carcinoma of the prostate gland, from genome-wide association studies, and also from studies undertaken in patients who have abnormalities in known cancer-associated genes such as BRCA1 and BRAC2. [4]

ProstateGene, the prostate cancer genetic testing, which is performed on saliva sample, is a genetic test which is used to analyse the DNA code of eight different genes that have been known to be associated with an increased risk for the development of carcinoma. [1] The genes that are assessed by

ISSN: 1694-1217 JMST. An open access journal

ProstateGene include: BRCA1, BRCA2, HOXB13, MLH1, MSH2, MSH6, PMS2 and EPCAM. [1]

Family studies

It has been stated that the risk for the development of carcinoma of the prostate gland is increased about two-fold in men who have one or more first-degree relatives (brother, father) affected by carcinoma of the prostate gland [7] [8]

Furthermore it has been stated that there tends to be a trend towards a further increased risk for the development of carcinoma of the prostate gland when there is a greater number of family members who are affected by prostate cancer, and that men who have two or three first-degree relatives affected by carcinoma of the prostate gland tend to have a 5 – and 11-fold increased risk for the development of prostate cancer, respectively. [9]

Additionally it has been stated that a family history of early age of onset of carcinoma of the prostate gland tends to increase the risk for the development of prostate gland [4] [8] [9] [10] [11] [12].

A study of 45,000 Scandinavian twin pairs, concordance for carcinoma in identical twins provided evidence that concordance for carcinoma in identical twins was higher for the development of prostate cancer in comparison with breast or colorectal cancer. [13] And the study also showed that as much as 42% of the risk for the development of prostate cancer could be explained by heritable factors [4] [13]

It has been stated that in addition to affecting the risk for the development of carcinoma of the prostate gland, genetic factors could influence the outcome in men who develop carcinoma of the prostate gland. A study that was undertaken in Sweden which was based upon 610 men who had carcinoma of the prostate gland, revealed that the survival of sons did correlate with that of their fathers [4] [14] and when the fathers survived for five years or more than five years the hazard ratio for death in their sons was 0.62 (95% CI 0.41-0.94), in comparison with those patients whose fathers had survived less than 24 months. [4] [14]

Genome-wide association studies

It has been stated that Genome-wide associated studies had identified alleles which are associated with an increased susceptibility for the development of carcinoma of the prostate gland [15] [16] [17] [18] [32 [19] [20] [21] [22] [23] [24] and that these studies rely on presence of genetic variations that are known as single nucleotide polymorphisms (SNPs). It has been documented that this approach had identified multiple foci in the 8q24 and in the 17 q region [23] [24] as well as in other chromosomes [4] [21] [22]

It has been intimated that despite the association of some genetic variants with the development of carcinoma of the prostate gland none of the five genetic variants was significantly associated with prognostic parameters in men who had carcinoma of the prostate gland including the Gleason score, serum prostate-specific antigen (PSA) level at the time of initial diagnosis, and the age. [4]. Sartor et al. [4] have had the opinion that despite the fact that the information from a panel of these markers could be useful with regard to the identification of men who are at high risk for the development of carcinoma of the prostate gland additional prospective evaluations would be necessary to establish the utility of this approach in additional populations. [4]

Sartor et al. [4] stated that deletion of sequences from chromosome 8p tends to be a common event in the genome of tumours of the prostate gland [25] and also that the results from genetic linkage studies had also provided some evidence that germ-line 8p alterations could be linked to hereditary carcinoma of the prostate gland [26] [27]

Sartor et al. [4] additionally stated that whether or not there is a linkage between the germline and somatic genetic changes would need to be conclusively demonstrated in the future.

It has been intimated that previous genetic associated studies had provided evidence in support of genetic complexity of carcinoma of the prostate gland. [28]

Sartor et al. [4] had stated the following: When multiple SNPs are considered in aggregate, the studies had a predictive power for carcinoma of the prostate which would appear to be similar to that provided by serum PSA levels and in view of this Sartor et al. [4] recommended that additional studies would need to be undertaken to ascertain whether multiple SNPs can be combined with serum PSA levels and clinical factors including age, race, family history, previous biopsies, to identify men who would

be at particularly high risk of being diagnosed as having carcinoma of the prostate gland.

DNA-repair gene mutations

It has been stated that Germline mutations in DNA-repair genes are more common in men who have carcinoma of the prostate in comparison with the general population. [4] Sartor et al. [4] stated that: It has been reported in a study which comprised of 692 men who had metastatic carcinoma of the prostate gland, and in which germline DNA was analysed for presence of mutation in 20 DNA-repair genes that have been known to be associated with cancer predisposition syndromes [29] And it was reported in this study in which the cohort was not selected upon the basis of a family history of carcinoma of the prostate gland, that mutations were found in 82 men (11.8%). This finding was significantly more frequent in comparison with a cohort of 499 men who had localized carcinoma of the prostate (4.6%) or in a cohort of 53,105 men who did not have any cancer (2.7%). Mutations had been found in 16 of the 20 genes that were studied. The commonest involved gene was BRCA2 in 37 men (5.3%). Some of the other frequently involved genes were ATM (11.16%), CHEK2 (10.19% of those analysed), and BRCA1 (6.09%). Mutations were also found in 11 other DNA-repair genes.

BRCA2

Sartor et al. [4] stated the following: The BRCA2" is the most frequently mutated DNA-repair gene and that reports from some authors had indicated that BRCA2 mutations would appear to be associated with higher Gleason score [30] [31] and also with a substantially worse outcome [32] [33] [34] [35] [36] In an Icelandic study which included 30 men with a 999 del5 mutation in BRCA2, a diagnosis of carcinoma of the prostate gland was made at an earlier age (69 years versus 74 years) and it was associated with a significant survival (2.1 years versus 12.4 years. Results of another study which was a multi-national cohort study of men who had carcinoma of the prostate gland which had included 183 men from BRCA2 families and 119 men from BRCA1 families, revealed that the men from BRCA2 families did have a significantly shorter survival of 4 years in comparison with 8.0 years in the case of men from the BRCA1 families. [33]

Sartor et al. [4] reviewed the results of the IMPACT study which has been looking at the feasibility and the role of serum PSA screening in men who are carriers of BRCA1 or BRAC2 mutations. [37] This study had included: 1520 men who were either carriers for either BRCA1 or BRCA2 mutations, and 959 men as controls who had tested negative for a pathogenic BRCA mutation in their family. The mean age of the men was 54 years at the time of their enrolment into the study. The men in the study were referred for biopsy of the prostate gland if their serum PSA levels were equal to or greater than, 3.0 ng/ml. With regard to the results of the study, 199 men (9%) had been referred to be considered for biopsy of the prostate gland at the baseline screening; In 59 cases which constituted 2.4% of the entire cohort, carcinoma of the prostate gland was detected and 75% of these did have intermediate- risk or high-risk disease; at the baseline phase of the study, there were no statistically significant differences between the carriers of mutation and the control group. Hopefully subsequent results from additional rounds of the study would supply further data relating to the biological behaviours of tumours related to both recruited groups in the study.

Sartor et al. [4] suggested that even though the overall risk for the development of carcinoma of the prostate at an age earlier than 50 years is low, and the fact that there is no convincing evidence to suggest that early detection of prostate cancer by means of screening does improve survival in any population, The American Society of Clinical Oncologists (ASCO) guidelines does advice that men who have inherited mutations should start undergoing screening for carcinoma of the prostate gland before the age of 50 years. [38] Furthermore, the National Comprehensive Cancer Network (NCCN) guidelines has advised that the risks as well as the benefits related to screening for carcinoma of the prostate gland should be discussed in the case of this high-risk group at 40 years of age. [39]

Lynch syndrome

Lynch syndrome is an autosomal dominant disorder which is caused by a germline mutation within one of many DNA mismatch repair (MMR) genes; the syndrome is characterized by a significantly increased risk for CRC and endometrial cancer as well as the development of many other malignancies; the syndrome has been described as commonest cause of inherited CRC [4]

Sator et al. [4] summarized a study by Raymond et al. [40] which reported their study which included 4127 men from familial cancer registries

which had shown that the cumulative risk for the development of carcinoma of the prostate gland was significantly higher in comparison with the general population (6.3% versus 2.6% at age 60 years, and 30% versus 18% at 80 years of age).

Tony Fanconi syndrome (Fanconi anaemia)

Fanconi anaemia has been defined as an inherited bone marrow failure syndrome which is characterized by pancytopenia, predisposition to malignancy, and presence of specific physical abnormalities [4] It has been stated that there is an association between Fanconi anaemia and mutations in many genes that are responsible for DNA repair [4] and that some authors [41] [42] [43] had suggested that there could be an association of Fanconi anaemia with an increased risk for the development of carcinoma of the prostate gland.

HOXB13

The homeobox B13 (HOXB13) gene codes for a transcription factor which is important in the development of the prostate. [4] The G84E variant of homeobox 13 (HOXB13) gene had been identified by means of sequencing of the 17q21-22 region in four families who had hereditary carcinoma of the prostate gland. [44] Subsequent studies which included 5083 unrelated subjects who had carcinoma of the prostate gland and 1401 controls did find a 20-fold increase in the frequency of the G84E variant in men who had carcinoma of the prostate gland in comparison with those who did not have carcinoma of the prostate gland (1.4% versus 0.1%). However, it has been stated that the molecular pathways and implications for the molecular pathogenesis of carcinoma of the prostate gland as a result of abnormalities in HOB13 is yet to be identified. [4]

(B) Miscellaneous narrations and discussions from reported studies and case reports / case series

Pritchard et al. [29] stated that inherited mutations in DNA-repair genes such as BRCA2 tend to be associated with increased risks for the development of lethal carcinoma of the prostate gland and that even though the prevalence of germline mutations in DNA-repair genes in men with localized carcinoma of the prostate gland who are unselected for family predisposition is not sufficient to necessitate routine testing, the frequency of such mutations in patients who have metastatic carcinoma of the prostate gland has not been established. Pritchard et al. [29] studied 692 men who had documented metastatic carcinoma of the prostate gland and who were unselected for family history carcinoma or age at the time of diagnosis of the metastatic carcinoma of the prostate gland. Pritchard et al, [29] isolated germline DNA and utilized multiplex sequencing assays to assess mutations in 20 DNA sequencing genes that are associated with autosomal dominant carcinoma-predisposition syndromes. With regard to the results, Pritchard et al. [29] reported that: they had identified a total of 84 germline DNA-repair gene mutations in 82 men (11.8%); they had identified mutations in 16 genes including BCRA2 in 37 men (5.3%), ATM in 11 men (1.6%), CHEK2 in 10 men (1.9%), out of 534 men whose data were available, BCRAC1 in 6 men (0.9%), RAD51D in 3 men (0.4%), PALB2 in 3 men (0.4%). Pritchard et al. [29] had stated that the frequencies of mutations did not differ according to whether or not there was a family history of carcinoma of the prostate gland and the frequencies did not depend upon the age of the patient at the time of the diagnosis. Pritchard et al. [29] further stated that on the whole, the frequency of germline mutations in DNA-repair genes in men who had been diagnosed with metastatic prostate cancer did significantly exceed the prevalence of 4.6% in 499 men who had localized carcinoma of the prostate gland ($P<0.001$), including men who had high-risk carcinoma of the prostate gland, and the prevalence of 2.7% in Exome Aggregation Consortium, which had included 53,105 men who did not have a known diagnosis of cancer ($P<0.001$). Pritchard et al. [29] concluded that their multi-centre study did show that: the germline mutations in genes mediating DNA-repair processes in men with metastatic carcinoma of the prostate gland was 11.8% which was higher in comparison with the incidence in patients who had localized carcinoma of the prostate gland; the frequencies of germline mutations in DNA-repair genes in men who had metastatic carcinoma of the prostate gland did not differ significantly based upon the age at the time of the diagnosis of the disease or upon the family history of prostate. It is worthwhile knowing that the frequencies of germ line mutations in DNA-repair genes is higher among patients who had metastatic prostate cancer in comparison with the frequencies in patients who had localized prostate cancer. What is not known is whether or not a prospective study related to patients who have localized prostate cancer would show whether or not there would be any significant difference in the outcome of the disease following observation and treatment with curative intent between patients who have germline mutations in genes mediating DNA-

repair processes and those patients who do not have any mutations or deletions.

Attard et al. [45] used fluorescence in situ hybridization (FISH) assays to assess ERG gene in 445 patients with carcinoma of the prostate gland who had been managed by means of the conservative approach. They stated that the FISH assays detected separation of 5' (labelled green) and 3' (labelled red) ERG sequences, which is a consequence of the TMPRSS2-ERG fusion, and additionally identified interstitial deletion of genomic sequences between the tandemly located TMPSS2 and ERG sequences on chromosome 21. With regard to outcome, Attard et al. [45] reported that the carcinomas that lacked ERG alterations did exhibit favourable cause-specific survival of 90% survival after 8 years. Attard et al. [45] also identified a novel category of carcinoma of the prostate gland, which was characterized by duplication of the fusion of TMPSS2 to ERG sequences together with interstitial deletion of sequences of 5' to ERG (called '2+Edel'), which on comparison did exhibit extremely poor cause-specific survival (hazard ratio = 6.10, 95% confidence ratio = 3.33-11.15, $p<0.001$, 25% survival at 8 years). They also reported that multivariate analysis did show that '2Edel' did provide significant prognostic information ($P=0.003$) in addition to that which was provided by Gleason score and the prostate-specific antigen level at the time of diagnosis. They additionally found that other categories of ERG alterations had been associated with intermediate or good prognosis. Attard et al. [45] concluded that determination of the ERG gene status, including duplication of the fusion of TMPSS2 to ERG sequences in 2+Edel in cases of carcinoma of the prostate gland, would allow stratification of carcinoma of the prostate gland into distinct survival categories.

Kote-Jarai et al. [46] screened 1864 men who had carcinoma of the prostate gland whose ages had ranged between 36 years and 88 years. Kote-Jarai et al. [46] analysed the BRCA2 gene utilizing a novel high throughput multiplex fluorescence hetero-duplex detection system which had been developed for the AB13130xl genetic analyser. With regard to the results Kote-Jarai et al. [46] did identify 19 protein truncating mutations, 3 in-frame deletions and 69 missense variants of uncertain significance (UV) within their sample sets. They further reported that all the carriers of truncating mutations did develop carcinoma of the prostate gland at an age equal to or less than 65 years, with a prevalence of BRCA2 mutation of 1.20% for cases in this age group. Kote-Jarai et al. [46] concluded that: Based upon the estimated frequency of BRCA2 mutations in the United Kingdom, they would estimate that germline mutations in the BRCA2 gene confer ~8.6 fold increased risk for the development of carcinoma of the prostate gland by the age of 65 years which would correspond to an absolute value of ~15% by the age of 65 years; Their results would indicate that routine testing of early onset carcinoma of prostate cases for germline BRCA2 mutations would be of additional help to refine the prevalence and risk associated with BRCA2 mutations and this may be useful in guiding patients with regard to management options of their disease. Kote-Jarai et al. [46] also alluded to the fact that they had previously estimated that approximately 2% of carcinomas of the prostate gland cases who were aged equal to or less than 55 years had harboured BRCA2 mutation and prostate cancer among BRCA2 carriers that had been shown to be more aggressive, with poorer prognosis.

Tomlins et al. [47] reported that they had used a bioinformatics approach to discover a candidate oncogenic chromosomal aberration on the basis of outlier gene expression and that they had identified two ETS transcription factors, ERG and ETV1 as outliers in carcinoma of the prostate gland. Tomlins et al. [47] did identify recurrent gene fusions of the 5' untranslated region of TMPRSS2 to ERG or ETV1 in tissues of carcinoma of the prostate gland with outlier expression. Tomlins et al. [47] reported that by using fluorescence in situ hybridization, they had found that 23 out of 29 carcinomas of the prostate gland samples did harbour re-arrangements in ERG or ETV1 and that cell line experiments did suggest that the androgen-responsive promoter elements of TMPRSS2 mediate the overexpression of ETS family members in carcinoma of the prostate gland. Tomlins et al. [47] additionally stated that their results had implications in the development of carcinomas as well as the molecular diagnosis and treatment of carcinoma of the prostate gland.

Edwards et al. [48] stated that studies undertaken on families with carcinoma of the breast had indicated that male carriers of BRCA2 mutations have an increased risk of carcinoma of the prostate gland especially at an early age. Edwards et al. [48] undertook a study to assess the contribution of BRCA2 mutations to early-onset carcinoma of the prostate gland by screening the complete coding sequence of BRCA2 for germline mutations, in 263 men who were diagnosed as having carcinoma of the

prostate gland who were aged 55 years old or younger than 55 years. Edwards et al. [48] reported that they had found protein-truncating mutations in six men (2.3%, 95% confidence interval 0.8% - 5.0%), and all of the mutations had been clustered outside the ovarian-cancer cluster region. Edwards et al. [48] stated that the relative cumulative risk for the development of carcinoma of the prostate gland by the age of 56 years from a deleterious germline BRCA2 mutation was 23-fold. Edwards et al. [48] further reported that four of the patients who had mutations did not have a family history of carcinoma of the breast or ovary; they had also identified twenty-two variants of uncertain significance. Edwards et al. [48] concluded that their results confirmed that BRCA2 is a high-risk prostate-cancer-susceptible gene and this has potential implications for management of early-onset carcinoma of the prostate gland with regard to both the patients and their relatives.

Gudmundsson et al. [17] stated that it had been reported that (a) in the developed countries, carcinoma of the prostate gland tends to be the most prevalent non-cutaneous carcinoma in males, and that (b) it had also been reported that African American men have among the highest worldwide incidence and mortality rates. Gudmundsson et al. [17] reported a second genetic variant in the 8q24 region which, in conjunction with another variant they had previously discovered, accounted approximately between 11% to 13% of cases of carcinoma of the prostate gland in individuals of European descent and 31% of cases in African Americans. Gudmundsson et al. [17] made their discovery through a genome-wide association scan of affected Icelandic men and 3,064 controls using the Illumina HumanHap300 BeadChip followed by four replication studies. Gudmundsson et al. [17] stated that a key step in their discovery was the construction of a 14-SNP haplotype which efficiently tags relatively uncommon (2% to 4%) susceptible variant individuals of European descent which happens to be very common (~42%) in African Americans. Gudmundsson et al. [17] further stated that the newly identified variant did show a stronger association with affected individuals who had an earlier age at diagnosis.

Yeager et al. [19] reported that they had conducted a genome-wide associated study in the Cancer Genetic Markers of Susceptibility project with 550,000 SNPs in a nested case-control study of 1,172 cases and 1,157 controls of European origin and that they had identified a new association at 8q24 which had an independent effect on susceptibility to carcinoma of the prostate gland. Yeager et al.[19] reported that the most significant signal was 70 kb centrometric to the previously reported SNP, rs1447295, but it showed little evidence of linkage disequilibrium with it. Their combined analysis with four additional studies that totalled 4,296 cases and 4,299 controls did confirm an association with carcinoma of the prostate gland for rs6983267 within the centromere locus (P = 9.42 x 10 -13; heterozygote odds ratio (OR) : 1.26, 95% confidence interval (c.i): 1.13 – 1.41); homozygote OR: 1.58; 95% c.i.: 1.40 – 1.78). Each SNP did remain significant in a joint analysis following adjustment for the other (rs1447295 P = 1.41 x 10 -11, rs6983267 P = 6.62 x 10 -10). Yeager et al. [19] made the ensuing iterations: Their observations, taken in combination with compelling evidence for a recombination hotspot between the two markers, did indicate the presence of at least two independent loci within 8q24 which contribute to the development of carcinoma of the prostate gland in men of European ancestry; It was their estimation that the population attributable risk of the new locus, marked by rs6983267, is higher in comparison with the locus marked by rs1447295 (21% versus 9%).

Stanbrough et al. [49] stated that androgen receptor [AR] does play a central role in carcinoma of the prostate gland and majority of patients do respond to androgen deprivation therapies; nevertheless; they invariably tend to relapse with the development of more aggressive carcinoma of the prostate which has been termed hormone refractory or androgen independent. In order to identify those proteins that mediate the tumour progression, Stanbrough et al. [49] compared the gene expression in 33 androgen-independent carcinomas of the prostate gland bone marrow metastases versus 22 laser capture-micro-dissected primary carcinomas by the use of Affymetrix oligonucleotide microarrays. They reported that multiple genes associated with aggressive behaviour were noted to be increased within the androgen-independent metastatic tumours including: MMP9, CKS2, LRRC15, WNT5A, EZH2, E2F3, E2F3, SDC1, SKP2, and BIRC5, but on the other hand a candidate tumour suppressor gene KLF6 was observed to be decreased. They also reported that consistent with castrate androgen levels, androgen-regulated genes were noted to be reduced 2- to 3-fold within the androgen-independent tumours. However, there were still major transcripts within these tumours which did indicate that there was partial reactivation of AR transcriptional activity

which was associated with increased expression of AR (5.8 fold) as well as multiple genes that mediate androgen metabolism including: HSD3B2, AKR1C3, SRD5A1, AKR1C2,AKR1C1, and UGT2B15. Additionally they reported an increase in aldo-keto reductase family 1, member C3 (AKR1C£), the prostate enzyme which reduces adrenal androstenedione to testosterone which was established by means of real-time reverse transcription-PCR and by means of immunohistochemistry studies. Stanbrough et al. [49] concluded that their results had indicated that enhanced intracellular conversion of adrenal androgens to testosterone and dihydrotestostorone is a mechanism through which cells of carcinoma of the prostate gland adapt to androgen deprivation and did suggest new therapeutic targets.

Carter et al. [50] stated that studies undertaken previously had illustrated familial clustering of carcinoma of the prostate gland. In order to ascertain and define, the nature of the aforementioned familial aggregation, and to determine whether Mendelian inheritance could explain clustering, Carter et al. [50] performed proportional hazards and segregation analyses on 691 families that had been ascertained through a single carcinoma of prostate gland pro-band. Carter et al. [50] reported that the proportional hazards analysis did reveal that two factors, namely, early age of onset of the disease in the pro-band as well as multiple affected members of the family, were adjudged to be important determinants for the development of carcinoma of the prostate gland in these families. Additionally, they had found that segregation analyses had shown that clustering could be best explained by autosomal dominant inheritance of a rare (q = 0.0030) high-risk allele which leads to an early onset carcinoma of the prostate gland. They further more stated the following: the estimated cumulative risk of carcinoma of the prostate gland for carriers showed that the allele was highly penetrant by the age of 85 years, 88% of carriers in comparison to only 5% of non-carriers had been projected to be affected by carcinoma of the prostate gland. The best fitting autosomal dominant model did additionally suggest that this inherited form of carcinoma of the prostate gland accounts for a significant proportion of early onset carcinoma of the prostate but overall is responsible for a small proportion of carcinoma of the prostate gland occurrence (9% by the age of 85 years). Carter et al. [50] made the following conclusions: Their data did provide evidence that carcinoma of the prostate gland was inherited in Mendelian fashion in a sub-set of families and did provide a deep foundation for gene mapping studies of heritable carcinoma of the prostate gland; Characterization of genes that are involved in inherited carcinoma of the prostate gland could provide important insight into the development of carcinoma of the prostate gland in general.

Eeles et al. [51] stated that carcinoma of the prostate gland shows evidence of familial aggregation, especially at young ages at diagnosis; nevertheless; the inherited basis of familial carcinoma of the prostate gland has been poorly understood and that evidence had been found of linkage to markers on 1q, at a locus which had been designated “HPC1” in 91 families that had multiple cases of early-onset carcinoma of the prostate gland. Eeles et al. [51] reported that they had attempted by using both parametric and non-parametric methods to confirm the aforementioned finding, in 60 affected related pairs and in 76 families who had three or more cases of carcinoma of the prostate gland, but they did not find any significant evidence of linkage. They found that the estimated proportion of linked families, under a standard autosomal dominant model, was 4%, with an upper 95% confidence limit of 31%. Eeles et al. [51] concluded that the HPC1 locus is responsible for only a minority of familial cases of carcinoma of the prostate gland and that it is likely to be the most important in families that have at least four cases of the disease.

Thomas et al. [22] reported that they had followed their initial genome-wide association study (GWAS) of 527,869 SNPs on 1,172 individuals who had carcinoma of the prostate gland and 1,157 controls of European origin – nested in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial prospective study by testing 26,958 SNPs in four independent studies that totalled 3,941 cases and 3,964 controls. They reported that in the combined joint analysis, they had confirmed three previously reported loci (two independent SNPs at 8q24, and one in HNF1B which was formerly known as TCF2 on 17q; $P < 10^{[10]}$. Additionally more loci on chromosome 7, 10 (two loci) and 11 were highly significant (between $P < 7.31vx\ 10^{[-13]}$ and $P < 2.14 \times 10^{[-6]}$. Loci on chromosome 10 had included MSMB, which encodes ß-microseminoprotein, a primary constituent of semen and a proposed prostate cancer biomarker, and CTBP2, a gene that had antipoptotic activity; the locus on chromosome 7 is at JAZF1, a transcriptional repressor which is fused by chromosome translocation to SUZ12 in carcinoma of

endometrium. Out of the nine loci which showed highly suggestive associations ($P<2.5 \times 10^{[-5]}$, four best fit a recessive model and had included candidate susceptibility genes including CPNE3, IL16 and CDH13. Thomas et al. [22] concluded that their findings point to multiple loci with moderate effects associated with susceptibility to carcinoma of the prostate gland that taken together, in the future might predict high risk in select individuals.

Ingles et al. [52] documented the association of risk of development of carcinoma of the prostate with Vitamin D Receptor and androgen receptor.

Gudmundsson et al. [23] performed a genome-wide association scan to search for sequence variants conferring-risk of carcinoma of the prostate gland using 1,501 Icelandic men who had prostate cancer and 11,290 controls. They reported that follow-up studies had involved three additional case-control groups that replicated an association of two variants on chromosome 17 with disease; These two variants, 33Mb apart, fell within a region that was previously implicated by family-based linkage studies on carcinoma of the prostate gland; The risks conferred by these variants were moderate individually (allele odds ratio of about 1.20) but because they tend to be common, their joint population attributable risk was substantial; One of the variants was in TCF2 (HNF1beta), a gene that is known to be mutated in individuals who have maturity onset diabetes of the young type 5; The results from eight case-control groups, including one West African, and one Chinese, did demonstrate that this variant confers protection against type 2 diabetes.

Cairns et al. [53] stated that sporadic prostate cancer is the commonest male cancer encountered in the Western world; nevertheless, many of the major genetic events involved in the progression of the disease which quite often tends to be fatal has remained to be elucidated. They also intimated that many cytogenetic and allelotype studies had reported frequent loss of heterozygosity on chromosomal arm 10q in sporadic prostate cancer. Cairns et al. additionally stated the following: Deletion mapping studies had identified unambiguously a region of chromosome 10q23 to be the minimal area of loss; A new tumour suppressor gene, PTEN/MMAC1, had been isolated at this region of chromosome 10q23 and found to be inactivated by mutation in three prostate cancer cell types. Cairns et al. [53] screened 80 carcinomas of the prostate gland by means of microsatellite analysis and found chromosome 10q23 to have been deleted in 23 of the cases. Cairns et al. [53] next proceeded with sequence analysis of the entire PTEN/MMAC1 coding region and tested for homozygous deletion with new intragenic markers in these 23 cases that had 10q23 loss of heterozygosity. They stated that the identification of the second mutational event in 10 (43%) tumours established PTEN/MMAC1 as a main inactivation target of 10q loss in sporadic carcinoma of the prostate gland.

Amundadottir et al. [15] stated that as a result of the increasing incidence of carcinoma of the prostate gland, the identification of common genetic variants which confer risk of disease is important. Amundadottir et al. [15] reported a variant on chromosome 8q24, a region which was in the first instance identified via a study of Icelandic families. Allele – 8 of the microsatellite DG8S737 was associated with carcinoma of the prostate gland in three case-control series of European ancestry from Iceland, Sweden, and the United States of America. The estimated odd ratio (OR) of the allele was 1.62 ($P = 2.7 \times 10^{-11}$). Approximately 19% of affected men and 13% of the general population carried at least one copy, which yielded a population-attributable risk (PAR) of -8%. Amundadottir et al. [15] also reported that the association was additionally replicated in an African American case-control group which had a similar odds ratio (OR), in 41% of affected individuals and 30% of the population were carriers. Amundadottir et al. [15] indicated that their finding led to a greater estimated PAR of 16% which could contribute to the higher incidence of carcinoma of the prostate gland in African American men in comparison with men who have European ancestry.

Dong et al. [54] reported that a gene from human chromosome 11p11.2 had been isolated and had been shown to suppress metastasis when it was introduced into rat AT6.1 carcinoma of prostate gland cells. Dong et al. [54] stated that expression of this gene, which had been designated KAH, was reduced to human cell lines that had been derived from metastatic tumours of the prostate gland and that KAI1 specifies a protein of 267 aminoacids which has four hydrophobic and presumably trans-membrane domains as well as one large extracellular hydrophilic domain which has three potential N-glycosylation sites. KAI1 tends to be evolutionarily conserved, is expressed in many human tissues and encodes a member of a structurally distinct family of leucocyte surface glycoproteins. Dong et al. [54] stated that decreased expression of the gene could be

involved in the malignant progression of prostate and other carcinomas.

Grönberg et al. [55] stated that it has been suggested that positive family history does constitute a risk factor for the development of carcinoma of the prostate gland and that familial clustering of carcinoma of the prostate gland might indicate that genetic factors are important with regard to the aetiology of the disease. Grönberg et al. [55] stated that in order to elucidate further the relative importance of genetic factors in the aetiology of carcinoma of the prostate gland, they did study carcinoma of the prostate gland among an unselected Swedish twin population. Grönberg et al. [55] used information from the Swedish Twin Registry and the Swedish Cancer Registry. Grönberg et al. [55] reported that in 4,840 male twin pairs, they had identified 458 carcinomas of the prostate gland between 1959 and 1989. They also reported that out of these 16 monozygotic and 6 dizygotic twin pairs had been concordant for carcinoma of the prostate gland. They found pro-band concordance rates of 0.192 and 0.043, and a correlation of liability of 0.40 and -0.05 for monozygotic and dizygotic pairs respectively. Grönberg et al. [55] further stated that the differences in pro-band concordance rates as well as correlations of liability for monozygotic pairs in comparison with dizygotic pairs are pronounced. Grönberg et al. [55] also said that their results indicated that genetic factors might be important with regard to the development of carcinoma of the prostate gland and that the results would allude to the need for further investigations of genetic factors related to carcinoma of the prostate gland, including large scale epidemiological studies and investigations of molecular genetics of risk families.

Visakorpi et al. [56] in 1995 stated that genetic changes that lead to the development of carcinoma of the prostate gland and factors which underlie the clinical progression of carcinoma of the prostate gland are poorly characterized. Visakorpi et al. [56] used comparative genomic hybridization (CGH) to screen for DNA sequence copy number changes along all chromosomes in 31 primary and 9 recurrent uncultured carcinomas of the prostate gland. Visakorpi et al. [56] stated that the aim of their study was to identify those chromosomal regions that contain genes that are important for the development of carcinoma of the prostate gland and to find genetic markers of tumour progression. Visakorpi et al. [56] reported the following results: Their CGH analysis did reveal that 74% of primary carcinomas of the prostate gland showed DNA sequences copy number changes; Losses were 5 times more common in comparison with gains and most often had involved 8p (32%), 13q (32%), 6q (22%), 16q (19%), 18q (19%); and 9p (16%). Visakorpi et al. [56] also reported the ensuing: Allelic loss studies with 5 polymorphic microsatellite markers for four different chromosomes had been undertaken from 13 samples and these showed a 76% concordance with CGH results. With regard to local recurrences that developed during endocrine treatment, there were significantly more gains ($P < 0.001$) and losses ($P < 0.05$) of DNA sequences in comparison with primary tumours, with gains of 8q (found in 89% of recurrences versus 6% of primary tumours), X (56% versus 0%), and 7 (56% versus 10%), as well as loss of 8p (78% versus 32%), being particularly involved. Visakorpi et al. [56] made the following conclusions: Their CGH results had illustrated that losses of several chromosomal regions tend to be common genetic changes in primary tumours suggestive of the fact that deletional inactivation of putative tumour suppressor genes in the aforementioned chromosomal sites would likely underlie the development of carcinoma of the prostate gland. Additionally, the pattern of genetic changes that were observed in recurrent tumours with the frequent gains of 7, 8q, and X would be suggestive of the fact that the progression of carcinoma of the prostate gland and development of hormone-independent growth might have a distinct genetic basis. The aforementioned chromosomal aberrations could have diagnostic utility as markers of progression of carcinoma of the prostate gland.

Zheng S L, et al. [24] conducted a population based, case-control study in Sweden, called CAPS (Cancer Prostate in Sweden). Patients with carcinoma of the prostate gland were identified and recruited from four of the six regional cancer registries within Sweden. Zheng et al. [24] included in the study, patients who had biopsy confirmed or cytologically diagnosed adenocarcinoma of the prostate gland that was diagnosed between July 2001 and October 2003. Zheng et al. [24] reported that out of 3648 men who had been identified as having carcinoma of the prostate gland 3161 (87%) did agree to participate in the study. Zheng et al. [24] intimated that DNA samples from blood specimens were obtained, the tumour-node-metastasis (TNM) stages of the patients, the Gleason grade determined from histological examination of the biopsy specimens, and the levels of serum prostate-specific antigen (PSA) at diagnosis of the disease was available in the

cases of 2893 of the men (92%). The men with adenocarcinoma of the prostate were classified as having advanced disease if they met any of the ensuing criteria: a grade 3 or 4 tumour, spread to nearby lymph nodes and metastasis, a Gleason score of 8 or more, or a serum prostate-specific antigen (PSA) level of greater than 50 ng per millilitre; otherwise the individuals were classified as having localized disease. With regard to the control subjects, they had been recruited contemporaneously with the case subjects and they were randomly selected out of the Swedish Population Registry and matched based upon the expected age distribution of the prostate cancer cases (groups of 5-year intervals) as well as geographic regions. Out of a total of 2149 of 3153 control subjects (68%) who had been invited subsequently accepted to participate in the study. DNA samples from blood were available for 1781 control subjects (83%). Serum PSA levels had been measured for all the control subjects but they were not used as an exclusionary variable. A history relating to carcinoma of the prostate gland among first degree relatives was obtained based upon a questionnaire for both the cases subjects with carcinoma of the prostate gland and control subjects who did not have carcinoma of the prostate gland. Sixteen SNPs had been selected from five chromosomal regions (three at 8q24 and one each at 17q12 and 17q24 which had been reported to be associated with carcinoma of the prostate gland. Polymerase-chain-reaction (PCR) assays and extension primers for the SNPs had been designed by means of MassARRAY software, version 3.0 (Sequenum). PCR and extension reactions had been performed based upon the manufacturer's instructions, and extension product sizes had been determined by using mass spectrometry with the use of the iPLEX system (Sequenum). Duplicate test samples and two water samples (PCR-negative controls), of which the technician was not aware were included in each 96 cell plate. The rate of concordant results between duplicate samples was more than 99%. With regard to the results Zheng et al. [24] reported that sixteen SNPs in five chromosomal regions (three at 8q24 and two at 17q which had been previously implicated in harbouring genes which centre susceptibility to carcinoma of the prostate gland were evaluated. Within the control, each SNP was in Hardy-Weinberg equilibrium (P equal to or greater than 0.05).

Eeles et al. [21] reported that in order to identify common alleles that are associated with the risk of carcinoma of the prostate gland they had undertaken a genome-wide associated study (GWAS) by using blood DNA samples from 1,854 individuals who had clinically detected carcinoma of the prostate gland that was diagnosed at an age equal to or less than 60 years, or with a family history of carcinoma of the prostate gland, and 1,894 population-screened controls who had low prostate-specific antigen (PSA) concentration that was less than 0.5 ng / ml. Eeles et al. [21] analysed the samples for 541,129 SNPs by the use of the Illumina Infinium platform. Eeles et al. [21] confirmed initial putative association with the use of a further 3,268 cases and 3,366 controls. Eeles et al. [21] reported that they had identified seven loci that were associated with carcinoma of the prostate gland on chromosomes 3, 6, 7, 10, 11, 19, and X ($P = 2.7 \times 10^{[-8]}$ to $P = 8.7 \times 10^{[-29]}$. Eeles et al. [21] made the ensuing concluding iterations: They had confirmed previous reports of common loci that are associated with carcinoma of the prostate gland at 8q24, and 17q. Furthermore, they had found that three of the newly identified loci contain candidate susceptibility genes: MSMB, LMTK2, and KLK3.

Taylor et al. [57] stated that annotation of prostate cancer genome does provide a foundation for discoveries which impact the understanding of disease and treatment. They further stated that concordant assessment of DNA copy number, mRNA expression, and focussed exon resequencing in 218 carcinoma of prostate gland tumours identified the nuclear receptor coactivator NCOA2 as an oncogene in ~ 11% of tumours. Taylor et al. [57] summarized findings from their study as follows: The androgen-driven TMPRSS2-ERG fusion was associated with a previously unrecognized, prostate-specific deletion at chromosome 3p14 which implicates FOXP1, RYBP, and SHQ1 as potential cooperative tumour suppressors. DNA copy-number data from primary tumours revealed that copy-number alterations robustly define clusters of low- and high-risk disease beyond that which was achieved by Gleason score.

McCarron et al. [58] stated that polymorphisms within the promoter regions of cytokine genes could influence the development of carcinoma of the prostate gland through regulation of the anti-tumour angiogenesis. McCarron et al. [58] reported 247 patients who had carcinoma of the prostate gland and 263 controls who were genotyped for interleukin (IL)-1ß-511, IL-8-251, IL-10-1082, tumour necrosis factor-a-308, and vascular endothelial growth factor (VEGF)-1154 single nucleotide polymorphs. McCarron et al. [58] reported that the patient control comparisons did reveal that

IL-8 TT and VEGF AA genotypes were decreased in patients in comparison with controls [23.9 versus 32.3%; P = 0.04, odds ratio (OR) = 0.66, 95% confidence interval (CI) 0.44-0.99 and 6.3 versus 12.9%; P = 0.01, OR = 0.45, 955 CI 0.24 – 0.86, respectively]. On the other hand, the IL-10 AA genotype was significantly increased in patients in comparison with controls (31.6 versus 20.6%; P = 0.01, OR = 1.78, 95% CI 1.14 – 2.77). Furthermore, McCarron et al. [58] reported that stratification according to prognostic indicators did reveal association between IL-8 genotype and log prostate-specific antigen level (P = 0.05). McCarron et al. [58] concluded that their results did indicate that single nucleotide polymorphisms was associated with differential production of IL-8, IL-10, and VEGF are risk factors for carcinoma of the prostate gland, by possibly acting through their influence on angiogenesis.

It has been stated by Berger et al [59] that carcinoma of the prostate gland is the second commonest cause of carcinoma in the male in the United States of America; nevertheless, the full range of carcinoma of prostate genomic alterations had been incompletely characterized. They reported the complete sequence of seven primary human carcinomas of the prostate gland and their paired normal counterparts. They stated that several tumours did contain complex chains of balanced (which is, 'copy-neutral') rearrangements which occurred within or adjacent to known cancer genes. They also said that rearrangement breakpoints had been enriched near open chromatin, androgen receptor and ERG DNA binding sites in the setting of ETS gene fusion TMPRSS2-ERG, but inversely correlated with these regions in tumours that lacked ETS fusions. They were of the opinion that their observations would suggest existence of a link between chromatin or transcriptional regulation and the genesis of genomic aberrations. Three tumours did contain rearrangements which disrupted CADM2, and four harboured events that disrupted either PTEN, (unbalanced events), a prostate tumour suppressor, or MAG12 (balanced events), a PTEN interacting protein which had not been previously implicated in prostate tumorigenesis. Hence, genomic rearrangements could arise from transcriptional or chromatin aberracies and engage prostate tumorigenesis mechanisms.

Magee et al. [60] stated that carcinoma of the prostate gland is the commonest diagnosed non-cutaneous cancer in men and despite this fact, many of the genetic changes that coincide with carcinoma of the prostate gland has remained enigmatic. Magee et al. [60] characterized the expression profiles of several benign and malignant samples of the prostate gland and from the specimens they identified several genes that are differentially expressed between the benign and malignant prostate gland specimens. Magee et al. [60] iterated that one gene which was overexpressed encodes the serine protease hepsin. Magee et al. [60] used an independent sample set to ascertain whether or not hepsin is overexpressed in tumours of the prostate gland and they found that in situ hybridization did demonstrate that hepsin is specifically overexpressed within the carcinoma cells themselves. Magee et al. [60] concluded that their findings taken in conjunction with the molecular properties of hepsin would make hepsin an ideal target for the treatment of carcinoma of the prostate gland.

Xu et al. [61] stated that more than 200,000 new cases of carcinoma of the prostate gland are diagnosed in the United States of America per year which would account for greater than 35% of all cases of cancer affecting men, resulting in 40,000 deaths per year in the United States of America. Xu et al. [61] also stated that attempts had been made to characterize genes that predispose to the development of carcinoma of the prostate gland but these attempts had been hampered by a high phenocopy rate, the age of onset of the disease and, in the absence of distinguishing clinical characteristics, the inability to stratify patients into sub-groups relative to suspected genetic locus heterogeneity. Xu et al. [61] further stated that they had previously undertaken a genome-wide search for the hereditary prostate cancer (HPC) genes and had found evidence of prostate cancer susceptibility locus on chromosome 1 which had been termed HPC1. Xu et al. [61] in 1998 also presented evidence for the location of a second prostate cancer susceptibility gene, which by estimates of heterogeneity account for about 16% of cases of HPC. Xu et al. [61] reported that the HPC locus resides on the X chromosome (Xq27-28, and the finding was consistent with the results of a previously undertaken population-based studies that suggested an X-linked mode of HPC inheritance. Xu et al. [61] intimated that linkage to Xq27-28 had been observed in a combined study population which included 360 families that had carcinoma of prostate gland that had been collected at four independent sites in North America, Finland and Sweden. Xu et al. [61] stated that a maximum two-point lod score of 4.60 was observed at DXS1113, 8=0.26, in the

combined data set. Parametric multipoint and non-parametric analyses did provide results that were consistent with the two-point analysis including: evidence for genetic locus heterogeneity was observed, with similar estimates of the proportion of linked families in each separate family collection. Xu et al. [61] concluded that Genetic mapping of the locus represents an important first step in the identification of an X-linked gene implicated in the aetiology of hereditary prostate cancer (HPC).

Eeles et al. [62] in 2009 stated that carcinoma of the prostate gland is the most frequently diagnosed carcinoma in the developed countries. Eeles et al. [62] stated that in order to identify common prostate cancer susceptibility alleles, they had previously undertaken a genome-wide association study in which 541,129 SNPs had been genotyped in 1,854 cases of prostate cancer in patients who had clinically detected disease and in 1,894 controls. Eeles et al. [62] reported that they had extended the study to evaluate promising associations in a second stage in which they had genotyped 43,671 SNPs in 3,650 cases of prostate cancer and3,940 controls and in a third stage involving 16,229 cases and 14,821 controls from 21 studies. Eeles et al. [62] reported that in addition to replication of their previous associations finding, they had also identified seven new prostate cancer susceptibility loci on chromosomes 2, 4, 8, 11, and 22 with P values of $P = 1.6 \times 10^{-8}$ to $P = 2.7 \times 10^{-33}$

Bubendorf et al. [63] stated that the development and progression of carcinoma of the prostate gland is driven by the accumulation of genetic changes, the nature of which has remained incompletely understood and that in order to facilitate high-throughput analysis of the molecular events that take place in primary, recurrent, and metastatic carcinoma of the prostate gland, they had constructed a tissue microarray which contained small 0.6 mm cylindrical samples that had been acquired from 371 formalin-fixed blocks that included 32 cases of benign prostatic hyperplasia, and 223 cases of primary carcinomas of the prostate gland, as well as 54 cases of locally recurrent prostatic carcinomas and 62 cases of metastatic prostatic carcinomas from patients who had hormone-refractory disease. Bubendorf et al. [63] applied Fluorescence in situ hybridization (FISH) to the analysis of consecutive tissue microarray sections with probes for five different genes. With regard to the results, Bubendorf et al. [63] reported the following: High-level (greater than or equal to 3X) amplification were very rare (less than 2%) in primary carcinomas of the prostate gland; nevertheless, within metastases from patients who had hormone-refractory disease, amplification of the androgen receptor gene was found in 22%, MYC in 11%, and Cyclin-D1 in 5% of the cases; within the specimens that were obtained from locally recurrent tumours, the corresponding percentages were 23%, 4%, and 8%. Furthermore, ERBB2 and MMYC amplifications had never been found at any stage of prostate cancer progression. Bubendorf et al. [63] made the following conclusions: FISH to tissue microarray sections do enable high-throughput analysis of genetic alterations that contribute to the development and progression of cancer; their results implicate a role for amplification of androgen receptor in hormonal treatment failure and that of MYC in the metastatic progression of human carcinomas of the prostate gland.

Gudmundsson et al. [64] conducted a genome-wide SNP association study on carcinoma of the prostate on over 23,000 Icelanders, which was followed by a replication study that included over 15,000 individuals from Europe and the United States of America. Gudmundsson et al. [64] reported that two newly identified variants were demonstrated to be associated with carcinoma of the prostate gland: rs5945572 on Xp11.22 and rs721048 on 2p15 (odds ratios (OR) = 1.23 and 1.15; $P = 3.9 \times 10^{-9}$, respectively). The 2p15 variant showed a significantly stronger association with more aggressive, rather than less aggressive, forms of the disease.

Rebbeck et al. [65] evaluated the effect of CYP3A4, a gene that is associated with the oxidative deactivation of testosterone, on the clinical presentation of carcinoma of the prostate gland. They used a polymerase chain reaction-based approach to identify sequence variants of the human CYP3A4 gene. In order to ascertain whether allelic variants of CYP3A4 gene were associated with the stage of tumour, the grade of the tumour, and the age of the patient at the time of diagnosis, Rebbeck et al. [65] determined CYP3A4 genotypes in 230 Caucasian men who had incidental carcinoma of the prostate gland. With regard to the results, Rebbeck et al. [65] reported that they had identified a novel genetic variant (CYP3A4-V), which had an altered 5' regulatory element that contained an A to G mutation, upstream of the CYP3A4 gene. Rebbeck et al. [65] compared the clinical characteristics of carcinomas of the prostate gland in men who did and those who did not carry this genetic variant and found

out that the presence of the CYP3A4-V allele had been associated with a higher tumour-lymph node metastasis (TNM) stage and Gleason grade. The association between CYP3A4 genotype and tumour stage was found to be most pronounced in men who were diagnosed at a relatively old age and who did not have any family history of carcinoma of the prostate gland. Within this group, 46% of men who had stage T3/T4 tumours carried CYP3A4-V, on the other hand, only 5% of the men with stage T1 tumours carried CYP3A4-V (adjusted odds ratio = 9.45; 95% confidence interval = 2.54 – 35.17; x^2 1 = 12.28; two-sided P < 0.001). Rebbeck et al. [65] made the following conclusions: They had determined that a single base change in the 5' flanking region of the CYP3A4 gene was associated with higher clinical stage and grade in men who had tumours of the prostate gland. Their results would suggest that mutations in the CYP3A4 gene could influence carcinogenesis of the prostate gland.

Ghoussaini et al. [66] stated that studies based upon genome-wide association, linkage, and admixture scan analysis had reported associations of a variety of genetic variants in 8q24 with susceptibility to carcinomas of breast, prostate, and colon and rectum. Ghoussaini et al. [66] also added that this locus lies within a 1.18-Mb region which contains no known genes but which is bounded at its centrometric end by FAM84B and at its telemetric end by c-MYC, two candidate cancer susceptibility genes. Ghoussaini et al. [66] stated that in order to investigate the associations of specific loci within 8q24 with specific cancers, they had genotyped, the nine previously reported cancer-associated single-nucleotide polymorphisms across the region in four case-control sets of prostate (1854 case subjects and 1894 control subjects), breast (2270 case subjects and 2280 control subjects), colorectal (2299 case subjects and 2284 control subjects), and ovarian (1975 case subjects and 3411 control subjects) cancer. With regard to the results, Ghoussaini et al. [66] reported that five different haplotype blocks within this gene desert had been specifically associated with risks for the development of carcinomas. One of the blocks was solely associated with risk for the development of carcinoma of the breast, three others were associated solely with the risk for the development of carcinoma of the prostate, and the fifth was associated with the risk for the development of prostate cancer, colorectal cancer, and ovarian cancer, but it was not associated with the risk for the development of breast cancer. Ghoussaini et al. [66] concluded that there are at least five separate functional variants in this region.

Rhodes et al [67] stated that the increasing availability and maturity of DNA microarray technology had led to an explosion of cancer profiling studies and that in order to extract maximum value from the accumulating mass of publicly available cancer gene expression data, methods would be required to evaluate, integrate, and inter-validate multiple datasets. Rhodes et al. [67] demonstrated a statistical model for undertaking meta-analysis of independent microarray datasets and they had reported that implementation of the model had revealed that four prostate cancer gene expression datasets shared significantly similar results, which was independent of the method and technology used (for example, spotted cDNA versus oligonucleotide). Rhodes et al. [67] stated that the inter-study cross-validation approach generated a cohort of genes which were consistently and significantly dysregulated in carcinoma of the prostate gland. Bioinformatic investigation of these genes showed a synchronous network of transcriptional regulation in polyamine and purine biosynthesis pathways. Rhodes et al. [67] also stated that beyond the specific implications for carcinoma of the prostate, their work had established a much-needed model for the evaluation, cross-validation, and comparison of multiple cancer profiling studies.

Conclusions

Genome-wide associated studies had identified alleles which are associated with an increased susceptibility for the development of carcinoma of the prostate gland and these studies rely on presence of genetic variations that are known as single nucleotide polymorphisms (SNPs). Multiple foci had been identified in the 8q24 and in the 17 q region as well as in other chromosomes. Mutations had been found in a number of genes in men with carcinomas of the prostate diagnosed at an early age or at risk for the development of the disease. Reports related to genetic studies undertaken globally are not many and there is no consensus yet regarding the global use of genetic studies relating to men at risk for the development of carcinoma of the prostate. Perhaps a global-wide multicentre trial is required on genetic testing in prostate cancer before oncologists and urologist could agree whether or not genetic testing could be recommended by various urology and oncology associations in the day to day practice of clinicians.

Conflict of Interest: None

References

1. ProstateGene – Genetic testing for prostate cancer URL: https://www.genehealthuk.com/services/prostategene?gclid=CJi_sd6e0M4CFQ2RGwod1zYPlw
2. Humphrey P A. Cancers of the male reproductive organs in: World Cancer Report, Stewart B W, Wild C P, (Eds), World Health Organization, Lyon 2014
3. Siegel R, Ward E, Brawley O, Jernal A. Cancer statistics 2011The impact of eliminating socioeconomic and racial disparities on premature cancer death. CA Cancer J Clin 2011 Jul-Aug; 61(4): 212 - 236
4. Sartor A O, Vogelzang N, Lee W R, Richie J P, Ross M E. Risk factors for prostate cancer UpTODate 2016 Jul 18; http://www.uptodate.com/contents/risk-factors-for-prostate cancer?source=preview&search=epidemiology+of+prostate+cancer&anchor=H41#H41
5. SEER Cancer Statistics Review, 1973 – 1999 http://seer.cancer.gov/csr/1973_1999/Accessed n August 28, 2016
6. Hankey B F, Feuer E J, Clegg L X, Hayes R B, Legler J M, Prorok P C, Ries L A, Merrill R M, Kaplan R S. Cancer surveillance series: interpreting trends in prostate cancer-part 1: Evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. J Natl Cancer Inst 1999 Jun; 91(12): 1017 - 1024
7. Whittemore A S, Wu A H, Kolonel L N, John E M, Gallagher R P, Howe G R, West D W, The C Z, Stamey T. Family history and prostate cancer risk in black, white, and Asian men in the United States and Canada. Am J Epidemiol 1995 Apr 15; 141(8): 732 - 740
8. Hamminki K, Czene K. Age specific and attributable risks of familial prostate carcinoma from the family-cancer database Cancer 2002 Sep 15; 95(6): 1346 - 1353
9. Steinberg G D, Carter B S, Beaty B H, Childs B, Walsh P C. Family history and the risk of prostate cancer. Prostate 1990; 17(4): 337 - 347
10. Zeegers M P, Jellema A, Ostrer H, Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis. Cancer 2003 Apr 15; 97(8): 1894 - 1903
11. Bruner D W, Moore D, Parlanti A, Dorgan J, Engstrom P. Relative risk of prostate cancer for men with affected relatives: systematic review and meta-analysis. Int. J Cancer 2003 Dec 10; 107(5): 797 - 803
12. Valeri A, Cormier L, Moineau M P, Cancel-Tassin G, Azzouzi R, Doucet L, Baschet F, Cussenot I, L'Her J, Berthon P, Mangin P, Cussenot O, Morin J F, Fournier G.. Targeted screening for prostate cancer in high risk families: early onset is a significant risk factor for disease in first degree relatives. J Urol. 2002 Aug; 168(2): 483 - 487
13. Lichtenstein P, Holm N V, Verkasalo P K, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer --- analysis of cohorts of twins from Sweden, Denmark, and Finland. N Engl. J Med. 2000 Jul 13; 343(2): 78 - 85
14. Hemminki K, Ji J, Forsti A, Concordance of survival in family members with prostate cancer. J Clin Oncol 2008; 26: 1705 - 1709
15. Amundadottir L T, Sulem P, Gudmundsson J, Sigurdsson A, Helgason A, Baker A, Agnarsson B A, Sigurdsson A, A, Benediktsdottir K R, Cazier J B, Sainz J, et al. A common variant associated with prostate cancer in European and African population. Mature Genetics. 2006 Jun; 38(6): 652 – 658
16. Freedman M L, Haiman C A, Patterson N, McDonald G J, Tandon A, Waliszewska A, Penney K, Steen R G, Ardlie K, John E M, Oakley-Girvan I, Whittemore A S, Cooney K A, Ingles S A, Altshuler D, Henderson B E, Reich D. Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men. Proc Natl Acad. Sci. USA 2006 Sep 19; 103(38): 14068 - 14073
17. Gudmundsson J, Sulem P, Manolescu A, Amundadottir L T, Gudbjartsson D, Helgason A, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant 8q24. Nature genetics 2007 May; 39(5): 631 – 637 DOI: 10.1038/ng1999
18. Haiman C A, Patterson N, Freedman M L, Myers S R, Pike M C, Waliszewska A, et al. Multiple regions within 8q24 independently affect, risk for prostate cancer. Nat Genet 2007 May; 39 (5): 638 - 644
19. Yeager M, Orr N, Hayes R B, Jacobs K B, Kraft P, Wacholder S, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nature Genetics 2007 May; 39(5): 645 – 649 DOI: 10.1038/ng2022

20. Zheng S L, Sun J, Cheng Y, Li G, Hsu F C, Zhu Y, et al. Association between two unlinked loci at 8q24 and prostate cancer risk among European Americans. J Natl Cancer Inst 2007 Oct 17; 99(20): 1525 - 1533
21. Eeles R A, Kote-Jarai Z, Giles G G, Al Olama A A, Guy M, Jugurnanth S K, et al. Multiple newly identified loci associated with prostate cancer susceptibility Nature Genetics 2008 Mar; 40(3): 316 – 321. DOI: 10.1038/ng.90
22. Thomas G, Jacobs K B, Yeager M, Kraft P, Wacholder S, Orr N, et al. Multiple loci identified in a genome-wide association study of prostate cancer. Nature genetics 2008 Mar; 40(3): 310 – 315: DOI: 10.1038/ng.91
23. Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson J T, Thorleifsson G, Manolescu A, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nature Genetics 2007 Aug; 39(8): 977 – 983. DOI: 10.1038/ng2062
24. Zheng S L, Sun J, Wiklund F, Smith S, Stattin P, Li G, et al. Cumulative Association of Five Genetic Variants with Prostate Cancer. The New England journal of Medicine (NEJM) 2008 Feb 28; 358: 910 – 919: DOI: 10.1056/NEJMoa075819
25. Dong J T. Chromosomal deletions and tumor suppressor genes in prostate cancer. Cancer Metastasis Rev 2001; 20(3-4): 173 - 193
26. Chang B L, Liu W, Sun J, Dimitrov L, Li T, Turner A R, Zheng S L, Isaacs W B, Xu J. Integration of somatic deletion analysis of prostate cancers and germline linkage analysis of prostate cancer families reveals two small consensus regions for prostate cancer genes at 8p Cancer Res 2007 May 1; 67: 4098 DOI: 10.1158/0008-5472.CAN-06-4570
27. Xu J, Dimitrov L, Chang B L, Adams T L, Turner A R, Meyers D A, et al, A combined genome wide linkage scan of 1,233 families for prostate cancer susceptibility genes conducted by the international consortium for prostate cancer genetics. Am. J Hum Genet 2005 Aug; 77(2): 219 - 229
28. Zheng S L, Sun J, Wiklund F, Gao Z, Stattin P, Purcell L D, et al. Genetic variants and family history predict prostate cancer similar to prostate-specific antigen Clin Cancer Res 2009 Feb 1; 15(3): 1105 – 1111 DOI: 10.1158/10778-0432.CCR-08-1743
29. Pritchard C C, Mateo J, Walsh M F, Sarkar N D, Abida W, Beltran H, et al. Inherited DNA-Repair Gene in Men with metastatic Prostate Cancer. N Engl. J Med 2016 Aug 4; 375: 443 – 453. DOI: 10.1056/NEJMoa1603144
30. Agalliu I, Gern R, Leanza S, Burke R D. Associations of high-grade prostate cancer with BRCA1 and BRCA" founder mutations. Clin Cancer Res 2009 Feb 1; 15(3): 1112 – 1120 DOI: 10.1158/1078-0432.CCR-08-1822
31. Mitra A, Fisher C, Foster C S, Jameson C, Barbachanno Y, Bartlett J, et al. Prostate cancer in male BRCA1 and BRCA2 mutation carriers has a more aggressive phenotype. Br J. Cancer 2008 Jan 29; 98(2): 502 – 507 DOI: 10.1038/sj.bjc.6604132
32. Tryggvadottir L, Vidarsdottir L, Thorngeirsson T, Jonasson J G, Olafsdottir E J, Olafsdottir G H, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. J Natl Cancer Inst 2007 Jun 20; 99(12): 929 - 935
33. Narod S A, Neuhausen S, Vichodez G, Armel S, Lynch H T, Ghadirian P, et al. Rapid progression of prostate cancer in men with a BRCA2 mutation Br J Cancer 2008 Jul 22; 99(2): 371 - 374
34. Edwards S M, Evans D G, Hope Q, Norman A R, Barbachano Y, Bullock S, et al. Prostate cancer in BRCA2 germline mutation carriers is associated with poorer prognosis. Br J Cancer 2010 Sep 7; 103(6): :918 – 924 DOI: 10.1038/sj.bjc.6605822
35. Castro F, Goh C, Olmos D, Saunders E, Leongarmornlett D, Tymrakiewicz M, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013 May 10; 31(14): 1748 – 1751 DOI: 10.1200/JCO.2012.43.1882
36. Castro E, Goh C, Leongamornlert D, Saunders E, Tymrakiewicz M, Dadaev T, et al. Effect of BRCA Mutations on Metastatic Relapse and Case-Specific Survival after Radical Treatment for Localized Prostate Cancer Eur. Urol. 2015 Aug; 68(2): 186 – 193 DOI: 10.1016/j.eururo.2014.10.022
37. Bancroft E K, Page E C, Castro E, Lilja H, Vickers A, Sjoberg D, et al. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. Eur. Urol. 2014 Sep; 66(3): 489 – 499 DOI: 10.1016/j.eururo.2014.01.003
38. Genitourinary cancer syndromes In: ASCO Curriculum Cancer Genetics and Cancer Predisposition Testing, 2nd Offitt K, Garber J,

Grady M (Eds), ASCO Publishing, Alexandria 2004; p.10
39. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (accessed on August 26, 2016.
40. Raymond V M, Mukherjee B, Wang F, Huang S H, Staffel E M, Kastrinos F, et al. Elevated risk of prostate cancer among men with Lynch syndrome. J Clin Oncol 2013 May 10; 31(14): 1713 - 1718
41. Tischhkowitz M, Easton D F, Ball J, Hodgson S V, Mathew C G. Cancer incidence in relatives of British Fanconi Anaemia patients. BMC Cancer 2008 Sep 11; 8: 257 DOI: 10.1186/1471-2407-8-257
42. Saunders E J, Dadae T, Leogamornlert D A, Al Olama A A, Benlloch S, Giles G G, et al. Gene and pathway level analyses of germline DNA-repair gene variants and prostate cancer susceptibility using the ICOGS-genotyping array. Br J Cancer 2016 Apr 12; 114(8): 945 - 952
43. Kumar A, Coleman I, Morrisey C, Zhang X, True L D, Gulati R, et al. Substantial interindividual and limited intraindividual genomic diversity among tumors from men with metastatic prostate cancer. Nat Med 2016 Apr; 22(4): 369 – 378.
44. Ewing C M, Ray A M, Lange E M, Zuhlke K A, Robbins C M, Tembe W D, et al. Germline mutations in HOB13 and prostate-cancer risk. N Engl. J Med 2012 Jan 12; 366(2): 141 – 149.
45. Attard G, Clark J, Ambroisine L, Fisher G, Kovacs G, Flohr P, et al. Duplication of the fusion of TMPSS2 to ERG sequences identifies fatal prostate cancer. Oncogene 2008 Jan 10; 27(3): 253 – 263.
46. Kote-Jarai Z, Leongamornlert D, Saunders E, Tymrakiewicz M, Castro E, Mahmud N, Guy M, Edward S, O'brien L, Sawyer E, Hall A, Wilkinson R, Dadnev T, Goh C, Easton D, The UKGPCS Collaborators, Goldgar D, Ecles R. BRCA2 is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients. Br J Cancer 2011 Oct 11; 105(8): 1230 – 1234.
47. Tomlins S A, Rhodes D R, Perner S, Dhanasekeran S M, Mehra R, Sun X-W, et al. Recurrent Fusion of TMPRSS2 and ETS transcription Factor Genes in Prostate Cancer. Science 2005 Oct 28; 310(5748): 644 – 648. DOI: 10.1126/science.1117679
48. Edwards S M, Kote-Jarai Z, Meitz J, Hamoudi R, Hope Q, Osin P, et al. Two Percent of Men with Early-Onset Prostate Cancer Harbor Germline mutations in BRCA2 Gene A J H G 2003 Jan; 72(1): 1 – 12
49. Stanbrough M, Bubley G J, Ross K, Golub T R, Rubin M A, Penning T M, Febbo F G, Balk S P. Increased Expression of Genes Converting Adrenal Androgens to Testtostorone in Androgen-Independent prostate Cancer. Cancer Research 2006 Mar; 66(5): 2815 – 2825. DOI: 10.1158/0008-5472.CAN-05-4000
50. Carter B S, Beatty T H, Steinberg G D, Childs B, Walsh P C. Mendelian Inheritance of familial prostate cancer. The Proceedings of the National Academy of Sciences of the United States of America (PNAS) 1992 Apr; 89(8): 3367 – 3371. DOI: 10.1073/pnas.89.8.3367
51. Eeles R A, Durocher F, Edwards S, Teare D, Badzioch M, Hamoudi R, et al. Linkage Analysis of Chromosome 1q Markers in 136 Prostate Cancer Families. A J H G 1998 Mar; 62(3): 653 – 658
52. Ingles S A, Ross R K, Yu M C, Irvine R A, La Pera G, Haile R W, Coetzee G A. Association of Prostate Cancer Risk With Genetic Polymorphisms in Vitamin D Receptor and Androgen Receptor. JNCI 1997 Jan 15; 89(2): 166 – 170.
53. Cairns P, Okami K, Halachmi S, Halachmi N, Esteller M, Herman J G, Jen J, Isaacs W B, Steven Bova G, Sidransky D. Frequent Inactivation of PTEN/MMAC1 in Primary Prostate Cancer. Cancer Research 1997 Nov; 57(22): 4997 – 5000
54. Dong J T, Lamb P W, Rinker-Schaeffer C W, Vukanovic J, Ichikawa T, Isaacs J T, Barrett J C. KAI1, a metastasis suppressor gene for prostate cancer on human chromosome 11p11.2 Science 1995 May 12; 268(5212): 884 - 886
55. Grönberg H, Damber L, Damber J E. Studies of genetic factors in prostate cancer in a twin population. The Journal of Urology 1994 Nov; 152(5 Pt 1): 1484 – 1487; discussion 1487 – 1491
56. Visakorpi T, Kallioniemi A H, Syvänen A-C, Hyytinen E R, Kahu R, Tammela T, Isola J J, Kallioniemi O-P. Genetic Changes in Primary and Recurrent Prostate Cancer by Comparative Genomic Hybridization Cancer Research 1995 Jan; 55(2): 342 – 347
57. Taylor B S, Schultz N, Hieronymus H, Gopalan A, Xiao Y, Carver B S, et al. Intergrative Genomic Profiling of Human Prostate Cancer.

Cancer Cell 2010 Jul 13; 18: 11 – 22. DOI: 10.1016/j.ccr.2010.05.026
58. McCarron S L, Edwards S, Evans P R, Gibbs R, Dearnaley D P, Dowe A, et al. Influence of Cytokine Gene Polymorphisms on the Development of Prostate cancer. Cancer Research 2002 Jun; 62(12): 3369 – 3372
59. Berger M F, Lawrence M S, Demichelis F, Drier Y. The genomic complexity of primary human prostate cancer Nature 2011 Feb 10; 470(7333): 214 – 220.
60. Magee J A, Araki T, Patil S, Ehrig T, True L, Humphrey P A, Catalona W J, Watson M A, Milbrand J. Expression Profiling Reveals Hepsin Overexpression in Prostate Cancer. Cancer Research 2001 Aug; 61(15): 5692 – 5696
61. Xu J, Meyers D, Freije D, Isaacs S, Wiley K, Nusskern D, et al. Evidence for a prostate cancer susceptibility locus on the X chromosome. Nature Genetics 1998 Oct; 20(2): 175 – 179.
62. Eeles R A, Kotei-Jarai Z, Al Olama A M, Giles G G, Guy M, Seven G, et al. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. Nature Genetics 2009 Sep 20; 41: 1116 – 1121.
63. Bubendorf L, Kunonen J, Kovisto P, Schrami P, Moch H, Gasser T C, Willi N, Mihatsch M J, Sauter G, Kallioniemi P-P. Survey of Gene Amplification during Prostate Cancer Progression by High-Throughput Fluorescence in Situ Hybridization on Tissue Microarrays Cancer Research 1999 Feb; 59(4): 803 – 806.
64. Gudmundsson J, Sulem P, Rafnar T, Bergthorsson J T, Manolescu A, Gudbjartsson D, et al. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer Nature Genetics 2008 Mar; 40(3): 281 – 283.
65. Rebbeck T R, Jaffe J M, Walker A H, Wein A J, Bruce Malkowicz S. Modification of Clinical Presentation of Prostate Tumors by a Novel Genetic Variant in CYP3A4 JNCI J Natl Cancer Inst 1998 Aug; 90(16): 1225 – 1229.
66. Ghoussaini M, Song H, Koessier T, Al Olama A A, Kote-Jarai Z, Driver K E, et al. Multiple Loci With Different Cancer Specificities Within the 8q24 Gene Desert JNCI J Natl Cancer Inst 2008 Jul; 100(13): 962 – 966.
67. Rhodes D R, Barrette T R, Rubin M A, Ghosh D, Chinnaiyan A M. Meta-Analysis of Microarrays Interstudy validation of Gene Expression Profiles Reveals Pathway Dysregulation in Prostate Cancer. Cancer Research 2002 Aug; 62(15): 4427 - 4433

