Abstract

Background: Benign prostate hyperplasia (BPH) is a classical age-related disease of the prostate, present in 20% of men at the age of 40 years with progression to 70% by the age of 60 years. BPH is associated with various lower urinary tract symptoms, which affect their day-to-day life.

Materials and methods: Our objective was to evaluate the association between HER-2/neu, c-myc, p53, and clinicopathological variables in 45 patients diagnosed with benign prostatic hyperplasia using fluorescence in situ hybridization (FISH). The patients underwent transurethral prostate resection to address their primary urological problem. All patients were evaluated by use of a comprehensive medical history and rectal digital examination. The preoperative evaluation also included serum prostate specific antigen (PSA) measurement and ultrasonographic measurement of prostate volume.

Results: The mean (± standard deviation) age of the 45 patients was 69.65 ± 8.97 years. The mean PSA value of the patients was 9.25 ± 5.12 ng/mL. The mean prostate volume was 65.46 ± 11.43 mL. Amplification of HER-2/neu was seen in 4/45 (8.9%) cases and amplification of c-myc was seen in 5 of 45 (11.1%) cases; both genes were not associated with adverse clinicopathological variables. Deletion of p53 was seen in 20/45 (44.4%) cases. p53 gene was significantly associated with a severe AUASI (American Urological Association Symptom Index) score.

Conclusion: In this study, we discussed important genetic markers in benign prostatic hyperplasia patients which may, in the future, be used as markers for diagnosis and prognosis, as well as targets for therapeutic intervention.

Keywords: benign prostatic hyperplasia, BPH, fluorescence in situ hybridization, FISH, genes, amplification, deletion

Zusammenfassung

Hintergrund: Benigne Prostatahyperplasie (BPH) ist eine klassische altersbedingte Erkrankung der Prostata, die in 20% der Männer im Alter von 40 Jahren auftritt mit einer Progression zu 70% im Alter von 60 Jahren. BPH ist mit verschiedenen Symptomen der unteren Harnwege assoziiert, die Auswirkungen auf das Alltagsleben haben.

Materialien und Methoden: Unser Ziel war es, die Verbindung zwischen HER-2/neu, c-myc, p53 und klinisch-pathologischen Variablen bei 45 Patienten mit benigner Prostatahyperplasie unter Anwendung von Fluoreszenz-in-situ-Hybridisierung (FISH) zu bewerten. Bei den Patienten wurde eine transurethrale Prostataresektion durchgeführt, um ihr primäres urologisches Problem zu behandeln. Alle Patienten wurden anhand einer umfassenden Anamnese und einer rektalen digitalen Untersuchung beurteilt. Die präoperative Auswertung umfasste auch die Messung des prostataspezifischen Antigens (PSA) sowie die sonografische Messung des Prostatavolumens.

Ergebnisse: Das mittlere (± Standardabweichung) Alter der 45 Patienten betrug 69,65 ± 8,97 Jahre. Der mittlere PSA-Wert der Patienten betrug
9,25 ± 5,12 ng/ml. Das mittlere Prostatavolumen betrug 65,46 ±
11,43 ml. Amplifikation von HER-2/neu wurde in 4/45 (8,9%) Fällen
und Amplifikation von c-myc in 5 von 45 (11,1%) Fällen gesehen; beide
Gene waren nicht mit nachteiligen klinisch-pathologischen Variablen
assoziert. Eine Deletion von p53 wurde in 20/45 (44,4%) Fällen beob-
achtet. Das p53-Gen war signifikant mit einem hohen AUASI (American
Urological Association Symptom Index)-Score assoziiert.
**Fazit:** In dieser Studie wurden wichtige genetische Marker bei benigner
Prostatahyperplasie diskutiert, die möglicherweise in Zukunft als Marker
für Diagnose und Prognose sowie als Ansatzpunkte für therapeutische
Intervention dienen können.

**Schlüsselwörter:** benigne Prostatahyperplasie, BPH,
Fluoreszenz-in-situ-Hybridisierung, FISH, Gene, Amplifikation, Deletion

### Introduction

Benign prostatic hyperplasia (BPH) is one of the most
common diseases found in adult men [1]. BPH is charac-
terized by the proliferation of smooth muscle cells and
epithelial cells within the prostatic transition zone [1].
The exact etiology and mechanisms underlying BPH de-
velopment and progression are not fully understood [1],
[2]. Benign prostatic hyperplasia mostly develops in a
small region, the transition zone, close to the urethra [3].
Prostatic cancer and benign prostatic hyperplasia are
often found at the same time in elderly men; however,
the relation between the two has been controversial since
their earliest descriptions [4]. The American Urological
Association Symptom Index (AUASI) score is a self-admin-
istered questionnaire, used to assess the severity of three
storage symptoms (frequency, nocturia, urgency) and
four voiding symptoms (feeling of incomplete emptying,
intermittency, straining, and a weak stream) and to help
diagnose BPH. How frequently the patient experiences
each symptom is rated on a scale of 1 to 5 [5].
Cytogenetic information on malignant and benign prostat-
ic tumors is limited because of the difficulties in culturing
prostatic epithelial cells. Although improvements in exist-
ing techniques have been achieved [6], 75% of cytogeneti-
cally investigated prostate tumors, almost exclusively
adenocarcinomas, have shown a normal male karyotype,
and no consistent chromosome change has been associ-
ated with this malignancy [7].

Few studies have been conducted on chromosomal ab-
normalities and gene polymorphisms in patients with BPH
[8], [9], [10], [11], therefore information regarding cyto-
genetic changes in these patients is scarce.

In the current study, we assessed the genetic alterations
of HER-2/neu, c-myc and p53 genes using fluorescence
in situ hybridization (FISH) in Egyptian benign prostatic
hyperplasia patients and investigated the prognostic role
of the three markers and their relation to each other and
to demonstrate their relation to the classical clinicopath-
ological factors.

### Materials and methods

#### Patients

The study protocol was reviewed and approved by the
Ethical Committee of National Cancer Institute, Cairo
University (IRB No. 00004025) and (FWA No. 00007284).
Forty-five consecutive samples from patients diagnosed
with BPH (n= 45) were obtained from the archived collection
at the National Cancer Institute, Cairo, Egypt. The
age of the patients ranged from 42 to 89 years. The pa-
tients were preoperatively considered to have BPH and
underwent surgery for their primary urological problem.
Preoperative evaluation consisted of rectal examination,
transrectal sonography, prostate specific antigen (PSA)
determination, and prostate biopsies, if warranted. Benign
hyperplastic prostate tissue samples were obtained from
adenomectomy (A) and transurethral resection of prostate
(TURP) or from cystoprostatectomy (CP) for invasive
bladder cancer.

#### FISH analysis

For each specimen, 5 µm tissue sections were cut and
placed on positively charged microscope slides. The
blocks were characterised by staining one out of 10
serial sections through the block with haematoxylin and
eosin (H&E) followed by examination by an expert patho-
ologist to confirm that no histological features of adenocar-
cinoma or prostatic intraepithelial neoplasia (PIN) are
present. The specimen slides used for the FISH assay
procedure were within 10 serial sections of the respective
H&E-stained slide to assure minimal separation of the
areas examined by FISH from the areas evaluated by
histopathology. Three slides were set for each case, and
each slide was used for hybridization with a probe cock-
tail, one probe specific for the gene under investigation
and the other specific for the chromosome containing
the gene. For example, the HER-2/neu probe cocktail
consists of a HER-2/neu probe (Spectrum Orange) and
a chromosome 17 centromere-specific probe (Spectrum
Green). All probe cocktails for HER-2/neu, c-myc, and p53
genes were purchased from Abbott Molecular (Des Plaines, IL). Slides were treated in xylene twice for 10 minutes to remove paraffin, denatured in 70% formamide at 70 °C for 3 minutes, and dehydrated in a cooled alcohol series of 70, 80, 90, and 100% for 2 minutes each. Ten microliters of the denatured probe were placed on each slide, covered with a glass coverslip, and sealed with rubber cement. Hybridization was continued overnight at 37 °C. Slides were washed twice in 50% formamide at 47 °C for 2 minutes and twice in 2x standard saline citrate at room temperature for 2 minutes. The slides were stained with DAPI as a counter stain and scanned using a 90i Nikon fluorescent microscope (Chroma Technology, Brattleboro, VT) at a magnification of 1000X. Only intact, non-overlapping nuclei were evaluated; positive signals were required to be bright and of approximately equal intensity among the nuclei. Genes were considered amplified if they showed a gene/centromere ratio of more than 2.2 after counting at least 100 nuclei. Ratio under 2.0 was considered unamplified [12],[13]. For p53, we also defined the FISH score as the percentage of cells for which the nuclei had lost at least one signal. The specificity of the probes and the validity of this method were checked by dual-color FISH using normal prostate sections from five individuals and normal human male peripheral lymphocytes.

Statistical analysis

Data were analyzed using SPSS version 23. Data were expressed as mean ± SD. Bivariate correlations were tested using Pearson’s correlation coefficient for parametric data or Spearman’s rho for non-parametric data. Portions were compared using chi-squared test. Two-tailed p-values were considered statistically significant if they were less than 0.05.

Results

To determine the efficiency of in situ hybridization, normal prostate sections from five individuals and peripheral lymphocytes from normal human male were hybridized with the three probe cocktails. In most of the cells, two orange signals for the single-copy probe (MYC, ERBB2, and TP53), and two green signals for chromosome 17 or 8 were observed.

Table 1 shows the major characteristics of the patients under the study. A total of 45 benign prostate tumor patients were included. The mean age was 69.55 ± 8.97 with a range of 42–89 years. PSA level was 9.25 ± 5.12 ng/mL with a range of 3.28–29.60 ng/mL. The volume of prostate was 65.46 ± 11.43 mL with a range of 47.0–88.0 mL. The PSAD, prostate specific antigen density, was 0.14 ± 0.09 ng/ml/cm³ with a range of 0.04–0.54 ng/ml/cm³. With respect to surgery techniques, 26 patients (57.8%) had adenomectomy, 11 (24.4%) had transurethral resection of prostate, 7 (15.6%) had cystoprostatectomy and one patient (2.2%) had radical retropubic prostatectomy. With respect to the previous treatments, 33 out of 45 (73.3%) had no treatment while 11 (24.4%) had treatment related to transitional cell carcinoma of the bladder. With respect to the severity of BPH, the American Urological Association Symptom Index (AUASI) was used. Three cases out of 45 (6.7%) were mild, 14 (31.1%) were moderate and 28 (62.2%) were severe.

Table 1: Major characteristics of benign prostatic hyperplasia patients

| Number          | 45          |
|-----------------|-------------|
| Age (yrs)       |             |
| Mean ± SD       | 69.55 ± 8.97|
| Range           | 42–89       |
| PSA (ng/mL)     |             |
| Mean ± SD       | 9.25 ± 5.12 |
| Range           | 3.28–29.60  |
| Prostate volume (mL) |         |
| Mean ± SD       | 65.46 ± 11.43|
| Range           | 47.0–88.0   |
| PSAD            |             |
| Mean ± SD       | 0.14 ± 0.09 |
| Range           | 0.04–0.54   |
| Surgery technique|             |
| Adenomectomy    | No (%)      |
| TURP            | 26 (57.8%)  |
| CP              | 11 (24.4%)  |
| RRPr            | 7 (15.6%)   |
| Previous treatment|            |
| Non             | No (%)      |
| TCC             | 33 (73.3%)  |
| Flut            | 11 (24.4%)  |
| AUASI score     |             |
| Mild (1–7)      | 3 (6.7%)    |
| Moderate (8–19) | 14 (31.1%)  |
| Severe (20–35)  | 28 (62.2%)  |

TURP: transurethral resection of prostate, CP: cystoprostatectomy, RRPr: Radical Retropubic Prostatectomy. TCC previous treatment related to transitional cell carcinoma of the bladder, Flut: 3 months Flutamide. PSAD: prostate specific antigen density = PSA (ng/ml)/prostate weight (g).

AUASI: American Urological Association Symptom Index.

Using FISH analysis, we found that 38 of 45 cases (84.4%) patients were disomic, 5 (11.1%) were monosomic, and 2 cases (4.4%) were polysomic for chromosomes 17 in at least 80% of their cells. Thirty-nine out of 45 patients (86.7%) were disomic, 4 (8.9%) were monosomic, and two (4.4) were polysomic for chromosome 8 in at least 80% of their cells (Table 2). Out of the 45 patients, 4 (8.9%) had amplification of HER-2/neu gene (Figure 1), 3 (6.7%) were lacking one HER-2/neu gene and (84.4%) had the normal two copies of the gene present in at least 80% of the cells. Also, out of the 45 patients, 5 (11.1%) patients had amplification of c-myc gene, 3 (6.7%) had one c-myc gene deleted and 37 (82.2%) had the normal two copies of the gene present in at least 80% of the cells. For the p53 gene, 20 patients (44.4%) had evident deletion of at least one copy of the...
gene in a high proportion of cells (Figure 2), whereas 25 (55.6%) patients had the normal two copies of the gene in at least 80% of the cells (Table 3).

**Previous treatment of patients**

Table 4 shows a comparison between patients previously treated from TCC and those without treatment. For chromosome 17, loss or gain was detected in 6 out of 11 (45.5%) patients treated, whereas, in patients with no treatment, only 2 patients out of 33 (6%) showed abnormal number of copies of chromosome 17; the difference in the proportion was significant (p=0.002). For chromosome 8, the proportion of abnormal cases in patients treated was 18.2% which was more than non-treated patients (12.1%) but insignificantly. For gene signals, HER-2/neu showed significant increase in the proportion of abnormalities in patients treated (45.5%) than those not treated (12.1%, p=0.01). For p53 and c-myc copy numbers, no significant difference could be detected.

**AUASI score**

Table 5 illustrates the association between the AUASI score and the copy number of chromosomes and gene signals. p53 gene copy number was the only factor significantly associated with the AUASI score where 71.4% of p53 abnormal copy number was focused in the severe cases whereas the mild and moderate cases had the normal number of gene copies.

**Correlation between the alteration of genes and clinicopathological characteristics.**

Univariate analysis revealed no association between aneuploidy and clinicopathological characteristics of patients. Univariate analysis failed to reveal any significant association between the oncogene copy number and clinicopathologic variables examined. Table 4 shows the correlation between the different variables. Significant correlations were observed between chromosome 8 and chromosome 17 copy numbers (r=0.315, p<0.05, Figure 3A), between chromosome 17 and p53 signals.
Figure 1: Hybridization of BPH sections with probes specific to Her-2/neu gene (orange) and chromosome 17 centromere (green). Two signals for chromosome 17 and more than two signals for the Her-2/neu gene can be seen.

Figure 2: Representative dual-color fluorescence in situ hybridization experiments of BPH patient with centromeric probe of chromosome 17 (green) and p53 gene (orange) showing two signals of chr17 and two or one or zero p53 signal(s).
(r=0.304, p<0.05, Figure 3B) and between chromosome 17 and HER-2/neu signals (r=0.649, p<0.01, Figure 3C). No statistically significant correlation could be detected chromosome 8 copies and HER-2/neu signals (r=0.289, p>0.05, Figure 3D). With respect to the severity of BPH cases (AUASI score), significant positive correlations were observed with the age (r=0.424, p<0.01), PSA (r=0.673, p<0.01), PV (r=0.322, p<0.05) and PSAD (r=0.534, p<0.01). Negative correlation was detected between the severity of cases and P53 copy numbers (r=−0.591, p<0.01, Table 6).
Discussion

Chromosomal changes in normal prostatic tissue and in BPH tissue have been investigated in few studies in contrast to prostate cancer tissues. Miyauchi et al. [14] studied 10 cases of BPH were karyotyped by the G-banding method. Structural analysis disclosed 2 cases of BPH were diploid whereas normal male karyotypes were seen in 6 BPH. Trisomy of chromosomes 7 and 16 were observed in 2 BPH in the same study. Aly et al. [9] found that out of 28 samples of BPH, loss of the Y chromosome was the most common chromosome change, followed by trisomy 7. Visakorpi et al. [15] demonstrated that out of 10 BPH patients, BPH specimens were diploid by DNA flow cytometry and showed no numerical chromosomal aberrations by FISH technique.

Balachandar et al. [16], in 2008, studied 63 BPH and 18 prostate cancer patients. Deletions, translocations, inversions and mosaics were the major chromosomal aberrations observed in the patients regardless their age. Chromosome 1, 7, 16 and Y were affected in BPH patients. In 2010, Balachandar et al. [8] reported major chromosomal aberrations like deletion, translocation, inversion in chromosomes 1, 6, 8, 13, 16, 18 in blood samples of BPH patients. Recently, Altok et al. [17] demonstrated that chromosomal abnormalities were noted in 5 of the 53 cases (9.4%). Loss of the Y chromosome was the most frequent chromosomal abnormality and was observed in three patients (5.7%).

In our study, although the statistical analysis failed to reveal any association between HER-2/neu gene amplification and clinicopathological data, FISH was demonstrated to be an appropriate technique for this type of study. Using FISH, amplification of the HER-2/neu gene was found in 8.9% of our samples. This rate is close to that detected in patients with cervical carcinoma and melanoma (5%–20%). This is in contrast to Edwards et al. [19] who found no abnormalities of HER-2/neu gene copy number, chromosome 17 copy or HER2 gene : chromosome ratio in their study of 28 BPH tissues.

and to estimate their eventual correlations with the genetic alterations of prostatic adenocarcinoma. If the genetic alterations of the adenocarcinoma (epithelial in origin) are also present in nonmalignant BPH (which usually do not evolve to malignancy) and in nonepithelial prostatic tissues, these changes cannot be considered relevant to the origin of prostatic adenocarcinoma.

HER-2/neu gene, a member of the epidermal growth factor receptor (EGFR) family, encodes a transmembrane phosphoprotein. The prognostic significance of HER-2/neu in breast cancer is well established [18]. Controversy remains regarding the significance HER-2/neu in prostate cancer. Edwards et al. [19] showed HER-2/neu amplification in 8% of prostate cancers (using FISH and IHC methods used for HER-2/neu diagnosis in breast cancer) suggesting that HER-2/neu is not involved in early prostate cancer and agrees with the data of Mark and colleagues who assessed HER-2/neu amplification using identical methods [20]. Ross and colleagues reported 41% of prostate tumors with an amplified HER-2/neu [21]. Three other studies found no HER-2/neu amplification [22], [23], [24], although this may be due to sampling errors.

In our study, although the statistical analysis failed to reveal any association between HER-2/neu gene amplification and clinicopathological data, FISH was demonstrated to be an appropriate technique for this type of study. Using FISH, amplification of the HER-2/neu gene was found in 8.9% of our samples. This rate is close to that detected in patients with cervical carcinoma and melanoma (5%–20%). This is in contrast to Edwards et al. [19] who found no abnormalities of HER-2/neu gene copy number, chromosome 17 copy or HER2 gene : chromosome ratio in their study of 28 BPH tissues.
The c-myc oncogene is a transcription factor that has pleiotropic effects on cell growth and differentiation. Amplification or overexpression of c-myc was detected in many human cancers including prostate cancer. Specifically, c-myc mRNA levels were found to be significantly higher in malignant tissues compared to BPH [25], [26]. Amplification of the c-myc locus has been found in some primary prostate tumors and in lymph node metastases [27], [28]. Other studies reported no significant amplification of c-myc expression [29], [30]. Fox et al. [31] showed by immunohistochemical that, detection of c-myc has not provided useful prognostic information for patients with early-stage prostate cancer. In our study, the c-myc oncogene was amplified in 11.1% of BPH samples. Bivariate analysis failed to reveal any significant association between oncogene amplification and the clinicopathologic variables examined. Thus, further study of c-myc gene is required to clarify the role of this oncogene in prostate cancer and in BPH.

p53 gene is the most frequently mutated gene in human cancers. The main function of p53 gene is the prohibition of entrance into the synthetic phase of the cell cycle and the promotion of apoptosis in cells that are incompetent or have damaged DNA [32], [33]. In primary prostate cancer, a relatively low incidence (10–20%) of p53 gene mutations has been described, however, in advanced stages of the disease, the p53 is mutated in 42% of the cases and it is associated with bone metastases and androgen-independent disease [34], [35]. Abnormal p53 expression correlates with high histological grade, high stage and clinical progression of the disease [36] while, it is also correlated with reduced survival after radical prostatectomy [37] and disease onset modulation [38]. p53 mutations are detectable in approximately 19.0% in patients with benign hyperplasia [39]. In our study, deletion of the p53 gene was the most significant finding. Twenty patients (44.4%) had evidence of deletion of at least one copy of p53 in a high proportion of the cells. Significant correlations were detected between chromosome 17 and p53 signals (r=0.304, p<0.05). p53 gene copy number was significantly associated with the AUASI score where 71.4% of p53 abnormal copy number was detected in the severe cases whereas the mild and moderate cases had the normal copy number.

O’Leary et al. [40] studied 4325 men with lower urinary tract symptoms caused by BPH with moderate to severe symptoms (AUASI score >12). Roehrborn et al. [41] found that men with lower urinary tract symptoms (LUTS) & clinical BPH and no history of urinary retention, the AUASI score are useful parameters for clinicians in identifying patients at risk for future prostate surgery.

Conclusion

This is the first report to demonstrate genetic alterations in Egyptian patients with BPH. The most important alteration detected is for p53; it showed abnormal copy number in the majority of our patients. Consequently, deletion of p53, when evident in prostatic adenocarcinoma, cannot be considered specific of or relevant for the genesis of this tumor, but although the patients studied had no evidence of carcinoma, they may still develop prostate cancer or may have a latent disease that was not detected. Indeed, future studies including larger databases of patients, which integrate clinical, pathologic, and molecular oncogene parameters are strongly recommended to identify the possible genetic abnormalities underlying BPH etiopathogenesis. The merging of these data may provide the clinician with an enhancement of prognostic information that accurately predicts the aggressive phenotype for benign prostatic hyperplasia.

Clinical practice points

- No previous reports have been obtained for genetic alterations studies performed on Egyptian BPH patients.
- We recorded 44.44% of deletion of p53 gene.
- The patients studied had no evidence of carcinoma, they may develop prostate cancer. Future studies are recommended to identify the possible genetic abnormalities underlying BPH etiopathogenesis.

Notes

Competing interests

The authors declare that they have no competing interests.

References

1. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, Foster HE Jr, Gonzalez CM, Kaplan SA, Penson DF, Utchaker JC, Wei JT. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol. 2011 May;185(5):1793-803. DOI: 10.1016/j.juro.2011.01.074
2. David M, Berman RR, Velti RW. Development, molecular biology, and physiology of the prostate. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh urology. 10th ed. Philadelphia: Saunders; 2012. p. 2533-69.
3. McNeal JE. Normal histology of the prostate. Am J Surg Pathol. 1988 Aug;12(8):819-33. DOI: 10.1097/00000478-198808000-00003
4. Armenian HK, Lilienfeld AM, Diamond EL, Bross ID. Relation between benign prostatic hyperplasia and cancer of the prostate. A prospective and retrospective study. Lancet. 1974 Jul;2(7873):115-7. DOI: 10.1016/S0140-6736(74)91551-7
5. AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. J Urol. 2003 Aug;170(2 Pt 1):S30-47. DOI: 10.1097/01.ju.0000078083.38675.79
6. Limon J, Lundgren R, Elfving P, Heim S, Kristoffersson U, Mandahl N, Mitelman F. An improved technique for short-term culturing of human prostatic adenocarcinoma tissue for cytogenetic analysis. Cancer Genet Cytogenet. 1990 Jun;46(2):191-9. DOI: 10.1016/0165-4608(90)9185-4

7. Lundgren R, Mandahl N, Heim S, Limon J, Henriksen H, Mitelman F. Cytogenetic analysis of 57 primary prostatic adenocarcinomas. Genes Chromosomes Cancer. 1992 Jan;4(1):16-24. DOI: 10.1002/gcc.2870040102

8. Balachandar V, Kumar BL, Devi SM, Sangeetha R, Manikantan P, Suresh Kumar S, Sudha S, Sasikala K, Dharwatur SN. Identification of chromosome aberrations among benign prostatic hyperplasia patients in Tamil Nadu, Southern India. Int J Hum Genet. 2010;1(1-3):159-64.

9. Aly MS, Dal Ci P, Van de Voorde W, van Poppel H, Ameye F, Baert L, Van den Bergh H. Chromosome abnormalities in benign prostatic hyperplasia. Genes Chromosomes Cancer. 1994 Apr;9(4):227-33. DOI: 10.1002/gcc.2870090402

10. Casalone R, Portentoso P, Minelli E, Righi R, Meroni E, Pozzi E, Chiariavalli AM. Chromosome changes in benign prostatic hyperplasia and their significance in the origin of prostatic carcinoma. Cancer Genet Cytogenet. 1993 Jul;68(2):126-30. DOI: 10.1016/0165-4608(93)90008-A

11. Brothman AR, Lesho LJ, Somers KD, Schellhammer PF, Ladaga LE, Merchant DJ. Cytogenetic analysis of four primary prostatic cultures. Cancer Genet Cytogenet. 1989 Feb;37(2):241-8. DOI: 10.1016/0165-4608(89)90185-4

12. Kallioniemi OP, Kallioniemi A, Kurisu W, Thor A, Chen LC, Smith HS, Waldman FM, Pinkel D, Gray JW. ERBB2 amplification in breast cancer analyzed by fluorescence in situ hybridization. Proc Natl Acad Sci USA. 1992 Jun;89(12):5321-5. DOI: 10.1073/pnas.89.12.5321

13. Sauter ER, Keller SM, Erner S, Goldberg M. HER-2/neu: a differentiation marker in adenocarcinoma of the esophagus. Cancer Lett. 1993 Nov;75(1):41-4. DOI: 10.1016/0304-383X(93)90205-N

14. Miyachi T, Nagayama T, Maruyama K. Chromosomal abnormalities in carcinoma and hyperplasia of the prostate. Nippon Hinyokika Gakkai Zasshi. 1992 Jan;83(1):66-74. DOI: 10.5980/jpnjrno.1989.83.66

15. Visakorpi T, Hyttinen E, Kallioniemi A, Isola J, Kallioniemi OP. Sensitive detection of chromosome copy number aberrations in prostate cancer by fluorescence in situ hybridization. Am J Pathol. 1994 Sep;145(3):624-30.

16. Balachandar V, Mohana SD, Lakshman KB et al. Cytogenetic analysis of benign prostatic hyperplasia (BPH) and prostate cancer (PC) patients from Tamil Nadu, South India. Scientific Research and Essay. 2008;3(5):212-4.

17. Atok M, Baço O, Uml M, Güneş M, Akuyüz M, Uruc F, Uz E, Soyuek S. Chromosomal aberrations in benign prostatic hyperplasia patients. Investig Clin Urol. 2016 Jan;57(1):45-9. DOI: 10.4111/icu.2016.57.1.45

18. Bartlett JM, Going JJ, Mailon EA, Watters AD, Reeves JR, Stanton P, Richmond J, Donald B, Ferrier R, Cocker TG. Evaluating HER2 amplification and overexpression in breast cancer. J Pathol. 2001 Nov;195(4):422-8. DOI: 10.1002/path.971

19. Edwards J, Mukherjee R, Munro AF, Wells AC, Almushatat A, Bartlett JM. HER2 and COX2 expression in human prostate cancer. Eur J Cancer. 2004 Jan;40(1):50-5. DOI: 10.1016/j.ejca.2003.08.010

20. Mark HF, Feldman D, Das S, Kye H, Mark S, Sun CL, Samy M. Fluorescence in situ hybridization study of HER-2/neu oncogene amplification in prostate cancer. Exp Mol Pathol. 1999 Jun;66(2):170-8. DOI: 10.1006/expm.1999.2242

21. Ross JS, Sheehan CE, Hayner-Buchan AM, Ambros RA, Kallakury BV, Kaufman RP Jr, Fisher HA, Ritkin MD, Muraca PJ. Prognostic significance of HER-2/neu gene amplification status by fluorescence in situ hybridization of prostate carcinoma. Cancer. 1997 Jun;79(11):2162-70. DOI: 10.1002/(SICI)1097-0414(19970601)79:11<2162::AID-CNCR14>3.0.CO;2-U

22. Fournier G, Latil A, Amet Y, Abalain JH, Volant A, Mangin P, Floch Ht, Lidereau R. Gene amplifications during advanced-stage human prostate cancer. Urol Res. 1995;23(2):343-7. DOI: 10.1007/BF00296872

23. Budendorf L, Kononen J, Koivisto P, Schraml P, Moch H, Gasser TC, Willi N, Mihatsch MJ, Sauter G, Kallioniemi OP. Survey of gene amplifications during prostate cancer progression by high-throughput fluorescence in situ hybridization on tissue microarrays. Cancer Res. 1999 Feb;59(4):803-6.

24. Sanchez KM, Sweeney CJ, Mass R, Koch MO, Eckert GJ, Geary WA, Baldridge LA, Zhang S, Eble JN, Cheng L. Evaluation of HER-2/neu expression in prostatic adenocarcinoma: a requested for a standardized, organ specific methodology. Cancer. 2002 Oct;95(8):1650-5. DOI: 10.1002/cncr.10839

25. Fleming WH, Hamel A, MacDonald R, Ramsey E, Pettigrew NM, Johnston B, Dodd JG, Matsuski RJ. Expression of the c-myc protooncogene in human prostatic carcinoma and benign prostatic hyperplasia. Cancer Res. 1986 Mar;46(3):1535-8.

26. Buttyan R, Sawczuk IS, Benson MC, Siegal JD, Olsson CA. Enhanced expression of the c-myc protooncogene in high-grade human prostate cancers. Prostate. 1987;11(4):327-37. DOI: 10.1002/pros.2990110405

27. Jenkins RB, Qian J, Lieber MM, Bostwick DG. Detection of c-myc oncogene amplification and chromosomal anomalies in metastatic prostatic carcinoma by fluorescence in situ hybridization. Cancer Res. 1997 Feb;57(3):524-31.

28. Qian J, Hirassawa K, Bostwick DG, Bergstralh EJ, Slezkaj JM, Anderl KL, Borell TJ, Lieber MM, Jenkins RB. Loss of p53 and c-myc overrepresentation in stage T2-3(N1-3)(M0) prostate cancer are potential markers for cancer progression. Mod Pathol. 2002 Jan;15(1):35-44. DOI: 10.1038/modpathol.3880487

29. Mark HF, Samy M, Santoro K, Mark S, Feldman D. Fluorescent in situ hybridization study of c-myc oncogene copy number in prostate cancer. Exp Mol Pathol. 2000 Feb;68(1):65-9. DOI: 10.1006/exmp.1999.2282

30. Savinainen KJ, Linja MJ, Saramäki OR, Tammela TL, Chang GT, Brinkmann AO, Visakorpi T. Expression and copy number analysis of TRPS1, EIF3S3 and MYC genes in breast and prostate cancer. Br J Cancer. 2004 Mar;90(5):1041-6. DOI: 10.1038/sj.bjc.6601648

31. Fox SB, Persad RA, Roys J, Kore RN, Silcocks PB, Collins CC. p53 and c-myc expression in stage A1 prostatic adenocarcinoma: useful prognostic determinants? J Urol. 1993 Aug;150(2 Pt 1):490-4. DOI: 10.1016/S0022-5347(17)35533-7

32. Hughes C, Murphy A, Martin C, Sheils O, O'Leary J. Molecular pathology of prostate cancer. J Clin Pathol. 2005 Jul;58(7):673-84. DOI: 10.1136/jcp.2002.003954

33. Karan D, Linja MJ, Saramäki OR, Tammela TL, Chang GT, Brinkmann AO, Visakorpi T. Expression and copy number analysis of TRPS1, EIF3S3 and MYC genes in breast and prostate cancer. Br J Cancer. 2004 Mar;90(5):1041-6. DOI: 10.1038/sj.bjc.6601648

34. Bookstein R, MacGrogan D, Hilsenbeck SG, Sharkey F, Allred DC. Identification of chromosome aberrations among benign prostatic hyperplasia and their significance in the origin of prostate cancer. Int J Urol. 2016 Jan;95(8):1650-5. DOI: 10.1002/icu.2016.57.1.45

35. Navone NM, Labate ME, Troncoso P, Pisters LL, Conti CJ, von Eschenbach AC, Logothetis CJ. p53 mutations in prostate cancer bone metastases suggest that selected p53 mutants in the primary site define foci with metastatic potential. J Urol. 1999 Jan;161(1):304-8. DOI: 10.1016/S0022-5347(01)62136-0
36. Voeller HJ, Sugars LY, Pretlow T, Gelmann EP. p53 oncogene mutations in human prostate cancer specimens. J Urol. 1994 Feb;151(2):492-5. DOI: 10.1016/S0022-5347(17)35000-0

37. Grignon DJ, Caplan R, Sarkar FH, Lawton CA, Hammond EH, Pilepich MV, Forman JD, Mesic J, Fu KK, Abrams RA, Pajak TF, Shipley WU, Cox JD. p53 status and prognosis of locally advanced prostatic adenocarcinoma: a study based on RTOG 8610. J Natl Cancer Inst. 1997 Jan;89(2):158-65. DOI: 10.1093/jnci/89.2.158

38. Rogler A, Rogenhofer M, Borchardt A, Lunz JC, Knoell A, Hofstaedter F, Tannapfel A, Wieland W, Hartmann A, Stoehr R. P53 codon 72 (Arg72Pro) polymorphism and prostate cancer risk: association between disease onset and proline genotype. Pathobiology. 2011;78(4):193-200. DOI: 10.1159/000326767

39. Schlechte H, Lenk SV, Lönig T, Schnorr D, Rudolph BD, Ditscherlein G, Loening SA. p53 tumour suppressor gene mutations in benign prostatic hyperplasia and prostate cancer. Eur Urol. 1998;34(5):433-40. DOI: 10.1159/000019778

40. O'Leary MP, Roehrborn C, Andriole G, Nickel C, Boyle P, Höfner K. Improvements in benign prostatic hyperplasia-specific quality of life with dutasteride, the novel dual 5alpha-reductase inhibitor. BJU Int. 2003 Aug;92(3):262-6. DOI: 10.1046/j.1464-410X.2003.03410.x

41. Roehrborn CG, McConnell JD, Saltzman B, Bergner D, Gray T, Narayan P, Cook TJ, Johnson-Levonias AO, Quezada WA, Waldstreicher J; PLESS Study Group. Proscar Long-term Efficacy and Safety Study. Storage (irritative) and voiding (obstructive) symptoms as predictors of benign prostatic hyperplasia progression and related outcomes. Eur Urol. 2002 Jul;42(1):1-6. DOI: 10.1016/S0302-2838(02)00210-5

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