RESEARCH COMMUNICATION

Role of Hypercholesterolemia in Prostate Cancer - Case Control Study from Manipal Teaching Hospital Pokhara, Nepal

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Abstract

Objective: The objective of this study was to appraise the role of hypercholesterolemia in prostate cancer among residents of Pokhara valley, Nepal. Materials and Methods: A hospital based retrospective study was carried out using data retrieved from the register maintained in the Department of Biochemistry of the Manipal Teaching Hospital, Pokhara, Nepal between 1st January, 2009, and 31st December, 2010. Descriptive statistics and testing of hypothesis were used for the analysis using EPI INFO and SPSS 16 software. Results: Of the 1,200 subjects, 600 were cancer patients and 600 were controls. In the 600 cases, the mean age was 69.4 ± SD10.21 years, with a preponderance in age group distribution between 65-69 years. The mean value of prostate specific antigen in cases (14.5 ± SD12.3 ng/ml) was markedly raised as compared to controls (1 ± SD 0.52ng/ml) (p= 0.0001). The mean value of total cholesterol levels (237.9 ± 31.2 mg/dl) was also increased along with raised PSA levels in cases when compared with controls (184 ± 33.8 mg/dl) (p= 0.0001). The percentage of cases with HDL normal limits (40 to 60mg/dl) was 72% which did not show much variation when compared to 79% in controls. However, the percentage of cases with LDL borderline high (150-190mg/dl) was 30% and markedly increased when compared to the 5% in controls. Conclusion: The identification of cholesterol as a vital module in signal transduction events in prostate cancer cells has not only bestowed us with new mechanistic insights but has also opened up new avenues for prostate cancer chemotherapeutic intervention.

Keywords: Hypercholesterolemia - prostate cancer - lipid prolife - Nepal

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Introduction

Prostate cancer is generally found to be rare before the age of 50 years and its frequency increases with age. Adenocarcinomas are localized in the peripheral part of prostate gland in 70% of cases and intraepithelial neoplasia is the pre-cancerous lesion observed in most adenocarcinomas (Fournier et al., 2004). Malignant alteration in the cells of prostate and further succession to carcinoma emerges due to series of initiation and promotional events under genetic and environmental influences. Major risk factors such as familial inheritance of prostate cancers, dietary factors, high intake of cholesterol, environmental carcinogens, hormonal milieu, racial and geographical differences, and ethnicity affects the progression of disease (Haas et al., 1997).

Serum PSA is a traditional marker for prostate cancer which allows early diagnosis and hence results in better prognosis. Western diet rich in cholesterol content promotes prostatic cancer development as suggested by epidemiological evidence (Di Vizio et al., 2008). High levels of cholesterol in proliferating tissues reflect their role in carcinogenesis as they have integral role in maintaining functions of biological membranes, cell growth and division, controls the activity of membrane bound enzymes and helps in stabilizing the DNA double helix (Bielecka-Dbrowa et al., 2011). Lovastatin and simvastatin are the inhibitors of rate limiting enzyme of cholesterol biosynthesis and also possess immunomodulatory, anti-inflammatory, antioxidant and growth inhibitory properties (Papadopoulos et al., 2011). They commendably decreased cell sustainability in three prostate cancer cell lines (PC3, DU145, and LnCap) by persuading apoptosis and cell growth arrest at G(1) phase (Hoque et al., 2008). The objective of our study is concerned primarily to evaluate the role of cholesterol in prostate cancer in Pokhara valley.

Materials and Methods

This hospital based retrospective study was carried out using data retrieved from the register maintained in

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Table 1. Distribution of Cases and Controls with Their Family History

	Cases(n=210)	Controls(n=72)	p Value
Father	78,13%	30,5%	0.001**
Brother	72,12%	24,4%	0.0001**
Grand father	6,1%	6,1%	1.000
Father and brother	18,3%	6,1%	0.079
Cousin or uncle	36,6%	6,1%	0.001**
None	390,65%	528,88%	0.0001**

the Department of Biochemistry of the Manipal Teaching Hospital, Pokhara, Nepal between 1st January, 2009 and 31st December, 2010. The variables collected were age, total PSA, total cholesterol, triglycerides, LDL, HDL. Approval for the study was obtained from the institutional research ethical committee.

Estimation of PSA was performed by ELISA reader for all cases and controls. The standard procedure was followed as per manufacturer's instructions for ELISA (Asafudullah et al., 2011). Estimation of total cholesterol and triglycerides was done by CHOD-PAP and GPO-PAP method respectively (Trinder, 1969). All these laboratory parameters were analyzed using Human reagent kits and with the help of ELISA and semi autoanalyser (Humalyser 3500, Germany). Analysis was done using descriptive statistics and testing of hypothesis. The data was analyzed using Excel 2003, R 2.8.0 Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and the EPI Info 3.5.1 Windows Version.

Inclusion criteria- Cases were men with incident, histologically confirmed prostate cancer. Controls were men without clinical cancer who were seen at the same hospital for an annual physical examination. Exclusion criteria- Patients suffering from any other cancer was excluded from our study.

Results

Of the 1200 subjects, 600 were having prostate cancer and 600 were controls. In the 600 cases , the mean age was 69.4 ± SD 10.2 years, with a preponderance in age group distribution between 65-69 years. The mean value of prostate specific antigen in cases (14.5 ± SD12.3 ng/ml) was markedly raised as compared to controls (1 ± SD 0.52ng/ml) (p= .0001). The mean value of total cholesterol levels (237.9 ± 31.2 mg/dl) were also increased along with raised PSA levels in cases when compared with controls (184 ± 33.8 mg/dl) (p= 0.0001). Out of six hundred cases, there was a preponderance of the age group between 65-69 years to develop prostate cancer, projecting the percentage to around 21.8%. Out of six hundred controls, there was a preponderance of age group between 75-79 years, projecting the percentage to around 21.0%.

Table 3. Descriptive Analysis of Variables in Cases and Controls

Variables	Cases(600) Mean values	Controls(600) Mean values	p value
Age (years)	69.4 ± 10.2	67 ± 9.44	0.221
PSA(ng/ml)	14.5 ± 12.3	1.0 ± 0.52	0.0001
Total cholesterol(mg/dl)	238 ± 31.2	184 ± 33.8	0.0001
HDL (mg/dl)	43.4 ± 6.57	43 ± 5.12	0.134
TG (mg/dl)	124.0 ± 29.2	117 ± 25.4	0.0001
LDL (mg/dl)	122.4 ± 35.0	108 ± 28.5	0.0001

PSA, Prostate specific antigen

Table 1 depicts that out of 1200 subjects, cases(217) and controls(72) were having the positive family history. The paternal side of patients have greater chances of getting prostate cancer. Table 2 shows that percentage of each variable in cases and controls differs considerably. The rise of percentage (55%) of serum total cholesterol of higher limits (>240mg/dl) in cases indicates hypercholesterolemia in prostate cancer when compared to percentage (6%) in controls. The percentage of cases with HDL normal limits (40 to 60mg/dl) was 72% and did not show much variation when compared to 79% in controls. Serum LDL level is usually elevated to a lesser degree than serum total cholesterol levels. The percentage of cases with LDL borderline high (150-190mg/dl) were 30% was markedly increased when compared to 5% in controls. The significant number of triglyceride values falls in normal limits both for cases and controls.

Table 2. Variations of Lipid Profile in Cases and Controls

	Cases(no.)	percentage	Controls(no.)	percentage	p value
Total cholesterol					
Desirable(5.17) <200mg/dl	80	13	430	72	0.0001**
Borderline high(5.17–6.21mmol/l) (200 to 240mg/dl)	190	32	130	22	0.0001**
High (>6.22mmol/l) >240mg/dl	330	55	40	6	0.0001**
High-density lipoproteins(HDL)					
Low(<1.03mmol/l) <(40mg/dl)	120	20	102	17	0.181
Normal (1.03- 1.55mmol/l) (40 to 60mg/dl)	430	72	475	79	0.002**
High (>1.55mmol/l) >60mg/dl	50	8	23	3	0.001**
Low-density lipoprotein(LDL)					
Optimal <4mmol/l (<150mg/dl)	402	67	558	93	0.0001**
BoderlineHigh (4.13–4.88mmol/l) (150-190mg/dl)	178	30	30	5	0.0001**
Very high (>4.91mmol/l) (>190mg/dl)	20	3	12	2	0.151
Triglycerides					
Normal (1.69mmol/l) (150mg/dl)	457	76	540	90	0.0001**
Borderline high (1.69–2.25 mmol/l) (150-200 mg/dl)	132	22	54	9	0.0001**
Very high (>2.26mmol/l)(>200mg/dl)	11	2	6	1	0.222

Discussion

The incidence of prostate cancer strongly corresponds to age and disproportionately affects the elderly. Prostate cancer in elderly men is particularly important because of the high incidence and prevalence of disease and mortality in this group of patients. Prostate cancer incidence rates rapidly rise with increasing age starting around age 50 years among Nepalese, with the highest rates seen in those aged between 65 to 80 years. Estimation of PSA has been considered as a very important tumor marker for prostate cancer. PSA level below 4 ng/ml has a low probability of having clinically detectable prostate cancer but its level above 4 ng/ml is considered abnormal. PSA level of 4-10 ng/ml is a diagnostic gray zone and greater than 10 ng/ml strongly suggests prostate cancer. The above results showed significant difference in mean levels of PSA (14.5 ± SD12.3 ng/ml, 1 ± SD0.523 ng/ml) in cases and controls respectively. The increased PSA levels (14.54 ng/ml) in cases indicates that patients were suffering from prostate cancer. Cholesterol as a neutral lipid exists within the lipid bilayer of all mammalian cells and plays an important role in signaling from the cell surface to various subcellular compartments. It accumulates in detergent-resistant membrane domains called lipid rafts. Lipid rafts in turn serve as membrane platforms for signal transduction mechanisms that promotes tumor cell growth, inhibits apoptotic signals and potentially stimulates other malignant cellular behaviors (Freeman et al., 2004).

Survival mechanism of prostate cancer cells is entirely processed via specialized membrane microdomains that are dependent on cholesterol for signal transduction. The present study revealed that majority of patients suffering from prostate cancer had increased levels of serum total cholesterol. The rise in mean levels of serum total cholesterol (237.92 ± SD31.23 mg/dl) was consistent with the increase in mean values of PSA (14.54ng/ml) in cases. In controls, the mean values of PSA (1ng/ml) and total cholesterol (184 ± SD33.77mg/dl) were significantly less when compared with cases. Our findings concurred with the findings of Maqura et al (2008). Hypercholesterolemia in prostate tumor cell membranes results in the coalescence of raft domains. This process inhibits positive regulators of oncogenic signaling within rafts, while maintaining negative regulators in the liquid-disordered membrane fraction (Hager et al., 2006).

The mevalonate pathway, which leads to cholesterol synthesis, plays a key role in controlling cell proliferation by generating prenyl intermediates, particularly farnesyl and geranyl moieties. These isoprenoids covalently modify and thus modulate the biological activity of signal transducing proteins, such as that of the Ras superfamily. The Ras and Rho proteins are known to be involved in cell proliferation, differentiation and apoptosis (Singh et al., 2003). Along with raised serum total cholesterol, mean LDL levels (122.4 ± SD35.0 mg/dl) also increased to some extent due to its enhanced susceptibility to oxidation in prostatic cancer when compared to controls (108± SD28.5 mg/dl). Malondialdehyde (MDA) is an endogenous genotoxic product of enzymatic and oxygen radical-induced lipid peroxidation may cross-link DNA on the same and opposite strands via adenine and cytosine and contributes to carcinogenecity and mutagenecity in mammalian cells (Niedernhofer, 2003). The mean values of HDL in cases (43.39± SD6.57mg/dl) did not show any statistical significance when compared to controls (43 ± SD5.12mg/dl) respectively. Therefore, it can be concluded that elevated plasma cholesterol levels can be a risk for prostate cancer.

In conclusion, the identification of cholesterol as a vital module in signal transduction events in prostate cancer cells has not only bestowed us with new mechanistic insights but has also opened up new avenues for chemotherapeutic intervention.

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