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ARTICLE

Prostatic Intraepithelial Neoplasia and Apoptosis in Benign Prostatic Hyperplasia Before and After the Chernobyl Accident in Ukraine

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The prevalence of prostatic intraepithelial neoplasia (PIN) in men who underwent surgery for benign prostatic hyperplasia (BPH) before and after the Chernobyl nuclear accident was studied. BPH samples were obtained by adenomectomy from 45 patients operated in 1984 before the accident (Group I), and 47 patients from the low contaminated Kiev City (Group II) and 76 from high contaminated area (Group III) operated between 1996 and 1998. Their BPH samples were examined histologically and immunohistochemically. The incidences of prostatic intraepithelial neoplasia (PIN) and high grade PIN (HGPIN) were 15.5 and 11.1% in Group I, 29.8 and 14.9% in Grpoup II, and 35.5 and 19.7% in Group III. The difference between the incidences of PIN in Group I and III is significant ($p<0.02$). There was increased apoptosis in areas of PIN in Group II and III as compared to Group I ($p<0.001$). Since apoptosis has been shown to be associated with ionizing radiation and it is now found to be associated with PIN in patients diagnosed after the Chernobyl nuclear accident, this suggests that long-term low dose internal ionizing radiation potentially may cause prostate cancer. (Pathology Oncology Research Vol 5, No 1, 28–31, 1999)

Key words: prostate, PIN, BPH, apoptosis, ionizing radiation

Introduction

The most serious accident in the history of the nuclear industry occurred on April 1986 at the Chernobyl power plant in Ukraine (70 km from Kiev). It took 10 days to control the disaster, and during this time large quantities of radionuclides were released into the environment with serious consequences to health, environment and the social and economic life of the people of Ukraine. It is important to note that radioactive contamination still exists, and continuously impacts the health of the Ukrainian population.

As of now, 12 years after the accident, about 10 million people who live in the radiocontaminated area of Ukraine have been exposed to low dose ionizing radiation. Cs-134 and Cs-137 constitute 80–90% of the internal exposure in the population. Ninety % of these radionuclides were concentrated and eliminated through urinary excretion.[1] An increase of the incidence of thyroid cancer has been shown in the clean-up workers and people, particularly children, who live in the radiocontaminated areas.[2-6] An increased incidence of bladder cancer in adults has also been reported.[7,8]

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Since the prostate gland is adjacent to the urinary bladder, it is plausible that this gland may also be a target of radionuclides. The present study investigated whether there is any increase in pre-malignant histological and molecular changes that can be associated with radiation exposure in the Ukraine population. HGPIN has been associated with carcinoma,[9-12] and it may be an early lesion identifiable by histological examination in the population exposed to radiation. We have selected three groups of population in Ukraine which represent a varying degrees of internal exposure to radiation for the present study.

Materials and Methods

All BPH patients underwent open adenomectomy in 1984, before the nuclear accident, (Group I) and between 1996 and 1998 (Group II and III) in the Institute of Urology and Nephrology in Kiev, Ukraine were included in this study. They were diagnosed to have BPH due to obstructive symptoms of this disease. No PSA screening was performed for these patients. All of them were smokers. Their characteristics were shown in *Table 1*. Group III patients were from the heavily radio-contaminated area and Group II were from less contaminated area. These patients resided in the same area during the pre- and post-Chernobyl accident.

Surgical specimens were fixed 24 hr in 10% buffered formalin solution, then embedded in paraffin. Sections were stained with hematoxylin and eosin for routine histological examination, as well as for immunohistochemical studies. A total of 12 specimens from each individual were evaluated independently by our co-authors in Budapest, Hungary and Syracuse, New York. PIN was classified into low and high grade according to the criteria defined by Bostwick.[10]

The ApopDETEK Cell Death Assay System (Enzo Diagnostics, USA) and Simply Sensitive Horseradish Peroxidase-DAB in situ Detection System (Enzo Diagnostics, USA) were used to identify apoptosis. Deparaffinized sections were treated with Proteinase K for 20 minutes, then used for detection of apoptotic bodies according to the procedure recommended by the provider. Slides were then counterstained with methyl green. About 2000 prostatic epithelial cells were evaluated for staining results and the index of immunoreactivity, defined as the percentage of positively stained cells, was calculated.

Chi square and students t-test were used for statistical analyses.[13]

Table 1. **Patient characteristics**

	Group I	*Group II*	*Group III*
No. of patients	45	47	76
Year being operated	1984	1996-1998	1996–1998
Median age (range)	67 (58–75)	67 (58–75)	61 (45–72)
Contamination level at inhabiting area (Ci/km^2)	NA	0.5–5	5–30

The contamination data are from ref. 20.

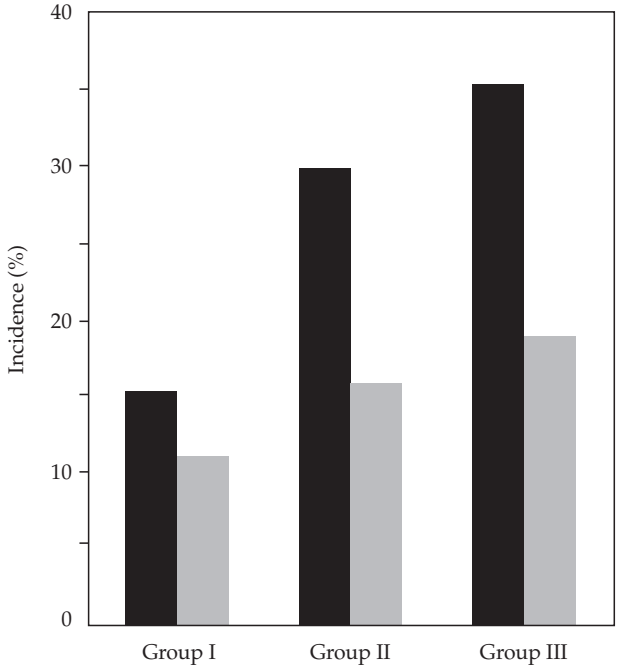

Figure 1. *Incidence of PIN in pre-Chernobyl group (I), low contaminated Kiev City (II), and high contaminated areas (III). Solid and shade bars stand for PIN and HGPIN, respectively. The incidence of PIN is significantly greater in Group III than in Group I ($p<0.02$).*

Results

The incidence of PIN

Microscopically, multiple foci of PIN were usually observed. They were characterized by significant proliferation of moderately or poorly differentiated epithelia within prostatic ducts and acini. PIN and HGPIN were observed in 7 and 5 of 45, 14 and 7 of 47, and 27 and 15 of 76 cases in Group I, II and III, respectively *(Figure 1)*. Only the difference between the incidences of PIN in Group I and Group III is significant ($p<0.02$). Although the incidences of HGPIN followed the order of Group III>Group II>Group I, the difference is not significant ($p>0.05$). None of the samples from any of these groups have lesions of carcinoma.

Apoptosis

The apoptotic indices were greater in PIN than in BPH in all groups. The majority of apoptosis occurred in basal layer cells in the area of PIN and BPH. The apoptotic indices in PIN in Group II and III *(Figure 2)* are significantly greater than in Group I ($p<0.01$ and $p<0.0001$, respectively).

Discussion

The present study has demonstrated a two-fold increase in incidence of PIN in BPH patients who underwent surgery during the period 1996-1998 from the radiocomtaminated areas as compared to analogous patients who have been operated before the Chernobyl accident *(Figure 1)*. However, the increase in the incidence of HGPIN was not statistically significant. Medical management of prostatic disease caused by benign obstruction has not become common in Ukraine, so most bladder outlet obstructions due to BPH are still managed by adenomectomy and the criteria for this procedure have not changed in the last decade. The observed difference in the incidence of PIN cannot be due to bias in clinical variances of BPH. The incidence of HGPIN found in the control group of this study was less than 50-60% reported by Sakr et al,[14] but was higher than 2.5% found in TURP samples from the comparable age group.[11,12] These differences in the incidence of HGPIN observed among these investigators may be due to the difference in the volume of prostatic tissue used for histological evaluation.

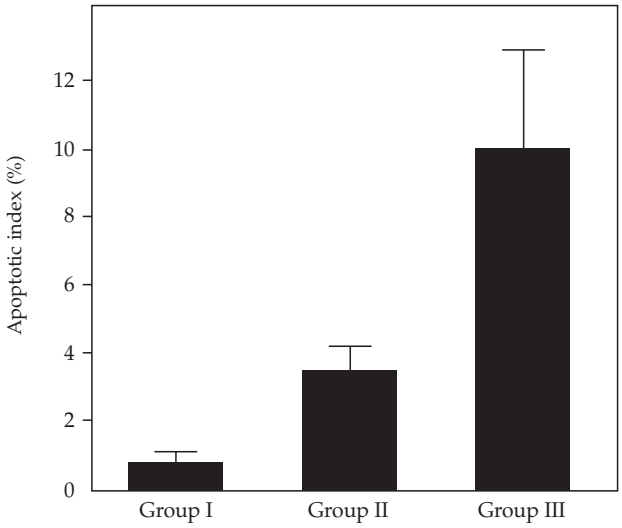

Figure 2. *Apoptotic index in areas of PIN in pre-Chernobyl group (I), low contaminated Kiev City (II), and high contaminated areas (III). The index is significantly greater in Group II and III than in Group I ($p<0.001$). The bar equal to one SD of the mean.*

Development of prostate carcinoma is a multistep process.[15] Alteration of genes, which control the processes of cell proliferation and apoptosis may lead to the appearance of PIN and invasive cancer. HGPIN is associated with progressive abnormalities of phenotype and genotype, which are intermediate between the normal prostatic epithelium and cancer.[10,16] Usually HGPIN arises after the accumulation of several genetic mutations, which include both mutations that activate dominant oncogenes and mutations that inactivate tumor suppressor genes.[15] G1-S arrest connected with DNA damage repair machinery can lead cells to apoptosis as a protective attempt in response to ionizing radiation.[17,18] The observed increase in apoptotic index in PIN *(Figure 2)* supports the interpretation that the PIN may be caused by long-term low dose internal ionizing radiation.

Since most prostate cancers develop in the peripheral zone which was not sampled in our study and PSA was not done on these men prior to surgery, it is quite probable that many early cancers could have been missed in our patients, particularly in the post Chernobyl group. It is interesting to note that neither the incidence nor the mortality of prostate cancer in atomic bomb survivors in the cities of Hiroshima and Nagasaki has increased over the last 50 years.[19] But the contamination level of the long-lived radiation element Cs-137 is thousands of times greater in Ukraine than in these two Japanese cities.[19-21] In summary, the presence in high frequency of histological and molecular changes associated with nuclear instability in the prostate of men exposed to ionizing radiation following the Chernobyl nuclear accident suggests that this type of radiation exposure may be a cause of prostate carcinoma.

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