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Serum Androgen Levels and Sexual Function Before and One Year After Treatment of Uterine Cervical Cancer: A Pilot Study

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ABSTRACT

Introduction: Radiotherapy or radical hysterectomy with salpingo-oophorectomy (SOE) as treatment for uterine cervical cancer causes estrogen deprivation in premenopausal women. The effects on androgen production have rarely been examined but could be relevant for survivors of cervical cancer because insufficiency has been associated with low sexual function.

Aim: To investigate the effects of pelvic radiotherapy, hysterectomy with SOE, or surgery without SOE on androgen levels and to explore potential associations with sexual function.

Methods: Patients with cervical cancer (N = 60) were prospectively examined through blood sampling and questionnaires before and 1 year after treatments.

Main Outcome Measures: Serum testosterone (measured by liquid chromatography and tandem mass spectrometry), sex hormone-binding globulin, androstenedione, dehydroepiandrosterone sulfate, follicle-stimulating hormone, luteinizing hormone, and estradiol levels and Female Sexual Function Index scores.

Results: In women treated with radiotherapy (n = 38), median total and free testosterone levels were significantly decreased at 1-year follow-up compared with baseline in premenopausal women (n = 16; total testosterone −29%, $P = .01$; free testosterone −22%, $P = .007$) and postmenopausal women (n = 22; total testosterone −25%, $P = .03$; free testosterone −29%, $P = .03$). Androstenedione was decreased in premenopausal women only and dehydroepiandrosterone sulfate was decreased in postmenopausal women only after radiotherapy. In women treated with hysterectomy and SOE (n = 10), testosterone levels were lower but not significantly lower, and there was no change in those having surgery without SOE (n = 12). Female Sexual Function Index scores lower than 26.5 in sexually active women were reported by 80% 1 year after radiotherapy, by 44% after hysterectomy with SOE, and by 40% after surgery without SOE, with no significant differences compared with baseline values. No direct correlation between androgen levels and Female Sexual Function Index scores were found at 1-year follow-up.

Conclusion: Total and free testosterone levels decreased slightly but significantly after pelvic radiotherapy in pre- and postmenopausal women. The clinical importance of this decrease is unclear, but androgen levels were not directly related to sexual function in this pilot setting.

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Key Words: Uterine Cervical Cancer; Testosterone; Sexual Function; Radiotherapy; Androstenedione; Female Sexual Function Index

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INTRODUCTION

Common treatments for uterine cervical cancer include radical hysterectomy with or without salpingo-oophorectomy (SOE) and/or radiotherapy in combination with chemotherapy (chemoradiotherapy). After surgical castration or radiotherapy, premenopausal women develop acute estrogen deprivation and are often prescribed hormone therapy (HT) to relieve menopausal symptoms.[1] However, the effects of treatments on androgen levels in this patient group have rarely been studied.

In premenopausal women, approximately 50% of circulating testosterone is produced by direct secretion from the ovary and

the adrenal gland in equal amounts. The remaining 50% is produced from peripheral conversion by adrenal and ovarian androgens (ie, androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate [DHEAS]). In postmenopausal women, testosterone originates mainly from the ovary (50%) and to a lesser extent from the adrenal gland (10%) and from peripheral conversion (40%).[2] Bilateral SOE eliminates all ovarian sources of androgens, and SOE has been associated with a 15% to 50% decrease in serum testosterone.[3–7] The effect of radiotherapy on serum androgen levels in women treated for cervical cancer has been examined in two previous small studies,[8,9] and a significant decrease in testosterone was found only in postmenopausal women.[9]

The term *female androgen insufficiency syndrome* was suggested in 2002 to describe women with low androgen levels and symptoms of fatigue, decreased well-being, and impaired sexual function.[10] In postmenopausal women, testosterone can be used to treat hypoactive sexual desire disorder,[11] and testosterone treatment should be considered for women with premature ovarian insufficiency for maintenance of bone and lean muscle mass and for sexual function.[12] Sexual dysfunction is a commonly reported symptom after cervical cancer treatment,[13] but whether potentially treatable androgen deficiency contributes to sexual dysfunction in survivors of cervical cancer is not known.

AIMS

In this pilot study, we investigated the effects of pelvic radiotherapy, hysterectomy with SOE, and surgery without SOE on androgen levels in women after treatment for cervical cancer. We also explored the potential associations with post-treatment androgen levels and sexual function.

METHODS

Participants

Women of all ages with incident cervical cancer referred to the Karolinska University Hospital (Stockholm, Sweden) from September 1, 2008 through August 31, 2009 were enrolled. Treatment of cervical cancer is centralized in Sweden and all diagnosed women are referred to a designated tertiary hospital that is required to offer an appointment within a few weeks. Women were asked to participate in the study at their first visit to the Karolinska University Hospital, before clinical staging and treatment. Exclusion criteria were inability to communicate in Swedish or World Health Organization performance status of at least 2. Ninety-two patients were eligible and asked to participate, of whom 71 consented (77%). The study was approved by the research ethics committee at the Karolinska University Hospital. Written informed consent was obtained from all participants.

Data Collection

Information on tumor stage (according to the International Federation of Gynecology and Obstetrics system of 1995) and treatment modality was obtained from the patients' medical charts. Blood samples were taken at baseline (before start of treatment) and 1 year after the last treatment. Plasma was stored at −20°C until analysis. For practical reasons, the blood sampling could not be performed systematically by time of day and by day of the menstrual cycle. Menopausal status was determined by baseline serum levels of follicle-stimulating hormone (FSH), and menstruating women with FSH levels no higher than 25 IU/L were considered premenopausal.

Radiotherapy

Chemoradiotherapy included external beam radiotherapy to a pelvic field at 1.8 to 2.0 Gy per fraction, with a total dose of 45 Gy (postoperative treatment) or 50 Gy (definitive treatment), and two to three brachytherapy insertions. Up to six weekly cycles of cisplatin 40 mg/m^2 were given concomitant with the radiotherapy. If brachytherapy was given in combination with chemoradiotherapy as definitive treatment, then the women received 8 Gy per fraction at a pulse-dose rate in an intracervical area. If brachytherapy was given postoperatively, then the women received 5 Gy per fraction vaginally at a high-dose rate. If brachytherapy was given preoperatively, then the women received 19 Gy in an intracervical area on two occasions.

Hormone Measurements

Each hormone analysis was performed at the same time point using the same batch. Serum levels of FSH, luteinizing hormone (LH), estradiol, sex hormone-binding globulin (SHBG), androstenedione, and DHEAS were determined by direct chemiluminescent immunometric assay (Immulite; Siemens, Munich, Germany). Total testosterone was determined by liquid chromatography and tandem mass spectrometry (MS Quattro Premier using Xevo TQ MS software; Waters Corp, Milford, MA, USA). The detection limit was 0.1 nmol/L and within- and between-assay coefficients of variation were 2.7 (7%) and 13 (6%), respectively. Free testosterone was determined by calculations including total testosterone, SHBG, and a fixed concentration of albumin (40 g/L) using the equation of Södergård et al.[14]

Questionnaire

The Female Sexual Function Index (FSFI) is an assessment tool for female sexual function[15] and has been validated in a cancer population that included women with cervical cancer.[16] The 19-item survey assesses six domains of sexual function: desire (two items), arousal (four items), lubrication (four items), orgasm (three items), satisfaction (three items), and discomfort or pain (three items). The responses are graded on a scale from 0 or 1 to 5. Domain scores are obtained by summing the scores of answers to questions in each domain and then multiplying the sum by the domain factor. The total score, which ranges from 2 to 36, is obtained by summing the six domain scores. A higher score means better sexual function. A total score no higher than