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Volatolome of the Female Genitourinary Area: Toward the Metabolome of Cervical Cancer

Miriam Rodríguez-Esquivel,^{a,1} Juan Rosales,^b Rafael Castro,^c Teresa Apresa-García,^a Ónix Garay,^d Pablo Romero-Morelos,^{a,2} Daniel Marrero-Rodríguez,^a Keiko Taniguchi-Ponciano,^{a,2} Ricardo López-Romero,^a Héctor Guerrero-Flores,^c Betsabé Morales,^b Mónica Mendoza-Rodríguez,^e Dejanira Mosso-Lara,^a Itzalia Núñez-Nolasco,^a Paola Castro-Alba,^f Sergio E. Meza-Toledo,^g and Mauricio Salcedo^a

^aLaboratorio de Oncología Genómica, Unidad de Investigación Médica en Enfermedades Oncológicas, UMAE Hospital de Oncología, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Ciudad de México, México

^bFacultad de Química, Universidad La Salle, Ciudad de México, México

^cSoluciones en Instrumentación, SA de CV, Monterrey, N.L., México

^dServicio de Braquiterapia, UMAE Hospital de Oncología, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Ciudad de México, México

^eUniversidad Politécnica de Huatusco, Veracruz, México

^fDirección de Prestaciones Médicas, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Ciudad de México, México

^gDepartamento de Bioquímica, Laboratorio de Quimioterapia Experimental, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Campus Lázaro Cárdenas, Ciudad de México, México

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Background and aims. Different Volatile Organic Compounds (VOCs) obtained from several human fluids (volatolome) has been reported as potential biomarkers for a great variety of diseases including cancer. At present, volatolomic profile data of the female genital area is scarce.

Methods. To identify the VOCs related to the female genitourinary area of healthy and Cervical Cancer (CC)-affected women used a pad, as a non-invasive tool for sample gathering was necessary. Used pads were analyzed by Gas Chromatography–Mass Spectrometry. The data were subjected to Principal Component Analysis looking for a possible spectrum of VOCs that could help identify CC-affected patients. The diagnostic role of the VOCs was validated through Receiver Operating Characteristic (ROC) analysis. The area below the curve and the diagnostic sensitivity and specificity values were also evaluated.

Results. The data showed great differences between female cancer and healthy patients groups; most of these VOCs belonging to the alkanes chemical classes. A group of VOCs were identified as common among CC patients, while others VOCs for healthy females. The ROC curve showed an optimal reach to diagnosis (89%), returning a 93% rate for sensitivity and specificity, indicating the VOCs identified in the samples could differentiate cancer patients from healthy females.

Conclusions. In summary, we have detected and identified specific VOCs from healthy women that are not present in CC-affected females and VOCs specific of CC-affected women. We are strengthening our findings to aid in the detection of VOCs that are potential biomarkers for cervical tumors. © 2018 IMSS. Published by Elsevier Inc.

Key Words: Volatolome, Genitourinary area, Cervical cancer, Biomarkers, Non-invasive.

¹Programa de Doctorado en Nanociencias y Micro-Nanotecnologías, Instituto Politécnico Nacional (IPN), CDMX, Mexico. ²Programa de Doctorado en Biomedicina y Biotecnología Molecular, Instituto Politécnico Nacional, CDMX, Mexico.

Address reprint requests to: Mauricio Salcedo, Laboratorio de Oncología Genómica, Unidad de Investigación Médica en Enfermedades Oncológicas, UMAE Hospital de Oncología, CMNSXXI-IMSS, Av. Cuauhtémoc 330, Col. Doctores, CDMX 06720, México; Phone: (+55) (55) 5627-6900 ext 22706; FAX: (+55) (55) 5627-6900x21210; E-mail: masava89@gmail.com

Introduction

Odorology is a method of identifying human scents, having been mainly applied by the forensic and police investigations, and often supported by trained canines (1–8). In terms of health, odorology has been used in the identification of odor-disease relationships, for example, in bacterial infections such as the rice-water scent in cholera, the scent of cedar in metabolic disease cedar diabetes, or the scent of chlorine in genetic disease and cystic fibrosis, etc. (9,10). There are many reports focused on female genitourinary-tract odor, describing different types of scents that result from personal or environmental factors such as the menstrual period, bacterial vaginosis, lifestyle, etc. These phenomena are still under study (11,12).

On the other hand, since many years ago, it has been proposed that in the carcinogenesis process, a change in cellular biochemistry is present, as well as the concentration and types of metabolites secreted by the cells (13–17). These metabolites, called Volatile Organic Compounds (VOCs), are produced by cellular chemical reactions and provide valuable information about their metabolic conditions (13,18–23). Thus, VOCs comprise a group of molecules with different physical, chemical, and toxicological properties and have been reported as potential biomarkers for a great variety of diseases, including several cancer types such as lung, colorectal, breast, and prostate (24–43). In most of these reports, breath analysis has been successfully used (44,45).

Cervical Cancer (CC) stands in second place in incidence among cancer types in Mexican female population at an alarming 15.5%. Furthermore, its mortality rate of 12.8% (46) makes it an even more important health problem in Mexico and worldwide.

Current standards in CC diagnosis are limited to cytological and colposcopic procedures, in addition to potential early detection of pre-invasive lesions. Nevertheless, a high percentage of false positives and negatives suggest deficiencies in the current diagnostic system, increasing the rate of mortality and aggravating economic impact. Moreover, early cancer diagnosis represents an area of opportunity particularly for developing countries that face more severe issues such as the lack of proper medical and testing facilities.

To this date VOCs associated with the healthy female genitourinary area and those related to CC are still scarce. Therefore, the goal of the present work is to improve current diagnosis system through the implementation of a non-invasive tool that is comfortable for the patient and capable of collecting metabolite to aid in the detection of VOCs of the genitourinary area.

Methods

The Present Work Represents a Descriptive Study in Two Phases

The first phase, the population studied was grouped as follows: a) healthy female volunteers ($n = 15$), some of whom

were recruited from among patients' relatives and hospital employees with no history of cancer (considered as an inclusion criteria for this group), and b) patients diagnosed with CC ($n = 15$) who were assisted or treated at the Brachytherapy Service at the Hospital of Oncology, Centro Médico Nacional Siglo XXI (CMN-SXXI), Mexican Institute of Social Security (Instituto Mexicano del Seguro Social, IMSS), in Mexico City. The Scientific and Ethics Committee of the IMSS (Comisión Nacional de Investigación Científica del Instituto Mexicano del Seguro Social) approved this study, and all samples were taken from participants after signing an informed consent form. In this phase, all subjects analyzed were well confirmed as healthy, or cancer patients previous to any treatment.

In the second phase of the work, the sample pool was broadened by a total of 108 new samples: 56 CC, 8 endometrial, 1 ovarian cancer samples, as well as 42 new healthy samples. Inclusion criteria for the CC group were the following: patients histologically confirmed for the disease through biopsy, any age, and any CC clinical stage. Habits or conditions during pad usage by participants included in some, but not all, cases: use of intimate vaginal soap, consumption of any food, consumption of any drug, use of contraceptives, and smoking. Most of these conditions were previously reported, however (44). The pads used are manufactured and commercially available, composed by cotton and cellulose, of 20×13 cm dimension. Patients with CC during or post-treatment were also included in this phase of the study. All women were always women over 20 years of age.

In general, collection process of cervical VOCs involved the following: to avoid any pitfall molecule (in the hospital rooms), all pads were used overnight at home, deposited by the participant into an individual, sealed packaging bag the following morning and taken to the hospital or clinic for its collection. Under no circumstance were bags opened in the hospital rooms and the latter were always cleaned before use to avoid any contamination. All determinations were conducted outside of the hospital (44).

To avoid if the background of the pad itself will affect in the detected VOCs, two pads not used by women were considered in the general analysis (as negative or internal control), one sterilized and directly analyzed, and another sterilized and deposited into the bag and then analyzed.

All assays were carried out in a double-blind procedure to discern between healthy and cancer cases. All samples were handled while wearing disposable polyethylene gloves. Staff members changed gloves between each pad to avoid sample contamination. Pads were analyzed by means of "HeadSpace" (HS) combined with Gas Chromatography-Mass Spectrometry (GC/MS).

VOCs analysis involved placing each sample in a glass vial and capped with a Teflon-coated silicon septum. Then, HS using the EST Analytical FLEX® Robotic Sampling Platform GC/MS autosampler at 100°C and 70 rpm for 30 minutes

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