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"TERRA DEI FUOCHI, THE STARTING POINT". THE ROLE OF PREVENTION AND COMPLEMENTARY MEDICINE IN THE CLINICAL PRACTICE

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Abstract – *In this issue, we highlight the most relevant discussion presented by speakers in the International Conference on theme Cancer and Pollution titled "Terra dei Fuochi, the starting point" which is held on July 7th, 2018 in Caserta, Italy. The expert faculty has presented the current reports from literature in the fields of newest genomic test suitable in clinical practice for detoxification and pollution. The purpose of the diet treatment and medical prevention was to promote the rebalancing of nutritional minerals, in order to increase the cellular capacity to defend against xenobiotics known to be hazardous. The speakers confirmed the hypothesis that promoting detoxification by changing lifestyle, diet, is the main way to influence the cellular physiology and the intestinal flora (microbiota). In addition, prevention programs by specific diagnostic tests, is necessary for early detect neoplasia, and chronic disease.*

KEYWORDS: *Heavy metal assay, Pollution in Caserta and Naples Area, Complementary medicine, Drug-nutrient interactions.*

INTRODUCTION

"Terra dei Fuochi, the starting point" leading scientists, researchers, politicians, experts and directors of health care services in the scope of cancer prevention to exchange information on their current research progress. Over the past 15 years, in the area of southern Italy called "Terra dei Fuochi" located between Napoli and Caserta town, emerging criticism for pollution and impact on the healthy. However, the clinical medicine has evolved into a multifaceted technology-driven activity whose major purposes are diagnosed and screening for disease, monitoring health and therapeutic response, and gauging deviations from ordinary physiology in humans. We are now toward the inside the era of personalized medicines, which is bringing forth the newest and most powerful science and technology available for the modern-day practice of diagnostic-based medicine. Among the numerous vital areas to consider with diagnostics there are the emerging issues concerning the development of genomic assays and their

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Fig. 1. Flyer of the conference.

use for testing individual patient responses for tailored therapy. Here, we highlight the most relevant discussion presented by speakers in the conference *"Terra dei Fuochi, the starting point"* (Figure 1). At the above faculty have been presented the most recent reports from literature in the fields of newest genomic test suitable in clinical practice.

ORAL SESSIONS

The scientific chief of the meeting Dr. Andrea Del Buono started the daily session.

Dr. Andrea Del Buono, clarifies the issue "Personalized and Detox Diet in the oncology field".

The current literature, accounting the relationship between diet and bioaccumulation of toxic elements, is still very lacking. However, the few works published in this field are extremely significant. Micronutrients intake have a significant effect on the toxicity and carcinogenesis caused by various chemical substances[1]. In addition, Jia et al[2] concluded that a diet low in micronutrients is predisposing to metal toxicity.

The kind of diet that we suggested to our patients is very close to a macrobiotic diet, such as whole grains beans, seasonal vegetables raw and cooked, vegetables, seasonal fruits, fish and white meat. The presence of a minimal quantity of animal protein is essential, on the second hand, because under some conditions the amino acids can modulate the absorption of toxic metals (e.g. Taurine)[3]. We also introduced short periods of caloric restriction, in which we used water and oils (occasionally butter)

to stimulate the mobilization of persistent lipophilic substances in oil reserves and to influence the enterohepatic circle to reduce the re-absorption of the xenobiotic[4]. In addition to the comparison of the percentages of subjects in shortage/excess and the ideal range in the first test and the retest, a control group (benchmark) consisting of residents of the Campania region that supposedly follow a standard diet (library Mineral Test) also used. The differences and the statistical significance in the distribution of individual trace elements was carried out between the study group at the first test and the control group (benchmark) and between the distributions of trace elements of the study group on the retest and the control group (benchmark). The purpose was to provide a statistical significance that went beyond differences in percentages. Nevertheless, which considered the entire distribution of individual trace elements recorded in the study group at the first test and second test (retest) and compare them with a "typical" distribution, that of a population living in the same area that follows a standard diet control group (Table 1).

Dr. A. D'Orta proceeded to examine "Relationship between diet and heavy metals in high-risk areas. The implication for cancer prevention".

Toxic metals are ubiquitous pollutants that enter our bodies through smoking, food, drink, air, water, cosmetics, dyes, orthopedic implants, piercings, tattoos, drugs, clothes, paints and daily objects that tend to bioaccumulate, thereby representing emerging health and environmental hazard[5]. In fact, when not balanced by adequate detoxification, the continuous exposure of the population to these toxins inevitably leads to accumulation along with the resulting increased risk of inflammaging and related chronic diseases[6]. The researchers aim to study dietary factors that modulate the effects of environmental toxicity related to the presence of "heavy metals" to minimize the risk of chronic damage in subjects who are exposing to high-toxicity risk areas[7]. The results show that proper food hygiene that leads to fundamental changes in lifestyle can effectively counter bio-accumulation, thereby representing not only a primary prevention strategy but also acquiring real drug value given the therapeutic effects it produces in existing cases of overt pathology.

Prof. Giulio Tarro, introduced the knowledge-base of "link between cancer mortality and congenital anomalies with the exposure of waste in Campania".

After the first "white" book on "Health and Environment in Campania" (1977), there is a clear failing of the healthy and environmental of populations. Illicit waste removal of toxic waste has led to an increase in tumor and body defect at birth[8]. It is not always known the whole substances contained in the illegal waste garbage. Thus, the incidence of some substances carrying expected carcinogenic effects[8]. Although there is no cancer record for the mapping of cancer cases in the area that can identify a correlation between the incidence of cancers and genetic/environmental cases directly, except for mesothelioma (exposure to asbestos). It is note that the exposure to mutagenic tumorigenic agents makes genetics and epigenetics damage (changes in the germline DNA) through the malfunction of the gene switches, which is transmitted immediately to the next generation. However, epigenetics are emerging fields to clarify tumor growth and progression[9]. This issue may answer the questions about the incidence of cancer and mortality in Campania, being higher than the Italian average.

TABLE 1. Variations between the distribution of the values of individual trace elements on the first hair test and the retest 90 days later.

	Control group resident in the same province (benchmark) (mineral test database first test) (135 subjects)				*Group study (16 subjects)*					
Continuous demographic variables	*Mean*	*Std. Dev.*	*Min*	*Max*	*Mean*	*Std. Dev.*	*Min*	*Max*	*Student's t test*	*p-value*
Years	38.5	18.583	3	72	35.23	19.212	1	75	0.646	0.519

*Between the mean of the distribution of the values of chromium (Cr) at the first examination and the mean of the distribution of the values of chromium (Cr) at the second examination (z = -2.017, p = 0.044). T end significant for the vanadium (V) (z = -1.706; p = 0.088), lead (Pb) (z = -1.810; p = 0.070), chromium (Cr) from 0.5354 ppm to 0.1384 ppm), mercury (Hg), increased from an average of 0.3913 ppm to an average of 1.4644 ppm (greatly increased after the treatment), cadmium (Cd) passes from an average of 0.0221 ppm to an average of 0, 0398 ppm, aluminum (Al) from 11.7045 to 10.1530 ppm

Of course, there is a need for scientific knowledge of polluted sites. We recognize numerous carcinogens present in the products available in this area. Dioxin-related pollution products, derived primarily from the pollution of the water source associated with illicit spills[3]. The most common biggest danger is Heavy metals involved in carcinogenesis, like mercury, tin, lead, antimony, arsenic, thallium, cesium and gadolinium[10].

Prof Paola Rossi, clarified the knowledge-base of "B-glucans from *Grifola frondosa* and *Ganoderma lucidum* in Breast Cancer: an example of Complementary and Integrative Medicine".

Medicinal mushrooms (MMs) are widely used in Asian countries, as a healthy food. Recently, it is emerged the importance of MM as a source of biologically active substances[11]. In particular, *G. lucidum* and *G. frondosa* have potential as immunomodulatory agent and antitumor properties[12]. The primary pharmacological activities are promoted by β-glucans[13]. β-glucans are constituent of the mushrooms wall and constitute a heterogeneous group of glucose polymers with a backbone of β-1,3-linked β-D-glucopyranosyl units with β-1,6-linked side chains of varying distributions and lengths. β-glucans extracted by *G. lucidum* and *G. frondosa* display immunomodulating[12], anti-inflammatory and direct anticancer activity[13]. In particular, in breast cancer, most of the data comes from *in vitro* studies with tumor cell lines and *in vivo* experimental animal models[14,15]. The data obtained has allowed scientists to begin to clarify the molecular mechanisms involved in anticancer activities. Only a minor quantity of research has been performed at the level of clinical trials in patients. More work needs to be completed to define the use of mushrooms, or their isolated compounds, for the prevention and treatment of cancer (Figure 2).

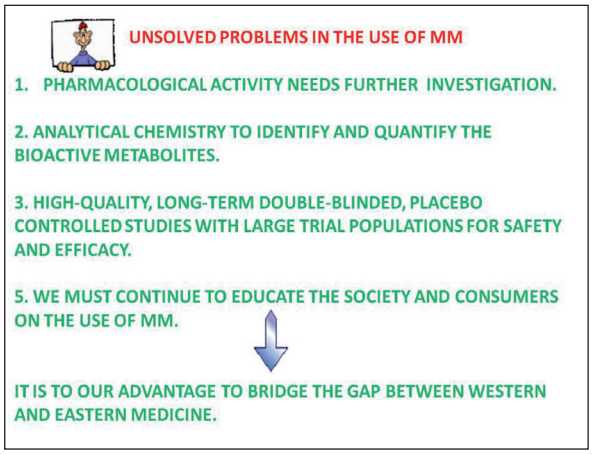

Fig. 2. Flow chart for the use of medical mushrooms.

Prof. Stefania Papa clarified the molecular knowledge-base of "exposure to environmental contamination: hair trace metals analysis".

Since metals are present in the air, soil, food and water, they can enter the body through the skin, the respiratory tract and the digestive system, being excess excreted directly through sweat, hair, urine and excrement. The use of non-conventional matrices, such as hair, in toxicological-environmental analyses, was linked to the possibility of increasing the range in which the investigated substance is detectable in that matrix, in addition to the non-sampling invasiveness. In fact, this range is only a few hours in the blood and it becomes a few days in the urine and months in the hair.

In addition, the xenobiotics deposition (organic substances, metals, etc.) in this tissue can occur both through endogenous and exogenous mechanisms. Sweat glands and direct contact of environmental contaminants with the outer hair surface determine exogenous deposition, in particular. Endogenous deposition, instead, is due to the bloodstream and the sebaceous glands.

The various substances are transported by the blood flow inside the hair matrix through the papilla with a mechanism that has not yet clarified. In particular, the keratinic sulfuryl groups sequester inorganic elements, such as metals. This union takes place continuously during hair growth. Any changes in their content in the fluids regularly recorded in the length direction. The study of these phenomena can provide information both from the diagnostic and toxicological point of view, as well as in the evaluation of nutritional and / or pathological conditions[16].

Hair reflects the total bodily accumulation of the elements better than biological fluids; in fact, the concentration of these is higher, even of an order magnitude, than that found in the blood, serum and urine. In contrast, hair, in addition to being significantly susceptible to exogenous contamination (powders, detergents, cosmetic treatments, etc.), is characterized by the remarkable biological variability (sex, age, ethnic origin, eating habits) that do not allow easy identification of "normal" reference values. In this respect, the aim of this study was to evaluate Sn, Cd, Pb, Se, Ba, Cr, Cu, Ni, Be, Al, V, Fe, Mn, Sb concentrations in women's hair fertile age (20-30 years) along a litoral areas, which falls into two provinces of Campania Region, Naples and Caserta. This area, according to the data provided by the ARPAC, is subject to a high human impact. In addition, since the hair allows us to evaluate the different inputs (endogenous and exogenous), it was also possible to evaluate this. Preliminary data have shown a not uniform accumulation[17]. An endogenous contamination for Cd, Pb, Ba, Cu, Ni, Be, Al, V, Fe, Mn, Sb; an exogenous for Cr; and a mixed one for Se and Sn were detected. Through Kruskal-Wal-

lis (p) test significance coefficient, the data showed a clear and significant accumulation of Sn, Cd, Se, Ni, Al, V and Sb.

Dr. Luigi Montano has presented "EcoFood-Fertlity Project, a new model for assessing environmental impact on human health and for primary prevention: detoxification strategies of the human body to protect the health of current and future generations in environmental risk areas".

EcoFoodFertility is a human biomonitoring study with multidisciplinary approaches involving, environment, life-style and diet, using the qualitative and quantitative alterations of human semen, as a key to understand both the level of environmental quality and its long-term modifications to set out health risks for populations. These conditions must be considered concerning with their living environment as well as diet and lifestyle[18]. We reported data of recent publications about human semen as an early and more sensitive marker than blood. Environmental impact on health, defining the male reproductive system as a "Sentinel Organ" particularly sensitive to exogenous and endogenous stress, is underlined. Ideal to seize the first signs of harmful effects on human health arising from the pollution and human semen as "key" to the relationship between the environment and health[19-21]. The project represents an example of citizen action supported by several environmental groups of the territory and involving different public research institutions. It was born as a response to an environmental and health crisis of so called "Terra dei Fuochi" (Campania Region, Southern Italy) and as a need for truth in the face of contradicting findings and media reports which generated a great deal of distrust in the healthcare system as well as anxiety and alarm within the population. Currently, the project is in progress in different environmentally challenged areas of Italy and Europe and part of it financed by Italian Ministry of Health. In particular, "human seminal model" was used by early detection and prevention of environmental health risks, useful in innovative programs on health surveillance especially in polluted areas. The second step of presentation pointed on lifestyle, dietary with the organic food chain (Eubiotic network of Environmental Health) and nutraceutical approaches with anti-inflammatory, antioxidant and detoxifying properties be effective in mitigating and reducing environmental impact (pollutant bioaccumulation) on human health[22].

Dr. Massimiliano Berretta introduced the known "Complementary and Alternative medicines"

The Complementary and Alternative Medicine (CAM), according to the National Center for Complementary and Integrative Health (USA), are all therapies program outside of the typical Western medicine. It comprises a wide range of products, such as herbs, vitamins, minerals, probiotics, and medical practices, such as acupuncture or magneto-therapy. Such methods or materials are defined 'alternative' when they are used in place of conventional medicine and 'complementary' when they are used together with conventional medicine[23].

Patients with cancer are more likely to choose to CAM, for a variety of reasons; firstly, the unfavorable outcome in a relevant percentage of cases leads patients to 'leave no stone unturned'; secondly, the heavy toxicities, often associated with the traditional antineoplastic therapies, induce them to look for something different from the prescribed therapy or more simply for substances supposed to reduce the side effects from such therapies. However, the literature about CAM in cancer patients is low, especially if we consider only the European publications[24]. Many patients do not declare that they use in auto-prescribing the CAM, probably they considering them 'natural' and unable to interact with the conventional drugs[24].

The use of CAM in oncologic patients is growing, so is fundamental to know the causes are inducing oncologic patients to use CAM, during chemotherapy, inappropriately. Furthermore, the promotion of the knowledge about CAM for the physicians that aim of alerting patients about the potential toxicities is very imperative. It is also significant from an economic issue, as its use is a various billion Euro. In the US was estimated to cost for patients that use CAM in US$ 27 billion (the year 1997)[25]. Finally, appropriate legislation and regulation of CAM therapies in the EU are also necessary. Therefore, information regarding which parameters influence the prognosis would be valuable in the interpretation and design of clinical trials. In the future it could also have implications for the clinical management decisions in the palliative setting care[26].

Dr Raffaele Di Francia, reported a study on "pharmacogenomics of cytochrome P450 family enzymes: implications for drug-nutrients interaction".

Current pharmacogenomics era, which integrates the uniqueness of an individual genetic profile concerning to the pharmacokinetics (PK) and pharmacodynamics (PD) of a drug, provide greater safety and efficacy in drug therapy[26]. Personalized medicine is particularly important in oncology and chronic disease, whereby most clinically used drugs have a narrow therapeutic window. It could be exhibit a large interindividual pharmacokinetic and pharmacodynamic variability when administered with others integrative agents and nutrients together[27]. Each drug, nutrients and xenobiotics from pollution (ie benzopyrenes) after its distribution in the body,

may interacts with several proteins, such as carrier proteins, transporters, metabolizing enzymes, and multiple types of receptors leading not-predictable variability in PK (ie, drug absorption, distribution, metabolism, and excretion) and PD (ie, target site of action, pharmacological and toxicological effects). As a result, the global response to a drug is unpredictability and may lead to therapeutic failure or severe toxicity. The variability could be determined by multiple genes variants that are involved in the PK and PD pathways of a drug/nutrients. An overview on the commonly occurring, functionally and/or clinically relevant genetic polymorphisms within the genes encoding Cytochrome P450 (CYP) superfamily, are necessary, and it is mandatory in the subset of so-called liver-frail patients[28, 29].

The retrospective and prospective trials evaluating the pharmacoeconomic impact of genotyping testing in this phase I and Phase II metabolizing enzymes will provide answers on the possibility to incorporate Pharmacogenomics testing into routine clinical practice[30, 31] .

CONCLUSION AND FUTURE OUTLOOK

This meeting did allow us to state that a change in lifestyle and adequate nutrition education can significantly improve reproducible metabolic parameters. The purpose of the diet treatment and medical prevention was to promote the rebalancing of nutritional minerals, to increase the cellular capacity to defend against xenobiotics known to be hazardous[32-35].The speakers confirmed the hypothesis that promoting detoxification by changing lifestyle, prevention and diet, it is possible to influence the cellular physiology and the intestinal flora (microbiota)[36].

This experience can also assess regarding political economy[37]. Published studies on the cost/benefit conducted with algorithms validated internationally, pose economic and ethical problems and allow to economically quantifying illnesses or deaths spared[37]. The use of these algorithms could contribute to the maximization of resources devoted to the protection of environment and health, transforming a context of uncertainty in a calculable risk[38]. Those who today are cost will become tomorrow for an increase in illnesses and deaths spared. Assuming that the benefits was observed after twenty years, and will last for the next thirty years, the algorithms allow estimating and to quantifying the resources to invest, which must be proportional to the expected result to avoid waste and poorly investments[39]. It is, in our view possible, first by diet control.

Hopefully, the future implementation of functional genomics, will result in personalized treatments, assuming that clinicians can interpret genetic results[40]. Furthermore, the clinical diagnostic laboratory makes assaying of patient samples, delivers the guidelines for standardizing test development, and is the site most likely to standardize genomics testing.

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Conflict of Interest:

None declared/applicable.

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