

INTRODUCTION

I am a medical doctor practicing internal medicine, hematology and oncology for more than 40 years, who has spent the recent 10 years in the field of cervical cancer because my wife, Dr. Olivera Markovic, has discovered that female cervical epithelium contains a bioactive protein (biomarker) which may lead and help them to conquer the fear from cervical cancer, and we together decided to devote our lives for bringing this biomarker to the benefit of all women.

During this period I've seen thousands of women coming to my office for help because of their concerns, fears, physical and psychological problems mostly related to cancer. Very early, I learned that the best way to deal with their problems is to hear the patient's complaints, to examine carefully and to teach them to understand the cause of their concerns and to help them deciding for the best treatment approach available. I also found how profound knowledge of human soul had Hippocrates of Kos (ca. 480–375 BC) who wrote, "In practicing his profession, a doctor can rarely cure, could improve the condition many times, but always must help those who ask for help."

Dr. Olivera Markovic is a medical doctor and a Ph.D. in biochemistry, who was practicing laboratory medicine, but has devoted the last two decades of her professional career to cancer research. She is also a lifetime educator teaching basic medical science, science and health related courses. During the recent years she has taught Women's Health and related courses at local colleges and universities in the Greater Washington Metro Area, where she learned how her students were unprepared for health challenges the adult life is bringing to them and learned how focused education could be both appreciative and successful.

When, because of the biomarker, we both dedicated our lives to women's health, we realized that the best way to accomplish new goals is to combine our research for bringing this biomarker to women's benefit with an appropriate education to help them understanding better the beauty and the risks of being a woman in the modern world, and the opportunities that all women have to protect themselves from cervical cancer. It is sad and unacceptable that millions of women, somebody's mothers, wives, sisters, daughters and granddaughters, still die from a preventable disease in the 21st century. In the period when we were in dilemma what to do first, came 2006 Experimental Biology Meeting in Washington, DC where we met the Springer representative Ms. Christine Dos Santos who inspired us to write a book for Springer who will make it available to all women worldwide.

In the meantime, a major change in the strategy for prevention of cervical cancer occurred. Two pharmaceutical giants, Merck and GSK developed vaccines to immunize women against oncogenic strains of HPV. This achievement has raised hopes for more effective protection from cervical cancer. However, since the way to reach those hopes is long to go (decades), in the meantime, the newest strategy for cervical cancer prevention placed the emphasis on the motto "*no women should be left without cytological screening protection.*"

Today, cytological screening for cervical cancer (Pap test) is not widely available. Only less than 10% of 1.7 billion women at risk have the opportunity to use this test in their developed and resourceful countries. The rest, most of them living in the low-resource

developing countries have not this opportunity. World Health Organization and many governments all over the world are aware of the problems and are struggling to find ways to protect their female population with less expensive screening – but all efforts to replace the standard Pap test have not yet produced convincing results. The alternatives have not been shown to be at least not worse than the cytological testing. Nevertheless, the news about vaccination has spread among women who are now increasingly asking whether, when and how to immunize themselves and their daughters against cervical cancer. Because of the inaccessibility of the best cytological test, the cost of vaccination, uncertainty of long term protection, ineffectiveness in all cancers and many still unresolved questions but great hopes, the public is alerted and women are upset which way to go and how. This is perfect environment for a book like ours to bring a comprehensive insight to the problems as a basic knowledge and reference to web sites where women will be able to follow the updated information.

Finally, because of the grave prognosis of cervical cancer, if not detected and treated on time, and the opportunity for cure if detected, the early detection of cervical cancer or precancerosis, the Pap test, became one of the most regulated medical diagnostic tests in the history. In addition to Federal regulations (CLIA*88 and amendments), many consensus conferences issued guidelines and guidance for medical procedures designed for early detection of cervical cancer and for products to be used in those procedures. All these documents are in public domain and are available for review on the Internet. As much as this “openness” is important for public education, reading this literature without prior knowledge could be a source of unnecessary misunderstanding, frustration and pain for readers. Our book will try to provide women with the basic knowledge, so they will read medical information with better understanding and, hopefully, will not regard the current medical strategies as biblical cannons, but as temporary recommendations made by groups of experts based on their best knowledge and understanding. Emphasizing the transition of rules, we would like to open a window that neither bad diagnostic news are always bad as they look, nor the good news should always be accepted as a total relief – a certain degree of uncertainty must always be present and second opinion asked. This makes the difference between educated and non-educated patient, and could be of importance for women to better protect themselves in their life-long struggle to avoid cervical cancer or to cure it if the first goal was not achieved.

Contents

A Story about This Book and the Authors	vii	
Acknowledgments	xiii	
Introduction	xv	
1 The Female Reproductive System in Health and Disease	1	
1.1 Basic Anatomy of the Female Reproductive System	1	
1.1.1 The Ovaries	1	
1.1.2 Fallopian Tubes	4	
1.1.3 The Uterus	4	
1.1.4 The Vagina	5	
1.1.5 The Vulva and the Perineum	5	
1.2 Basic Physiology of the Female Reproductive System	6	
1.2.1 Female Hormones	6	
1.2.2 The Menstrual Cycle	6	
1.2.3 Pregnancy	8	
1.2.4 Menopause	9	
1.3 An Overview of the Most Common Women's Diseases	10	
1.3.1 Menstrual Disorders	10	
1.3.2 Other Disorders	12	
1.3.3 Common Infections in Women	13	
1.3.4 Sexually Transmitted Diseases	15	
1.4 Tumors of the Female Genital System	18	
1.4.1 Benign Tumors	19	
1.4.2 Malignant Tumors Other than Cervical Cancer	20	
2 Cervical Cancer	23	
2.1 About Cervical Cancer and Pre-cancerosis in this Book	23	23
2.1.1 Introduction	23	
2.1.2 Definition	24	
2.1.3 Interpretation	26	
2.2 Epidemiology of Cervical Cancer	29	29
2.3 Prevention and Control of Cervical Cancer	41	
2.3.1 Risk Factors and Education to Reduce Their Influence	43	
2.3.2 Cancer Control: Cervical Cancer/Pre-cancerosis Screening	54	
2.3.3 Non Cytology-Based Cervical Cancer Screening	82	
2.3.4 Management of Women When the Pap Test Result Returns	88	
2.3.5 Biomarkers and Cervical Cancer	96	
2.3.6 Human Papilloma Virus and Cervical Cancer	110	
2.4 Diagnosis and Treatment of Cervical Cancer	119	119
2.4.1 Diagnostic Methods	120	

2.4.2 Staging System	128	
2.4.3 Planning Therapy	131	
2.4.4 Cervical Cancer Treatment	132	
2.5 Prognosis of Cervical Cancer and How to Improve it	140	
3 Coping and Living with Cervical Cancer	149	
3.1 Coping	149	
3.1.1 How to Cope When the Result is Abnormal Pap Test?	150	
3.1.2 The Diagnosis is Cervical Cancer	152	
3.1.3 Support from Caregivers and Close Family in Day-by-Day Coping with the Disease	153	
3.1.4 Support of Extended Family and Friends	156	
3.1.5 Support Groups	156	
3.2 Living with Cancer		157
3.2.1 Complementary and Alternative Medicine	158	
3.2.2 Holistic View of Health and Wellness	160	
3.2.3 Which are Other Dimensions of Health Described as a Holistic Health Model?	162	
3.2.4 How We can Achieve a Higher Level of Wellness Across all Dimensions of Health?	162	
3.2.5 Understanding the Mechanism of Stress	166	
3.2.6 Stress Release Strategies	168	
3.2.7 An Overview on Eating for Optimal Health in Cancer Prevention and Cervical Cancer	174	
3.3 Stories from Real People	175	
3.4 Survey on What Women Think About Pap Test	184	
3.4.1 Background	184	
3.4.2 Identifying the Problem	185	
3.4.3 Addressing the Problem – Study	185	
3.4.4 Study Results and Analysis	186	
3.4.5 Interim Conclusion	188	
3.5 Where to Read More?	189	
Literature Cited	195	
Afterword	207	
Index	211	

AFTERWORD

The manuscript for the book *What Every Woman Should Know about Cervical Cancer* was submitted for publishing on September 30, 2007. The next month, the *2006 Consensus Guidelines for the Management of Women with Abnormal Cervical Cancer Screening Tests*, were published in the October, 2007, issue of the *Journal of Lower Genital Tract Disease* and in the October, 2007, issue of the *American Journal of Obstetrics and Gynecology*.

The major difference between these 2006 Guidelines and the previous 2001 Guidelines, recommended by the same consensus conferences, is (1) the introduction of HPV DNA testing in the primary screening for cervical cancer and (2) adjustments made in the management of women with HPV DNA +/- tests. The adjustments were necessary to limit the fast mounting cost of cervical cancer screening caused by the HPV testing. It is important to note that the authors of this clinical practice guidance document, in the preamble stated clearly "these guidelines should never substitute for clinical judgment" giving back the power of decision to doctors and ultimately to patients themselves. This statement is a great support to our book and to our objective to help women understand the value of testing and medical options and to make them educated patients who could contribute to the right diagnosis and treatment of their own conditions.

In the follow-up, along with the promotion of HPV testing, many limitations were noted, and the regulatory agencies (FDA, CDC), professional societies (CAP, ASC, ASCP) and even manufacturers of HPV vaccines and HPV tests, indicated that the annual cytological testing should be considered as the gold standard not as an unnecessary alternative to the more complicated new testing. American Cancer Society (ACS) acknowledged the HPV testing, but did not change their 2003 *ACS Guidelines for Early Detection of Cancer*, where Pap test (cytological screening) is the pivotal laboratory instrument to measure women's risk for cervical cancer.

Introduction of HPV DNA testing into the primary screening has brought one big accomplishment; the Pap test is again recognized as the best test for cervical cancer control worldwide. Together with HPV vaccination (cancer prevention) the Pap test is becoming our hope for eradication of cervical cancer in 21st Century. This change of perception has set aside the work of WHO, IARC Cervical Cancer Screening Group, PAHO, PATH, JHPIEGO and other members of the Alliance for Cervical Cancer Prevention who considered Pap test as an unaffordable luxury for cervical cancer screening in low resource countries, and recommended alternative methods such as visual inspection with acetic acid (VIA), DNA HPV testing alone, and/or one-visit screen-and-treat approaches. Now, Pap test (cytological cervical cancer screening) is again the first priority, but the new question is what type of primary screening to be used. All of these options are addressed in our book.

Another major event, already discussed in this book, was the introduction of HPV vaccines (Merck's Gardasil, and Glaxo SmithKline's Cervarix). This accomplishment has risen hopes that cervical cancer could be prevented by global vaccination (eliminate the HPV viral strains that can cause cervical cancer by eliminating them from the population) and lot of money and effort was given to recruit people worldwide to accelerate the access of vaccines to the developing world.

The difference, between the day the manuscript for this book was submitted and the day it is published, was made by an enormous effort given to support those universal noble hopes. Supported by Melinda and Bill Gates Foundation, PATH has launched worldwide marketing to raise awareness of the preventability of cervical cancer deaths among all women in the world (1.7 billion at risk). A *Call to Stop Cervical Cancer*, which has been a logo for this campaign, is now beginning to institutionalize these activities into marketing entities coordinated by PATH. More information is available at <http://www.cervicalcanceraction.org>

We have joined the campaign *Call to Stop Cervical Cancer* with a wish to contribute to this noble cause providing women with evidence-based information, which could educate them for making better decision about their own protection from cervical cancer. Namely, stopping cervical cancer with vaccination, today, is only a wish until more effective vaccines are developed. Current vaccines cover only four HPV strains (out of at least 100) and are intended only for sexually naïve girls. Once infected with HPV, a woman remains infected for life with a weak natural immunity that clears the clinical signs until reinfection or reduction of immunity occurs. The current vaccine cannot add to or change this immunity. New vaccines are necessary. We hope that in the 21st Century this technical barriers will be overcome and there will be vaccines for all types of HPV and vaccines or other immuno-therapies for non-infected and infected women alike; but, this time has not come yet, and a caution is needed to prevent general public disappointment (with all negative repercussions) when vaccinated women will start getting cervical cancers. To prevent this disappointment, all agencies involved in cervical cancer prevention and control insist on keeping cervical cancer screening programs alive for 10, 20 and more years

On the 4th of February, World Cancer Day, the International Agency for Research on Cancer (IARC) has published *2007 Annual World Cancer Data Update* and *2008 Cancer Challenges*. The first, among General Challenges is “To prevent those cancers that can be prevented.” Two Specific Priorities are also related with cervical cancer, “To implement what is known to reduce risk” and “To develop concerted action against cancer of the cervix.”

The call for “concerted action” was long due. Today, we have available tools for successful cervical cancer control (cytological screening in different versions), tools for cervical cancer prevention are in the beginning of promising development (HPV vaccination), but we lack a substantial progress in cervical cancer therapy—surgical removal of early lesions that could develop into cancer is still the only therapy providing cure. This is why IARC is highlighting cervical cancer prevention and control.

The *Call to Stop Cervical Cancer* is also dedicated to prevention and control. The programs for development of new vaccines and programs to increase the awareness of vaccine protection are underway and well organized. Cervical cancer control is entangled with some confusion because of different options. The major dilemma is what examining procedure and what type of laboratory technique to recommend for mass cervical cancer screening worldwide. The stance of this book is to keep the tradition until the new option proves its superiority. It means, regular annual cervical cancer screening with a biomarker-based cytological test, similar to the conventional Pap test or liquid-based Pap with HPV testing in addition (if necessary).

We see our contribution in this direction with development of Home Test and MarkPap Digital, two options available only because of our biomarker previously discussed in this book. We also believe that the medical device industry and the health care providers will join our vision to do whatever is possible to:

- Make the collection of material and primary screening more affordable and more comfortable for every woman via development of new devices (e.g., Home Test).
- To improve the accuracy of diagnosis by introducing telecytology digital screening procedures (based on biomarker-based cytology, digital imaging and on-line communication) between field sites where specimen is taken and processed and the remote screening sites where digital images of positive specimens are examined.

In addition to the better and new HPV vaccines, we expect, these two accomplishments, Home Test and Digital Screening to become operational new tools for response to the unmet goals summarized in the *Call to Stop Cervical Cancer* in the 21st Century.