MATERNAL AND CHILD HEALTH: A GLOBAL PERSPECTIVE

Editors

Uwe Gross
- Institute for Medical Microbiology, Gerog-August University Goettingen, Germany

Yadi
- Department of Microbiology Faculty of Medicine Mulawarman University, Indonesia

Ni Nyoman Ayu Dewi
- Department of Biochemistry Faculty of Medicine Udayana University, Indonesia

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LIST OF AUTHORS

A.A. Raka Budayasa
Department of Obstetrics and Gynecology,
Sanjiwani Hospital, Gianyar-Bali
Email: rakabudayasa@ymail.com

Andri Pramesyanti Pramono
Department of Biology. Faculty of Science and Technology,
University of Al-Azhar Indonesia, Jakarta. email:
apramesyanti@gmail.com, pramesyanti@yahoo.com

Andrew Joachim Makoi
Dar-Es-Salaam, Tanzania
email: amakoi2001@yahoo.com

Bate Betsy Efudem
Paediatric Unit, Regional Hospital,
Buea Cameroon

Citra Dewi
Department of Obstetrics and Gynecology,
Faculty of Medicine, University of Indonesia
email: wang.cide@gmail.com

Dwi Bahagia Febriani
Department of Child Health, Medical Faculty,
Hasanuddin University

Edward Nketiah-Amponsah
Department of Economics
University of Ghana, Legon, Accra
email: enamponsah@ug.edu.gh, enamponsah@daad-alumni.de

Eric Bertrand Fokam
Department of Zoology and Animal Physiology,
University of Buea, Cameroon,
email: efokam@yahoo.com

Geraud Canis Tasse Taboue
Department of Zoology and Animal Physiology,
University of Buea, Cameroon

Gerhard Jahn
University Hospital of Tübingen Institute for Medical Virology and Epidemiology of Viral Disease Elfriede-Aulhorn-Str. 6 D-72076 Tübingen
email: gerhard.jahn@med.uni-tuebingen.de

Gloria Afful-Mensah
Department of Economics, Management and Quantitative Methods, University of Milan
E-mail: gloria.afful@unimi.it, gaffulmensah@yahoo.com

Hasanuddin
Department of Obstetrics and Gynecology, Medical Faculty of Syiah Kuala University, Banda Aceh, Indonesia.
email: hasan.spog@yahoo.co.id

Henry Dilonga Meriki
Tuberculosis Section, Laboratory Unit, Regional Hospital,
Buea Cameroon

Lily Pertiwi Kalalo
Department of Clinical Pathology, Faculty of Medicine,
Mulawarman University Samarinda East Kalimantan
email: lilypertiwi@ymail.com

Matthias Grade
Christliches Krankenhaus Quakenbrück GmbH
Department for Gastroenterology, General Internal Medicine and Infectious diseases, Teaching Hospital of the Medical School of Hannover (MHH), Quakenbrück
m.grade@ckq-gmbh.de

Nelly Al Audhah
Medical Fakulty of Lambung Mangkurat University,
South Kalimantan, Indonesia
email: Audhah_fkunlam@yahoo.co.id

Ni Nyoman Ayu Dewi
Department of Biochemistry, Faculty of Medicine, Udayana University, Denpasar-Bali.
email: ayu.dewi@unud.ac.id

Rahmat Bakhtiar
Departement of Public Health Faculty of Medicine
Mulawarman University Samarinda East Kalimantan
email: bakhtiar_rahmat@yahoo.com.sg

Roudhotul Ismaillya Noor
Department of Clinical Pathology
Medical School of Airlangga University - Dr. Soetomo Hospital Surabaya, email: emilya009@gmail.com

Swandari Paramita
Faculty of Medicine Mulawarman University
Samarinda, East Kalimantan, Indonesia
swandariparamita@gmail.com

Yolande Djike Puepi Fokam
Paediatric Unit, Buea Regional Hospital Annex, Buea, Cameroon
email: yolandep2000@yahoo.fr

PREFACE

The dynamic and mobility of modern society have increased substantially over the past decades throughout the world. Among the consequences are major sociological changes, massive ecological repercussions, and climate change, all having a major impact on health. In foreseeing the future, world leaders declared the Millennium Development Goals (MDG) at the United Nations Headquarters in New York in the year 2000 thereby giving the commitment of their nations to reduce poverty and to define important health-related time-bound goals to be reached by the year 2015.

It is not long ago that former EU Commissioner for Health, John Dalli, gave the important statement that *"Health is a prerequisite for economic development and goes hand in hand with prosperity"* at a Global Health Conference in Brussels. And indeed, improving health care, food production and the economic situation are key aims of international development politics. Although several of the goals have indeed been successfully followed up, MDG 4 and 5, related to maternal-child-health were most far away from having reached track in 2015.

As a consequence - and building on the MDGs - the Sustainable Development Goals (SDG) were put in place in 2015 in which SDG 3 requests to "ensure healthy lives and promote wellbeing for all at all ages". Unfortunately even today, one out of every 10 children in low-income countries still dies before it reaches the age of five, whereas in high-income countries only one out of 143 dies before this age. As a consequence, SDG 3 aims **to meet the following targets by 2030:**

- Reduce the global maternal mortality ratio to less than 70 per 100,000 live births
- End preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births
- Ensure universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes

Knowledge and information should go hand in hand, when considering how to improve health. The Indonesian-German Health Education Partnership (IGHEP), established in 2010 is aiming to contribute to the improvement of maternal-child health by education and information. As one result of our initiative we here present a global perspective of maternal-child health. Twenty-four authors from Asia, Africa, and Europe contribute to this book which tries to understand infectious diseases not as stand-alone problems but rather being interconnected with environmental and economic issues.

- Uwe Gross -

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Swandari Paramita
Faculty of Medicine Mulawarman University
Samarinda, East Kalimantan, Indonesia
swandariparamita@gmail.com

INTRODUCTION

Cervical cancer is the second biggest cause of female cancer mortality worldwide with 288,000 deaths yearly. About 510,000 cases of cervical cancer are reported each year with nearly 80% in developing countries: 68,000 in Africa, 77,000 in Latin America, and 245,000 in Asia[1]. The incidence of cervical cancer varies widely around the world, with the highest burden of disease occurring in less developed regions, largely reflecting lack of screening programs. The Asia Oceania region accounts for just more than 50% of all cases and deaths from the disease worldwide, with South Central and Southeast Asia having the highest incidence and mortality rates. Every year across the Asia Oceania region almost 315,000 women are diagnosed with cervical cancer giving an overall incidence of 15.2 of 100,000: this is likely an underestimate[2]. Cervical cancer ranks as the 3rd most frequent cancer among women in Indonesia, and the 2nd most frequent cancer among women between 15 and 44 years of age. Indonesia has a population of 79.14 million women ages 15 years and older who are at risk of developing cervical cancer. Current estimates indicate that every year more than 13,500 women are diagnosed with cervical cancer and almost 7,500 die from the disease[3].

Cervical cancer is caused by HPV infection. The causal role of human papillomavirus (HPV) infections in cervical cancer has been documented beyond reasonable doubt. Compelling epidemiologic and experimental evidence has clearly established a causative role of HPV in this human malignancy[4]. However, in addition to HPV infection, other factors exist that influence the risk of developing cervical cancer. In particular, high parity and long-term oral contraceptive (OC) use have been found to increase the risk of cervical cancer and its precursor lesions. Interestingly, these associations have also been confirmed in analyses restricted to HPV-positive women. The results from International Agency for Research on Cancer Multicenter Cervical Cancer Study Group, found cofactors that showed statistically significant associations with cervical carcinoma including long-term use of hormonal contraception and high parity[5].

A role of estrogen in human cervical cancer has been hypothesized on the basis of two observations. First, extended use of oral contraceptives, which contain synthetic estrogens

and or progesterone, increases cervical cancer risk 2-to-4-fold, depending upon the length of use. The synthetic estrogens found in oral contraceptive formulations have increased estrogenic activity compared with endogenous estrogen in some tissues, as well as enhanced bioavailability. Second, parity increases cervical cancer risk up to 3.8-fold for seven or more pregnancies. During pregnancy, women are exposed to continuously elevated levels of estrogen[6]. Based on that, the paper made to explain the role of estrogen on cervical cancer carcinogenesis.

RISK FACTORS OF CERVICAL CANCER

Several cofactors, including long-term use of oral contraceptives and high parity, have been implicated in the genesis of HPV-associated cervical cancer, suggesting a potential role of female steroid hormones, such as estrogen, in cervical carcinogenesis. Oral contraceptives is the most common form of effective and reversible contraception in the world. However, oral contraceptive use is not without risks. Many studies show serious adverse events associated with oral contraceptive use. In addition to the risk of acute harms, the use of oral contraceptives may influence the risk of certain cancers[4].

Oral contraceptive use may promote or initiate tumors of the cervix. Assessing the risk of cancer associated with oral contraceptive use is fraught with difficulties. For example, cancer is a disease with a long latency period, and the time between exposure to oral contraceptives and diagnosis of cancer may span decades. Also, temporal variations in oral contraceptive formulations available on the market and used over a woman's lifetime may influence associations between cancer risk and oral contraceptive use. Furthermore, patterns of oral contraceptive use over a lifetime may be influenced by factors that also affect cancer risks (e.g., gravidity, parity, breastfeeding)[7].

Duration of oral contraceptive use was significantly associated with cancer incidence such that HPV-positive women who used oral contraceptives for 5 to 9 years (OR=2.82; 95%CI=1.46–5.42) and 10 years (OR=4.03; 95%CI=2.09–8.02) experienced a significant increase in the risk of cervical cancers compared with never users. Women who had an HPV infection and who have used OC for over 5 years have a 3-fold increase in the risk of cervical cancer compared with never users. A meta-analysis of 28 studies on hormonal contraceptives and cervical cancer showed an increased relative risk of cervical cancer of 2.2 (95% CI=1.9-2.4) for long-term (z10 years) OC users. The results of these studies were confirmed when the analyses were restricted to HPV-positive women[8].

Parity also contributed as risk factors of cervical cancer. During pregnancy, women are exposed to continuously elevated levels of estrogen.The data demonstrated that women who had five children or more had a 3-fold increase in risk compared with women with no children. Parity also increases cervical cancer risk up to 3.8-fold for seven or more pregnancies[8].

ROLE OF HUMAN PAPILLOMAVIRUS (HPV)

Based on genome type, viruses can be grouped into two major categories: RNA viruses and DNA viruses. Examples of RNA viruses are influenza virus, severe acute respiratory syndrome (SARS) virus, and human immunodeficiency virus (HIV); examples of DNA viruses are SV40, human papillomavirus (HPV), and adenovirus (Ad). Owing to the lack of particular enzyme activities in host cells, it is essential for most RNA viruses to encode either viral RNA-dependent RNA polymerases or viral RNA-dependent DNA polymerases (also known as reverse transcriptase) to achieve viral genome replication via an RNA or a DNA intermediate, respectively. In contrast to RNA viruses, DNA viruses utilize the DNA replication machinery of the host cell in order to propagate their respective viral genomes[9].

HPV from *Papillomaviridae* are one of the most-studied types of DNA viruses that are also known as tumor viruses due to the cancer-causing proteins that they encode. HPVs are small circular double-stranded DNA viruses that belong to the Papovaviridae family. More than 130 HPV genotypes have been cloned from a wide variety of clinical lesions. Of the >100 different HPV types, 40 are known to infect the genital tract. HPV have a predilection for either cutaneous or mucosal epithelial surfaces. These mucosal types are classified as low-risk and high-risk based on their prevalence in cervical cancer and its precursors. Low-risk HPV predominantly generate benign squamous epithelial lesions, commonly known as warts, whereas the high-risk types are associated with malignant diseases such as cervical cancer, skin tumours in patients with epidermodysplasia verruciformis, anal and rectal cancers, and head and neck squamous cell carcinoma (HNSCC), including oral cavity cancer. Low-risk HPV types, such as 6 and 11, induce benign lesions with minimum risk of progression to malignancy. By contrast, high-risk HPVs (HR-HPV) have higher oncogenic potential.The two most common low-risk viruses causing warts on the anogenital epithelium are HPV-6 and HPV-11; the two major high-risk or oncogenic viruses are HPV-16 and HPV-18[10,11].

Infection with ‘‘high-risk’’ mucosal-tropic or human papillomaviruses (HPV) is etiologically associated with the development of several human cancers, including cervical cancer, the second leading cause of cancer-related deaths among women worldwide. The vast majority of cervical cancers are associated with the so-called high-risk human papillomaviruses (HPV), among which HPV-16 is most common, being found in 60% of all cervical cancers. HPV-16, one of the dozen or so high-risk HPVs, is associated with more than half of all cases of HPV-related cervical cancer. The relative contribution of the 8 most common types in cervical cancer worldwide are reported consistently for HPV 16/18 (70.8%); 16/18/45 (76.7%); 16/18/45/33/31 (84.2%); whereas the proportional attribution of 16/18/45/33/31/52/58/35 is 91.3%[12].

Over the last decade, astonishing progress has been made in understanding the pathogenesis of cervical cancer. An overwhelming body of evidence shows that infection with distinct types of the human papillomavirus (HPV) is the primary risk factor for the development of cervical cancer and its precursor lesions. HPV is a double-stranded, circular DNA virus approximately 8,000 base pairs in size. The HPV genome encodes eight open reading frames, which are transcribed as polycistronic mRNAs. The gene products can be divided into ‘‘early’’ (E) and ‘‘late’’ (L) proteins, depending on the time of expression during the viral life cycle[10,13].

All oncogenic HPV types code for 6 early genes involved in viral gene expression and replication, and 2 late genes [L2 and L1 gene of human papillomavirus (L1)] involved in capsid formation.The HPV genome can be divided into three regions: an early region encoding six nonstructural proteins (E1, E2, E4, E5, E6 and E7); a late region encoding two structural proteins (L1 and L2); a noncoding long control region. The E1, E2, E4 and E5 proteins are required for viral DNA replication, the E6 and E7 oncoproteins cooperate to transform and immortalize infected cells, and the L1 and L2 proteins are needed for the production of viral particles. The L1 protein self-assembles into viral-like particles and is the active component in the currently licensed HPV vaccines. The upstream regulatory region (URR) located between the L1 and E6 genes, contains the E6 promoter and an enhancer region with cis-responsive elements that regulate viral gene expression, replication, and packaging into viral particles[13].

In HPV-associated cervical cancers, two HPV oncogenes, E6 and E7, are commonly up-regulated in their expression. E6 and E7, both multifunctional proteins, display transforming properties in tissue culture, including an ability to contribute to the immortalization process. HPV E6 and E7 proteins are oncogenic early genes encoded by

DNA tumor viruses that are capable of subverting for viral replication the otherwise tightly controlled host cell cycle.Specifically, E6 and E7 oncoproteins expressed by high-risk HPV can immortalize primary human keratinocytes and cause cancers in transgenic mouse models in a cofactor-dependent manner. In addition, E6 and E7 are required for the continued proliferation of cervical cancer cell lines[9].

The tumorigenic potential of HPV E6 and E7 oncoproteins depends, at least in part, on their ability to inactivate p53 and pRb tumor suppressor protein, respectively.Good examples are the interactions of HPV E6 and E7 oncoproteins with tumour suppressors p53 and pRb, respectively, leading to their degradation and inactivation, and contributing to persistent viral infection, cellular transformation, immortalization and carcinogenesis.The critical molecules in viral replication are E6 and E7, which functionally inactivate the products of two important tumor suppressor genes, p53 and pRb, respectively. Both oncoproteins induce proliferation, immortalization, and malignant transformation of the infected cells[10,11].

Two HPV genes, E6 and E7, are consistently up-regulated in human cervical cancers upon integration of the viral genome into the host chromosome. High-risk HPV E6 and E7 are considered potent oncogenes based on their transforming and immortalizing activities in tissue culture systems and their capacities to induce tumors in various animal models. High-risk HPV E6 and E7 are multifunctional proteins and are best known for their abilities to bind and inactivate p53 and pRb, respectively. The primary HPV oncogenes, E6 and E7, interact with a large number of cellular targets, including the cellular tumor suppressor proteins p53 and pRb, which are central regulators of apoptosis and cell cycle, respectively. During productive infection, E6 and E7 are expressed at relatively low levels, in part due to transcriptional repression by E2 gene of human papillomavirus (E2). During the carcinogenic process, transcription of E6 and E7 is deregulated, leading to their overexpression. This deregulation may be mediated by the integration of HPV DNA into the host genome, often resulting in disruption of the E2 gene with increased E6 and E7 transcripts spliced into host sequences, causing increased HPV oncogene expression[12,13].

The hallmark of cancer is uncontrolled cell division resulting in tumor formation. Thus, the molecular mechanisms that control cell division have been a major focus of basic cancer research. The fidelity of cell division is maintained in a process called the cell cycle that contains four distinct phases, G1, S, G2, and M. During the S phase, DNA replication takes place; the M phase is when cells divide during a process called mitosis; and G1 and G2 are two gaps that precede the S and M phases, respectively. Intrinsic checkpoints function to

protect cells from aberrant proliferation along cell cycle procession, and loss of checkpoint control is the cause of many human cancers[9].

The p53 and retinoblastoma protein (pRb) play key roles in controlling progression through the cell cycle, whereby p53 exerts its effect on the G2–M and G1–S transition and pRb exerts its effect on the G1–S transition. Mutations that inactivate p53 or pRb function result in uncontrolled cell division leading to cancer, and so these proteins are called tumor suppressors. Not surprisingly, mutations of both tumor suppressors are observed frequently in human cancers of various types, and p53, also called "guardian of the genome", is mutated in the majority of human cancers. p53 is regarded as the ''guardian of the genome'' because it mediates the response of DNA damage and other stress response pathways.p53 is a transcription factor that responds to cellular stresses such as DNA damage by binding to DNA and regulating the transcription of genes involved in cell cycle arrest, apoptosis, or senescence[12].

Correspondingly, HPV E6 viral oncoproteins mediate p53 inactivation, by promoting ubiquitination-mediated p53 degradation, as is the case with HPV E6. In contrast to the situation with pRb, considerably less is known about the mechanism of viral oncoprotein inactivation of p53, as there have been no structures reported of p53 bound to a viral oncoprotein. It is interesting to note that HPV E6 also disrupts p53 function through its interaction with the p53 core domain, although the mechanism for this is unknown, even with the recent report of the NMR structure of the HPV E6 C-terminal zinc-binding domain. It seems clear that viral oncoproteins use a variety of mechanisms to target host tumor suppressor proteins for inactivation[9].

The pRb transcriptional repressor is a member of the "pocket protein" family, binds and represses transcriptional activation by the E2F/DP family of DNA-binding proteins.Viruses have developed an efficient way to inactivate the pRb checkpoint, by stimulating the disassembly of the pRb/E2F/DP complex during the G1–S cell cycle transition, leading to the production of host enzymes required for replication of the virus genome. Together, structures of pRb, HPV E7, and their respective complexes have provided important clues about viral inactivation of pRb function, although further studies are still required to derive more detailed mechanistic information[9].

The E7 oncogene synergizes with the loss of p53 to induce cancer.In addition, HPV E7 shortened tumor latency and fostered more aggressive tumor progression when placed on the p53-deficient genetic background. Thus, HPV E7 cooperates with the loss of p53 to increase cancer incidence, shorten tumor latency, and promote extensive tumor invasion. p53-

independent activities of HPV E6 contribute to the development of nonreproductive tumors independent of HPV E7 but only contribute to cervical carcinogenesis in the presence of HPV E7. The p53-independent activities of E6, however, became apparent in the presence of E7, they contribute to cervical carcinogenesis but only do so in synergy with some function(s) of HPV E7[12].

ROLE OF ESTROGEN

Despite the robust carcinogenic potential of E6 and E7, HPV infection alone is not sufficient for the development of cervical cancer because only a minor fraction of patients infected with HPV develop cervical cancer. In agreement with epidemiologic studies, findings from HPV-16 transgenic mice and in vitro models also suggest that high estrogen levels are involved in the regulation of early viral promoters and malignant transformation of HPV-infected cells. On account of the central role of HPV infection in cervical carcinogenesis, any risk factor other than HPV may play a role by either increasing the risk of acquisition or duration of the infection, or by increasing the risk of progression from HPV infection to cervical cancer[6].

Cervical cancers develop only in a minority of women who have been infected with high-risk HPVs, take on average decades to arise, and follow a progressive histopathological disease pattern that involves acquisition of multiple genetic changes to the cancer cell. These facts indicate that development of cervical cancer is a multifactorial process and likely involves other contributing factors in addition to HPVs, such as environmental, genetic, biological, and hormonal factors[14].

An essential role of estrogen in cervical cancer, however, has been clearly defined in mouse models for HPV-associated cervical cancer that make use of transgenic mice expressing HPV-16 E6 or E7, or both. In these mouse models, either a HPV oncogene or estrogen alone is insufficient to cause cervical cancers, whereas a HPV oncogene in conjunction with physiologic levels of exogenous estrogen can promote the development of cervical cancer. In both HPV-infected women and these mouse models, cervical cancer is preceded by cervical intraepithelial neoplasia (CIN) of increasing severity that arises preferentially in the transformation zone of the endocervix, at which is found the normal transition from columnar epithelium to stratified squamous epithelium. The transformation zone is hypothesized to be the preferential site of carcinogenesis by HPV because therein lie the reserve cells, which are thought to be multipotential progenitor cells from which cervical cancer is argued to arise[4].

The in vivo properties of high-risk HPV E6 and E7 oncoproteins have been evaluated through the generation and characterization of HPV transgenic mouse strains. In E6 and E7 transgenic mice, respectively, expression of the E6 and E7 genes of the high-risk HPV type16 (HPV-16) was directed to stratified epithelium. A role of E6 and E7 in cervical cancer, however, was elucidated when these transgenic mice were treated with exogenous estrogen. When treated chronically for 6 months with 17-estradiol, the E7 transgenic mice, but not the E6 transgenic mice or nontransgenic mice, developed cervical cancer. The E6 oncoprotein contributed to increased tumor size in estrogen treated E6/E7 doubly transgenic mice. In conclusion, estrogen synergizes with high-risk HPV oncogenes to cause cancer in this mouse model for human cervical cancer. Thus, both in the HPV transgenic mouse model for human cervical cancer and in women, a role of estrogen in the genesis of cervical cancer is evident, that estrogen plays a critical role not only in the genesis of cervical cancer but also its persistence and continued development[14].

HPV-transgenic mice treated for 6 months with exogenous estrogen developed cervical cancer. The prolonged treatment of HPV transgenic mice for 9 months with estrogen, compared with the 6-month treatment regimen used in our prior study, led to an increase in the size of tumors in the HPV transgenic mice. This finding could be a consequence of the continued exposure to exogenous estrogen, the presence of the viral oncogenes, or both. These results indicate that the high cervical tumor incidence, tumor growth, and invasive character of the tumors seen after 9 months of treatment with estrogen are dependent upon the continued exposure of the HPV transgenic animals to exogenous estrogen. Here we present evidence that estrogen contributes not only to the onset but also to the persistence and malignant progression of cervical cancer in an HPV-transgenic mouse model[15].

The cervix contains the transformation zone, the physical junction of the squamous and columnar cells, which in women is the location of the majority of HPV-induced cervical tumors.The transformation zone is hypothesized to contain multipotent stem cells that can give rise to both endocervical and exocervical epithelial cell types. Infection by HPVs is hypothesized to contribute to long-term viral persistence, a requisite for cervical carcinogenesis, which takes decades to develop in most women[14].

The risk of squamous-cell cancer of the cervix increases with increasing number of pregnancies and with number of years of oral contraceptive use. Thus, hormonal changes associated with pregnancy and oral contraceptive use likely influence the risk of cervical cancer, similar to how estrogen influenced markedly the development of cervical cancer in our mouse model. Estrogen has been shown to be a direct carcinogen, and therefore could

contribute to initiation of lesions. Estrogen also is a recognized mitogen, and therefore it could contribute to tumor promotion.In the context of HPVs, a potential role of estrogens has been made in the context of altering the efficiency of viral gene expression[15].

CONCLUSION

Estrogen contributes in cervical cancer carcinogenesis.Parity and hormonal contraception indicates relationships with cervical cancer. A role of estrogen in human cervical cancer has been hypothesized on the basis of two observations.First, extended use of oral contraceptives, increases cervical cancer risk. The synthetic estrogens found in oral contraceptive formulations have increased estrogenic activity. Second, parity increases cervical cancer risk. During pregnancy, women are exposed to continuously elevated levels of estrogen. It recommended that cervical cancer screening can be focused on high-risk groups, i.e. women with the high number of children born, or women in particular long users of hormonal contraception methods. Our conclusions may imply that multiparous women and women on long-term hormonal contraception use may need closer surveillance for cytologic abnormalities and HPV infections than women in the general population may.

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