



Oslo
University Hospital

Research on gynaecologic oncology in Norway

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The gynaecologic cancer milieu in Norway is quite active in research, both more basic research and clinical research.

An important prerequisite for basic research is access to biological material, such as tissue, blood and other material. Prospective collection of biologic material is resource demanding but necessary and has been done for several years. In recent years, we have used image material from MRI, CT and PET as well.

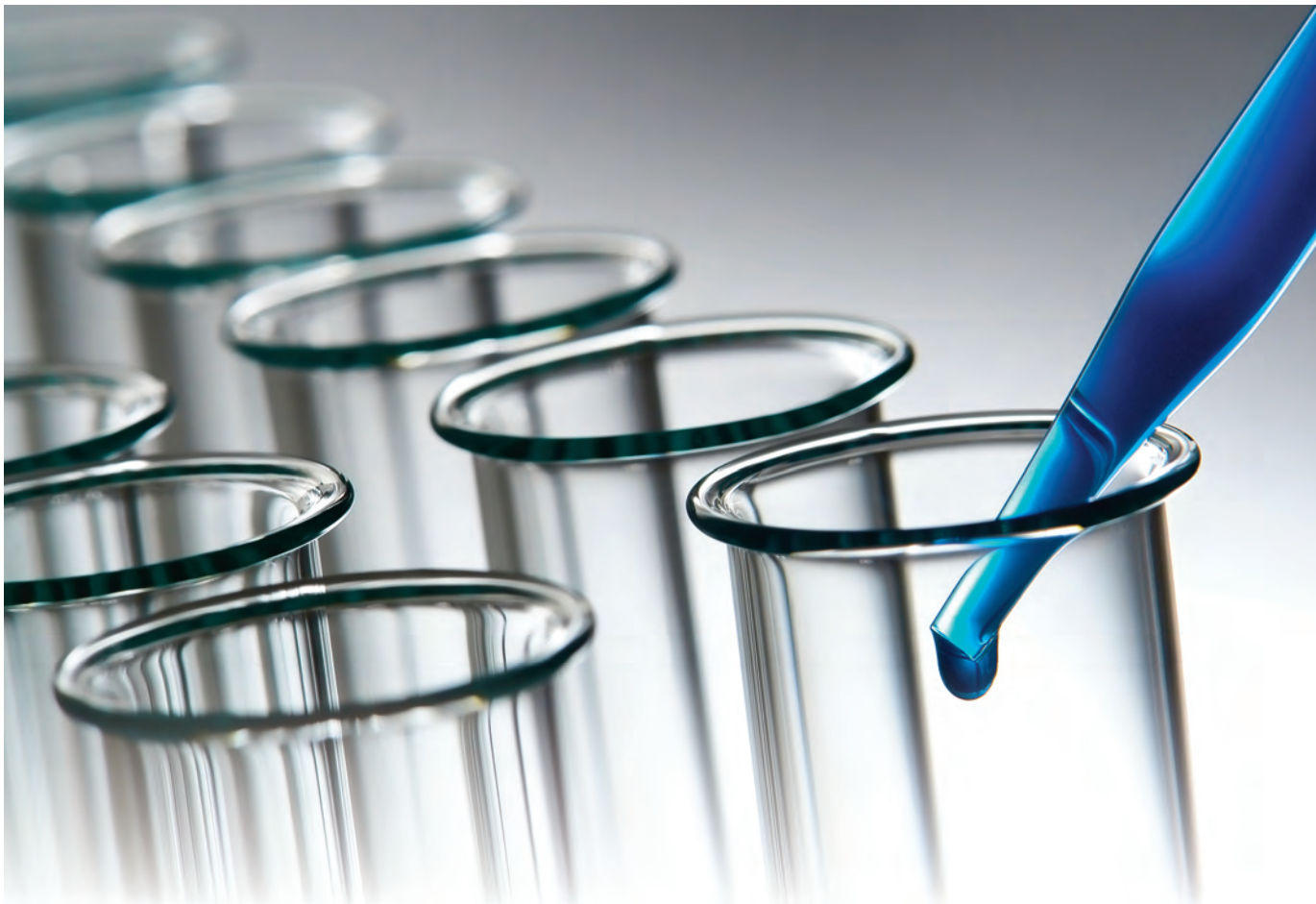
“Immunotherapy has been of interest for many years but so far without any major breakthrough in gynecologic cancer. In recent years immune checkpoint inhibitors have had a major breakthrough, especially in malignant melanoma. Activity has been shown also in other cancer types. The time has come to test these drugs in gynecologic cancer. Norwegian centers are participating in several of these studies.”

In Norway we have 4 cancer centres, with Oslo University Hospital being the largest followed by Bergen, Trondheim and Tromsø. Due to space limitations I will restrict this presentation to the 2 biggest university hospitals.

At Oslo University Hospital we especially focused our translational research on cervical and ovarian cancer and gynaecological sarcoma, in addition to clinical studies.

In cervical cancer, we have performed a number of studies to better understand the biology of the disease and especially relating to radiation treatment of locally advanced tumours. Low oxygen saturation (hypoxia) in the tumour makes the tumour more resistant to radiation, even when chemotherapy is added. We have identified tumour genes related to hypoxia. Increased activity of these genes also makes the tumour more aggressive with a higher potential of spread to other parts of the body (metastases). We have shown how hypoxic areas of the tumour can be visualised on MRI pictures. Further, we have shown a close relationship with activation of the hypoxia related genes and the hypoxia indicators we can visualise on MRI. This is of clinical importance, as we need to find some kind of extra treatment for the tumours with hypoxic areas. Using MRI visualisation of hypoxia would allow us to focus that extra treatment on patients with this kind of tumour and avoid giving this additional treatment to all patients. Unfortunately, we do not have any good candidate for such additional treatment, but research is ongoing.

Brachytherapy is an important part of radiotherapy for cervical cancer. This is radiation given directly to the neck (cervix) of the uterus. It is given in such a way that the cervix receives a high radiation dose, while the dose to the intestines is low. Over the years, we have spent a lot of resources and research to be able to give a sufficiently high dose of radiation to all tumour tissue while sparing the healthy tissue surrounding the tumour. Follow up of patients after treatment to learn about their side effects and complications and



relating that to treatment details is important. This was the topic of a PhD a few years ago. We are now running new studies after further optimisation of the radiation technique.

In ovarian cancer, we have been running a number of studies to learn about the biology of these tumours. One of our pathologists has done extensive studies on tumour cells from ascites (fluid accumulated in the abdominal cavity) of patients with advanced ovarian cancer. This has been possible as we have prospectively collected ascites from such patients over many years. Together with studies on tumour tissue, this has given great insight into tumour biology. A number of genes related to response to chemotherapy and to prognosis have been identified. Also the importance of interplay between tumour and stroma has been evaluated on tumour specimens. On blood specimens, circulating tumour DNA, MRA and microRNA can be evaluated. We have found that some microRNA may be related to tumour aggressiveness and thereby to the prognosis for the patient. It will be interesting to see, whether some of these microRNA will be predictive for different kinds of treatment, as

this may have clinical relevance. It is of great value to know about genes and other factors of importance in response to treatment, as this can be used in the decision about type of treatment and can be used to guide development of new drugs and new treatment types.

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In gynaecologic sarcoma, we have studied the importance of clinical and biological factors for the outcome of patients. We are presently studying the importance of different types of treatment, both surgical and medical treatments.

In endometrial cancer, the research group in Bergen has done a tremendous job in translational research, while we in Oslo have mainly focused on clinical studies. The clinical treatment of endometrial cancer patients has very much been



based on convention and to a lesser extent on randomised studies. The primary treatment is surgery with removal of the uterus and adnexa. There is a risk of spread of the disease outside the uterus, related to clinico-pathologic factors. Removal of lymph nodes for evaluation of spread is commonly done in patients with increased risk of spread. This is associated with some morbidity and has not been shown to increase survival. In Norway and in many other countries, we are working on a technique to only remove one or a very few lymph nodes representing the status of all relevant lymph nodes; the so-called sentinel node technique. Another question is whether removal of lymph nodes should be done at all. Maybe the surgical procedure could be replaced by imaging and chemotherapy given to patients with apparently normal nodes, but having a high risk of micro metastases. Work is ongoing to perform a randomised study on this topic.

The value of adjuvant treatment after surgery is

controversial. The traditional adjuvant treatment has been radiation, which can reduce the frequency of pelvic relapses, but does not increase survival. For this reason, many departments have chosen to give chemotherapy instead of radiation to patients with a particularly high risk of relapse. We are in the progress of publishing the results of such a change in a large group of patients.

For clinical studies, all Norwegian centres for gynaecologic oncology are working together. The number of patients with gynaecologic cancer is relatively low, so to be able to perform larger clinical studies we must work together. For studies on rare conditions with a limited number of patients, only one or two centres participate and patients from other parts of the country travel to one of these centres. The government considers it of importance that all patients in the country have the possibility to participate in studies on new treatments and facilitates this by paying for travel.

Most clinical studies are performed as a member of the European network for clinical studies in gynaecologic cancer (ENGOT). Some studies are purely industry driven. We do have a number of clinical questions that could best be solved by randomised clinical trials. Unfortunately, it is very difficult to get funding for such academic trials. Almost all funding for clinical studies comes in some way from the industry, which naturally has an economic perspective. A better opportunity to get funding for academic clinical trials from government or at the European level is needed.

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In clinical studies, we have participated in studies on the value of blocking growth signals for new vessels. Tumours need nutrition and thereby blood vessels to grow. In ovarian cancer it has been shown that such treatment slows down the regrowth of tumours after surgery (VEGF inhibition). Such inhibition can be obtained either by IV infusions or by tablets. A study to evaluate such treatment in advanced or metastatic endometrial cancer will start soon. For patients with a partial defect in their ability to repair DNA damage, treatment with a group of drugs called PARP inhibitors shows promise. The drug Olaparib has recently been licensed in Europe for treatment of ovarian cancer after successful treatment with chemotherapy. The license was based on results a randomised phase II study. We are performing a similar study on patients with relapsed ovarian cancer and will soon start a study on treatment after end of first line chemotherapy.

Inhibition of signal pathways that are crucial for the tumour is called targeted therapy. The molecular biology of most cases of ovarian cancer is quite heterogeneous and so far no treatable common pathway has been found. In patients with low grade serous ovarian cancer, some important pathways are known. We participate in a study targeting such a pathway. This is a rare tumour group with few patients so only Oslo and Bergen participate. Patients from other regions thus travel to one of these two hospitals. Travel costs are paid by the government to allow for equal opportunity for all inhabitants in the country to participate in this kind of study. In endometrial cancer some pathways are also known and clinical studies blocking these pathways are of interest. We are participating in such a study.

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In regard of surgical studies, we have participated in a randomised study to evaluate the benefit of surgery before chemotherapy for relapsed cancer. The results of that study are pending. We are awaiting the start of a study to evaluate the benefit of removing lymph nodes in endometrial cancer.

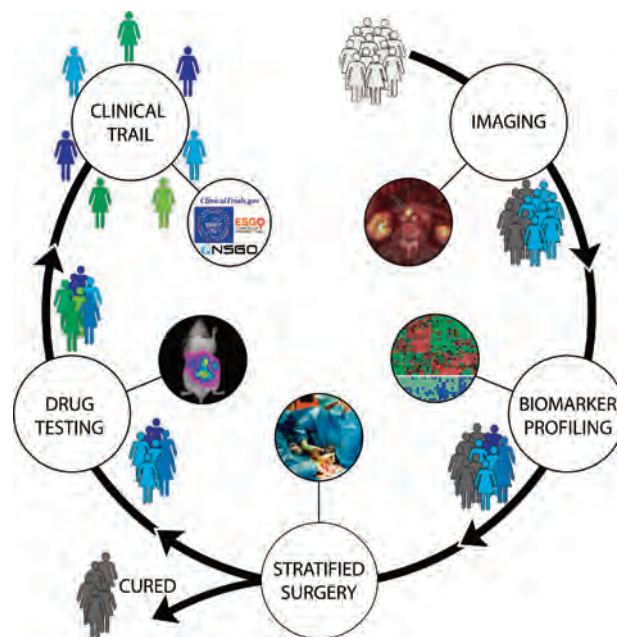
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Presentation of the Bergen group

The Bergen gynaecological cancer research group has 23 active members focusing on clinical and molecular aspects of gynaecological cancers. The group is embedded in Haukeland University Hospital, being a Norwegian ESGO¹ accredited training centre for gynaecologic oncology and the Center of Excellence CCBIO, co-directed by Professor Helga B Salvesen. The group has generated break throughs published in top ranked general (Nature, PNAS, NEJM) and specialised cancer journals (JCO, CR, CCR)², and contributed to the discovery of new potential treatment targets and markers for individualising gynaecological cancer care.

Resources: A gynaecological cancer biobank with well-annotated fresh frozen samples, blood and urine from >3000 consented patients with extensive follow-up is applied to generate a range of input data using array techniques, and sequencing in parallel with functional imaging studies by fMRI and PET-CT. Candidate biomarkers are validated in preclinical models and clinically-annotated formalin-fixed paraffin-embedded samples by immunohistochemistry and fluorescence in situ hybridisation. Such additional validation cohorts include the international prospective multicentre study Molecular Markers in the Treatment of Endometrial Cancer (MoMaTEC trials).

Key clinical challenges in gynaecological cancers show significant overlap for histological subtypes and clinical phenotypes, also recently supported by comprehensive molecular tumour profiling. The challenge is now to translate this knowledge into clinically meaningful and applicable tests to improve and individualise patient care. Our research environment is presently in a unique position to take some of this new knowledge to clinical implementation studies.



The graphical abstract summarises the research strategy to contribute to more precision in gynaecological cancer care: By exploring primary and metastatic lesions, in parallel with comprehensive clinical annotation, advanced imaging and drug testing in preclinical models, we will define promising targets and conduct molecularly based clinical trials. Individualised treatment and follow-up based on biomarker-determined risk profiles will be implemented in studies in parallel, whilst assessing quality of life and costs.

¹ ESGO: European Society of Gynaecological Oncology, ENITEC: European Network of Individual Treatment in Endometrial Cancer

² Ojesina AISalvesen* and Meyerson* (*joint senior authors): Nature; 2014;506:371-5; Salvesen et al. PNAS 2009; 106:4834-4839; Dutt A, Salvesen et al, PNAS 2008; 05:8713-7; Salvesen et al, JCO 1999; 17:1382-90; Hoshida Y et al. NEJM 2008;539:1995-2004

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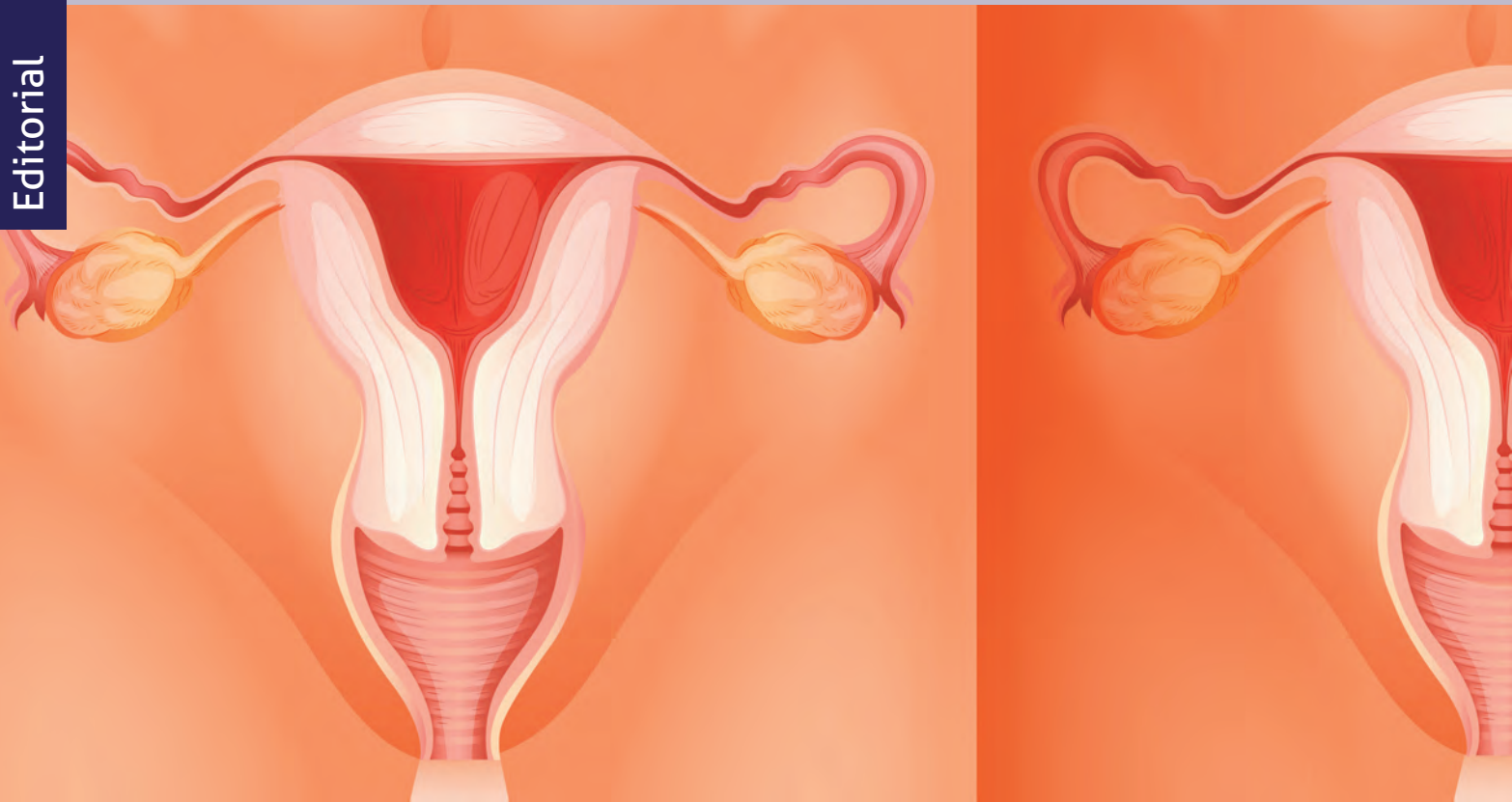
Gynaecological cancers – prevention and early detection

Murat Gultekin, Vice-President of the European Society of Gynaecological Oncology (ESGO) highlights the importance of early detection of gynaecological cancers for prevention...

According to World Cancer Report 2014 (IARC), at least one third of cancers are preventable. This is true for gynaecological cancers, especially cervical cancer. However, less than 5% of the whole cancer control budget in the EU is spared for prevention. A great majority of the total budget is still spent on treatment of cancer and only 25 of the 28 EU member states have a strategic cancer control plan.

Based on the UN General Assembly Resolution in 2011, cancer control and prevention will be the main focus for all countries within the next decade. New data estimates that the \$18bn increase in funding per year by the international community could result in a 30% reduction in cancer deaths in low and middle-income countries by 2030.

In this respect scientific and non-scientific societies including ESGO have initiated new awareness campaigns. ESGO is the principal European society of gynaecological oncology contributing to the study, prevention and treatment of gynecological cancer which also organises state of the art symposiums to upgrade the knowledge and skills about the highlighted topics, via the world's most famous experts. In order to lead in several gynaecological cancers prevention, ESGO has decided to organise a 2016 symposium focusing on the prevention of gynaecological cancers, with specialised lectures on primary, secondary and tertiary prevention of cervical, endometrial, breast and ovarian cancers. In addition to the up to date scientific reviews, this meeting will also give an opportunity to reach and train all relevant groups such as cancer



patients, their relatives and the young generation of European doctors. With almost 30 worldwide famous scientists, lecturers and 500 attendees from all around Europe and the Middle East Region, the 2016 ESGO State of Art Symposium-Antalya/Turkey will be a trademark and a cornerstone on gynecological cancer prevention strategies.

Cervical Cancer

Cervical cancer is the 4th most common cancer of women around the world. Although it is a preventable, 2 women every 1 hour in the European Union, currently lose their lives because of this type of cancer.

HPV is the main causative agent of cervical cancers and more than 70% of these cancers are related to HPV type 16 and 18. This is important because it means that a great majority of these cancers can be prevented via HPV vaccination and cancer related deaths can be avoided by early diagnosis through screening.

HPV Vaccination

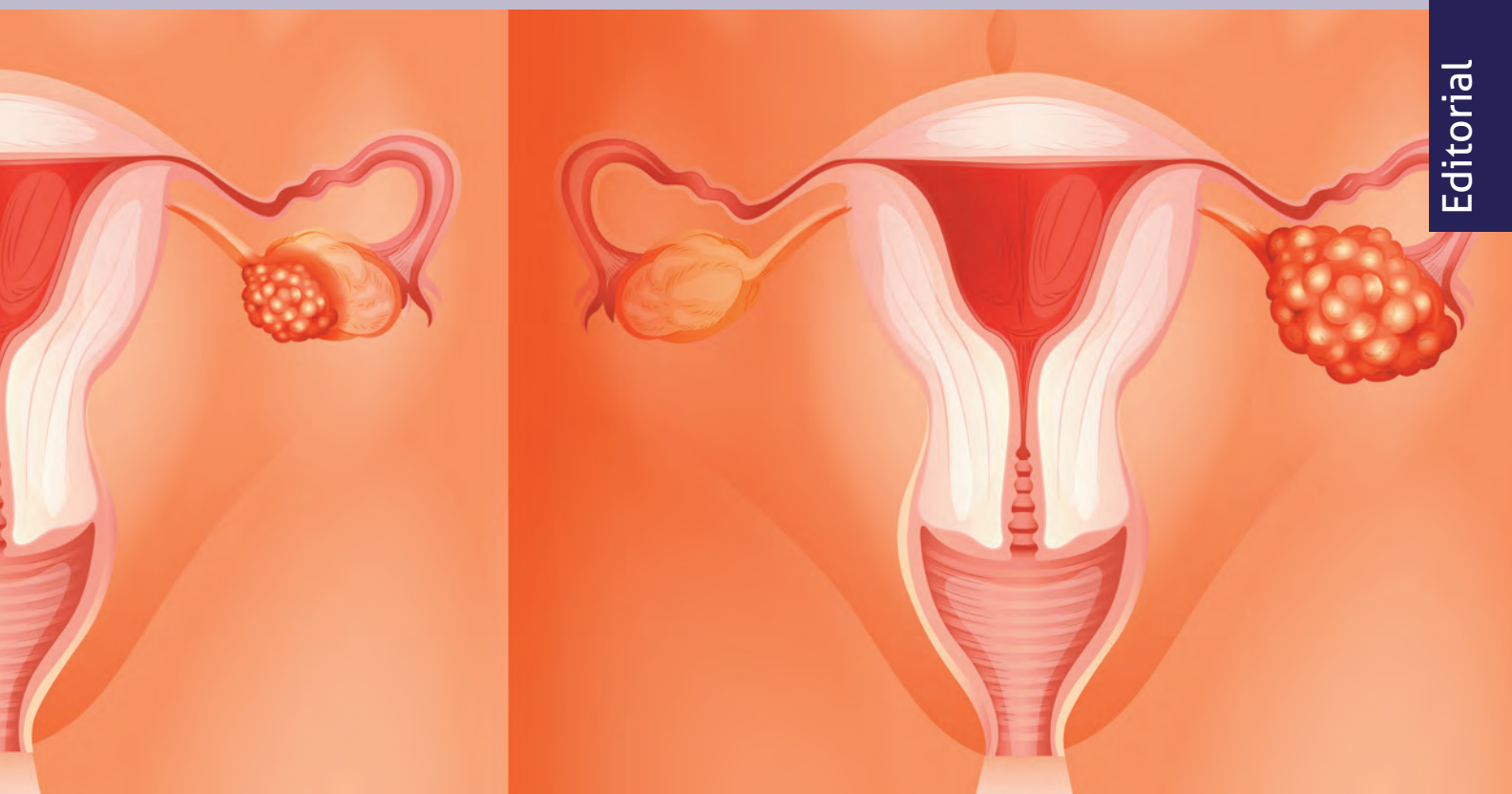
Cervical cancer can be prevented and this can begin from childhood. We can save our children's lives by vaccinating our children and avoid at least 3 out of 4 deaths by an effective HPV vaccination. These vaccinations are FDA approved,

effective and safe vaccines, against to known oncogenic HPV types. Unlike most other vaccines, which are administered to children under the age of 5, HPV vaccines are inoculated to girls aged 9 to 13.

In contrast with the fact that HPV vaccines can prevent every 4 of 5 deaths from the cervical cancer and don't have serious side effects, vaccination rates are still low around the world. According to VAERS (Vaccine Adverse Event Reporting System) about 92% of the side effect reports were classified as non-serious. The most common side effects are; injection problems, fever, headache, nausea and muscle or joint pain. Despite speculations the vaccine was found to not have any relation to a risk of multiple sclerosis in many scientific studies.

Screening

Besides prevention, early detection by screening still remains important. Population based, effective and well-designed screening programs should be the goal of achievement for all countries in a view of public health. In addition to the ongoing cytology programs, countries have many different screening strategies such as VIA/ VILI/ HPV DNA or a combination of all. Recent evidence shows HPV DNA can be safely used alone



for cervical cancer, with its high scientific value and scientifically proven success.

Uterine Cancer

The most common type of uterine corpus cancer is endometrial cancer, which is the 5th most common cancer of women in the world. It is mostly symptomatic and could be easily diagnosed and totally curable at early stages. It is generally seen after the menopause with only 5% of the cases under 40 years of age. Most of these cancers are related to obesity and high estrogen exposure. There aren't any feasible and acceptable screening methods for endometrial cancer, however it is important to be aware of the fact that any post-menopausal bleeding may be an early sign of it.

Ovarian Cancer

Ovarian cancer is the 7th most common cancer among women in the world and it is the most deadly gynecologic cancer. Although there are not any adoptable screening methods for this cancer at a community level, it is curable if diagnosed in the early stages. It is important to raise public awareness about the symptoms of ovarian cancer so it can be detected earlier. There is also a genetic proportion of this cancer but only 10% of ovarian cancer cases have this liability. Women who have a family history of

ovarian, endometrial or colorectal cancer could be screened for genetic predisposition and be prevented by some measures. There are many studies on ovarian cancer which may lead screening and early diagnosis or new treatment options.

Conclusion

More than 70% of gynecological cancers can be prevented and the harm caused by them can be reduced by several measures such as screening and vaccination programs. It is important to be aware of first the importance of prevention then the importance of early diagnosis.

In conclusion; "Raising Awareness" should be our first as this is the most important initial point for saving more people's life.

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