Screening and primary prevention of gynaecological malignancies

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Europe-women
Estimated number of cancer cases

1.606.252
GLOBOCAN 2008, International Agency for Research on Cancer
http://globocan.iarc.fr/ 21/1/2011

Gynecological cancer 222,941 (13.88%)
Gynecological and Breast cancer 681,659 (42%)
Most of these cancers have favorable prognosis, if diagnosed early.

Survival rates by stage
Cervical cancer
Every 2 minutes one woman dies due to cervical cancer, the disease that can be prevented!
Facts about Cervical cancer

- Commonest among women in developing world
- 80% of new cases and deaths occur
- Less than 5% of global cancer resources
- Disease of *inequality of access* to health care

- Curable if detected early

Parkin, 2000
Cervical cancer in Europe - incidence

ASR per 100,000

- < 4.99
- 5-9.99
- 10-14.99
- 15-19.99
- >20

< 5: Finland, Greece, Malta, Switzerland

>20: Romania, Lithuania, Bulgaria, Serbia...


http://globocan.iarc.fr/ 9/9/2015
Cervical cancer in Europe – Globocan 2008 and 2012

Incidence

- 2012: 11.4
- 2008: 10.6

Mortality

- 2012: 3.8
- 2008: 3.9
Burden of Cervical Cancer in Europe

Number of new cases: 59,115
Number of deaths: 25,592

Two key reasons:

1. The vast majority of women still know little about cervical cancer or what they should do to prevent it.

2. Many countries have ineffective prevention programmes or no prevention programmes at all.
From old Egypt, 2200 B.C…

• The first known description of uterine cancer
• Documentation of linen sheath as condom for prevention of disease

Nobel Prize, 2008

Human papilloma virus (HPV) and Cervical cancer

Harald Zur Hausen
Cervical cancer

Human papiloma virus (HPV) infection has a causal role in the development of cervical cancer.

99.7%!
Human papilloma virus (HPV) has causal role in the development of cervical cancer

The association between HPV infection and cervical cancer is stronger than the connection between smoking and lung cancer.
The prevalence of HPV infection in the age of 20 - 25 years reaches 50%

HPV positivity does not mean cancer, and not even a precancer

Wheeler et al., IJC, 2012
Majority of HPV infections is transitory and spontaneously disappear during the period of two years.

5-year rate of spontaneous elimination is HPV 92%
Human papilloma virus (HPV) infection is necessary for the development of H-SIL and invasive cancer but it is not a sufficient cause.
• Immunodeficiency
• Smoking
• Nutrition (vitamin deficiencies)
• Infections with other microbial agents
• Hormonal influences
are believed to act as co-factors in cervical carcinogenesis.
Cervical carcinogenesis

Normal

HPV

H-SIL

10 years

> 5 years

Cancer
HPV infection

Low-grade changes

High-grade lesions

Cancer

Number of cases

300 millions

30 millions

10 millions

0.5 millions

Many years
8-15

HPV E6, E7 Cellular changes

0.15% !


Prevention of Cervical Cancer

Is it possible?
Natural history of cervical cancer and prevention

Primary - vaccination

Normal Cervix

Initial HPV infection

Persistent infection with HR types HPV

Secondary - screening

Tertiary – treatment of precancer

Invasive disease

Precancerous lesion
Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial

Diane M Harper, Eduardo Fraschina, Susan Heliwell, David S Ferrell, David Jenkins, Anne Scheindlin, Toufik Zahrif, Brigitte Brahim, Paulo Mamede, Newton S De Carvalho, Cecilia M Roque-Martins, Julie Taviera, Mark M Blatter, Ahmer P Khan, Wim Quinl, Gary Dolin, for the GlobalSmithKline HPV Vaccine Study Group

Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices

Emiko Petrosky, MD; Joseph A. Bocchini Jr, MD; Susan Harton, PhD; Harrell Cheauson, PhD; C. Robinette Curtis, MD; Mona Saraiya, MD; Elizabeth R. Unger, PhD; MD; Lauri E. Markowitz, MD (Author affiliations at end of text)
HPV Vaccination

7 studies about efficacy with female subjects an overall sample size of 58,625 patients
• 26,547 for bivalent vaccine
• 17,863 for quadrivalent and
• 14,215 for ninevalent HPV vaccine

10 studies about safety, an overall sample size of 10,820 patients were reached,
• 4,365 for bivalent vaccine
• 6,455 for quadrivalent
HPV Vaccination

The available vaccines are safe and also efficacious (90-100%), but......

... their real efficacy would be confirmed after a total period of 20 years follow up.
HPV Vaccination in Europe

HPV vaccines are being delivered to the low-risk populations that already have extensive screening programs while the high-risk countries are not getting the vaccines.
We do not know yet if HPV vaccines are effective in preventing cervical cancer.
Vaccination is not a substitute for routine cervical cancer screening

Vaccinated females should have cervical cancer screening as recommended
Screening !
Cytology
Standard Papanicolaou test

✓ Proven in practice
✓ High specificity (70-95%)
✓ Low cost, easy to perform

➢ Moderate sensitivity (~ 50%)
   increases by regular testing

➢ Accuracy depends on:
   technique of smear taking (endocervical cells)
   interpretation of findings
HPV testing

✓ High sensitivity for high grade lesions (80-100%)

➤ Low specificity

➤ High cost, sophisticated equipment

Application:
• Not as a primary test
• Triage of women with ASCUS and L-SIL (age > 30)
• Follow-up after treatment of H-SIL lesions

If used in primary screening, not before 30 years of age

Risk for CIN 3+ after negative test
Countries where primary HPV screening is introduced

1. Netherlands*
2. Mexico
3. Ruanda
4. U.S. (co-testing)
5. Turkey*
6. Italy
7. British Columbia and Ontario, Canada

Many pilot studies and trials are ongoing
(Australia/New Zealand, Sweden and Finland)
Conclusions:

• Most European countries should consider switching from primary cytology to **HPV screening** for cervical cancer.

• HPV screening must, however, only be implemented in situations where screening is well controlled.
Effective cervical cancer screening requires not only a good screening test, but also a good screening program.
In the populations where the screening quality and coverage have been high, invasive cervical cancer is reduced by as much as 90 percent!
Only 16 countries in Europe have organized screening!

Epidemiol Biomarkers Prev; 2012; 21(9): 1423–33
By 2030 cervical cancer will be responsible for the death of 474 000 women annually with over 95% of these deaths anticipated to occur in low- and middle-income countries.

HPV-FASTER concept: combined HPV screening of women older than 30 godina and vaccination of women in the age of 25–45

Integrated HPV Vaccination & Screening
The Beginning of the End for Cervical Cancer?

Incidence of invasive cervical cancer in UK

The success of screening depends on social mobilisation!
Education about Cervical Cancer

Politics, Women, and Medical professionals

- Education is crucial for early detection and prevention of cervical cancer.
- Healthcare providers should engage with policymakers to increase awareness and resources.
- Women should be educated about the importance of regular screenings.

Supporting images: Various urban and cityscapes around the world.
The incidence of cervical cancer in one country is an indicator of how much the whole society takes care about its women.
Endometrial cancer

Corpus uteri

Age-Standardized incidence rate per 100,000

GLOBOCAN 2002, IARC
What do we know about Endometrial cancer?

- Predominantly postmenopausal disease
- 25% of patients are premenopausal (4% < 40)
- Bleeding is the most common symptom
- Diagnosis in early stage in more than 80%
- Excellent survival

- No screening
Classical risk factors for Endometrial cancer

- Obesity
- Hypertension
- Diabetes
Risk factors for Endometrial cancer

- Obesity
- Nulliparity
- Unopposed estrogen exposure
- Tamoxifen
- Hypertension
- Type-2 diabetes
- Insulin resistance
- Infertility
- PCOS
- Genetics (Lynch II)
Obesity and Endometrial Cancer

Strength of association between obesity and cancer risk increases with increasing BMI: RR for

- overweight ..... **1.32** (95% CI 1.16-1.50)
- obesity ........... **2.54** (95% CI 2.11-3.06)

24;29(1):e21-9
Infertility risk factors

- Age
- Stress
- Poor diet
- Athletic training
- Overweight
- Underweight Tobacco
- ETOH
- STDs
- Health problems

Percent of women ages 15-44 with impaired fecundity: 10.9%
Causes of female infertility

- Ovulatory disorders
- Tubal damage
- Uterine or peritoneal disorders

70%
PCOS associated disorders

- Subfertility
- Abnormal menstrual cycles
- Obesity
- Hyperinsulinaemia
- Diabetes
- Hyperlipidemia (LDL, Tryglicerides)
- Cardiovascular disease
- Sleep apnoea

a common, complex metabolic disorder affecting approximately **10% of reproductive age**

Endometrial hyperplasia
Endometrial cancer
Women with PCOS have 2.89 fold increased risk for Endometrial cancer!

Evaluating the association between endometrial cancer and polycystic ovary syndrome
Zeina Haoula¹, Maida Salman², and William Atiomo¹

This translates into a 9% lifetime risk of EC in women with PCOS compared with 3% in women without it.
Mechanisms in pathogenesis of Endometrial cancer
Hypotheses to explain the link between PCOS and Endometrial cancer

- Raised estrogen levels
  - Hyperinsulinemia
  - Reduced apoptosis
Why the link between PCOS and EC is important?

- Screening of PCOS patients for EC
- Regulation of insulinemia may contribute to
  - prevention of EC
  - improved survival
- Potentially, maintenance therapy after conservative treatment of EC
Metformin: A Hopeful Promise in the Aging

Marta G. Novella1,2,*, Ahmed Ali1, Carlos Díaz-Gómez1, Michel Bernier1, and Rafael de Cabo1

Research

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Tamoxifen and endometrial cancer

The relative risk of developing endometrial cancer is two to three times (2.53) greater in women receiving Tamoxifen.

This risk varies depending on menopausal status.

- Pre-menopausally: no increased risk
- Postmenopausis: the risk is 4.0 times higher.

In about 10% of the cases Endometrial cancer develops as a component of familial malignant syndrome (Lynch syndrome II-HNCCS) due to the inheritance of the germ cell lines with predisposition for genetic abnormalities.
Hereditary non-polyposis colorectal cancer syndrome
HNCCS

- Autosomal dominant inheritance
- Genetic basis of the mutation is 5 genes (MSH2, MLH1, PMS1, PMS2, MSH6 genes) involved in DNA basis mismatch repair
- Except colorectal cancer, carcinoma of the small intestine, ureter, kidney, endometrial and ovarian cancer can occur
- 40-60% women with Lynch syndrome develop endometrial cancer
Risk map for cancer in Lynch syndrom

www.myriadpro.com/hereditary-cancer-testing, last accessed 22/09/2016
Screening in women with high risk for endometrial cancer

• Surveillance of the endometrium by gynaecological examination, transvaginal ultrasound and aspiration biopsy **starting from the age of 35 years** (annually until hysterectomy) should be offered to all LS mutation carriers (IV, B).

• **Prophylactic surgery** (hysterectomy and bilateral salpingo-oophorectomy), preferably using a minimally invasive approach, should be discussed at the age of 40 as an option for LS mutation carriers to prevent endometrial and ovarian cancer. All pros and cons of prophylactic surgery must be discussed (IV, B).
ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up

N. Colombo*, C. Creutzberg†, F. Amant‡, T. Bosse§, A. Gonzalez-Martín¶, J. Ledermann#, C. Marth#, R. Nout##, D. Querleu###, M.R. Mirza#### & C. Sessa#### the ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group†

ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer
Diagnosis, Treatment and Follow-up

Nicoletta Colombo, *Carien Creutzberg, †Frederic Amant, §Tjalling Bosse, ¶Antonio Gonzalez-Martín, ||Jonathan Ledermann, #Christian Marth, ##Remi Nout, ###Denis Querleu, ####Mansoor Raza Mirza, ######Cristina Sessa, ######and the ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group
Malignant tumors of the ovary

Ovarian cancer usually produces no signs or symptoms in the early stages.
Second most common gynecological cancer accounting 26% of tumors, but 52% of the total mortality

- Prevalence 30-50/100 000
- Life time risk 1.4% (i.e. 1 in 71)
- Most common in women aged 55-59 years

Average survival time 1.4 years
Total 5-year survival 35-40%
Ovary develops from mesonephric system and retains a special vascular system, different from the rest of the genital organs.

Structure of the ovary:
- epithelium
- germ cells
- stroma
Established risk conferring factors

- Increasing age
- Family history (breast cancer or HNPCC)
- BRCA1 and BRCA 2
Risk factors for ovarian cancer

- Family history of ovarian cancer - BRCA gene (5-10%)
- History of breast cancer or HNPCC
- Advancing age

BRCA, breast cancer associated
HNPCC, hereditary nonpolyposis colorectal cancer
**Risk of inheritable ovarian cancer**

<table>
<thead>
<tr>
<th>Number of first degree relatives affected</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>2.5</td>
</tr>
<tr>
<td>Two</td>
<td>30.0</td>
</tr>
</tbody>
</table>

Women with the genetic trait have a greater than 80% chance of developing epithelial ovarian cancer by the age 70 (median age 48)

Risk factors for ovarian cancer

- Family history of ovarian cancer - BRCA gene
  - 5-10%
- History of breast cancer or HNPCC
- Advancing age
- Nulliparity

BRCA, breast cancer associated
HNPCC, hereditary nonpolyposis colorectal cancer
Etiology of sporadic ovarian cancer

- Excessive gonadotrophin secretion
- Unsuppressed ovulation

Fathalla MF. Incessant ovulation- A factor in ovarian neoplasia?
Lancet, 1971; 2: 163
Ovulation
Established protective factors

- Increasing parity
- Oral contraceptive use (50% ↓, >10y)
- Hysterectomy
- Sterilization
- Oophorectomy

Ovarian cancer

STIC- Serous tubal intraepithelial cancer
Possible risk factors

- Age at menarche/menopause
- Hormon replacement therapy (RR 1.43)
- Infertility and infertility treatment drugs
- Endometriosis
- IUD (RR 1.76)
- Obesity
- Smoking (mucinous cancer)
- Talc
- Viral infections in childhood
- Ionizing radiation
If diagnosed in early stages ovarian cancer has favorable prognosis.
Stage of ovarian cancer at diagnosis

- Stage IIIA-IV: 59%
- Stage IC-IIC: 10%
- Stage IA-IB: 26%
- Unstaged: 6%

SEER data: Ries et al 2001
Diagnostics of Ovarian tumors

- Gynecological examination
- WBC and CRP
- Tumor markers
- Ultrasound
- CT/MR
Ca-125

- Elevated (>35 U/mL) in 80% of all cases
- Elevated in only 50% of stage I cases
- Low specificity
- Most useful: follow-up

- Elevated in tubal, endometrial and cervical cancer
- It may be elevated in non-gynecologic malignancies (pancreas, colon, breast, lung, liver, lymphoma, mesothelioma)
Ca 125 can be elevated in benign conditions!

- Endometriosis
- Adenomyosis
- Fibroid
- PID
- Menstruation
- Pregnancy
- Diverticulitis
- Pancreatitis
- Renal failure
- Appendicitis
- IBD
- Cirrhosis
- Ascit
Ultrasound assessment of adnexal mass
Screening for ovarian cancer

- Bimanual vaginal examination
- Transvaginal ultrasonography (TVS)
- Tumor markers (Ca 125)
- Ultrasound scanning (color Doppler imaging CDI)

Currently none of these techniques, either alone or in combination has proved to be suitable for screening the general population.
Multimodal screening strategy
St Barth’s / Royal London Hospital
Jacobs et al, 2000
22,000 volunteers

Ca 125 > 30 U/ml
Ultrasound volume > 8.8 ml
Surgery

Sensitivity 71%
Specificity 99.8%
PPV = 30%
~ 3 operations per case of OC
Serum levels of CA 125 are interpreted applying Algorithm risk of ovarian cancer (ROCA)
Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial


Summary

Background Ovarian cancer has a poor prognosis, with just 40% of patients surviving 5 years. We designed this trial to establish the effect of early detection by screening on ovarian cancer mortality.

Figure 3: Rates of ovarian cancer

The figure including confidence limits is in the appendix (p.14). MMS = multimodal screening. USS = ultrasound screening.
Healthy life style
Physical activity and prevention of cancer

It is estimated that 20-30% of cancer associated with overweight and lack of physical activity.

Global data show a 25% reduction of risk for cancer in physically active women.
"The doctor of the future will give no medicine, but will interest his patients in the care of the human frame, in diet and in the cause and prevention of disease."
~ Thomas Edison