VACCINAZIONE E TUMORI HPV CORRELATI: PERCHE' VACCINARSI

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Oncologia

- Cervical cancer is the fourth most common cancer in women;
- **528.000 new cases every year in the world;**
- The second largest cause of mortality due to cancer in women in the developing world (Ferlay et al., 2015);
- **The human papillomavirus (HPV)** represents one of the most common sexually transmitted infections **and it has been related to cervical cancer;**
- 50-80% of sexually active women will be infected with one or more of the 100 different existing types of genital HPV;
- Peak prevalence in young (16-25 anni) sexually active individuals (Stanley, 2010; WHO 2009);
- 70% of cervical cancers are actually exclusively caused by **HPV 16** and **18** viruses worlwide

Human papillomavirus & cancer

➢ **Cancer of cervix**	**100%**
➢ Cancer of anus	90%
➢ Cancer of vulva, vagina	40%
➢ Cancer of penis	40%
➢ Cancer of throat	12%
➢ Cancer of mouth	3%
➢ Cancer of esophagus	.
➢ Cancer of skin	.
➢ Cancer of X,Y,Z….	.

Graphical elaboration from Parkin DM, et al. CA Cancer J Clin 2005; 55(2): 74-108.

Cervical Cancer

Pathology

Epidemiology

Prevention and screening

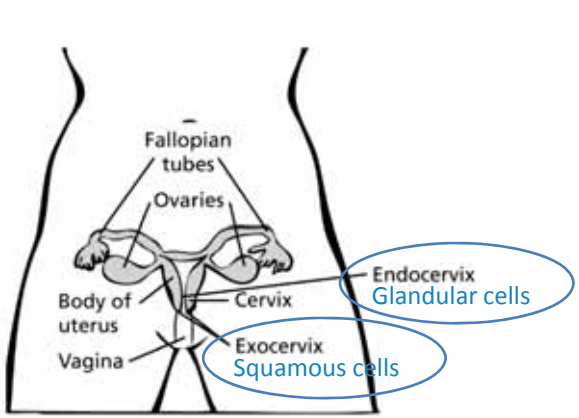
PATHOLOGY

The cervix: from precancerous lesions to cervical cancer

The cervix

- **Endocervix:** part of the cervix closest to the body of the uterus.
- **Exocervix (or ectocervix):** part next to the vagina is the (or ectocervix).[1]
- Main types of cells covering the cervix:
  - **squamous cells** (on the exocervix)
  - **glandular cells** (on the endocervix).[1]
- These two cell types meet at the **transformation zone**, where most cervical cancers start.

Figure 1



Two main types of cervical cancer: **squamous cell carcinoma** and **adenocarcinoma**. They develop from the squamous cells and the glandular cells, respectevely.[1]

1. Adapted from American Cancer Society 2013, http://www.cancer.org/acs/groups/cid/documents/webcontent/003094-pdf.pdf - Last access December 2014.

From in situ to invasive cancer: a process quite slow

- Longitudinal studies show that in untreated patients with precancerous lesions (in situ). 30-70% will develop invasive carcinoma over a period of **10-12** years.[1]
- In ~ **10**% of patients lesions can progress from in situ to invasive in less that 1 year.[1]

Precancerous lesions

- Precancerous changes of the normal cells:[2]
  - *cervical intraepithelial neoplasia (CIN)*[2] (CIN1, 2 3 grades)
  - *squamous intraepithelial lesion (SIL)(low-grade [LSIL] and high-grade [H*SIL] [2,3]
  - *dysplasia*(mild, moderate, severe).[2]

Cervical cancer

- 3 categories of epithelial tumours of the cervical cancer (WHO):[4]
  - *squamous cells carcinoma (70-80%)*[4]
  - *Adenocarcinoma* (heterogeneous group of tumours - *10-15%)*[4]
  - other epithelial tumours, (incl. neuroendocrine and undifferentiated carcinoma).[4]

1. National Cancer Institute: PDQ®Cervical Cancer Treatment 2014 available at http://cancer.gov/cancertopics/pdq/treatment/cervical/HealthProfessional - Last access December 2014; 2. American Cancer Society 2013 - Cervical Cancer available at http://www.cancer.org/acs/groups/cid/documents/webcontent/003094-pdf.pdf - Last access December 2014; 3. Mukhopadhyay S, et al. J Cytol. 2013; 30: 33-35; 4. Colombo N, et al. Ann Oncol 2012; 23 (Suppl 7): vii27-32.

Cervical cancer is a lethal disease associated with few key risk factors

1. Key risk factor

Persistent infection with HPV

•99% of cervical tumours (of whom 70% from genotypes HPV16 and 18)[1]

2. Key risk factor

Socio-economic factors[2]

•Indirectly linked to persistent HPV infection

•Early sexual activity and multiple partners, poverty, early and/or multiple pregnancies, smoking and poor access to health care[2]

3. Key risk factor

Familial history

•2-3 fold increase of risk of developing with cervical cancer in the near family[2]

1. Colombo N, et al. Ann Oncol 2012; 23 (Suppl7): vii27-32; 2. American Cancer Society 2013 - Cervical Cancer available at http://www.cancer.org/cancer/cervicalcancer/detailedguide/cervical-cancer-risk-factors Last access December 2014; 3. Cancer Research UK 2013 http://www.cancerresearchuk.org/cancer-help/type/cervical-cancer/ - Last access December 2014; 4. National Cancer Institute SEER Fact Sheet 2013 http://www.cancer.gov/cancertopics/factsheet/disparities/cancer-health-disparities - Last access December 2014.

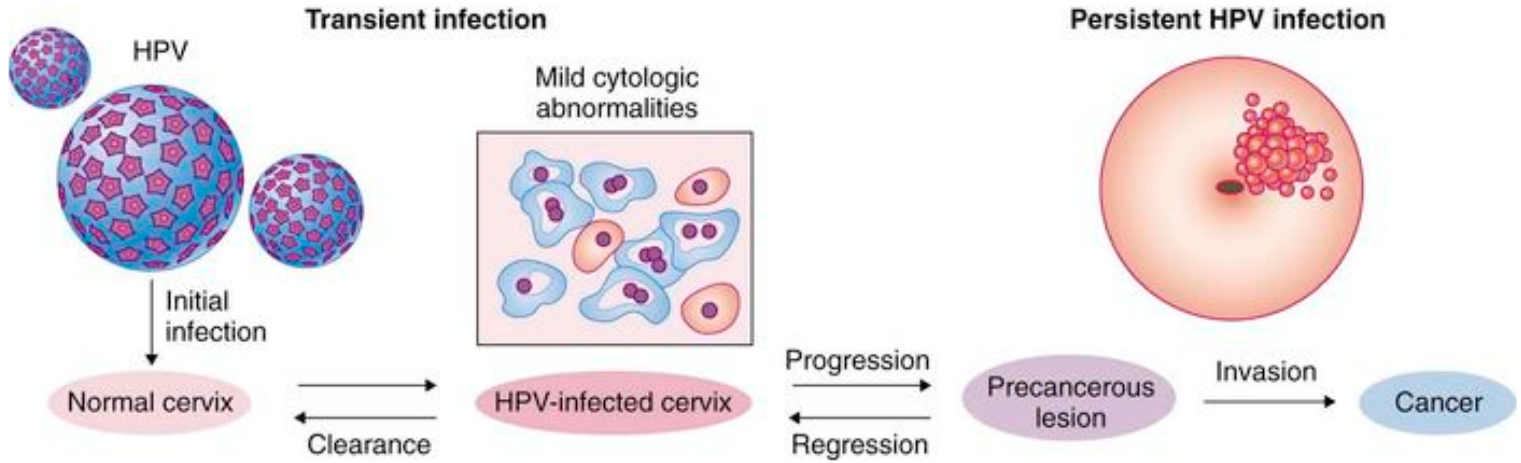
High risk HPV is the most important etiologic factor in cervical cancer

- Nearly 100% of cervical cancer cases test positive for HPV.2

3 Different phases[1-3]

Persistent HPV infection → Progressive displasia → Invasive Cancer

Role of human papillomavirus infection in the development of cervical cancer[3]



Adapted from Ref 2

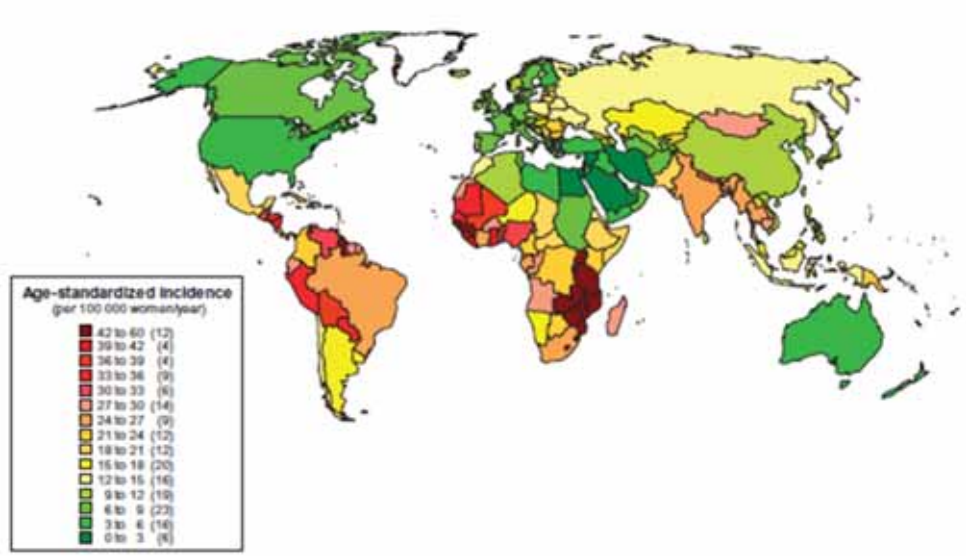
*1. Saslow D, et al. Am J Clin Pathol 2012; 137(4): 516-542; 2. Wright TC Jr, Shiffman M. *N Engl J Med 2003; 348(6): 489-490; 3. Colombo N, et al. Ann Oncol 2012; 23 (Suppl7): vii27-32.*

EPIDEMIOLOGY

Cervical cancer is the 4rd most common cancer in women[3]

Figure 1. Geographic distribution of the world ASIR of cervical cancer, by country, estimated for 2008 (per 100 000 women-years). The counts in brackets in the legend correspond to the number of countries in each ASIR range. ASIR, age-standardised incidence rate.[2]

- **530,000** new cases (8.8%) and **275,000** deaths[1]
- **4rd** most common cancer in women, (1° BC -22.9%; 2° CRC - 9.4%)[1,3]
- **2nd** most frequent cancer in women aged 15-44[4]
- **> 85%** in developing countries (**13%** of all female cancers)[1,3]
- Incidence and mortality rates (per 100.000 cases/ year)[1]:
  - developed world:
    inc, **9**%; mort., **3.2**%
  - developing countries:
    inc, **17.8**%; mort., **9.8**%

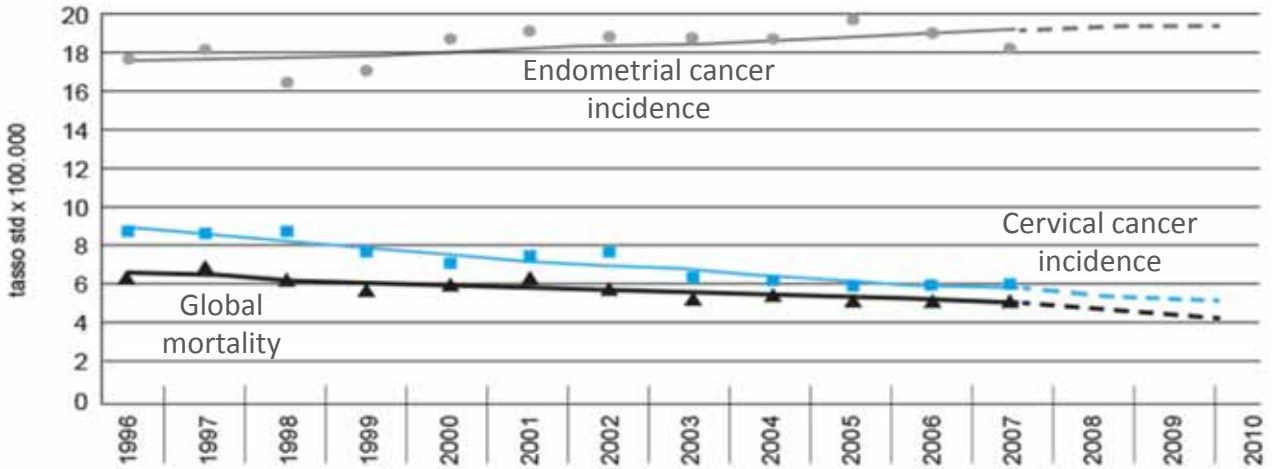


1. IACR Globocan Cervix uteri fact sheet. 2008. available at http://onlinelibrary.wiley.com/doi/10.1002/ijc.25516/pdf - Last access December 2014 2. Arbin M, et al. Ann Oncol 2011; 22(12): 2675-2686; 3. American Cancer Society Global Cancer Facts and Figures 2008 available at http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-027766.pdf - Last access December 2014; 4. sexually transmitted diseases European Commission – Public Health available at http://ec.europa.eu/health/sexual_health/hpv/ - Last access December 2014

Cervical cancer in Italy: the fifth tumor in women before the age of 50

- 4% of all tumors in women < 50 years.[1,2]
- 5th position for prevalence after: breast [23.3%], colon-rectum [13.2%], bladder [10%] and prostate [9.7%] cancers.[1,2]
- 3,000 new cases in 2013 (-3.8% in incidence and -2.1% in global mortality).[2]
- 5 year-survival for cervical carcinoma increased from 63% to 71% in the last 2 decades.[1,2]

Adapt from Ref. 2 - Endometrial and cervical cancer: trend in incidence and global mortality in the last decade (1996-2010)[2]



1. AIOM Guidelines 2015: Neoplasie dell'utero: endometrio e cervice; 2. AIOM-AIRTUM. I numeri del cancro in Italia 2013. Intermedia Editore available at http://www.registri-tumori.it/PDF/AIOM2013/I_numeri_del_cancro_2013.pdf - Last access December 2014

Developed vs developing countries: half of incidence and one-third of mortality

Developed countries experience half of the incidence rate and one-third of the mortality rate compared to developing countries.[1,2]

- Incidence and mortality are substantially higher in certain populations in developed countries with higher risk factors and poor access to health care.[1]
- Overall age-standardised cervical cancer incidence and mortality rates (per 100,000 cases/year) are shown in Figure 1:
  - **developed world**: incidence, 9.032; mortality, 3.232
  - **developing countries**: incidence, 17.733; mortality, 9.732.

Figure 1. Overall age standardised cervical cancer incidence and mortality in developed and developing countries

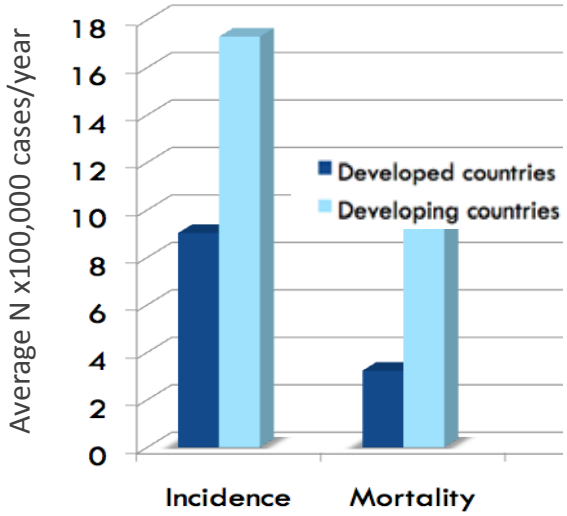


Figure adpted from Ref. 1 American Cancer Society 2013.

1. American Cancer Society 2013; 2. National Cancer Institute Factsheet 2013; 3. Arbyn M, et al. Ann Oncol. 2011; 22(12): 2675-86.

Women of lower socio-economic status have a higher incidence of cervical cancer

- Women of lower socio-economic status (defined by income, educational status or housing) have an increased risk of cervical cancer.[1]
- Prevalence of HPV infection appears to be greater in women of lower educational and income levels.[1]
- Correlates of social status such as poor nutrition, smoking, other genital infections and the lack of use/access to preventative services (especially screening) are linked to increased risk.[1]
- In the US, African-American women are more likely to be diagnosed with cervical cancer than white women; the highest incidence rate is in Hispanic/Latino women (13.8 per 100,000) and the highest mortality rate is among African-American women (4.9 per 100,000).[2]
- The incidence in African-American/black women is approximately 1.3 times that in white women.[3]
- Differences are, in part, due to socio-economic indicators such as income and education; adjustments for such factors greatly reduce the black-white difference.[1]

HPV, human papillomavirus.

1. IARC Handbooks of Cancer Prevention 2005; 2. National Cancer Institute Fact Sheet 2013; 3. US SEER 2000-2010.

Cervical cancer is a lethal disease with a high mortality rate if diagnosed at an advanced stage

- Stage at diagnosis will influence prognosis, with only 20% of patients diagnosed at stage IV surviving ≥5 years.[1]
- Overall, the mortality/incidence ratio is **52%** in developing countries and only about **25%** in developed countries.[2]
- Individuals from medically underserved populations are more likely to be diagnosed with late-stage disease that might have been treated more effectively or cured if diagnosed earlier. The 5-year survival rates for patients diagnosed with different stages of disease are:[3]
  - local-disease: **91%**
  - regional spread: **57%**
  - distant disease: **19%**

1. Cancer Research UK. http://www.cancerresearchuk.org/cancer-help/type/cervical-cancer/; 2. Globocan, 2015. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx; 3. National Cancer Institute SEER Fact Sheet. http://www.cancer.gov/cancertopics/factsheet/disparities/cancer-health-disparities - Last Access Feb 2015.

PREVENTION AND SCREENING

HPV16 and 18 are the most carcinogenic genotypes

- **HPV 16** most carcinogenic HPV genotype (~55-60% of all cervical cancers – 68% squamous cell carcinomas).[1]
- **HPV 18** is the next most carcinogenic HPV genotype (~10-15% of cervical cancers - 71% adenocarcinomas and adenosquamous carcinomas).[1]
- Studies suggest that acute infection with HPV types 16 and 18 conferred an 11 to 16,9 fold risk of rapid development of high grade CIN.[2]
- The remaining 25-35% of cervical cancers caused by approximately 10 other HPV genotypes.[1]

  - (including HPV16 related 31, 33, 35, 45, 52 and 58 genotypes and HPV18 related 39, 45, 59 and 68 genotypes).[3]

1. Saslow D, et al. Am J Clin Pathol 2012; 137(4): 516-542; 2 Colombo N, et al. Ann Oncol 2012; 23(Suppl 7): vii27-32; 3. National Cancer Institute: PDQ®Cervical Cancer Treatment 2014 for Health Professionals Available at: http://cancer.gov/cancertopics/pdq/treatment/cervical/HealthProfessional - Last access Feb 2015.

HPV 18 is associated to poor prognosis and is more common in adenocarcinomas

- Squamous cells carcinomas and their precursor (CIN) are related to HPV infection in almost all the cases and the presence of HPV 18 DNA is associated with poor prognosis.[1]

- Endocervical adenocarcinoma of usual type and its precursor, adenocarcinoma in situ, are positive for HPV in nearly 90-100% of cases.[1]

- HPV 18 is more common in adenocarcinomas and adenosquamous carcinomas than in squamous carcinomas1 (approximately 32% vs 8% respectively).[2]

1. Colombo N, et al. Ann Oncol 2012; 23 (Suppl 7): vii27-32.; 2. Saslow D, et al. Am J Clin Pathol 2012; 137(4): 516-542..

HPV acquisition and persistence

- Genital HPV is acquired through sexual and genital skin-to-skin contact.[1]
- In most populations prevalence peaks within a few year after the median age of sexual debut.[1]
- 90% HPV infections are transient, becoming undetectable within 1-2 years.[1]
- One-two year HPV persistence, especially HPV16, strongly predict CIN3 or more severe diagnosis (CIN3+) in the subsequent years.
- Untreated CIN3 has a 30% probability of becoming invasive cancer over a 30-year period, although only about 1% of treated CIN3 will become invasive.[1]

1. Saslow D, et al. Am J Clin Pathol 2012; 137(4): 516-542.

High prevention with prophylactic vaccination against HPV16/18

- A prophylactic vaccination against HPV 16/18 has the potential to prevent more than two-thirds of worldwide cervical carcinomas and half of high grade squamous intraepithelial lesions.[1]

- These proportions may be even higher due to cross-protection against other high risk HPV-type infections.[1]

- Two vaccines against HPV for females aged 12–25 years are now available:[1,3]
  - Gardasil® (Merck) that protects against HPV types 6, 11, 16 and 18
  - Cervarix® (GlaxoSmithKline) that protects against HPV types 16 and 18

- Both vaccines work to prevent HPV infection and requires a series of 3 injections over a period of 6 months.[1,3]

- December 2014, US Food and Drug Administration has approved a new nonavalent vaccines against HPV genotypes

1. Cancer Research UK. 2013; 2. Colombo N, et al. Ann Oncol 2012; 23(Suppl 7): vii27-32; 3. American Cancer Society 2013.

HPV vaccination programs developed worldwide

- HPV vaccination programs have been implemented in 33 countries worldwide, including 19 countries in the European Union/European Economic Area, Australia, Canada, New Zealand and the USA.

- HPV vaccination does not prevent all cervical cancers, because a proportion are not associated with HPV infection, or all HPV-associated cancers, because not all HPV subtypes are covered by the vaccine
  - Gardasil is **96-100%** effective in preventing CIN, adenocarcinoma in situ and cervical cancer related to HPV 16 and 18
  - Cervarix is **92-95%** effective in preventing CIN related to HPV 16 and 18
  - However HPV 16 and 18 are responsible for only 70% of cervical cancers.

1. Saslow D, et al. Am J Clin Pathol 2012; 137(4): 516-542; 2. Cancer Research UK. 2013.

CRITICITA’

- Costi;
- Durata dell’efficacia e l’eventuale necessità di richiami nel tempo;
- Identificazione del target (età e sesso dei soggetti a cui offrire la vaccinazione);
- Compliance non ottimale perchè non tutte le ragazze effettuano le 3 dosi;
- Uno studio recente (PATRICIA trials)ha dimostrato che, dopo 4 anni di vaccinazione, donne tra 15-25 anni sottoposte a 1-2 dosi hanno la stessa protezione della schedula a 3 dosi (Kreimer et al., 2015);
- Maggiori effetti collaterali: dolore, fatigue, febbre, disturbi GI, cefalea, artralgie e mialgie;
- Circa 30% dei tumori della cervice non sono correlati all’infezione da HPV 16 e 18;
- La vaccinazione non previene la totalità delle infezioni da HPV ad alto rischio: proseguire con le attività di screening organizzato

Universal HPV vaccination in adolescents: efficacious, safe and cost-effective

- Adolescent cervical cancer prevention programs should focus on universal HPV vaccination, which is safe, highly efficacious and - when used in adolescents before they become sexually active - highly effective and cost-effective.[1]

- The American Cancer Society guidelines recommend that the HPV vaccine be routinely given to females aged 11 to 12 and as early as age 9 years at the discretion of doctors.[2]

- Even without cervical cancer screening it is crucial that adolescents continue to have access to appropriate health care, including assessment of health risks, family planning,contraception and prevention counselling, screening and treatment of sexually transmitted infections (STIs).[1]

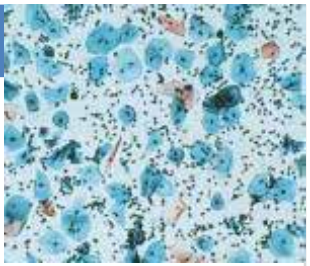
1. Saslow D, et al. Am J Clin Pathol 2012; 137(4): 516-542; 2. Cancer Research UK. 2013 http://www.cancerresearchuk.org/cancer-help/type/cervical-cancer/.

Screening

Conventional Pap Smear[1]

- Widely available
- Inexpensive
- But not perfect
- Screening test – not diagnostic
- 7-10% of women need further evaluation
- Low sensitivity – need regular repeats

New Liquid Pap Tests[2-3]



- More accurate test
- Thin, uniform layer of cells
- Screening errors reduced by half
- Screening needed less often
- Can test for HPV with same specimen if abnormal cells found
- Expensive

2012 Cervical Cancer Screening Recommendations[4]

- Women younger than 21 should not be screened.
- Women between ages 21 and 65 without risk factors (such as DES exposure or immunodeficiency) should undergo cytologic screening every 3 years.
- Those aged 30 to 65 wishing to extend the screening interval could undergo screening with both cytologic exam and human papillomavirus testing every 5 years.
- Women older than 65 who have been adequately screened previously should not be screened.

1. Cervical Cytology Screening. ACOG Practice Bulletin No. 45. 2003; 102: 417-27. 2. Linder J, et al. Arch Pathol Lab Med. 1998; 122(2): 139-144; 3. ACOG Practice Bulletin. Cervical Cytology Screening. 2003; 45: 1-11; 4. Cervical Cancer Screening Reccomandation available at http://www.cdc.gov/cancer/cervical/pdf/guidelines.pdf - Last access Feb 2015.

Weighing the benefits and harms of cervical cancer screening

Benefit outcomes

- Efficient and accurate identification of women with pre-cancer who are at significant risk for developing cancer (CIN3).[1]

Potential harms

- Anxiety associated with detecting transient lesions (CIN1 and 2) which could be erroneously considered “positive” for cancer.[1]
- Stigmatization from the diagnosis of a sexually transmitted infection.[1]
- Discomfort from additional diagnostic and treatment procedures.[1]
- Increased risk of pregnancy complications such as preterm delivery due to treatment.[1]

CIN, cervical intraepithelial neoplasia .

1. Saslow D, et al. Am J Clin Pathol 2012; 137(4): 516-542.

Screening for prevention and early detection of cervical cancer: no evidence to begin before 21

Population	Recommended screening method	Comments
Aged < 21 years	No screening	HPV testing should not be used for screening or management of atypical squamous cells of undetermined significance (ASCUS) in this age group[1]

Rational

- Cervical cancer is rare in adolescents and young women and may not be prevented by cytology screening[1]
- The incidence of cervical cancer screening in this age group has not changed with increased screening coverage over the last 4 decades[1]
- Screening adolescents leads to unnecessary evaluation and potentially to the treatment of preinvasive cervical lesions that have a high probability to regressing spontaneously[1]

Tabular elaboration from text data.
Saslow D, et al. Am J Clin Pathol 2012; 137(4): 516-542.

Pap test alone every 3 years in young women

Population	Recommended screening method	Comments
Aged 21-29 years	Citology (PAP test) alone every 3 years[1]	HPV testing should not be used for screening in this age group[1]

Rational

- For women aged younger than 30 year few studies specifically address the optimal interval for cytology-based screening[1]
- Annual screening results in twice the number of colposcopies compared with screening every 3 year, while affording slightly greater cancer risk reduction[1]
- No significant difference in cancer reduction between 2 and 3 year screening interval
- Screening every 3 years provides the best balance of benefits and harms of screening this age group

Tabular elaboration from text data.
Saslow D, et al. Am J Clin Pathol 2012; 137(4): 516-542.

HPV and cytology cotesting every 5 year in adult women

Population	Recommended screening method	Comments
Aged 30-65 years	• HPV and citology (PAP test) cotesting every 5 year (preferred)[1] • Citology alone every 3 years (acceptable)[1]	Screening by HPV testing alone is not recommended for most clinical settings[1]

Rational

- In the majority of studies the addition of HPV testing to cytology resulted in an increased detection of prevalent CIN3 with a concomitant decrease in CIN3+ or cancer detected in subsequent rounds of screening[1]
- Cotesting at 5-year intervals provides similar or lower cancer risk as cytology at 3-year intervals[1]

Tabular elaboration from text data.
Saslow D, et al. Am J Clin Pathol 2012; 137(4): 516-542.

HPV and cytology cotesting every five year in adult women

Population	Recommended screening method	Comments
Aged>65 years	• No screening following adequate negative prior screening[1]	Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 years[1]

Rational
• In well screened women aged older than 65 years the prevalence of CIN2+ is low and cervical cancer is rare[1]
• The potential harms for screening include anxiety, discomfort during citology sampling and false positive tests[1]
• Based on the extended natural history it is improbable that incident HPV infections will have sufficient time to progress to invasive cancer in the woman's lifetime[1]

Tabular elaboration from text data.
Saslow D, et al. Am J Clin Pathol 2012; 137(4): 516-542.

How PAP test results are reported

- According to Bethesda cervical cytology reporting system1 PAP test results are reported in 3 main categories[2]

  - Negative for intraepithelial lesion or malignancies
  - Epithelial cell abnormalities
    - Atypical squamous cells (ASC) and ASC of uncertain significance (ASCUS)
    - Squamous intraepithelial lesions (SILs), divided into low-grade (LSIL) and high-grade (HSIL)
    - Squamous cell carcinoma
    - Adenocarcinoma (cancers of the glandular cells)
    - Atypical glandular cells
  - Other malignant neoplasms.

1. Wright TC, et al. 2nded New York: Springer-Verlag, 2004, pp 89-121; 2. Cancer Research UK 2013 http://www.cancerresearchuk.org/cancer-help/type/cervical-cancer/ - Last Access Feb 2015.

2001 Bethesda System Terminology for Reporting Results of Cervical Cytology

SPECIMEN ADEQUACY
- Satisfactory for evaluation (*note presence/absence of endocervical/transformation zone component*)
- Unsatisfactory for evaluation . . . (*specify reason*)
  - Specimen rejected/not processed (*specify reason*)
  - Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (*specify reason*)

GENERAL CATEGORIZATION (*Optional*)
- Negative for intraepithelial lesion or malignancy
- Epithelial cell abnormality
- Other

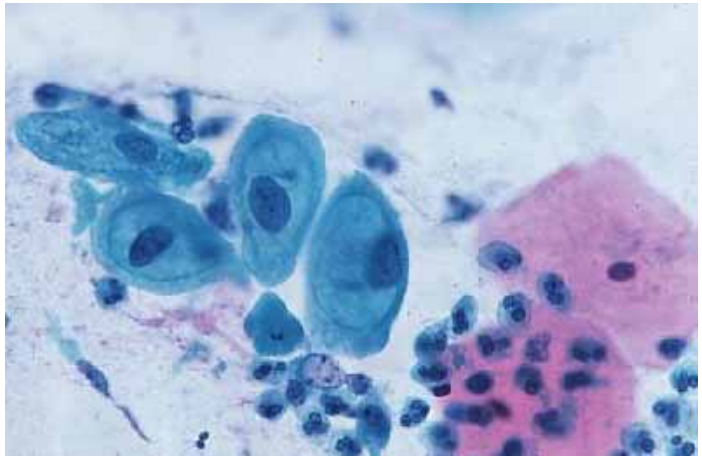
INTERPRETATION/RESULT

Negative for Intraepithelial Lesion or Malignancy
- Organisms
  - *Trichomonas vaginalis*
  - Fungal oganisms morphologically consistent with *Candida* species
  - Shift in flora suggestive of bacterial vaginosis
  - Bacteria morphologically consistent with *Actinomyces* species
  - Cellular changes consistent with herpes simplex virus
- Other non-neoplastic findings (*Optional to report; list not comprehensive*)
  - Reactive cellular changes associated with
    - inflammation (includes typical repair)
    - radiation
    - intrauterine contraceptive device
  - Glandular cells status posthysterectomy
  - Atrophy

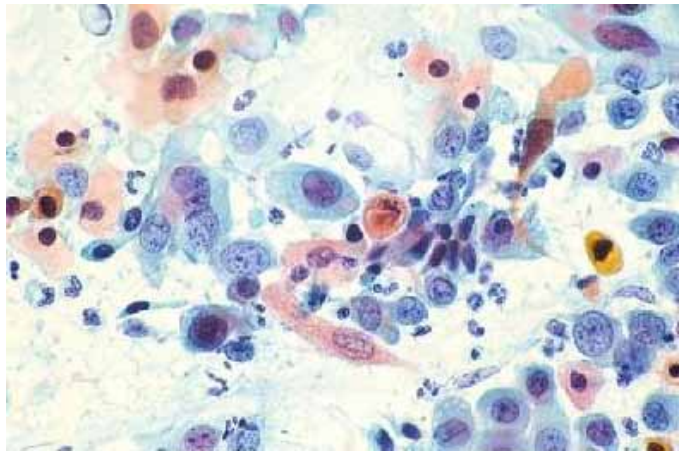
Epithelial Cell Abnormalities
- Squamous cell
  - Atypical squamous cells (ASC)
    - of undetermined significance (ASC-US)
    - cannot exclude HSIL (ASC-H)
  - Low-grade squamous intraepithelial lesion (LSIL)
    - encompassing: human papillomavirus/mild dysplasia/cervical intraepithelial neoplasia (CIN) 1
  - High-grade squamous intraepithelial lesion (HSIL)
    - encompassing: moderate and severe dysplasia, carcinoma in situ; CIN 2 and CIN 3
  - Squamous cell carcinoma
- Glandular cell
  - Atypical glandular cells (AGC) (*specify endocervical, endometrial, or not otherwise specified*)
  - Atypical glandular cells, favor neoplastic (*specify endocervical or not otherwise specified*)
  - Endocervical adenocarcinoma in situ (AIS)
  - Adenocarcinoma
- Other (*List not comprehensive*)
  - Endometrial cells in a woman ≥40 years of age

AUTOMATED REVIEW AND ANCILLARY TESTING (*Include as appropriate*)

EDUCATIONAL NOTES AND SUGGESTIONS (*Optional*)



Atypical squamous cells



Squamous cell carcinoma

Figures from American Society of Cytopathology Available at http://nih.techriver.net/view.php?patientId=25 - Last Access Feb 2015.
Solomon D, et al. JAMA. 2002; 287(16): 2114-9.

CONCLUSIONI

- Il carcinoma della cervice è una malattia trasmessa sessualmente;
- E' in calo per incidenza in Italia;
- Rappresenta ancora una problematica assistenziale rilevante, ++ nelle aree con minore efficacia dello screening e nella popolazione immigrata;
- L'infezione da HPV ha un ruolo determinante nello sviluppo della neoplasia cervicale anche se è condizione necessaria ma non sufficiente nella patogenesi del tumore della cervice;
- Il picco di prevalenza dell'infezione è tra i 16 e i 25 anni, poi l'incidenza cala progressivamente;
- Non esiste un' età nella quale l'infezione da HPV possa essere esclusa, pertanto un'efficace protezione contro l'HPV deve iniziare **precocemente;**
- **In Italia la vaccinazione viene offerta gratuitamente e attivamente alle bambine nel dodicesimo anno di vita in tutte le Regioni fin dalla fine del 2007;**

- Necessità di promuovere l'educazione alla vaccinazione con:
  - Maggior informazione;
  - Maggior coinvolgimento degli specialisti e dei medici di base;
  - Riduzione dei costi;
  - Programmi di vaccinazione meglio strutturati;
  - Ricerca;
  - Maggiori risorse per aumentare la vaccinazione e lo screening nei paesi in via di sviluppo

Impatto positivo per ridurre:

incidenza di tumori invasivi;

mortalità;

costi correlati all'assistenza e alle terapie

Rimane un importante problema sanitario