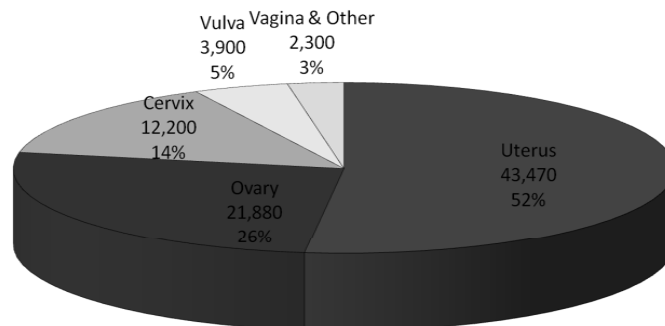


Cervical Cancer

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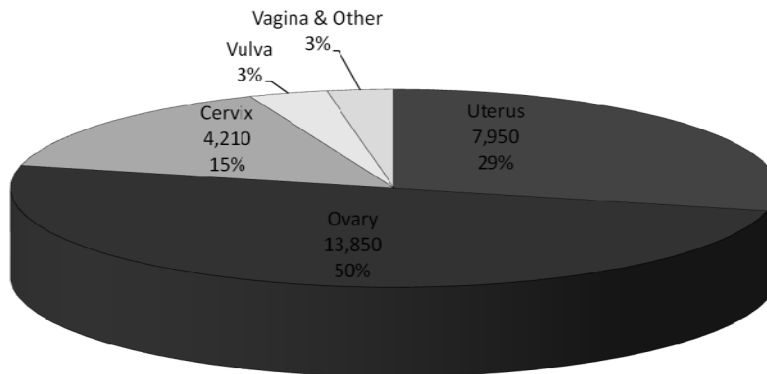
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Estimated gynecologic cancer cases United States 2010



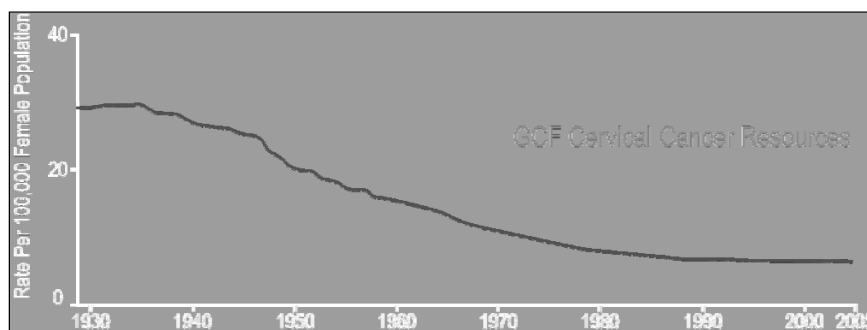
Jemal, A. et al. *CA Cancer J Clin* 2010; 60:277-300

Estimated gynecologic cancer deaths United States 2010



Jemal, A. et al. *CA Cancer J Clin* 2010; 60:277-300

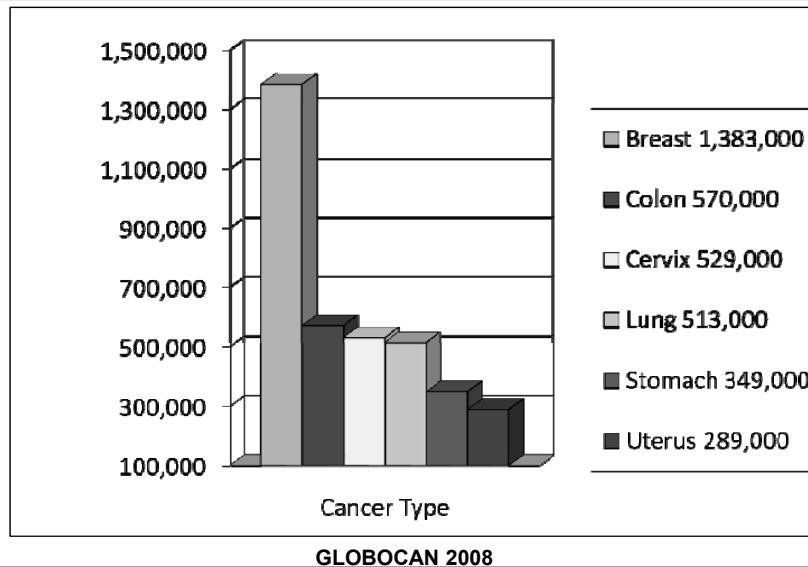
Decreasing Trends of Cervical Cancer Incidence in the U.S.



- With the advent of the Pap smear, the incidence of cervical cancer has dramatically declined.
- The curve has been stable for the past decade because we are not reaching the unscreened population.

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Cancer incidence worldwide



Cervical Cancer

	New cases	Deaths
United States	12,200	4,210
Developing nations	530,000	275,000

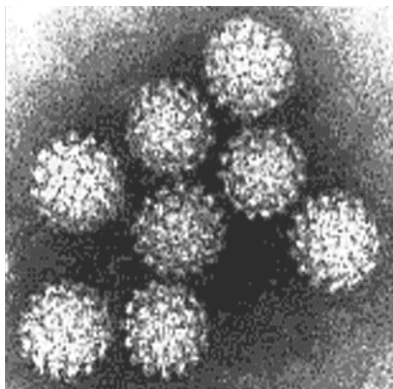
- **85% of cases occur in developing nations**

¹Jemal, *CA Cancer J Clin* 2010
GLOBOCAN 2008

Cervical Cancer

- **Histology**
 - Squamous cell carcinoma (80%)
 - Adenocarcinoma (15%)
 - Adenosquamous carcinoma (3 to 5%)
 - Neuroendocrine or small cell carcinoma (rare)

Human Papillomavirus (HPV)

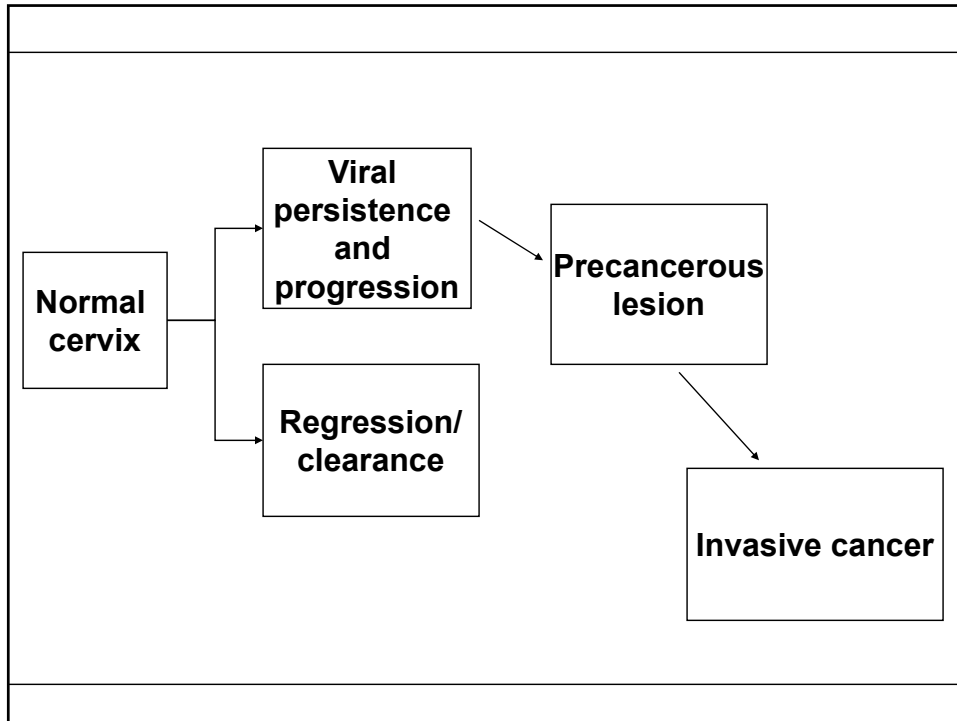


- Etiologic agent of cervical cancer
- HPV DNA sequences detected in more than 99% of invasive cervical carcinomas
- High risk types: 16, 18, 45, and 56
- Intermediate types: 31, 33, 35, 39, 51, 52, 55, 58, 59, 66, 68

HPV 16 accounts for ~80% of cases

HPV 18 accounts for 25% of cases

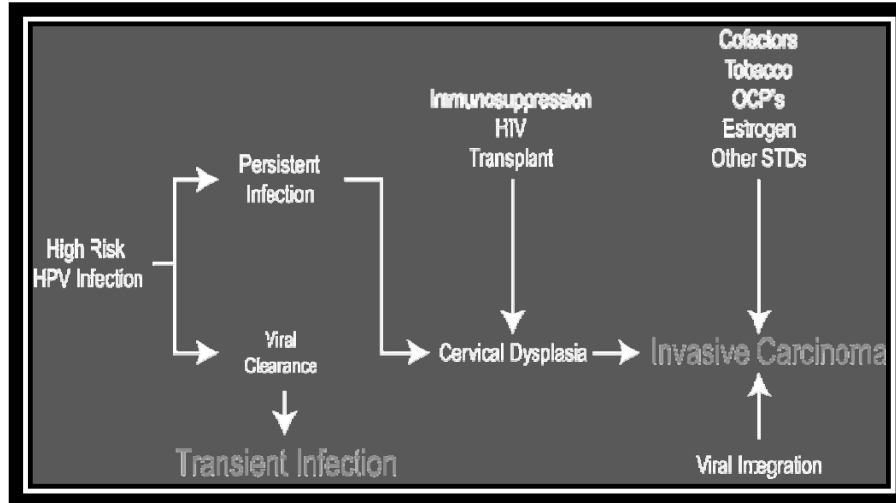
Walboomers JM, Jacobs MV, Manos MM, et al. *J Pathol* 1999;189(1):12-9.



Risk factors

- **Early age of sexual activity**
- **Cigarette smoking**
- **Infection by other microbial agents**
- **Immunosuppression**
 - **Transplant medications**
 - **HIV infection**
- **Oral contraceptive use**
- **Dietary factors**
 - **Deficiencies in vitamin A and beta carotene**

Multi-Stage Cervical Carcinogenesis



Rosenthal AN, Ryan A, Al-Jehani RM, et al. *Lancet* 1998;352(9131):871-2.
Smith JS, Green J, Berrington A, et al. *Lancet* 2003;361:1159-67.

Presentation

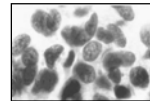
- Asymptomatic
- Vaginal bleeding
 - Post coital bleeding
- Vaginal discharge
- Pelvic pain, pressure
- Vaginal passage of urine or feces

Cervical Cancer

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Screening



- Goal
 - Detect high risk lesions (CIN 2,3+) that could progress to invasive cancer
- Reliability
 - Pap smear has broad range of sensitivity (30-87%)¹
 - Improved with repeated testing
 - Improved with HR HPV testing
- Triage²
 - ASC-H, LSIL, HSIL, AGC, repeat ASC-US
 - Refer for colposcopy and biopsy

¹Smith AE et al. *Cancer* 2000

²ACOG Practice Bulletin 99. *Obstet Gynecol* 2008.

Diagnosis



- **Most women with invasive cancer have a visible lesion**
 - However, broad range of clinical appearances
- **Grossly visible lesions should be biopsied**
 - Pap alone is inadequate for visible lesions
- **Firm, expanded cervix should undergo biopsy and endocervical curettage**
- **Women with symptoms or abnormal cytology without a visible lesion should undergo colposcopy and directed biopsy**

Diagnosis



- **Adequate colposcopy**
 - Squamocolumnar junction and all lesions completely visualized
 - Biopsy results explain the abnormal cytology
 - Cone biopsy if colposcopy is inadequate
- **Limitations of colposcopy**
 - Less sensitive than presumed¹
 - Poor correlation between colposcopic impression and biopsy grade²
 - Sensitivity improved with ≥ 2 biopsies³

¹Cox JT et al. *Am J Obstet Gynecol* 2003.

²Ferris DG et al. *Am J Obstet Gynecol* 2006.

³Gage JC et al. *Obstet Gynecol* 2006.

Diagnosis



- **Conclusion**
 - **Multiple biopsies**
 - **Repeat colposcopy if abnormalities persist**
 - **Cone if inadequate colposcopy**

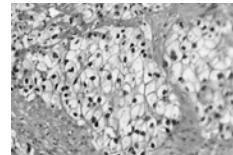
¹Cox JT et al. *Am J Obstet Gynecol* 2003.

²Ferris DG et al. *Am J Obstet Gynecol* 2006.

³Gage JC et al. *Obstet Gynecol* 2006.

Diagnosis

• Histopathology	<u>Incidence¹</u>
– Squamous cell carcinoma	67%
– Adenocarcinoma	25%
– Adenosquamous carcinoma	5%
– Rare histologies:	3%
• Neuroendocrine carcinoma	
• Adenoid cystic carcinoma	
• Undifferentiated carcinoma	
• Sarcoma or lymphoma	



¹SEER data 2004-2008. <http://seer.cancer.gov/>

Staging



- **Cervical cancer can spread by:**
 - **Direct extension to uterine corpus, vagina, parametria, peritoneum, bladder or rectum**
 - **Lymphatic spread to pelvic or aortic lymph nodes**
 - **Hematogenous dissemination**
- **Staging is a clinical evaluation to assess the extent to which the cancer has spread**

Staging

- **Accurate pretreatment staging of cervical cancer determines the therapeutic approach**
- **International Federation of Gynecology and Obstetrics (FIGO) system¹**
 - Physical exam
 - Hysteroscopy
 - Intravenous pyelogram
 - Xray evaluation of lungs and skeleton
 - Biopsy
 - Cystoscopy
 - Proctoscopy
- **Optional testing modalities such as CT and PET scan are widely used in US, and results used to plan treatment²**
- **Most US gyn oncologists still report FIGO stage**

¹Benedet JL et al. *Int J Gynaecol Obstet* 2000.

²Amendola MA et al. *J Clin Oncol* 2005.

FIGO Staging of Cervical Cancer

Stage		
I	Cervical carcinoma confined to uterus	⇒ “Early stage”
IA	Invasive carcinoma diagnosed only by microscopy (microinvasive)	
IB	• Clinically visible lesions	
II	Cervical carcinoma invades beyond uterus but not to pelvic wall or lower third of vagina	⇒ “Locally Advanced”
III	Tumor extends to pelvic wall and/or <ul style="list-style-type: none"> • - Involves lower third of vagina • - Causes hydronephrosis or nonfunctioning kidney 	
IV	Tumor spreads to other parts of the body, such as the mucosa of the bladder or rectum and/or distant metastasis	⇒ “Distant” or “Advanced”

Prognosis

Stage Distribution and Survival¹

Stage	Distribution	5 Year Survival
IA	9%	97%
IB	35%	85%
II	30%	68%
III	19%	41%
IV	6%	15%

¹Quinn MA et al. *Int J Gynaecol Obstet* 2006.

Prognosis

- Stage is the most important prognostic factor
- Lymph node metastasis is the second
 - 5 year survival with stage IB/IIA disease^{1,2}
 - Negative LN – 88-96%
 - Positive LN – 64-74%
 - Number of involved nodes may be important
- HPV subtype 18 may have a worse prognosis
- Smoking may increase the risk for treatment-related complications

¹Delgado G et al. *Gynecol Oncol* 1990.

²Averette HE et al. *Cancer* 1993.

Cervical Cancer

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Treatment

- **Based on stage of disease**
- **Categories**
 - **Early stage**
 - **Locally advanced**
 - **Advanced/Metastatic disease**

Treatment-Early stage FIGO IA, IB1

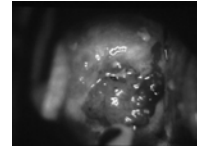
- **Non-radical surgery**
 - **Microinvasive disease**
 - **Conization**
 - **Simple hysterectomy**
 - **Fertility-preserving surgery**
 - **Discussed later**



Treatment-Early stage

FIGO IA, IB1, nonbulky IIA1

- **Surgery versus chemoradiation**
 - **Outcomes comparable**
 - **Decision based on**
 - **Childbearing plans/preservation of ovarian function**
 - **Comorbidities**
 - **Physician and patient preference**
 - **Quality of life (QOL) issues (higher in surgery)**

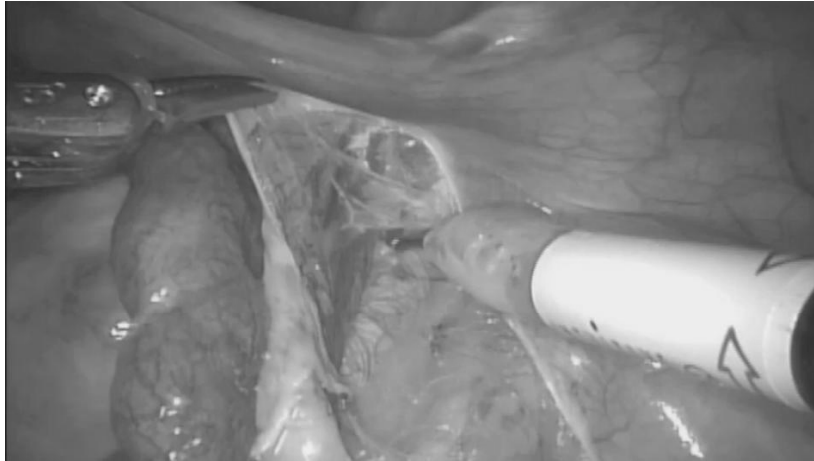


Treatment-Early stage

FIGO IA, IB1, nonbulky IIA1

- **Radical hysterectomy**
 - **Radical hysterectomy refers to the excision of the uterus en bloc with the parametrium (ie, round, broad, cardinal, and uterosacral ligaments) and the upper one-third to one-half of the vagina, with the ovaries left intact.**
 - **Open, vaginal, laparoscopic, or robotic approach**

Video



Lymphadenectomy

- **Pelvic and para-aortic lymph node dissection**
 - Resection of bulky pelvic lymph nodes
 - Assessment of lymphatic spread
 - Indication for post-operative chemoradiation
- **Not performed for stage IA1 SCC**
 - Less than 1% risk of nodal metastases
- **Stage IA2, IB1, IB2, and IIA disease**
 - Lymphadenectomy indicated

Adjuvant therapy

- **Intermediate risk factors**
 - Deep stromal involvement (to the middle or deep one-third)
 - Lymph vascular space invasion
 - Tumor size >4 cm
- **High risk factors**
 - Positive or close resection margins
 - Positive lymph nodes
 - Microscopic parametrial involvement

Treatment-Early stage

FIGO IA, IB1, nonbulky IIA1

- **Primary chemoradiation therapy**
 - RT consists of external beam radiation therapy +/- brachytherapy
 - Treatment field includes the whole pelvis
 - Extended field if known or suspected para-aortic metastases
 - The addition of weekly cisplatin to radiation resulted in superior results than RT alone

Complications of treatment

Radical hysterectomy

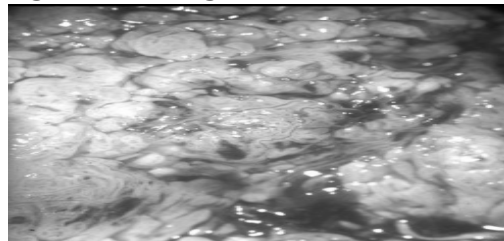
- Mortality: <2%
- Fistula:
 - Higher with prior RT
 - 1/3 to 1/2 heal spontaneously
- Bladder atony and delay in removal of the catheter: 4%
- Lymphedema

Chemoradiation

- Major complications 3-15%
- GI toxicity
 - Diarrhea
 - Enteritis
- GU toxicity
 - Frequency
 - Hematuria
- Nerve pain
 - Lumbosacral plexus

Treatment-Advanced stage FIGO IB2-IVB

- Lymphadenectomy may be performed to determine disease spread and treatment
- Primary chemoradiation followed by brachytherapy



Special circumstances

- **Role of postchemoradiotherapy hysterectomy**
 - Little to no benefit
- **Management of incidentally diagnosed cervical cancer after simple hysterectomy**
 - Radical parametrectomy and upper vaginectomy, lymph node dissection
 - Radiation therapy

Special circumstances

- **Cancer in a cervical stump**
 - Post supra-cervical hysterectomy
- **Cervical cancer in pregnancy**
 - Factors considered
 - Stage of disease
 - Gestational age
 - Patient preference

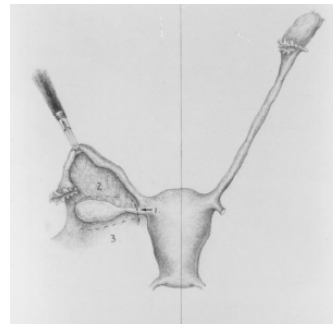
Cervical Cancer

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Ovarian Transposition

- Standard pelvic radiation doses cause ovarian ablation
- “Transposition”, or “oophoropexy”, can preserve ovarian function by surgically relocating ovaries out of the radiation field¹
- Minimally invasive
- Up to 50% success rate
- Predictive factors²:
 - Reproductive age
 - Radiation doses and fields

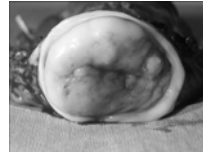


¹Tulandi T et al. *Fertil Steril* 1998.

²Stroud JS et al. *Fertil Steril* 2009.

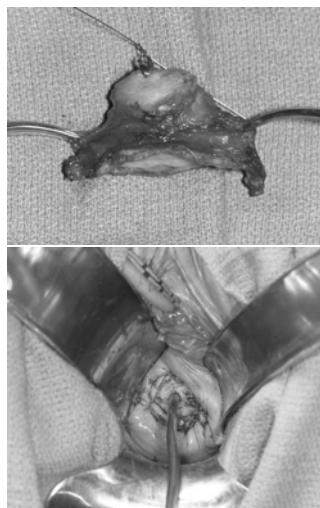
Fertility-sparing surgery

- Eligibility
 - Early cervical cancer < 4 cm
 - No evidence of metastasis
 - Desire for future child-bearing
- Options
 - Cervical conization for non-visible lesions
 - Radical trachelectomy and pelvic lymphadenectomy



Fertility-sparing surgery

- Radical trachelectomy
 - Removal of cervix, upper vagina and parametrium, but not uterus
 - Abdominal or vaginal
 - Frozen section
 - Cervical cerclage
 - Lower uterine segment reattached to upper vagina



Fertility-sparing surgery

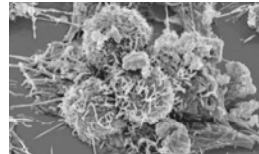
- Fertility outcomes after radical trachelectomy¹
 - As many as 50% of well-selected patients are able to achieve successful pregnancy
 - Rates of 1st and 2nd trimester loss are comparable to general population
 - May have increased incidence of preterm delivery



¹Plante M et al. *Gynecol Oncol* 2005.

Prevention

- HPV Subtypes
 - HPV types 16 and 18 cause 70% cervical cancers
 - HPV types 6 and 11 cause 90% of genital warts



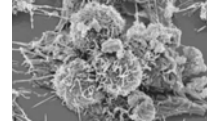
¹Future II Study Group. *N Engl J Med* 2007.

²Paavonen J et al. *Lancet* 2009.

Prevention

- **HPV Vaccines**

- **Quadrivalent Vaccine (HPV 16/18 + 6/11)**
 - In HPV naïve women, 98% effective to prevent CIN2+¹
 - 95% effective even if all 3 doses were not received
- **Bivalent Vaccine (HPV 16/18)**
 - In HPV naïve women, 93% effective to prevent CIN2+²
- **Both are FDA approved**
- **Neither contain live virus and are pregnancy category B**

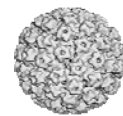


¹Future II Study Group. *N Engl J Med* 2007.
²Paavonen J et al. *Lancet* 2009.

Prevention

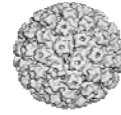
- **Recommendations for HPV Vaccination**

- **Girls and young women ages 9-26**
- **Maximum benefit before onset of sexual activity**
- **Age-specific recommendations regardless of sexual activity**
- **Given as 3 doses at 0, 1-2 and 6 months follow-up**
- **Reasonable efficacy even if not all doses administered**



Prevention

- **Conclusions**



- Demonstrated efficacy to prevent CIN 2/3, AIS and cervical cancers, as well as anogenital dysplasia and neoplasia
- No evidence of vaccine effect on pre-existing infections

Cervical Cancer

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Surveillance

- **Clinical evaluation every 3-6 months**
- **Review of symptoms**
- **Thorough examination**
 - **Lymph nodes assessment**
 - **Speculum examination**
 - **Rectovaginal**
 - **Abdominal**
- **Cytology**
 - **Low yield**

Post treatment considerations

- **Menopausal symptoms**
 - **Hormonal therapy**
- **Acute postradiation vaginal mucositis**
- **Sexual dysfunction**
 - **Vaginal shortening**
 - **Decreased vaginal lubrication**

Healthy lifestyle

- **Routine cancer screening**
 - Increased risk of developing a second cancer
 - Continued surveillance for development of new lower genital tract disease
- **Exercise**
- **Maintenance of a healthy weight**

Healthy lifestyle

- **Smoking cessation**
 - Over 35% of patients continue to smoke after cervical cancer treatment
- **Bone density monitoring**
 - Assess menopausal status