



2° CONGRESSO NAZIONALE
Verso la medicina genere specifica

LA DONNA E LA COPPIA DOPO L'ETA' FERTILE

La salute che cambia:
prevenzione, stili di vita, fragilità

19 - 20
settembre 2018

HOTEL MICHELANGELO
MILANO

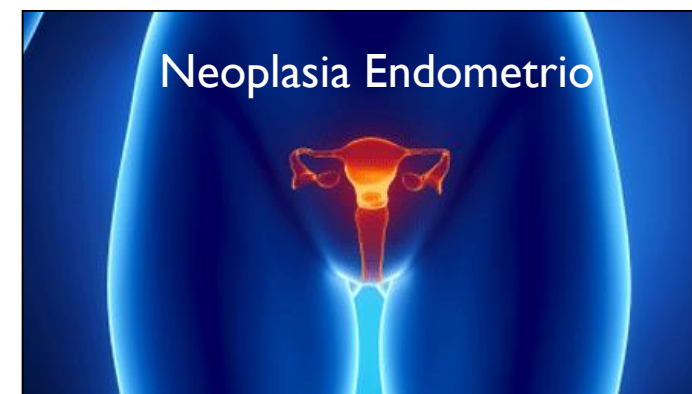
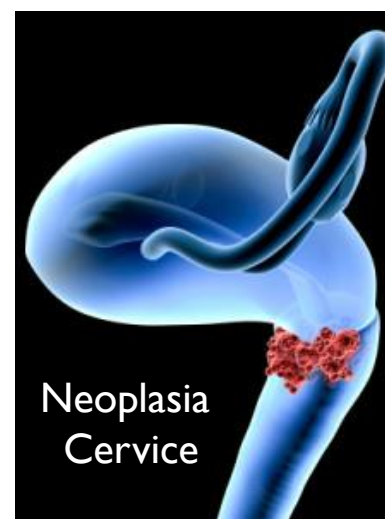
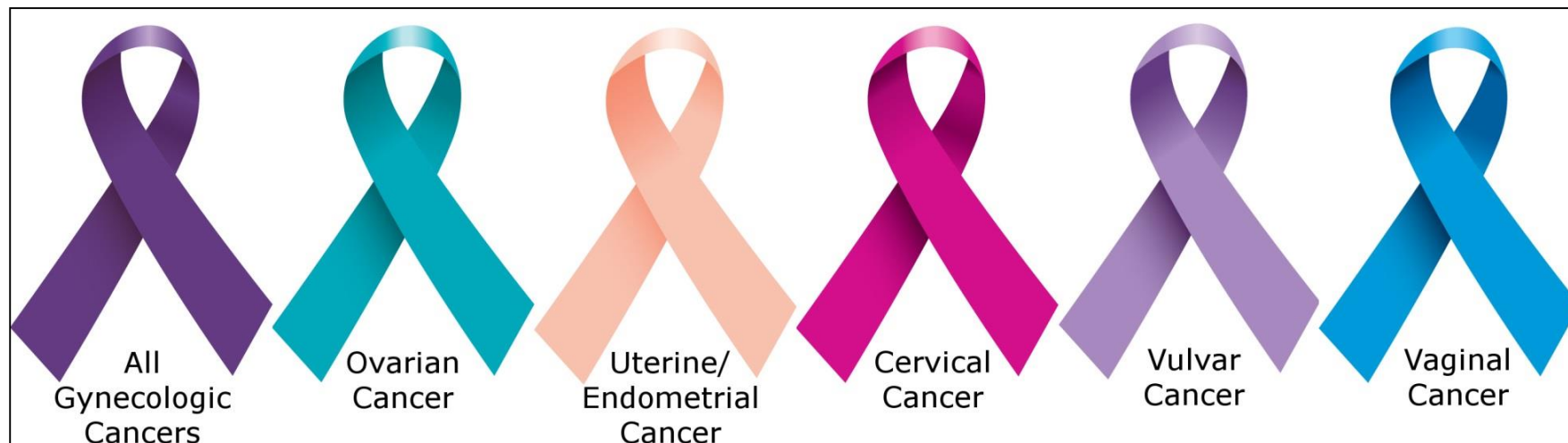


TUMORI GINECOLOGICI: UPDATE NELLA PREVENZIONE,
NELLA DIAGNOSI PRECOCE E NEL TRATTAMENTO




Prof. Massimo Candiani – Dr. Luca Bocciolone

IRCCS Ospedale San Raffaele, Milano





Neoplasia Endometrio

New Cases – US 2018			
Females			
	Breast	266,120	30%
	Lung & bronchus	112,350	13%
	Colon & rectum	64,640	7%
	4° Uterine Cancer	63,230	7%
	Thyroid	40,900	5%
	Melanoma of the skin	36,120	4%
	Non-Hodgkin lymphoma	32,950	4%
	Pancreas	26,240	3%
	Leukemia	25,270	3%
	Kidney & renal pelvis	22,660	3%
	All Sites	878,980	100%

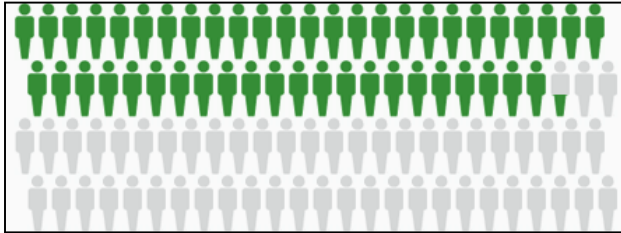
- Le neoplasie uterine sono i tumori ginecologici più frequenti (55% del totale)

- I tumori dell'ovaio sono causa del 50% delle morti per neoplasia ginecologica

- Incidenza e mortalità del cancro della cervice uterina si sono ridotte di circa il 50% tra il 1975 e il 2011



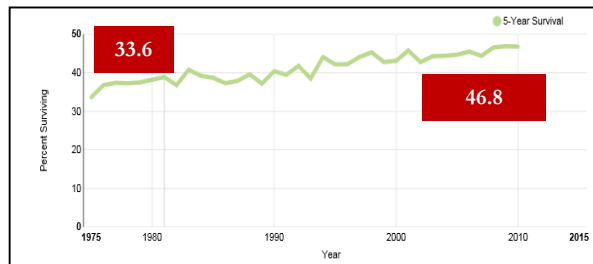
Neoplasia Ovaio



SEER – US: 2008 - 2014

Sopravvivenza
a 5 anni

47.4%



SEER – US: 1975 - 2015

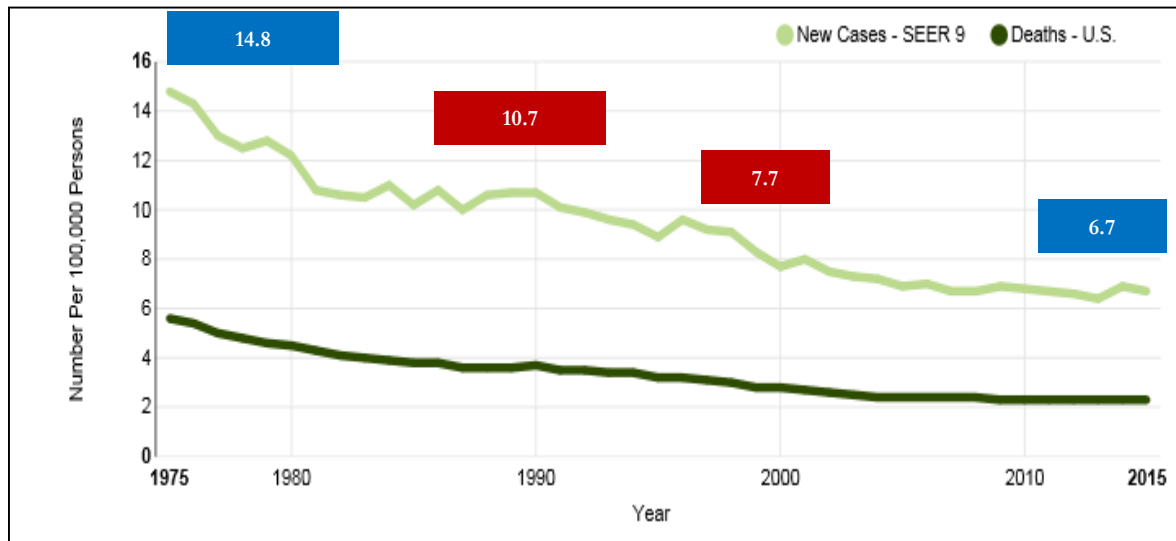
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Neoplasia Cervice Uterina

Nuove Diagnosi
100.000 donne / anno

6.7

- Le neoplasie uterine sono i tumori ginecologici più frequenti (55% del totale)
- I tumori dell'ovaio sono causa del 50% delle morti per neoplasia ginecologica
- Incidenza e mortalità del cancro della cervice uterina si sono ridotte di circa il 50% tra il 1975 e il 2015



SEER – US: 1975 - 2015

OBIETTIVO: MIGLIORARE LA CURA DEI TUMORI GINECOLOGICI



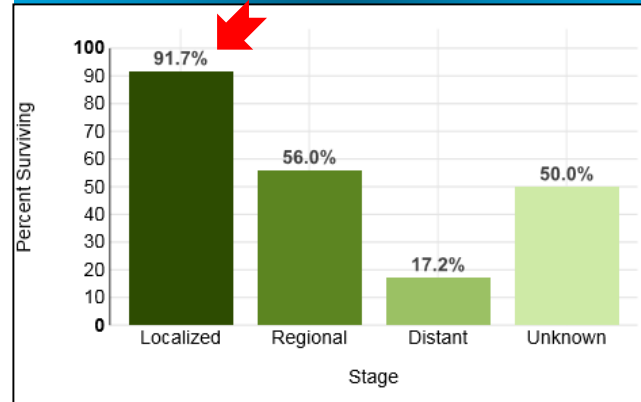
- Programmi di prevenzione e diagnosi precoce
- Approccio multidisciplinare
- Introduzione di nuovi farmaci
- Evoluzione delle tecniche chirurgiche

QUALI SONO LE PRINCIPALI NOVITA'?

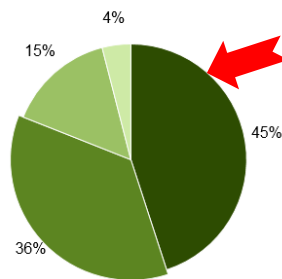
Diagnosi Precoce

Cervice

Sopravvivenza a 5 anni
Stadio alla diagnosi



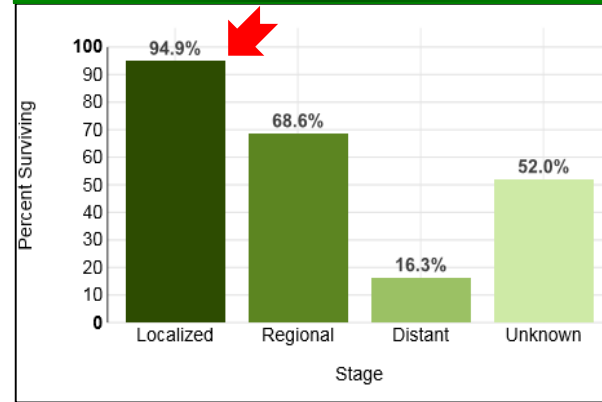
Stadio alla diagnosi



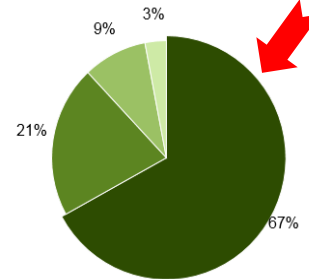
**Confinato a cervice
(45%)**
**Metastasi linfonodi
(36%)**
**Metastasi distanza
(15%)**
**Non stadiato
(4%)**

Endometrio

Sopravvivenza a 5 anni
Stadio alla diagnosi



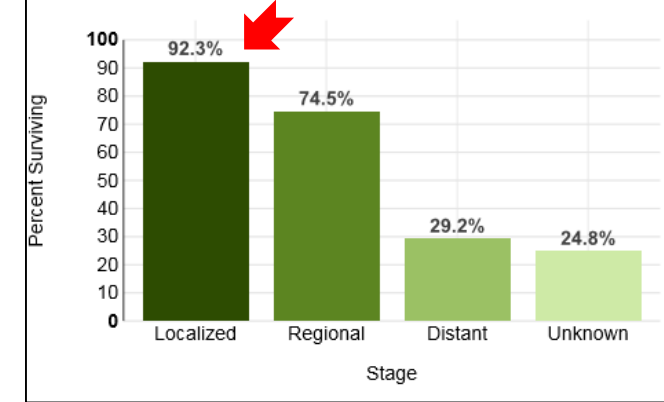
Stadio alla diagnosi



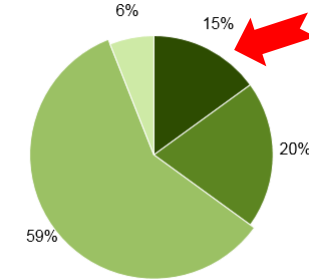
**Confinato a utero
(67%)**
**Metastasi linfonodi
(21%)**
**Metastasi distanza
(9%)**
**Non stadiato
(3%)**

Ovaio

Sopravvivenza a 5 anni
Stadio alla diagnosi



Stadio alla diagnosi



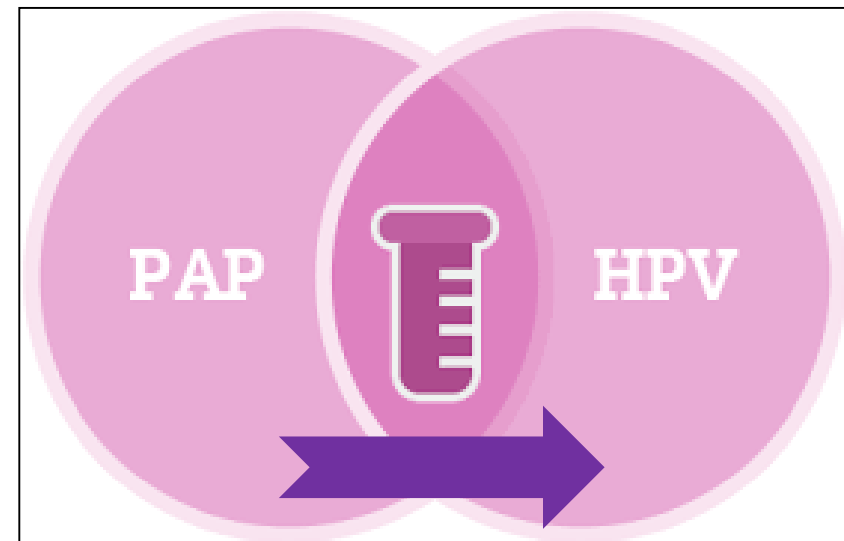
**Confinato a ovaio
(15%)**
**Metastasi a linfonodi
(20%)**
**Metastasi a distanza
(69%)**
**Non stadiato
(6%)**

TUMORI GINECOLOGICI: UPDATE NELLA PREVENZIONE, NELLA DIAGNOSI PRECOCE E NEL TRATTAMENTO

- HPV test
- Vaccinazione anti-HPV
- Ricerca mutazione BRCA 1-2
- Nuovi farmaci: PARP inibitori
- Nuovi approcci chirurgici: Linfonodo Sentinella

Test di Screening

Pap Test
HPV Test

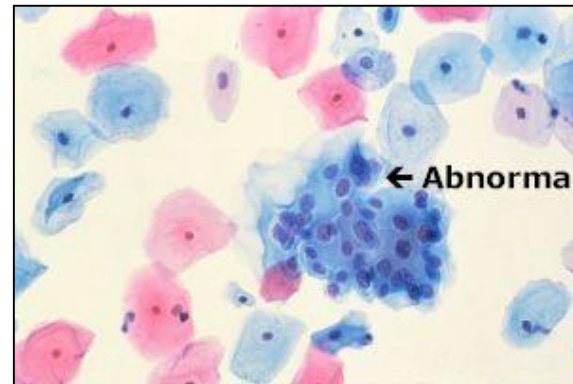
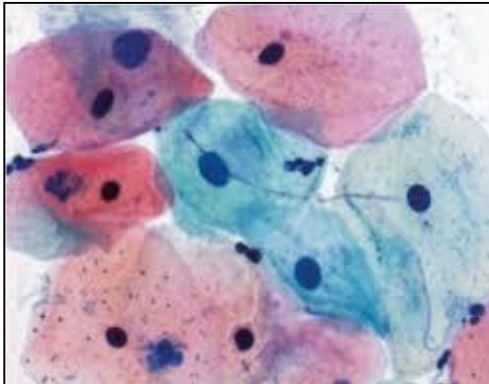


Il test di screening consiste in un
Pap-test



His monumental contribution proved
that **cancer can be beaten...**

The Papanicolaou screening test
will remain one of the **most powerful
weapons** against cervical cancer.



Dr. George Papanicolaou
Women's benefactor

Giovane età a 1^a
gravidanza

Gravidanze
multiple

Inizio precoce
attività sessuale

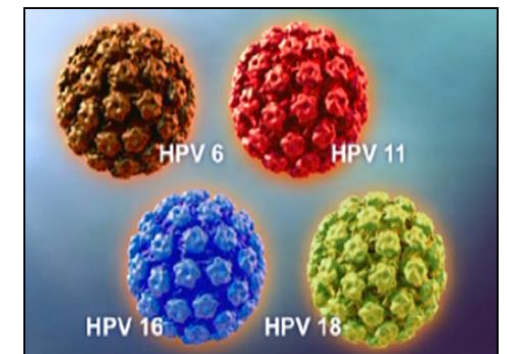
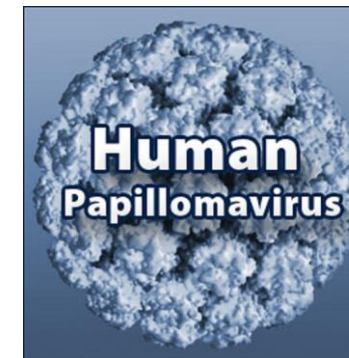
Elevato numero
di partner

Infezioni genitali
HIV - Herpes

Scarsa igiene
genitale

Contraccettivi orali
Pillola

Fumo

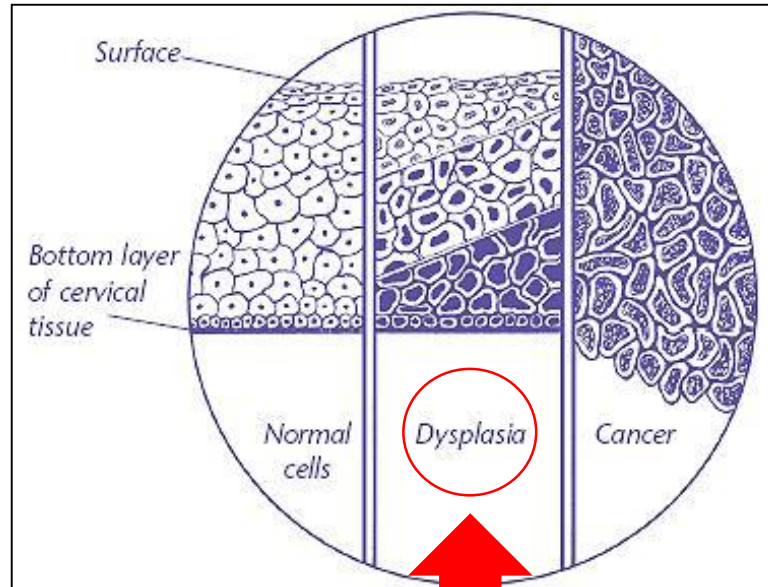


Neoplasia
Cervice

Neoplasia Cervice Uterina

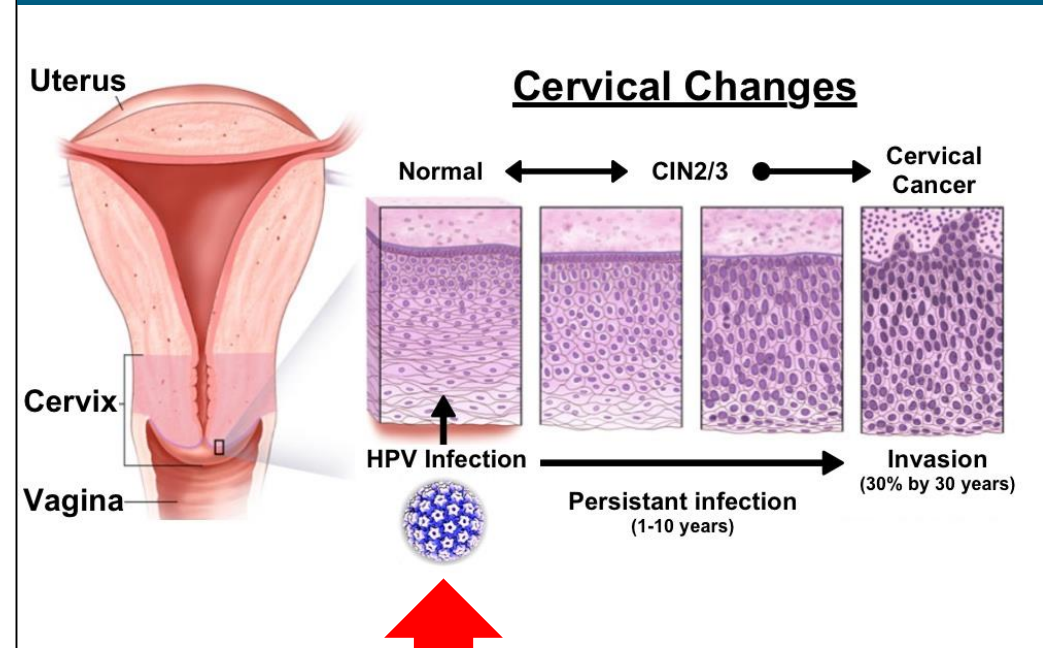
Biologia

Lesioni Pre-invasive
Displasie / CIN



Pap
Test

Infezione → Displasia → Neoplasia



HPV
Test



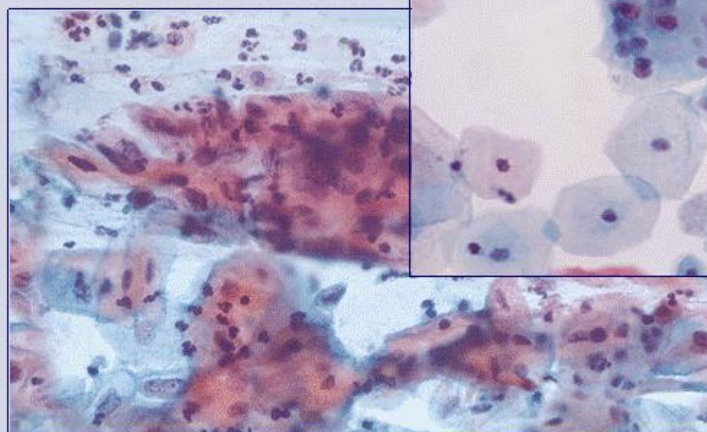


- Pap Test
- HPV Test
- Genotipizzazione

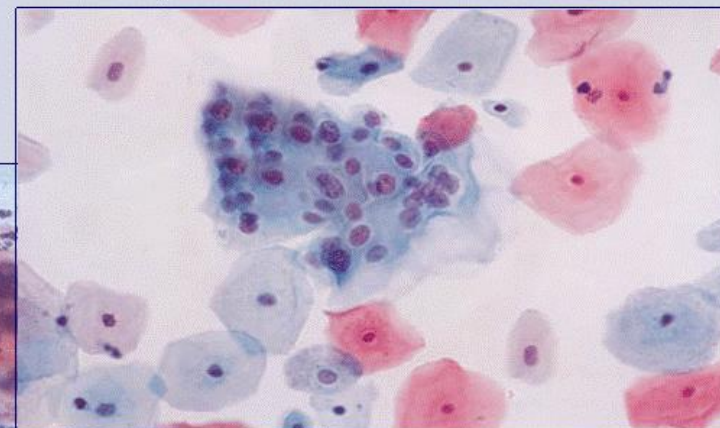


Traditional vs ThinPrep Technology

Traditional Slide



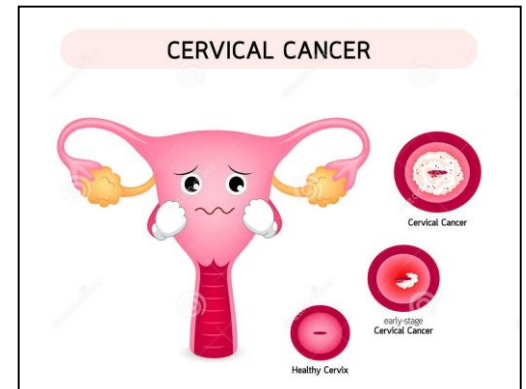
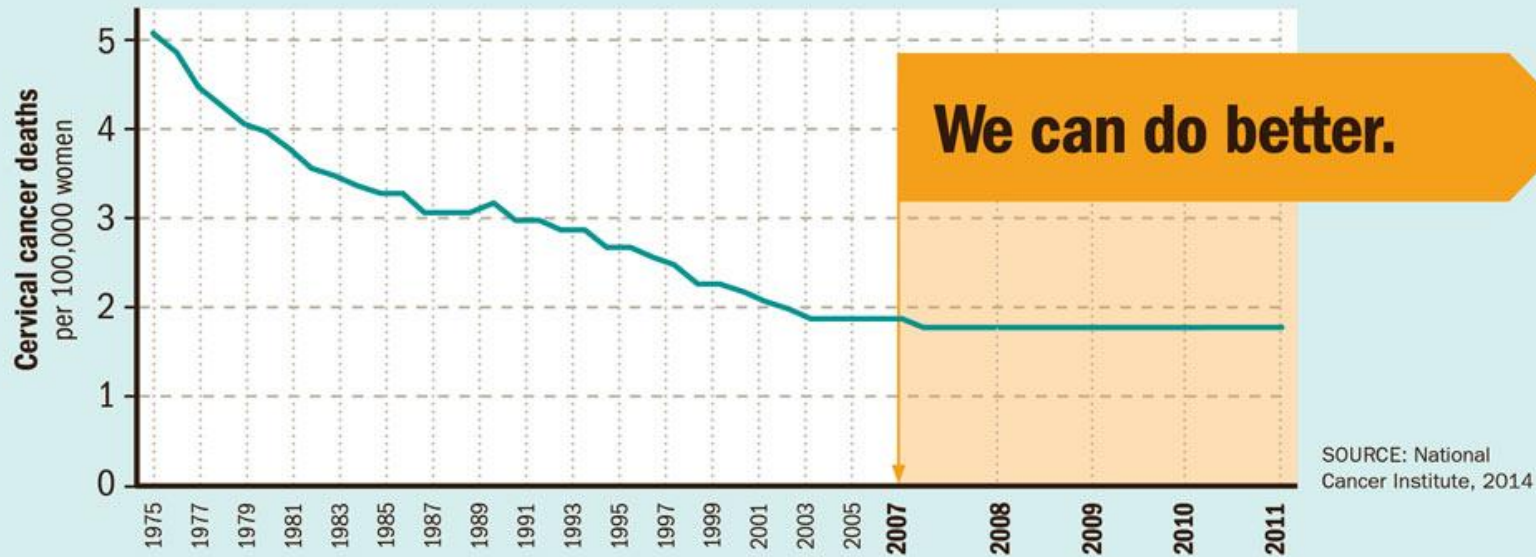
ThinPrep Slide



Vaccinazione Anti HPV

No woman should die of cervical cancer

Screening leads to fewer deaths

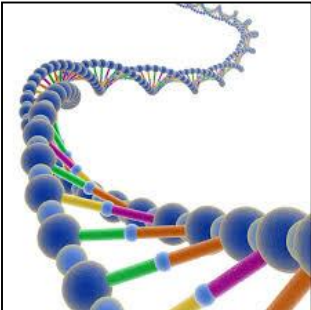


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- Nuovi farmaci: PARP inibitori
- Nuovi approcci chirurgici: Linfonodo Sentinella

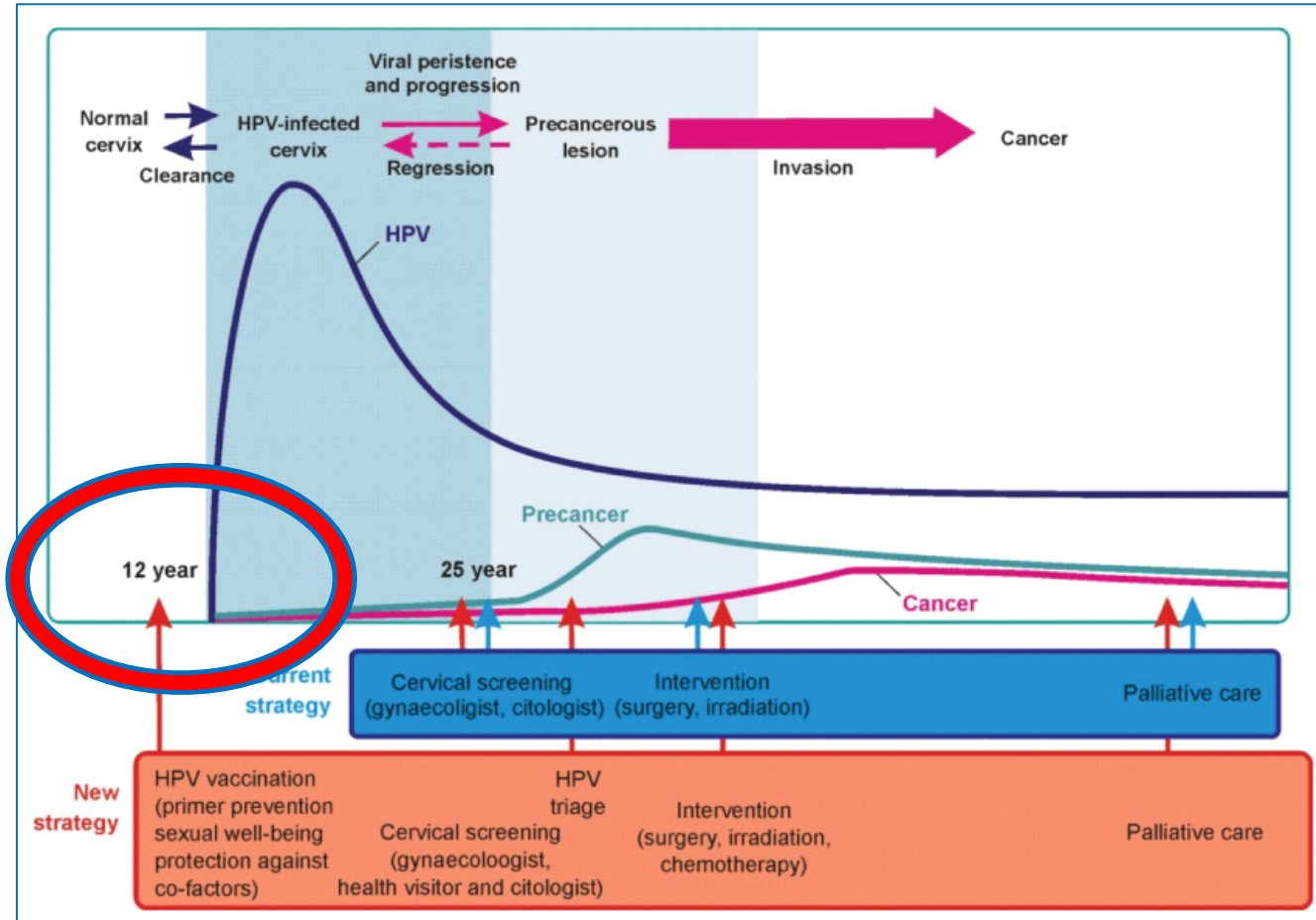
Prevenzione

Vaccinazione Anti-HPV



A word cloud with 'CERVICAL CANCER' as the central, largest text. Other prominent words include 'GYNECOLOGY', 'DISEASE', 'MEDICAL', 'HUMAN', 'DISORDER', 'HEALTH-CARE', 'REPRODUCTION', 'TUMOUR', 'UTERINE', 'DIAGNOSIS', 'SYMPTOM', 'PSYCHOLOGICAL', 'PSEUDOPAPILLARY', 'CELLULOSE', 'TUMOR', 'HEALTHY', 'DANGEROUS', 'LIFE', 'CANCER', 'HUMAN', 'DISEASE', 'GYNECOLOGY', 'REPRODUCTION', 'TUMOUR', 'UTERINE', 'DIAGNOSIS', 'SYMPTOM', 'PSYCHOLOGICAL', 'PSEUDOPAPILLARY', 'CELLULOSE', 'TUMOR', 'HEALTHY', 'DANGEROUS', 'LIFE'. The words are in various shades of brown and tan, with different orientations and sizes, creating a dense, circular arrangement.

Prevenzione Primaria



Italia - Piano Vaccinale

Da 2007
Femmine
12 anni

2017 - 2019
Femmine & Maschi
12 anni

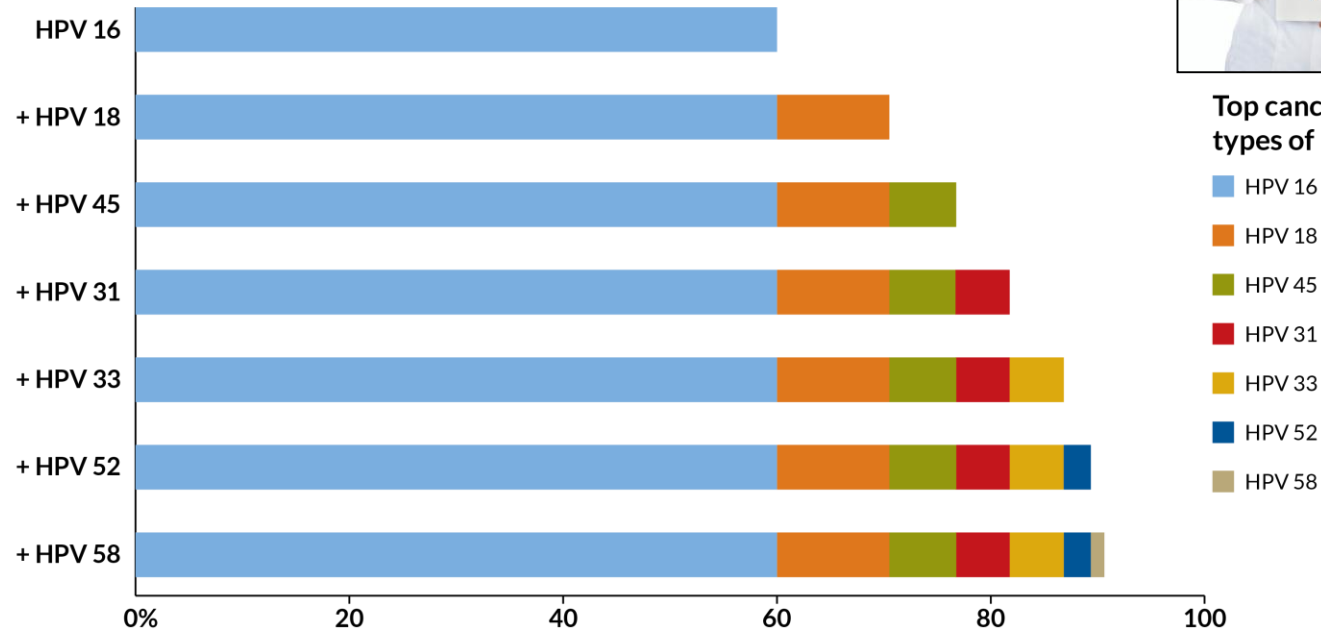


Döbrössy et al. 2016

Prevenzione Primaria



Percent of cervical cancers worldwide caused by HPV type



Top cancer-causing types of HPV

- HPV 16
- HPV 18
- HPV 45
- HPV 31
- HPV 33
- HPV 52
- HPV 58

Vaccino Bivalente

HPV 16 - 18

Vaccino Quadrivalente

HPV 16 – 18

HPV 6 - 11

Vaccino Nonavalente

HPV 6,11,15,18

HPV 31,33,45,52,58

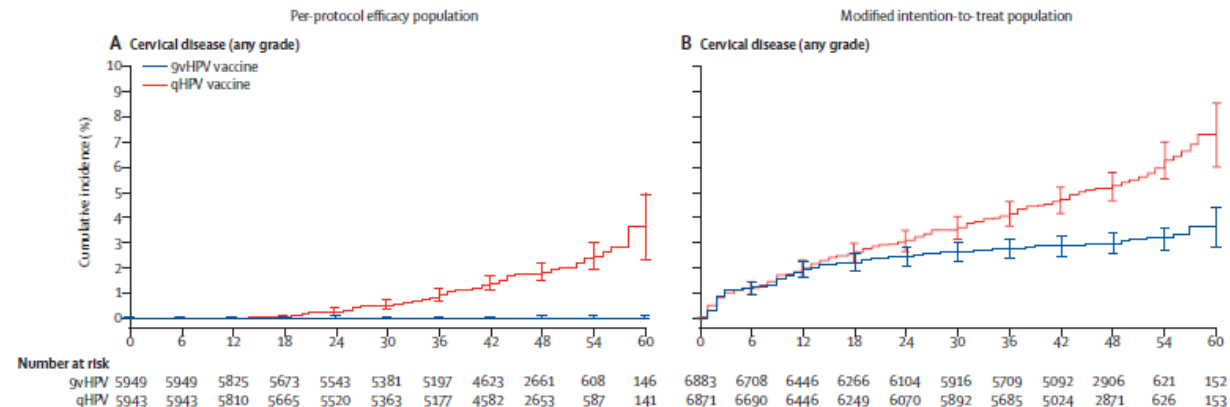
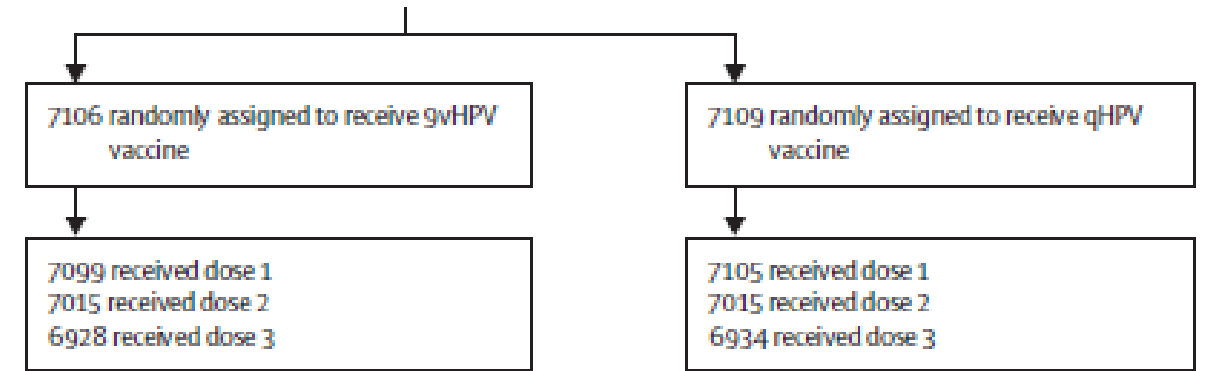
VACCINAZIONE ANTI-HPV



Lancet. 2017 Nov 11;390(10108):2143-2159. doi: 10.1016/S0140-6736(17)31821-4. Epub 2017 Sep 5.

Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial.

Efficacy of 9vHPV vaccine
97.4% (95% CI=85.0–99.9)



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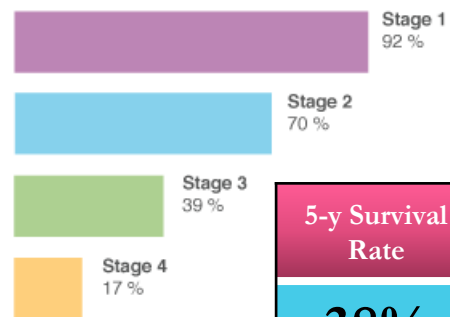
Neoplasia Ovaio



ESTIMATED DEATHS - US, 2018		
Females		
Lung & bronchus	70,500	25%
Breast	40,920	14%
Colon & rectum	23,240	8%
Pancreas	21,310	7%
Ovarian Cancer	14,070	5%
Uterine corpus	11,350	4%
Leukemia	10,100	4%
Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	7,340	3%
All Sites	286,010	100%

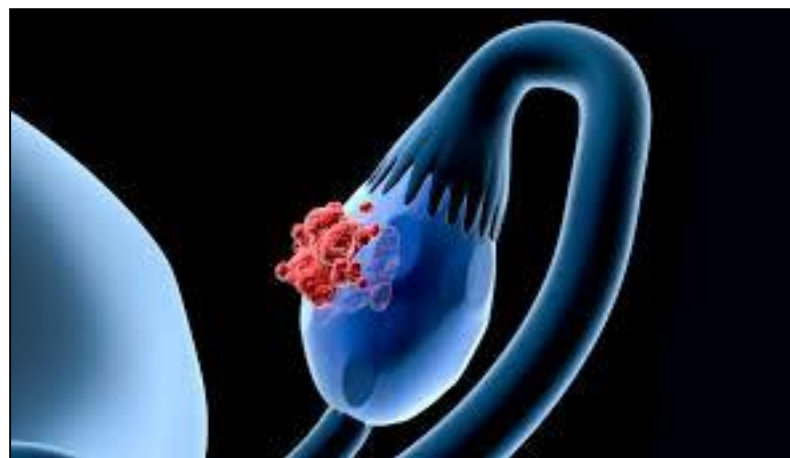
5°

Five-Year Survival Rate



5-y Survival Rate

38%



Eziologia

Insorgenza Spontanea

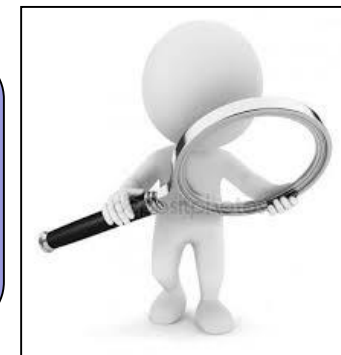
90%



Alterazione Genetica

10%

Sindrome Familiare
Carcinoma Mammario
& Ovarico
BRCA1 - BRCA2



Rischio di
Neoplasia

1.6%

Rischio di
Neoplasia

20 – 60%



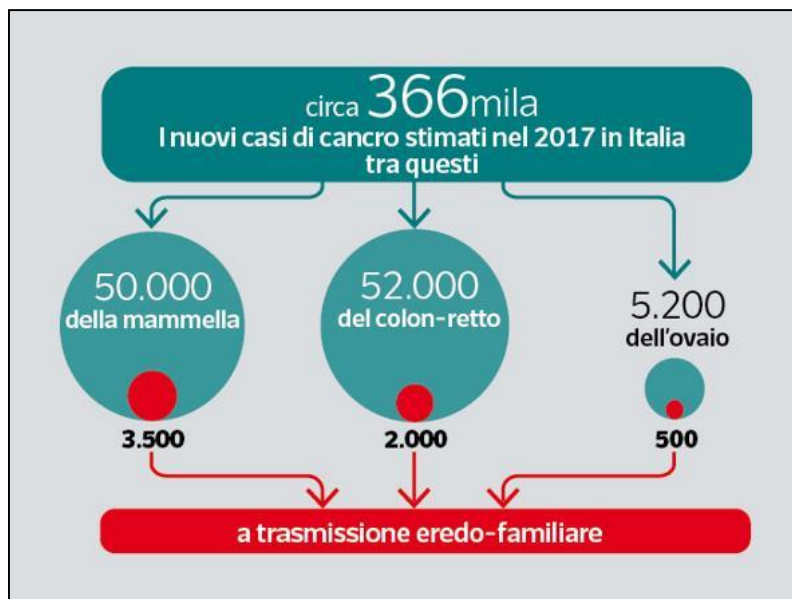
BRCA1

BRCA2

Geni Oncosoppressori

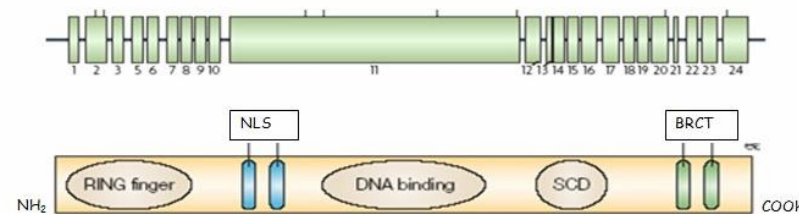
Cromosoma 17

Cromosoma 13



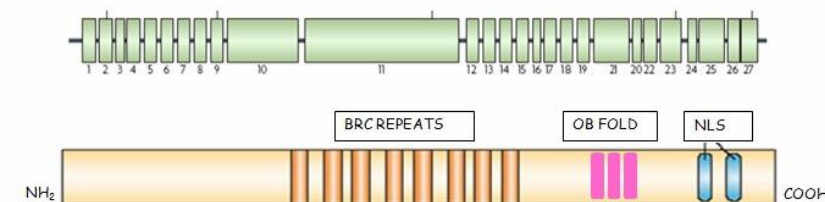
BRCA1

- 7.8 kb
- 1863 aa

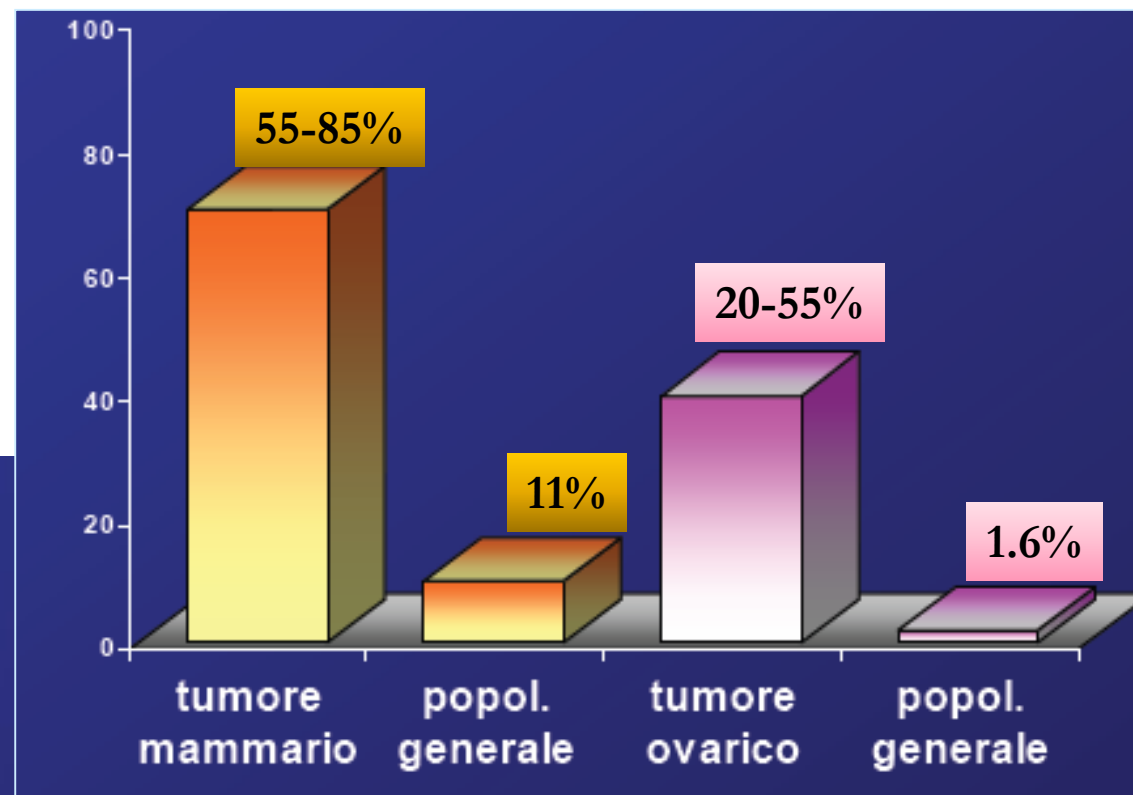
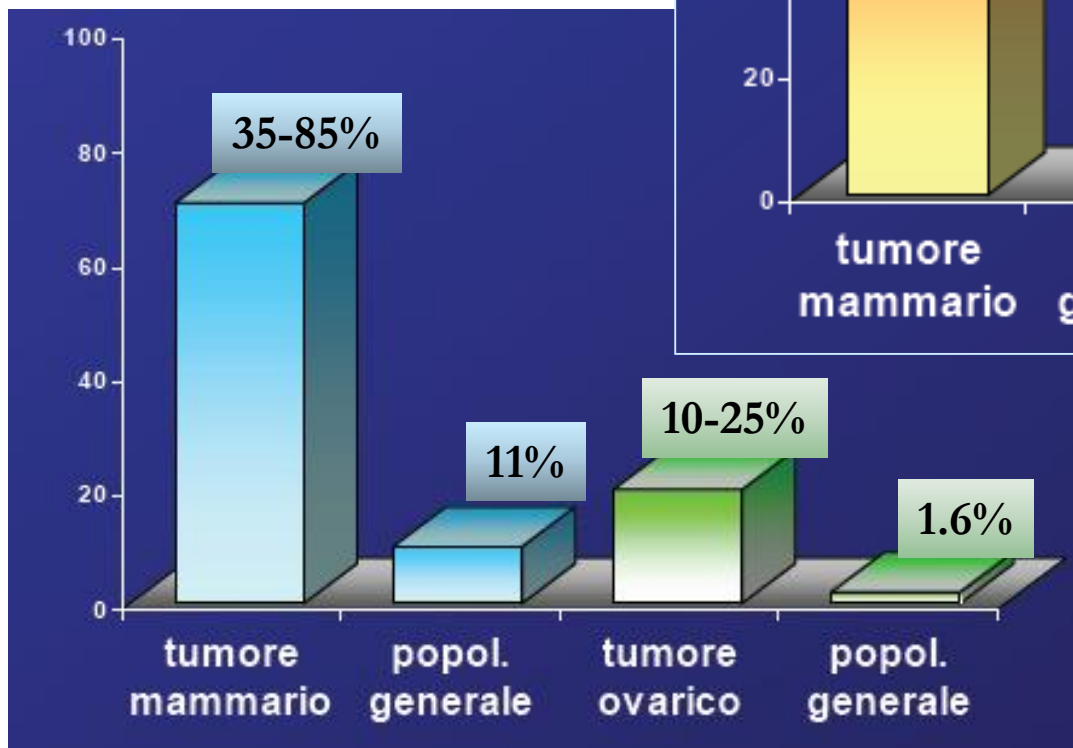


BRCA2

- 11-12 kb
- 3418 aa



BRCA1



BRCA2

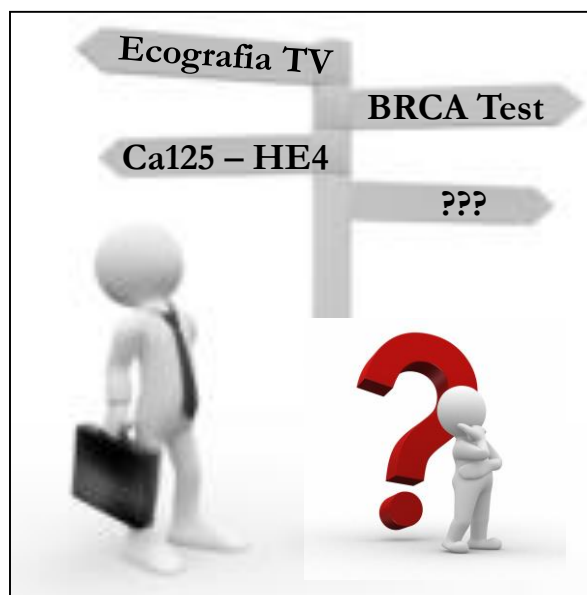
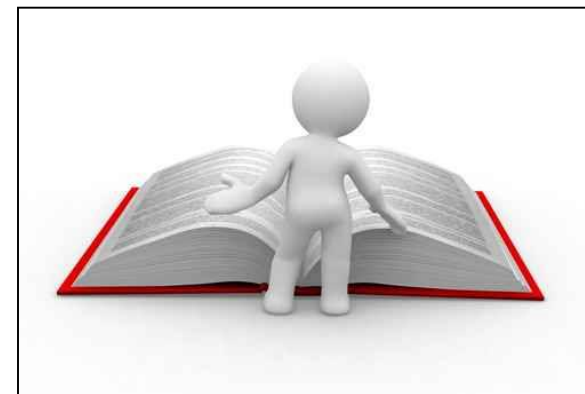
Prevenzione Secondaria

Test Screening

NO

Diagnosi Stadio Avanzato

70 – 80%



Diagnosi Clinica

Asintomatica
Disturbi aspecifici
Segni clinici tardivi

NO

**Diagnosi Strumentale
& Biochimica**

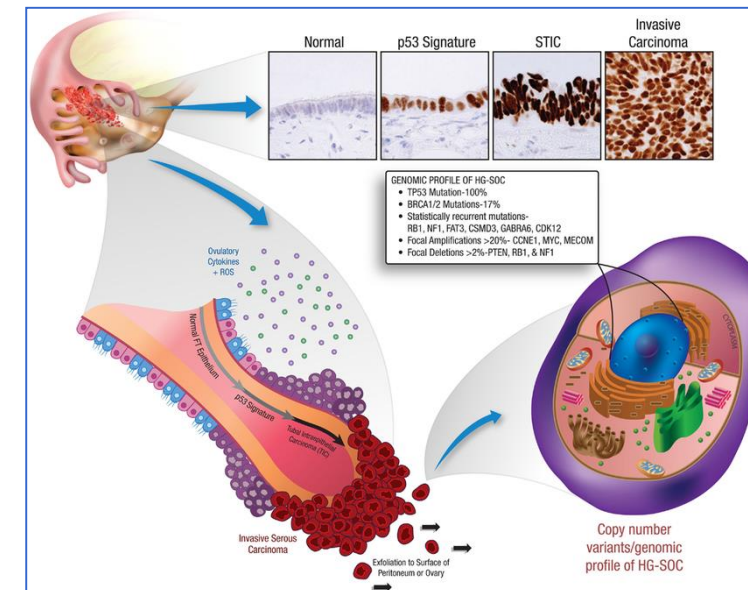
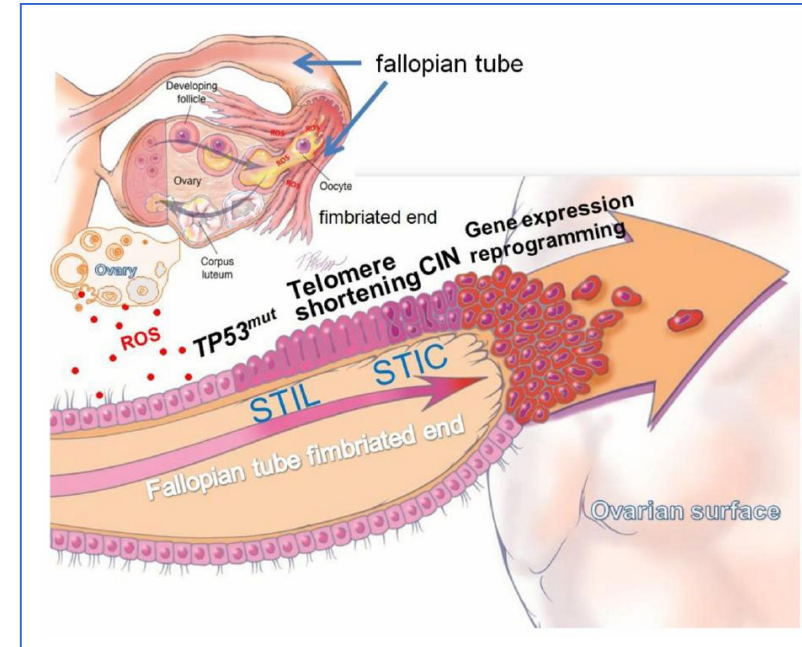
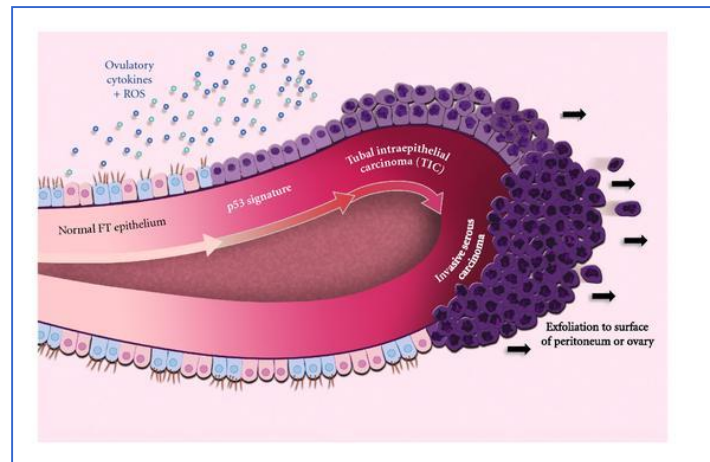
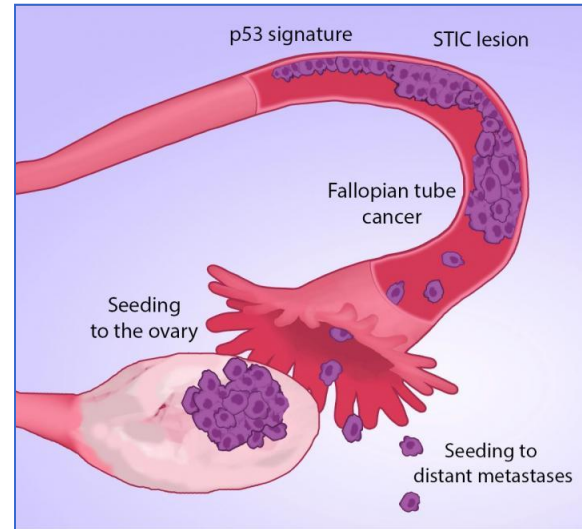
Ecografia Transvaginale
Markers (Ca125 – HE4)

NO

The Origin and Pathogenesis of Epithelial Ovarian Cancer: A Proposed Unifying Theory

Robert J. Kurman, MD and Ie-Ming Shih, MD, PhD

(*Am J Surg Pathol* 2010;34:433-443)



RICERCA MUTAZIONE BRCA



- Possibili strategie volte alla riduzione del rischio nelle pazienti BRCA mutate

Intervention	Estimated risk-reduction provided	Level of evidence [104]	Grade practice recommendations [105]
rrBSO	~80% [9–11]	Level 2 (Observational studies with dramatic effect)	Grade A = strong recommendation
Oral contraceptives	50% [86]	Level 4 (Case-control studies)	Grade B = Recommendation



Screening [82]	NPV = 99.9% [81] Adherence to screening associated with a lower chance of being diagnosed at stage 3C and above	Level 4; graded down from Level 3 due to inconsistencies with other studies (Nonrandomized controlled cohort)	Option
PSDO	Risk-reduction comparable with rrBSO [66]; Offers higher quality-adjusted life expectancy compared with rrBSO [65]	Level 5 (mechanism-based reasoning)	Option May be considered for carriers reluctant to undergo rrBSO, preferably in the context of a clinical trial
Chemoprevention with NSAIDs, vitamin D, or fenretinide (4-HPR)	No data on risk-reduction in mBRCA carriers	Level 5 (mechanism-based reasoning)	Option

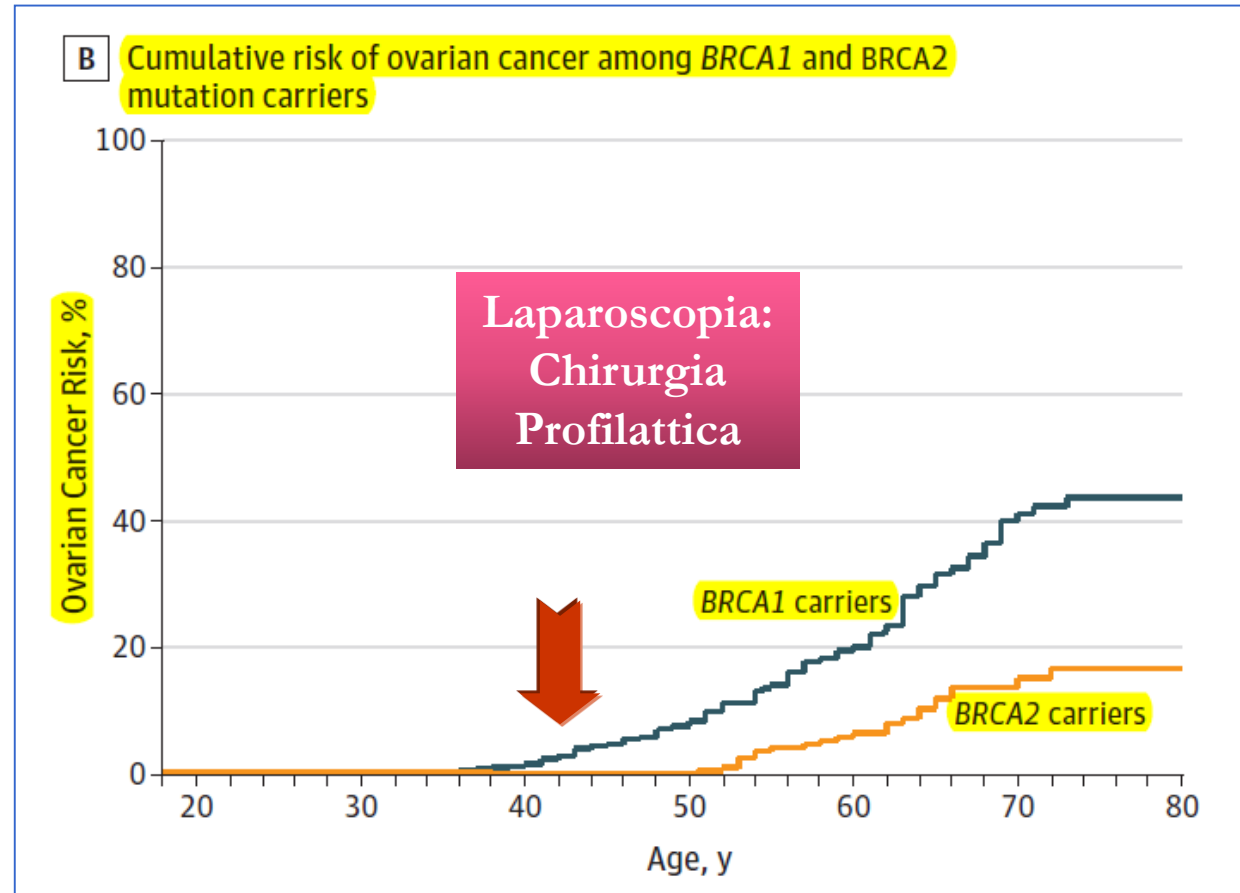
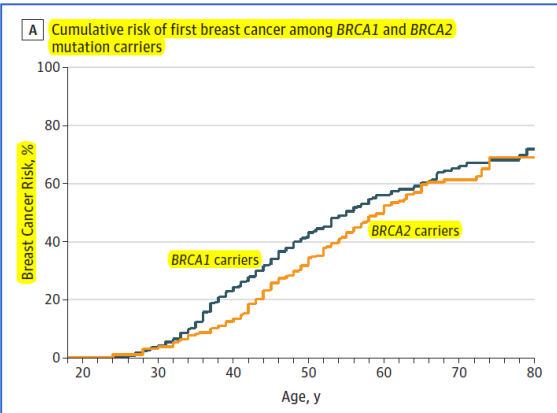
Abbreviations: mBRCA, BRCA mutation; NSAIDs, nonsteroidal anti-inflammatory drugs; PSDO, prophylactic salpingectomy with delayed oophorectomy; rrBSO, risk-reducing bilateral salpingo-oophorectomy.

JAMA | Original Investigation

JAMA. 2017;317(23):2402-2416.

Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers

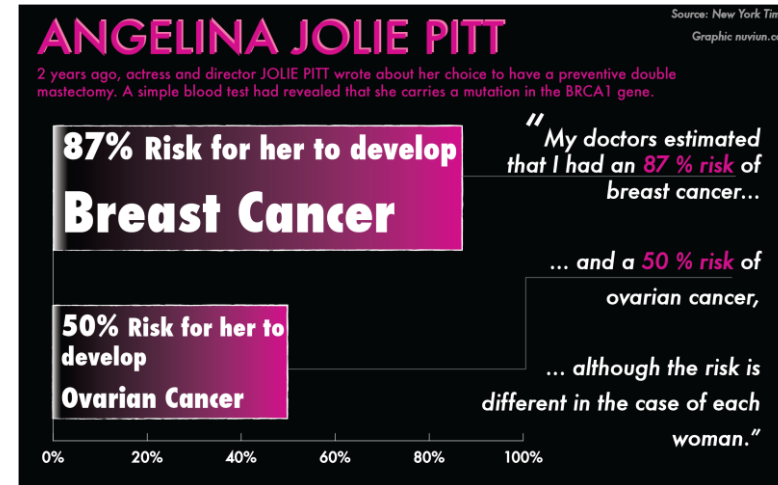
Karoline B. Kuchenbaecker, PhD; John L. Hopper, PhD; Daniel R. Barnes, PhD; Kelly-Anne Phillips, MD; Thea M. Mooij, MSc; Marie-José Roos-Blom, MSc; Sarah Jarvis, PhD; Flora E. van Leeuwen, PhD; Roger L. Milne, PhD; Nadine Andrieu, PhD; David E. Goldgar, PhD; Mary Beth Terry, PhD; Matti A. Rookus, PhD; Douglas F. Easton, PhD; Antonis C. Antoniou, PhD; and the *BRCA1* and *BRCA2* Cohort Consortium



Annessiectomia
Profilattica

Laparoscopy:
Chirurgia
Profilattica

Annessiectomy Profilattica



Angelina Jolie's decision

- "The truth is I carry a 'faulty' gene, BRCA 1, which sharply increases my risk of developing breast cancer and ovarian cancer."
- ➔ Her mother had previously battled breast cancer, but then developed ovarian cancer at age 49 and died of the disease at age 56
- ➔ Her Grandmother died of ovarian cancer at age 45
- ➔ Her maternal aunt died of breast cancer
- She chose to have bilateral preventive double mastectomies.
- She plans to have her ovaries removed once she has decided that she does not want any more children.

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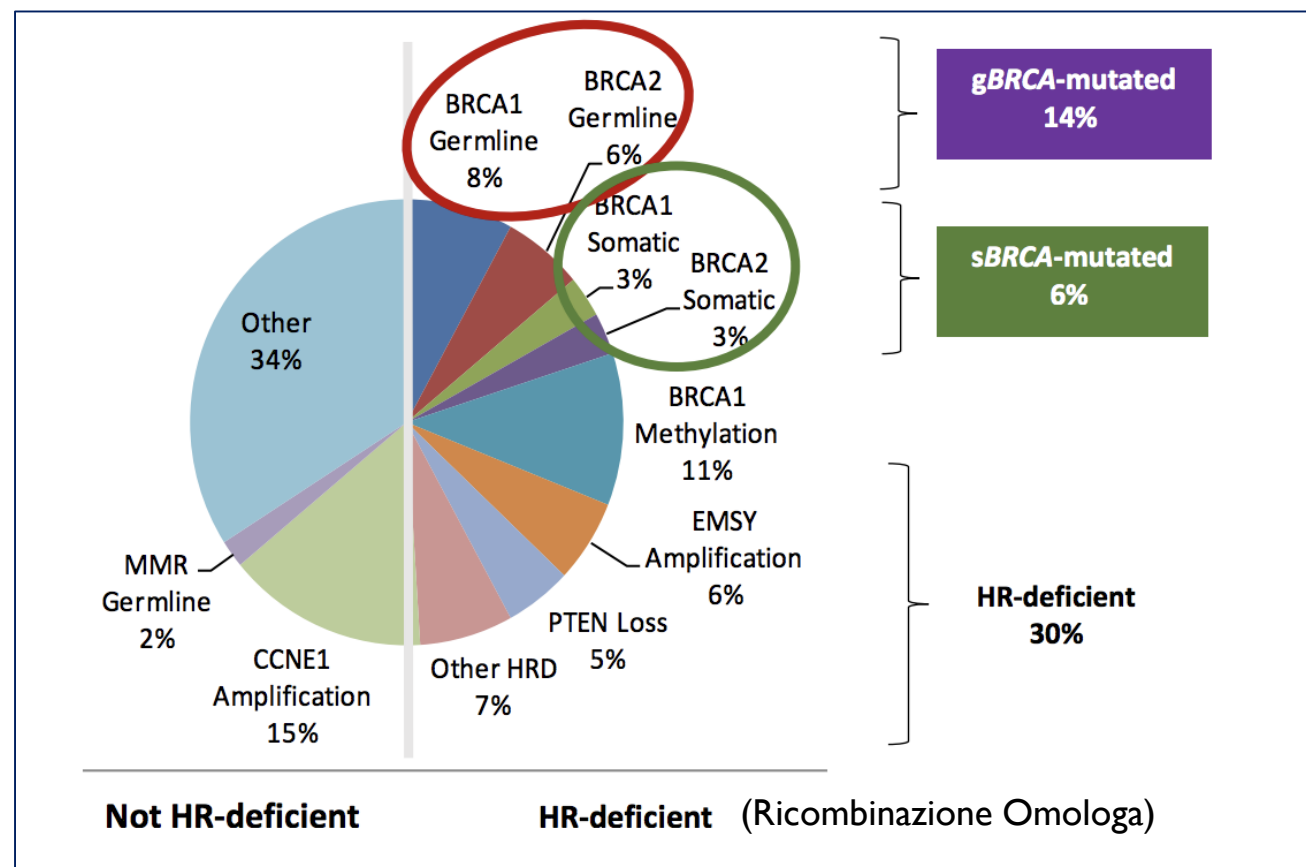
- HPV test
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- Nuovi farmaci: PARP inibitori
(Poli-ADP-Ribosio Polimerasi)
- Nuovi approcci chirurgici: Linfonodo
Sentinella



NUOVI FARMACI



- L' introduzione della medicina molecolare nella cura dei tumori ovarici permette di individuare farmaci target specifici per le portatrici di determinate mutazioni



NUOVI FARMACI



DNA SSBs occur all the time in cells
and PARP detects and repairs them

Poli-ADP-Ribosio Polimerasi

During the replication process
unrepaired SSBs are converted into
DSBs

Replicating cells

Normal cell

Cancer cell with HRD

Repair by
Homologous
Recombination

No effective repair
(No HR pathway)

Survival

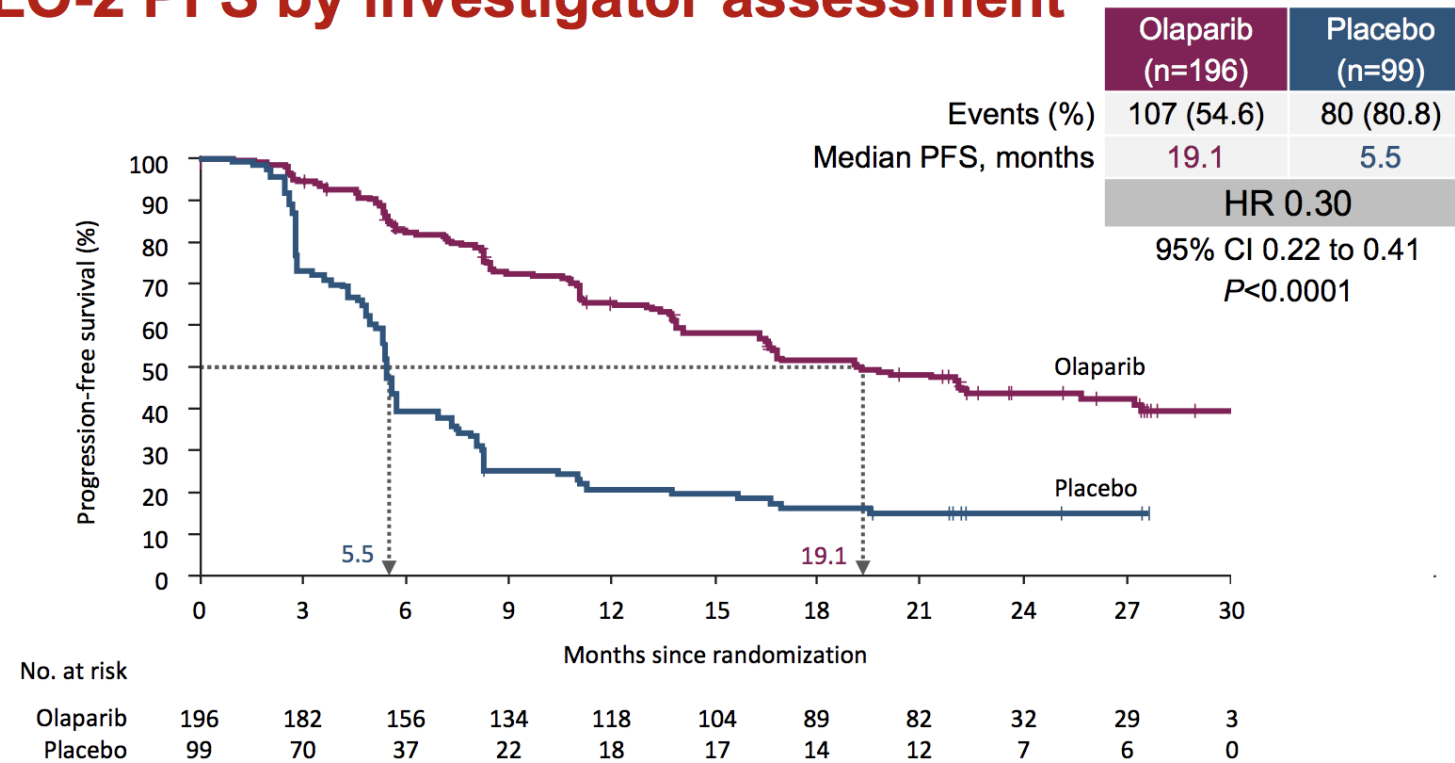
Tumour specific
killing by PARP
inhibitor

Cell death

NUOVI FARMACI



SOLO-2 PFS by investigator assessment



Median follow-up was 22.1 months in the olaparib group and 22.2 months for placebo

Pujade-Lauraine et al SGO 2017

NUOVI FARMACI



PARP inibitori approvati da FDA

Trattamento				
	Approval date	Rx	Indication	Data
Olaparib	12/2014	400 mg BID (50 mg CAPSULES)	Deleterious germline BRCA mut ≥3 more priors	Study 42
Rucaparib	12/2016	600 mg BID (200 mg, 300 mg capsules)	Deleterious germline OR somatic BRCA mutation & ≥2 more priors	Study 10, ARIEL2

Mantenimento				
Niraparib	3/2017	300 mg daily (100 mg capsules)	Recurrent ovarian cancer & complete or partial response to platinum based chemotherapy	NOVA
Olaparib	8/2017	300mg BID (150mg, 100mg TABLETS)	Recurrent ovarian cancer & complete or partial response to platinum based chemotherapy	SOLO-2 Study 19

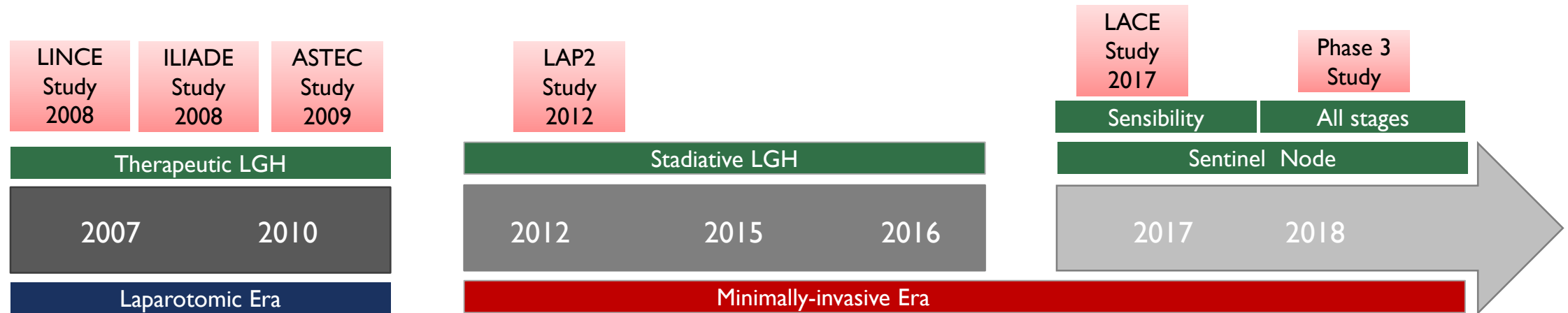
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Linfonodo Sentinella Neoplasia Endometrio



NEOPLASIA ENDOMETRIALE: NUOVI APPROCCI CHIRURGICI



Systematic Pelvic Lymphadenectomy vs No Lymphadenectomy in Early-Stage Endometrial Carcinoma: Randomized Clinical Trial

Pierluigi Benedetti Panici, Stefano Basile, Francesco Maneschi, Andrea Alberto Lissoni, Mauro Signorelli, Giovanni Scambia, Roberto Angioli, Saverio Tateo, Giorgia Mangili, Dionyssios Katsaros, Gaetano Garozzo, Elio Campagnutta, Nicoletta Donadello, Stefano Greggi, Mauro Melpignano, Francesco Raspagliesi, Nicola Ragni, Gennaro Cormio, Roberto Grassi, Massimo Franchi, Diana Giannarelli, Roldano Fossati, Valter Torri, Mariangela Amoroso, Clara Crocè, Costantino Mangioni

Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study

The writing committee on behalf of the ASTEC study group*

VOLUME 30 · NUMBER 7 · MARCH 1 2012

JOURNAL OF CLINICAL ONCOLOGY

Recurrence and Survival After Random Assignment to Laparoscopy Versus Laparotomy for Comprehensive Surgical Staging of Uterine Cancer: Gynecologic Oncology Group LAP2 Study

Joan L. Walker, Marion R. Piedmonte, Nick M. Spirtos, Scott M. Eisenkop, John B. Schlaerth, Robert S. Mannel, Richard Barakat, Michael L. Pearl, and Sudarshan K. Sharma

JAMA | Original Investigation

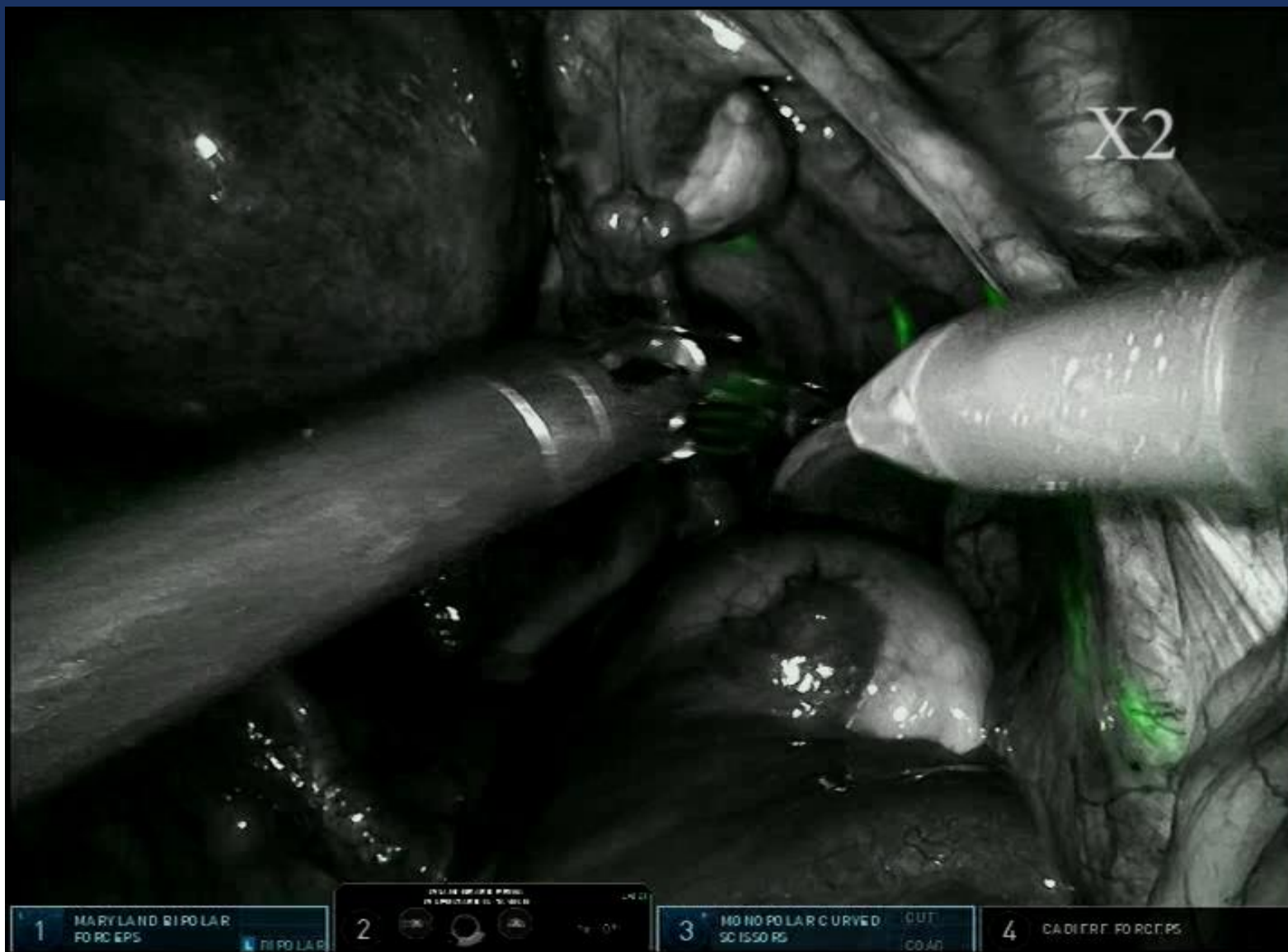
Effect of Total Laparoscopic Hysterectomy vs Total Abdominal Hysterectomy on Disease-Free Survival Among Women With Stage I Endometrial Cancer: A Randomized Clinical Trial

A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study

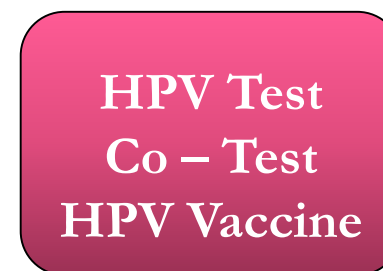
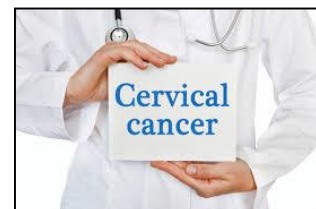
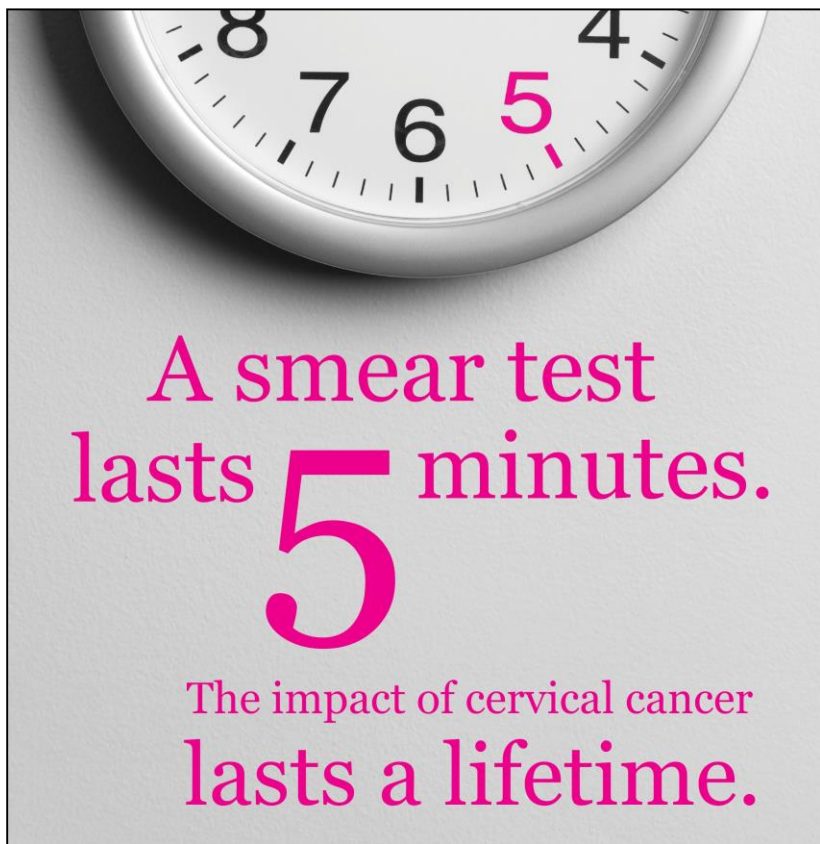
Emma C Rossi, Lynn D Kowalski, Jennifer Scalici, Leigh Cantrell, Kevin Schuler, Robbie K Hanna, Michael Method, Melissa Ade, Anastasia Ivanova, John F Boggess

Evaluation of Sentinel Node Policy in Early Stage Endometrial Carcinomas at Intermediate and High Risk of Recurrence. (SENTIRAD)

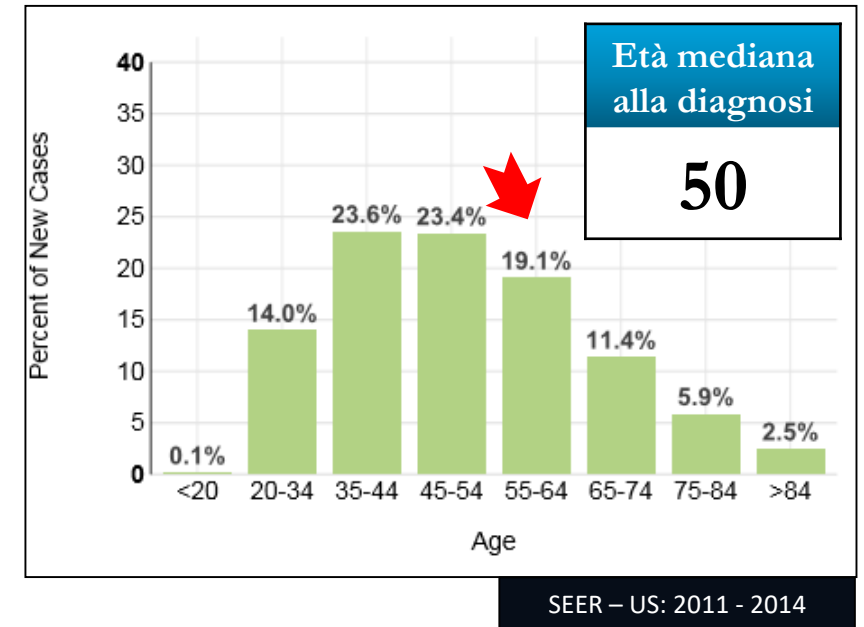
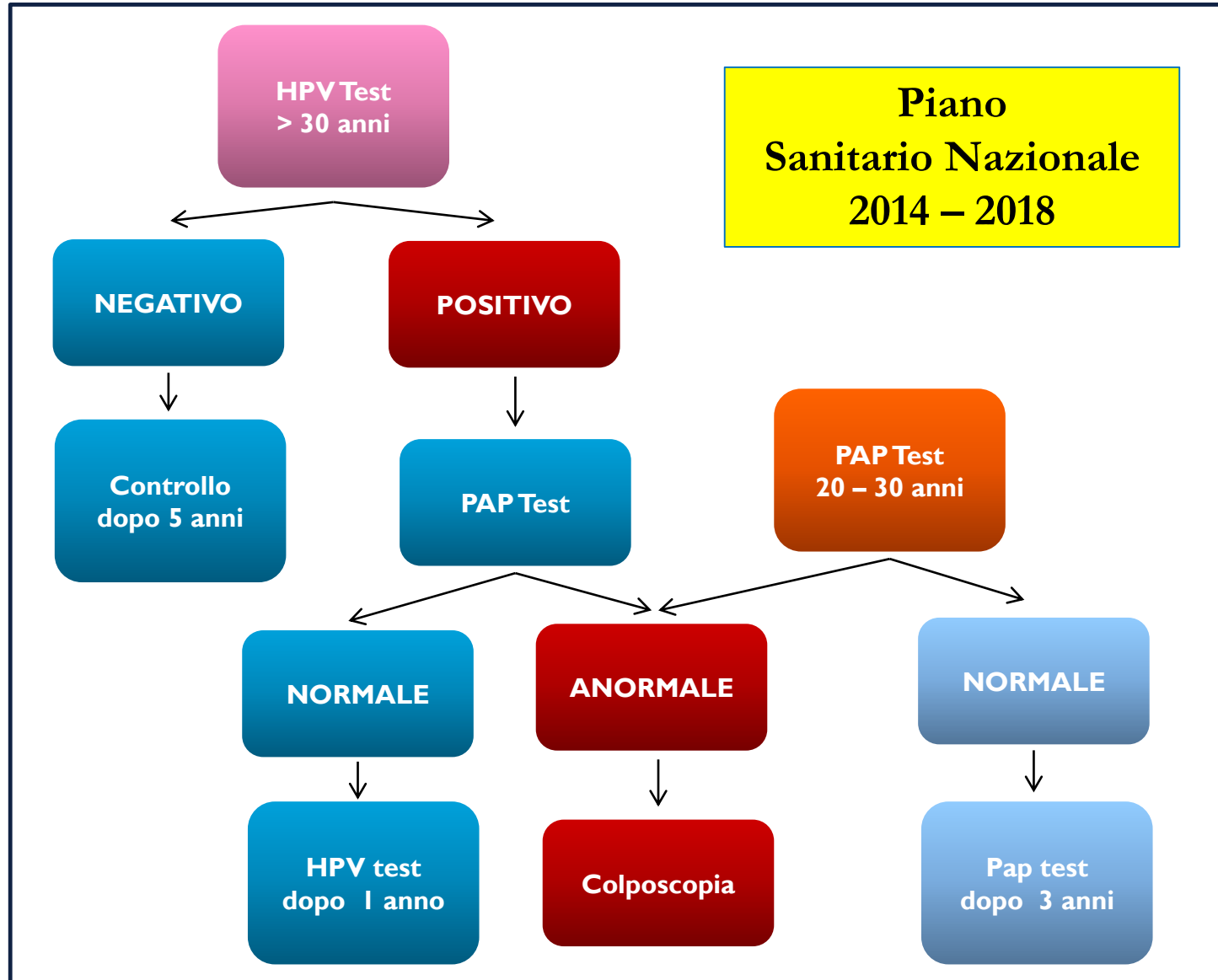
Eric LEBLANC; Hélène GAUTHIER



Take-Home Message: Cervice Uterina



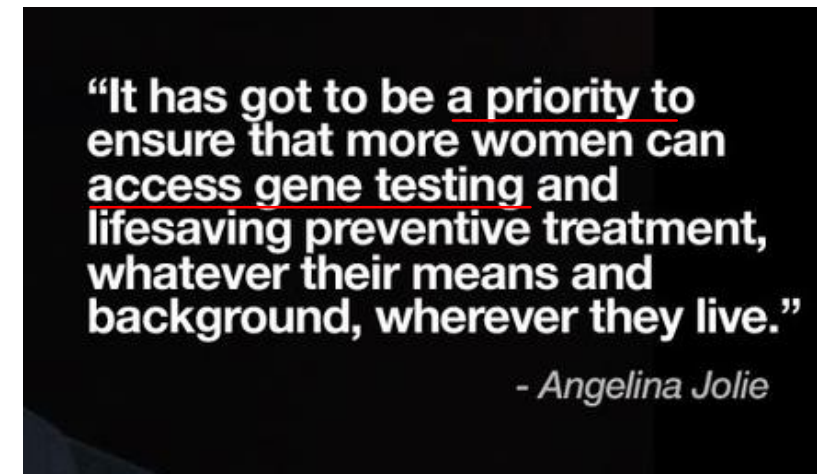
Take-Home Message: Neoplasia Cervice



Età più frequente alla diagnosi

35 - 44

Take-Home Message: Neoplasia Ovaio



Take-Home Message: Neoplasia Ovaio

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v103–v110, 2016
doi:10.1093/annonc/mdw327

Prevention and screening in *BRCA* mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening[†]

S. Paluch-Shimon¹, F. Cardoso², C. Sessa³, J. Balmana⁴, M. J. Cardoso², F. Gilbert⁵ & E. Senkus⁶,
on behalf of the ESMO Guidelines Committee*

[†]Division of Oncology and the Dr Pinchas Borenstein Talpiot Medical Leadership Program, Sheba Medical Center, Ramat Gan, Israel; ²Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal; ³Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland; ⁴Vall d'Hebron University Hospital Institut d'Oncologia, Barcelona, Spain; ⁵School of Clinical Medicine, University of Cambridge, Cambridge, UK; ⁶Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland

Arch Gynecol Obstet (2015) 292:231–234
DOI 10.1007/s00404-015-3697-y



POSITION STATEMENTS AND GUIDELINES

Opportunistic salpingectomies for the prevention of a high-grade serous carcinoma: a statement by the Kommission Ovar of the AGO

Martin Pölcher¹ · Steffen Hauptmann² · Christina Fotopoulou³ · Barbara Schmalfeldt⁴ ·
Ivo Meinhold-Heerlein⁵ · Alexander Mustea⁶ · Ingo Runnebaum⁷ ·
Jalid Sehoul⁸

Take-Home Message: Neoplasia Endometrio

Prevalence, Classification, and Risk Factors for Postoperative Lower Extremity Lymphedema in Women With Gynecologic Malignancies

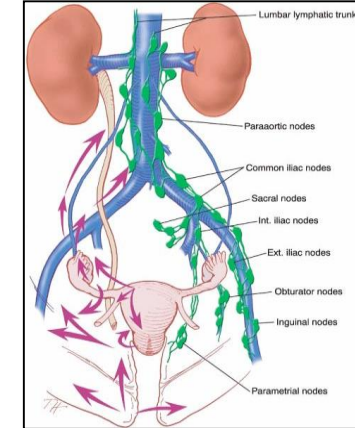
A Retrospective Study

Hitoshi Hareyama, MD, PhD, Kenichi Hada, MD, Kumiko Goto, MD, Sawako Watanabe, MD, Minako Hakoyama, MD, Kikuo Oku, MD, Yukitoki Hayakashi, MD, Emi Hirayama, MD, PhD, and Kazuhiko Okuyama, MD, PhD

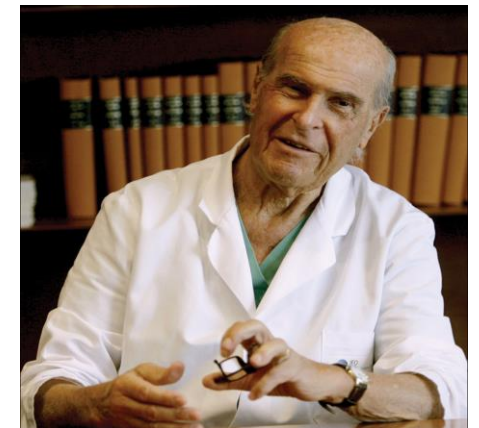
Int J Gynecol Cancer 2015

Incidenza

21.8%



“Da massimo
trattamento tollerato
a minimo
trattamento necessario”

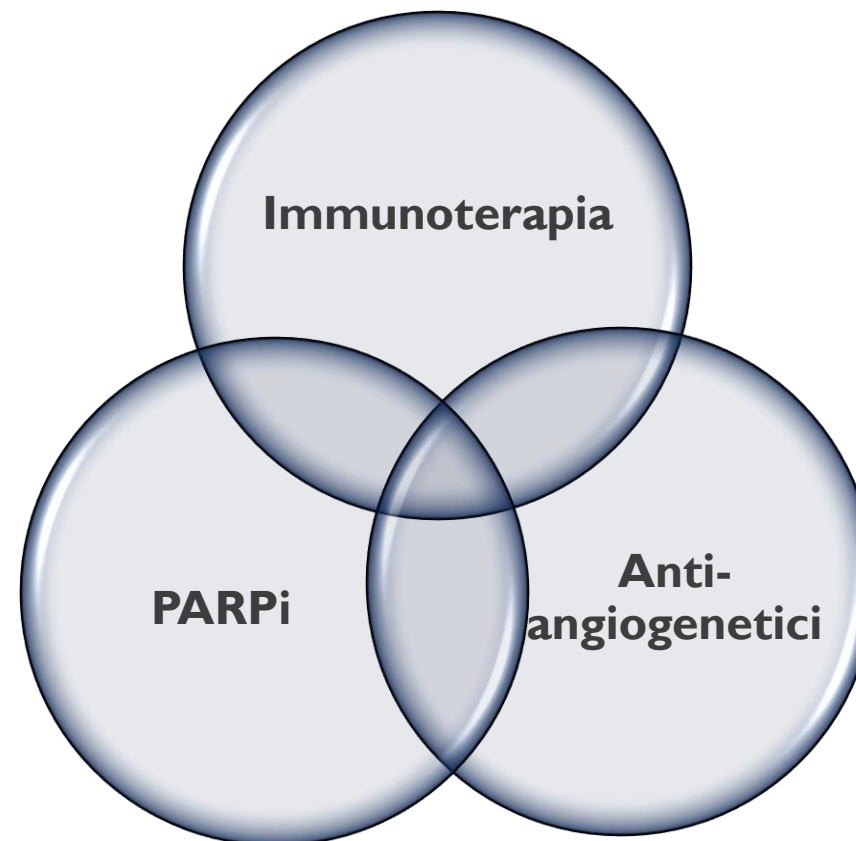


Prof. Umberto Veronesi

NUOVI FARMACI



In futuro...





**“Stay hungry,
stay foolish”**

S. Jobs, 2005

**“Siate dubbiosi e siate trasgressivi, se
trasgredire significa andare oltre limite del
dogma o la rigidità della regola.**

**L'importante non è sapere, ma cercare.
Continuate a cercare fino alla fine, con la consapevolezza
che non potete fare a meno del bene e della vita”.**

U. Veronesi, 2016

