Tumori dell’ovaio nel 2014 tra difficoltà e speranze

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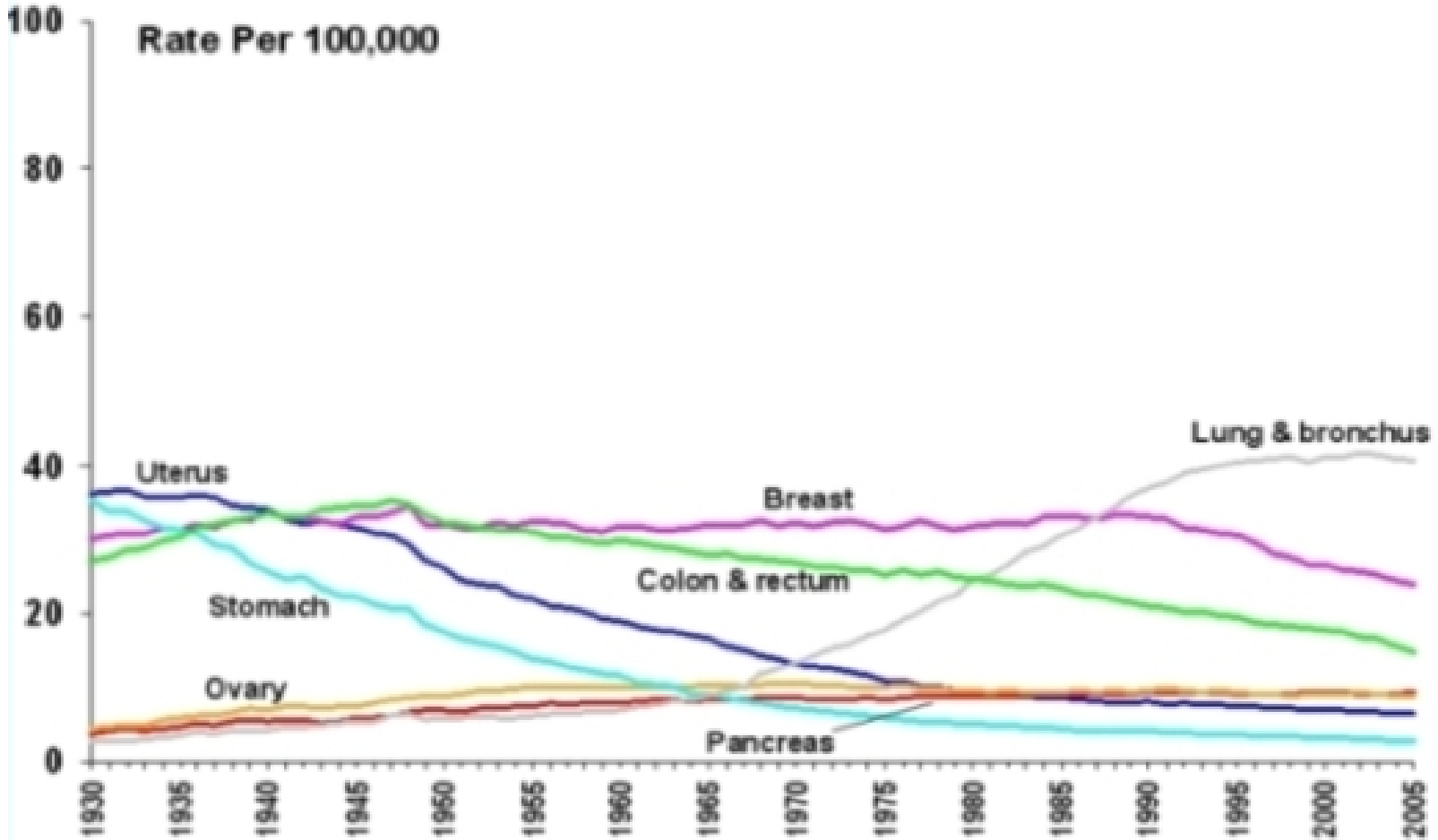
Le difficoltà

Ricordiamo che il cancro ovarico è..

- colpisce 1 donna su 70-75 (1.4%)
- 5-6° tumore per incidenza nelle donne (3% di tutti i tumori nella donna)
- 1° causa di morte per neoplasia ginecologica
- 5° causa di morte per cancro nella donna
- In Italia 3000 morti l'anno.
- Sopravvivenza a 5 anni cica il 30-35%

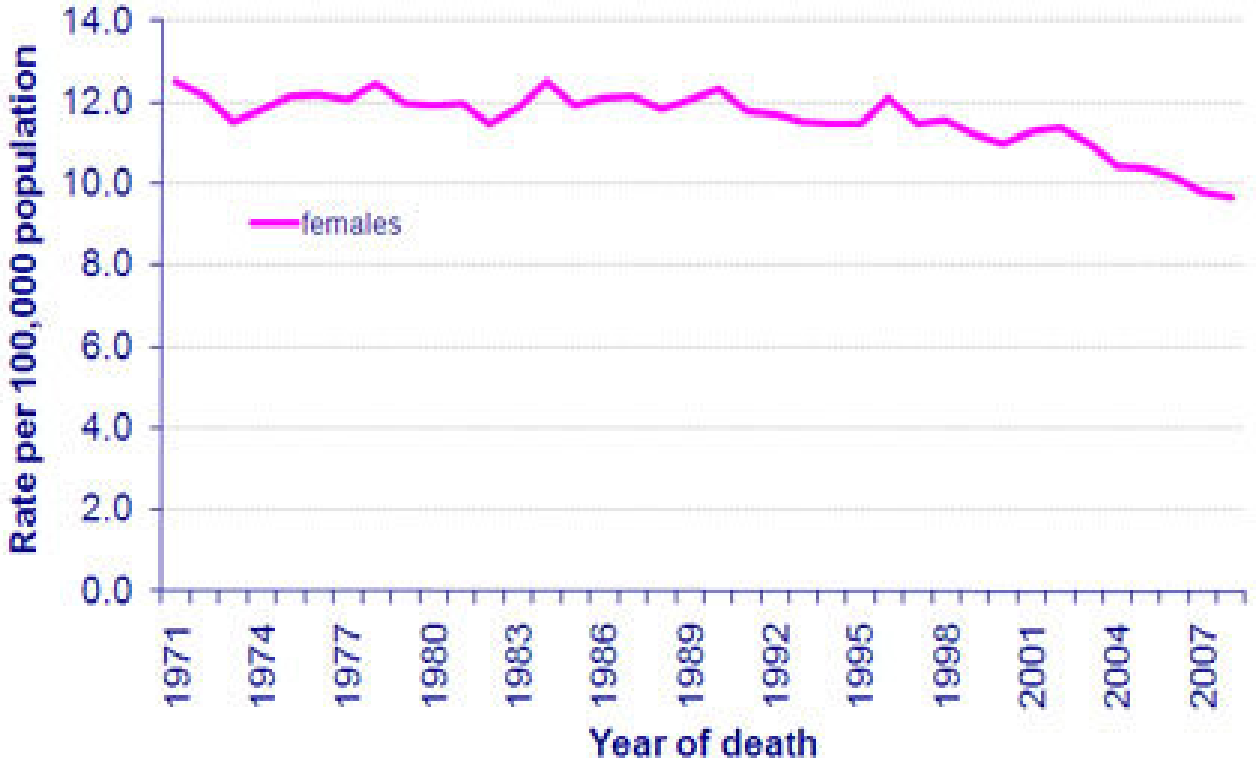
Dati di mortalità per le donne1935-2005 USA



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2005, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2008.

Cosa è cambiato in Europa?

Figure 2.2: Age-standardised (European) mortality rates, ovarian cancer, UK, 1971-2008



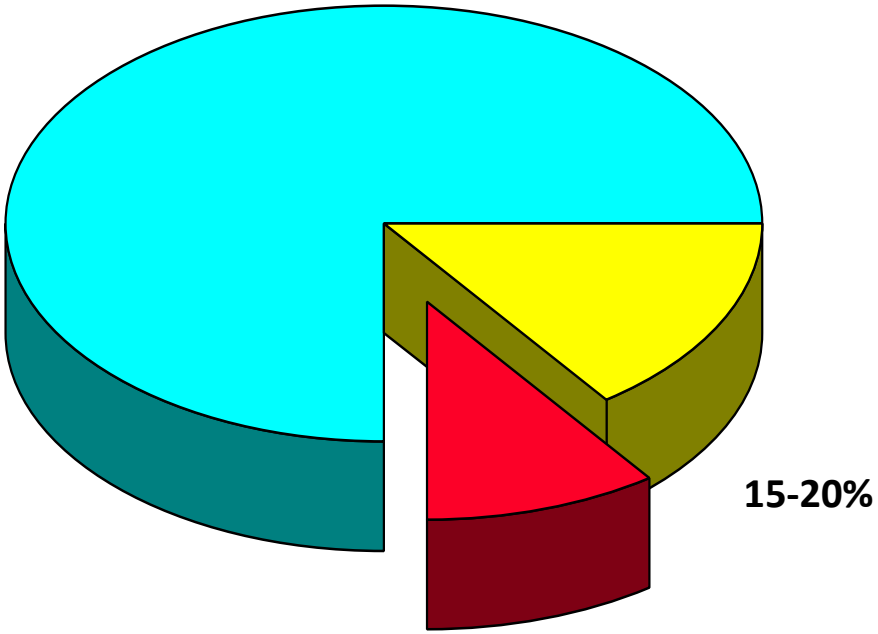
eziologia

- Aumento del rischio:
- Fattori genetici (15% BRCA1/2, Mlh1, Msh2, RAD51)
- Ormonoterapia (stimolazione per sterilità)

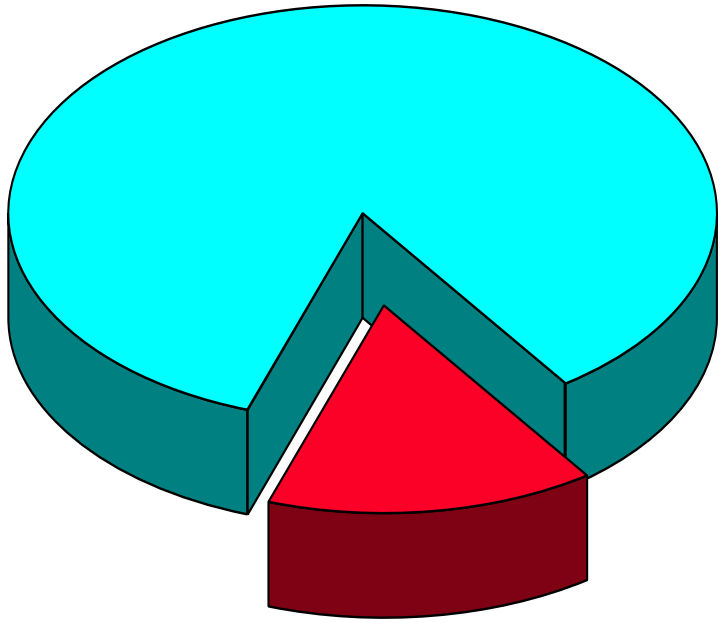
- Diminuzione del rischio
- N° Gravidanze
- Contraccettivi orali
- Allattamento

Tumori mammella e ovaio su base eredo-familiare

Carcinoma mammario



Carcinoma ovarico



Sporadici

Familiari

Ereditari

Il tumore dell'ovaio "killer silenzioso"

- la mortalità in mancanza di fattori eziologici prevenibili può diminuire per……

1. Migliore diagnosi precoce e screening

2. Migliore terapia

   – chirurgica (standardizzazione)
   – medica (miglioramento della chemioterapia, farmaci biologici ..)

sintomi

- **Dolore addominale**
- **Minzione frequente o impellente**
- **Aumento della circonferenza addominale, gonfiore**
- **Difficoltà nel mangiare, senso di ripienezza**

sintomi

OVARIAN CANCER
Older Women

What Are The Barriers To Detection And Treatment?

- Older women often do not have regular gynecologic checkups which improve chances of early diagnosis.
- Many older women have poorer access to quality testing and treatment due to limited income and supplemental health insurance or Medicare restrictions.
- Older women are less likely to receive aggressive treatment.

What Should You Look For?

Ovarian cancer has symptoms, even in its early stages. Take action and see your doctor if the following symptoms are unusual for you and last more than three weeks:

- Pelvic and abdominal pain
- Urinary frequency and urgency
- Difficulty eating and feeling full quickly
- Increased abdominal size and bloating

* Other symptoms may include constipation or diarrhea; nausea, indigestion or gas; abnormal vaginal bleeding; unusual fatigue; unexplained weight loss or gain; shortness of breath; or low back pain

What Can You Do To Detect It?

Until a screening test is found:

- Have a vaginal/rectal pelvic exam every year. Discuss regular monitoring with your doctor.
- If you have symptoms, ask for a transvaginal ultrasound and a CA125 blood test.
- If ovarian cancer is suspected, consult a gynecologic oncologist. To find one in your area, call the Gynecologic Cancer Foundation at 1-800-444-4441.

Where Can You Get More Information?

Ovarian Cancer National Alliance

910 17th Street, NW, Suite 1190
Washington, DC 20006
866.399.6262

www.ovariancancer.org

OVARIAN CANCER
Older Women

Ovarian Cancer National Alliance

The Facts

- Ovarian cancer is the deadliest of the gynecologic cancers.
- Ovarian cancer is one of the five leading causes of cancer death in American women.
- Chances of survival are better if the cancer is found early.
- A Pap smear is ***NOT*** a test for ovarian cancer; it detects cervical cancer.
- Risk for ovarian cancer increases with age; a personal or family history of ovarian, breast or colon cancer; and not bearing a child.

Why Is Ovarian Cancer A Concern For Older Women?

- Risk increases as a woman gets older; the risk peaks around age 70.
- Ovarian cancer generally develops after menopause; around two-thirds of women diagnosed are over age 55.
- Women over the age of 65 are more likely to be diagnosed with an advanced stage.
- Women under the age of 65 with ovarian cancer have better survival rates.

www.ovariancancer.org

Perché lo screening/diagnosi precoce fino ad ora non hanno funzionato?

Table 2. World Health Organization's Criteria for Disease Screening.*

The condition that is screened for should represent a major cause of death and have a substantial prevalence in the population.
The natural history of the disease, from latency to overt disease, should be well characterized.
There should be a treatment for the disease's latent or early stage that improves the outcome.
The screening test should be acceptable to the population.
Effective treatments should be available for those with overt disease.
Facilities for diagnosis and treatment should be available.
There should be agreement among clinical guidelines on whom to treat.
Screening should be cost-effective.
Screening tests should have a high positive predictive value, negative predictive value, sensitivity, and specificity.

* Data are from Wilson and Junger.[5]

Perché non usare il marcatore Ca 125?

Table 4. Conditions Associated with an Elevated Level of Cancer Antigen 125.

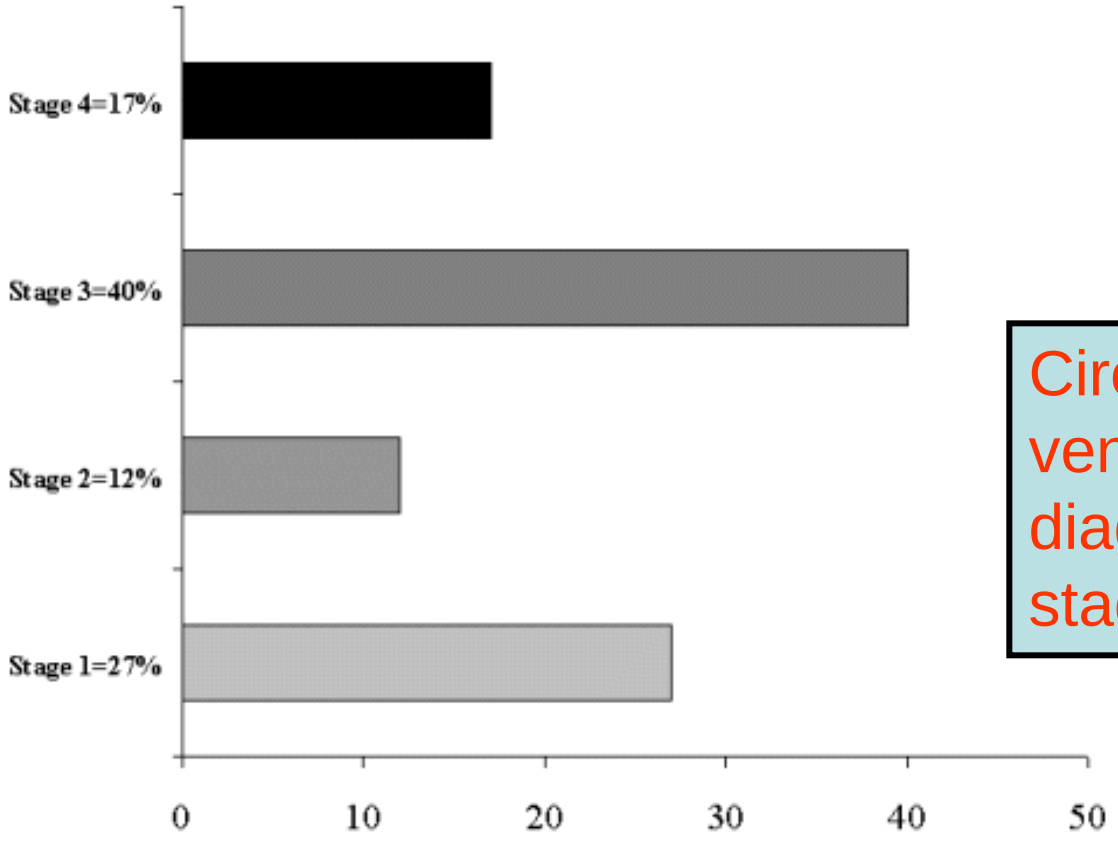
Noncancer	Cancer
Endometriosis	Breast
Fibroids	Pancreatic
Pelvic inflammatory disease	Colon
Hepatitis	Lung
Pregnancy	Endometrial
Menses	
Peritonitis	
Recent abdominal surgery	

- Picco di incidenza tra 60-70 anni
- Difficoltà dell’intervento chirurgico nelle pazienti più anziane
- Sopportabilità della chemioterapia con l’aumento dell’età?

Identikit della paziente tipica con carcinoma ovarico

- Donna > 55 anni con ascite e carcinosi peritoneale
- Decadimento delle condizioni generali
- Ritardo diagnostico di alcuni mesi
- Rialzo cospicuo del Ca 125

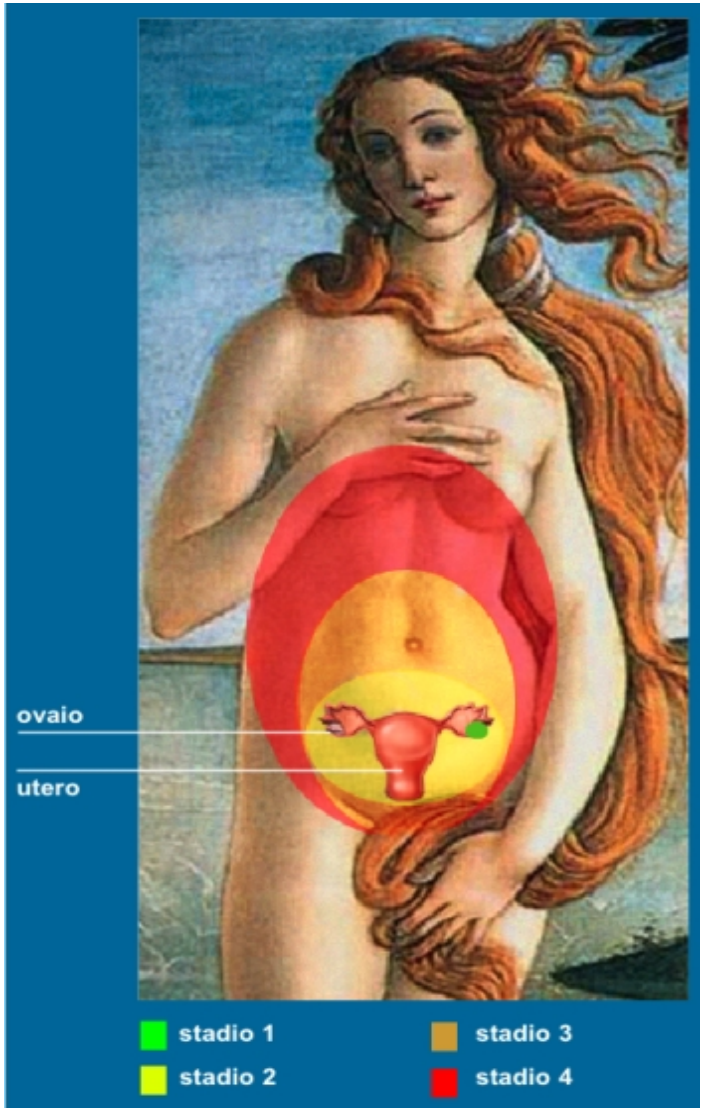
Stadio alla diagnosi



Circa i 2/3 dei casi vengono diagnosticati in stadio III o IV

- **Stadiazione carcinoma ovarico**

- **Stadio I:** confinato ad una o entrambe le ovaie.
- **Stadio II:** diffuso agli organi pelvici (utero, tube), ma non agli organi addominali.
- **Stadio III:** diffuso agli organi addominali (linfonodi, peritoneo, superficie epatica).
- **Stadio IV:** diffuso a distanza (polmone, fegato intraepatico, linfonodi sovradiaframmatici etc).



Stadio e sopravvivenza

Table 1. Stage of Ovarian Cancer at Diagnosis and Survival at 5 Years.*

Tumor Stage	Patients with Tumor Stage at Diagnosis	5-Yr Survival
	percent	
I	37	83–90
II	8	65–71
III†	44	
A	3	47
B	5	42
C	36	33
Outcome of initial surgery‡		
No residual tumor	NA	63
Residual disease		
Optimal debulking (<2-cm nodules)	NA	33
Suboptimal debulking (≥2-cm nodules)	NA	25
IV	11	19

Clarke-Pearson DL. N Engl J Med 361; 2 2009

Table 5. Recommendations for Ovarian-Cancer Screening.*

Professional Group	Recommendation
U.S. Preventive Services Task Force[45]	Does not recommend routine screening, concluding that "the potential harms outweigh the potential benefits"
American Cancer Society[46]	Does not recommend routine screening; possible screening for women with a family history of ovarian cancer, although "it is not known how helpful" the tests will be in improving survival
American College of Obstetricians and Gynecologists[47]	Does not recommend routine screening; suggests evaluation of signs and symptoms of ovarian cancer (e.g., pelvic mass, pelvic or abdominal pain, urinary frequency or urgency, increased abdominal size or bloating, or difficulty eating or feeling of fullness)
National Comprehensive Cancer Network[36]	Does not recommend routine screening; recommends screening of high-risk women (i.e., those with either a family history of ovarian or breast cancer or a documented *BRCA* mutation) with transvaginal ultrasonography and CA-125 measurements every 6 mo, starting at the age of 35 years or 5 to 10 years before the earliest age at diagnosis of ovarian cancer in relatives; recommends strong consideration of risk-reducing prophylactic salpingo-oophorectomy at the completion of childbearing in women with a *BRCA* mutation

E’ possibile diminuire la mortalità nel carcinoma ovarico?

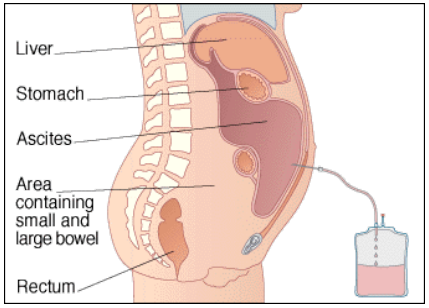
- In assenza al momento di uno screening efficace
- Come migliorare il trattamento?

Problemi principali

- Le pazienti arrivano spesso in fase molto avanzata e con performance in scadimento

- Sintomi presenti da mesi/settimane mal interpretati→ritardo diagnostico

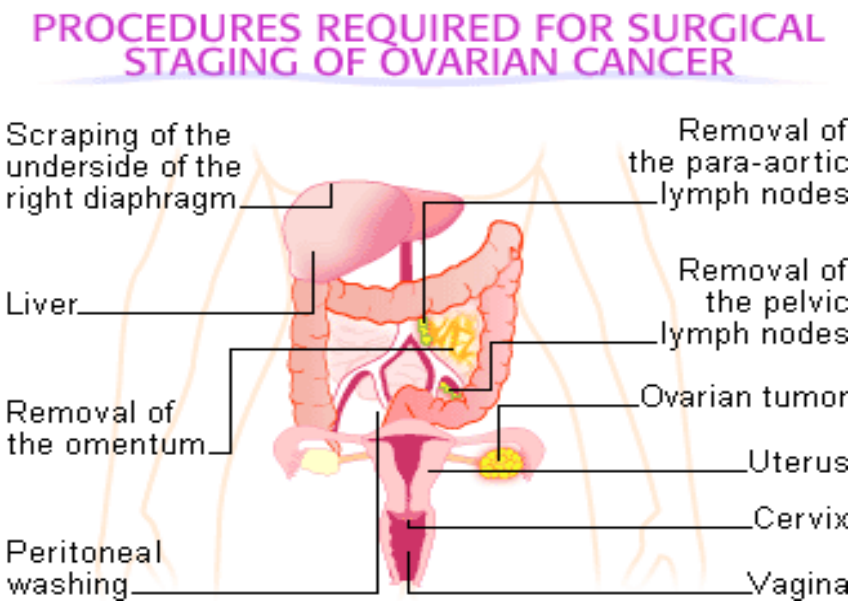
- Possono essere ricoverate in un qualsiasi reparto, spesso non in oncologia o in ginecologia→ritardo nel trattamento



Problemi

- Difficoltà, anche logistiche, nel mettere insieme un team interdisciplinare (ginecologo-oncologo-radiologo) che valuti la situazione per verificare la operabilità

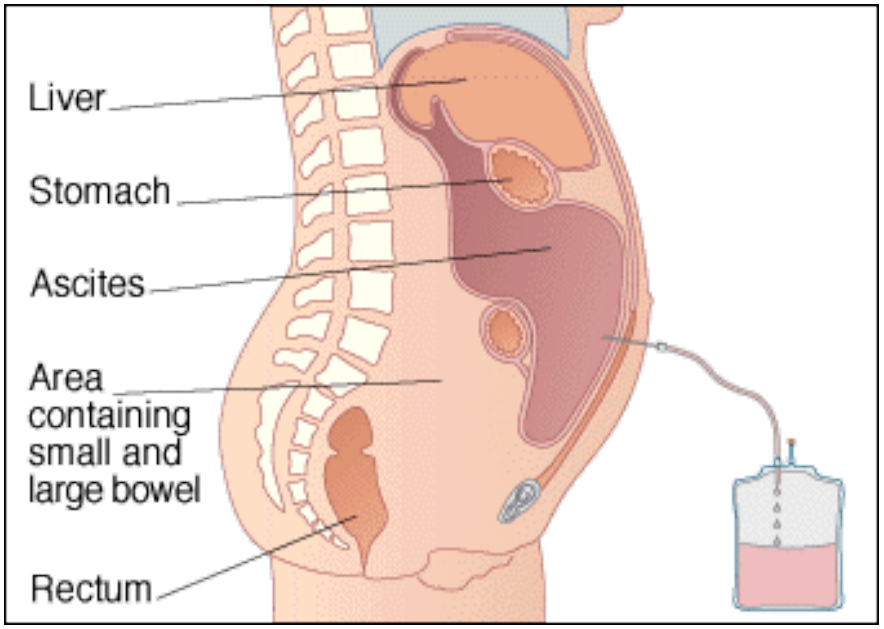
- Disomogeneità nel tipo di intervento chirurgico (..dipende da chi lo fa)



Il lavoro in team…
Perché è così importante?

- Difficoltà diagnostiche
- La paziente ha veramente un cancro ovarico?Attenzione nel valutare possibili diagnosi alternative→biopsia!!
- E’ operabile?

No alla diagnosi citologica!



Possibili errori diagnostici con carcinosi peritoneali da altre neoplasie (stomaco, mammella, pancreas etc)!!

IMPORTANZA DELLA DIAGNOSI ISTOLOGICA

Come migliorare?

- Valutazione multidisciplinare rapida
- valutazione accurata stadio
- Utilizzare criteri di inoperabilità iniziale del ca ovarico (coinvolgere un radiologo dedicato?)
- Intervento chirurgico secondo gli standard

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Gynecologic Oncology
www.elsevier.com/locate/ygyno

Role of CT and MR imaging in predicting optimal cytoreduction of newly diagnosed primary epithelial ovarian cancer

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Fig. 5. Contrast-enhanced CT demonstrating metastatic ovarian cancer involving small bowel mesentery (arrow).

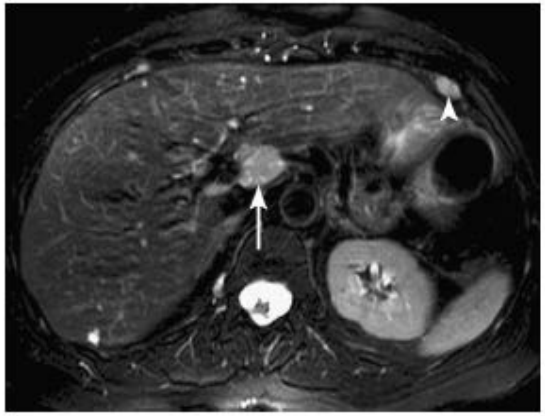


Fig. 3. T2-weighted MR image demonstrating hyperintense implant in the porta hepatis (arrow) and anterior peritoneal surface (arrowhead).

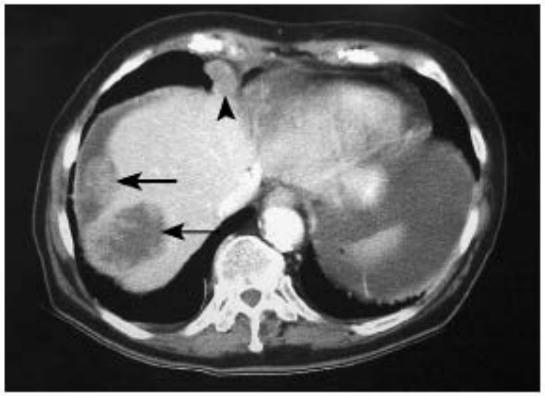


Fig. 4. Contrast-enhanced CT demonstrating surface implants at liver dome (arrows) and peridiaphragmatic tumor implant (arrow head).

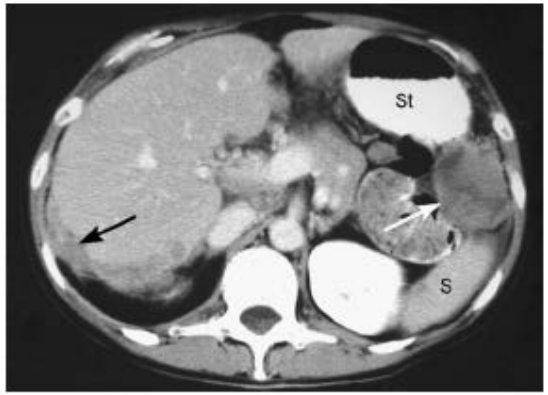


Fig. 2. Contrast-enhanced CT demonstrating metastatic ovarian cancer involving the gastrosplenic ligament (white arrow) and liver surface implants (black arrow); stomach (St); spleen (S).

Stadiazione adeguata

- La stadiazione vera di un carcinoma ovarico viene fatta solitamente durante l'intervento chirurgico

- Lo staging chirurgico adeguato ci consente di valutare la necessità di una chemioterapia adiuvante negli stadi precoci

Stadi Iniziali I-II

Impact of Adjuvant Chemotherapy and Surgical Staging in Early-Stage Ovarian Carcinoma: European Organisation for Research and Treatment of Cancer–Adjuvant ChemoTherapy in Ovarian Neoplasm Trial

J. Baptist Trimbos, Ignace Vergote, Giorgio Bolis, Jan B. Vermorken, Constantino Mangioni, Caterina Madronal, Massimo Franchi, Saverio Tateo, Gerardo Zanetta, Giovanna Scarfone, Livia Giurgea, Petra Timmers, Corneel Coens, Sergio Pecorelli

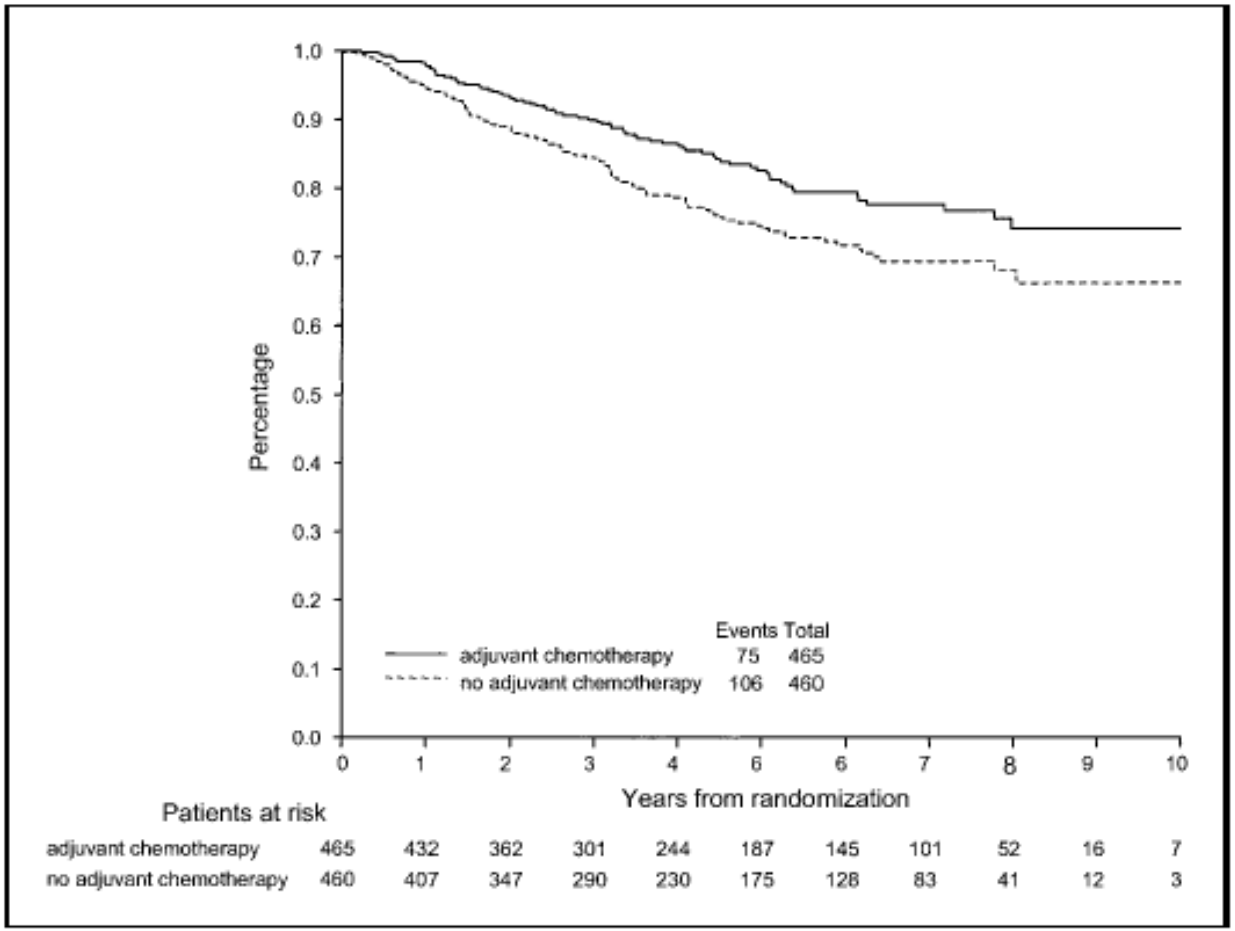
For the EORTC–ACTION collaborators

International Collaborative Ovarian Neoplasm Trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm Trial: Two Parallel Randomized Phase III Trials of Adjuvant Chemotherapy in Patients With Early-Stage Ovarian Carcinoma

International Collaborative Ovarian Neoplasm 1 (ICON1) and European Organisation for Research and Treatment of Cancer Collaborators–Adjuvant ChemoTherapy In Ovarian Neoplasm (EORTC–ACTION)[1]

Journal of the National Cancer Institute, Vol. 95, No. 2, January 15, 2003

Sopravvivenza con CHT

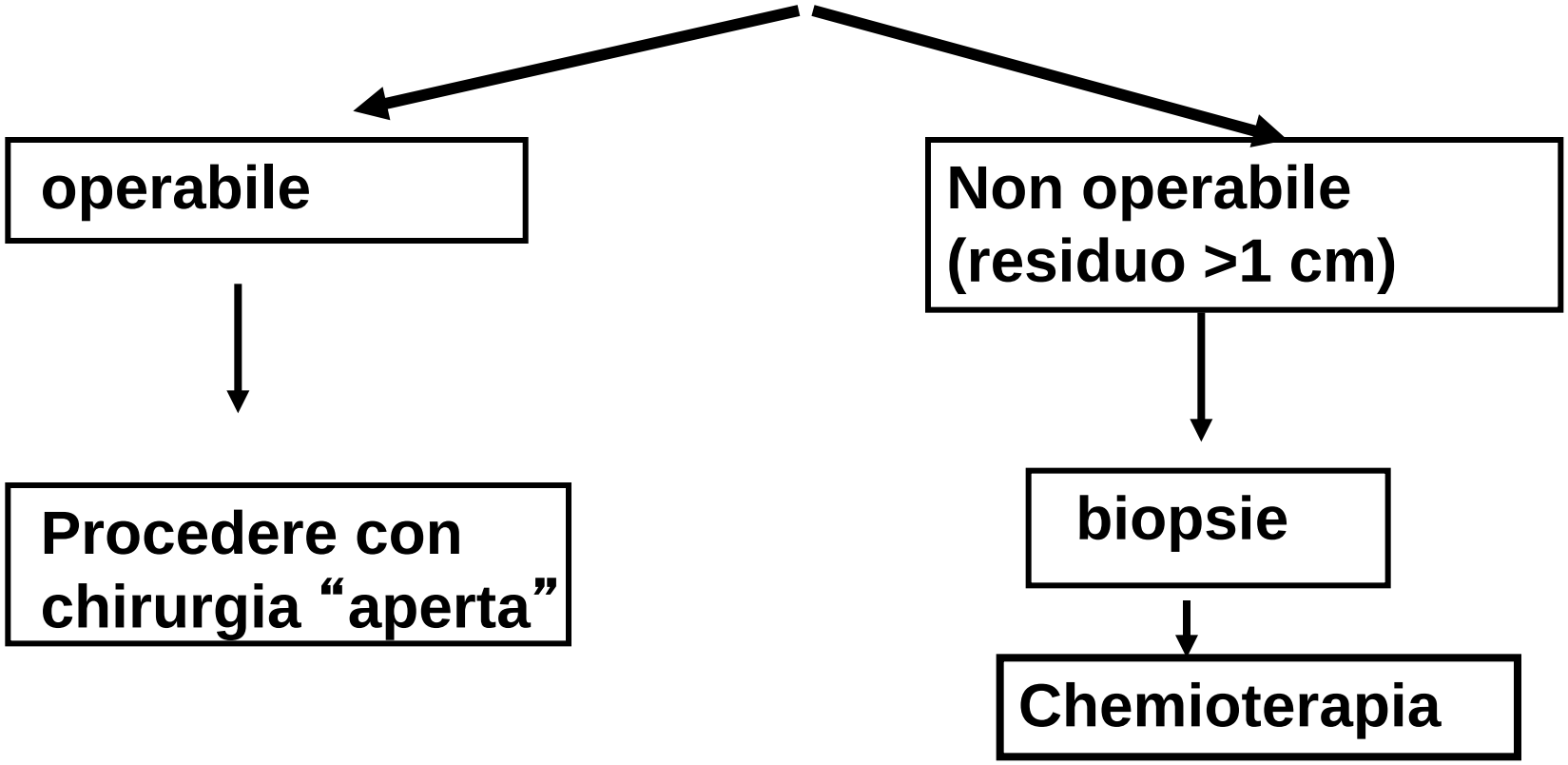


significance were two-sided. *Results:* After a median follow-up of over 4 years, 245 patients had died or had a recurrence (ICON1: 133, ACTION: 112). Overall survival at 5 years was 82% in the chemotherapy arm and 74% in the observation arm (difference = 8% [95% confidence interval (CI) = 2% to 12%]; hazard ratio [HR] = 0.67, 95% CI = 0.50 to 0.90; P = .008). Recurrence-free survival at 5 years was also better in the adjuvant chemotherapy arm than it was in the observation arm (76% versus 65%, difference = 11% [95% CI = 5% to 16%]; HR = 0.64, 95% CI = 0.50 to 0.82; P = .001). Subgroup analyses provided no evidence of a dif-

Quale trattamento chirurgico negli stadi più avanzati?

Trattamento chirurgico

- Il trattamento chirurgico iniziale potrebbe anche essere laparoscopico



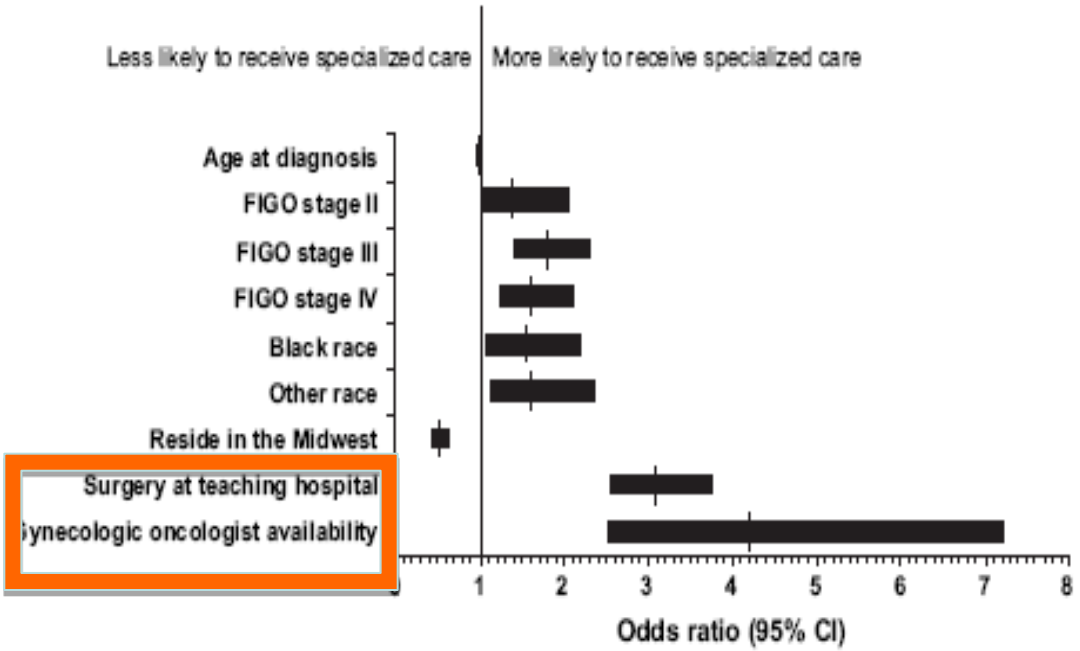


Fig. 1. Predictors of having a gynecologic oncologist perform primary surgery. **Vertical lines** = odds ratios; **horizontal bars** = 95% confidence intervals. FIGO = International Federation of Gynecology and Obstetrics; gynecologic oncologist availability = per capita state concentration of gynecologic oncologists; CI = confidence interval.

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Gynecologic Oncology 105 (2007) 801–812

Gynecologic Oncology

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Review

The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: A systematic review

Flora Vernooij [a,*], Peter Heintz [a], Els Witteveen [b], Yolanda van der Graaf [c]

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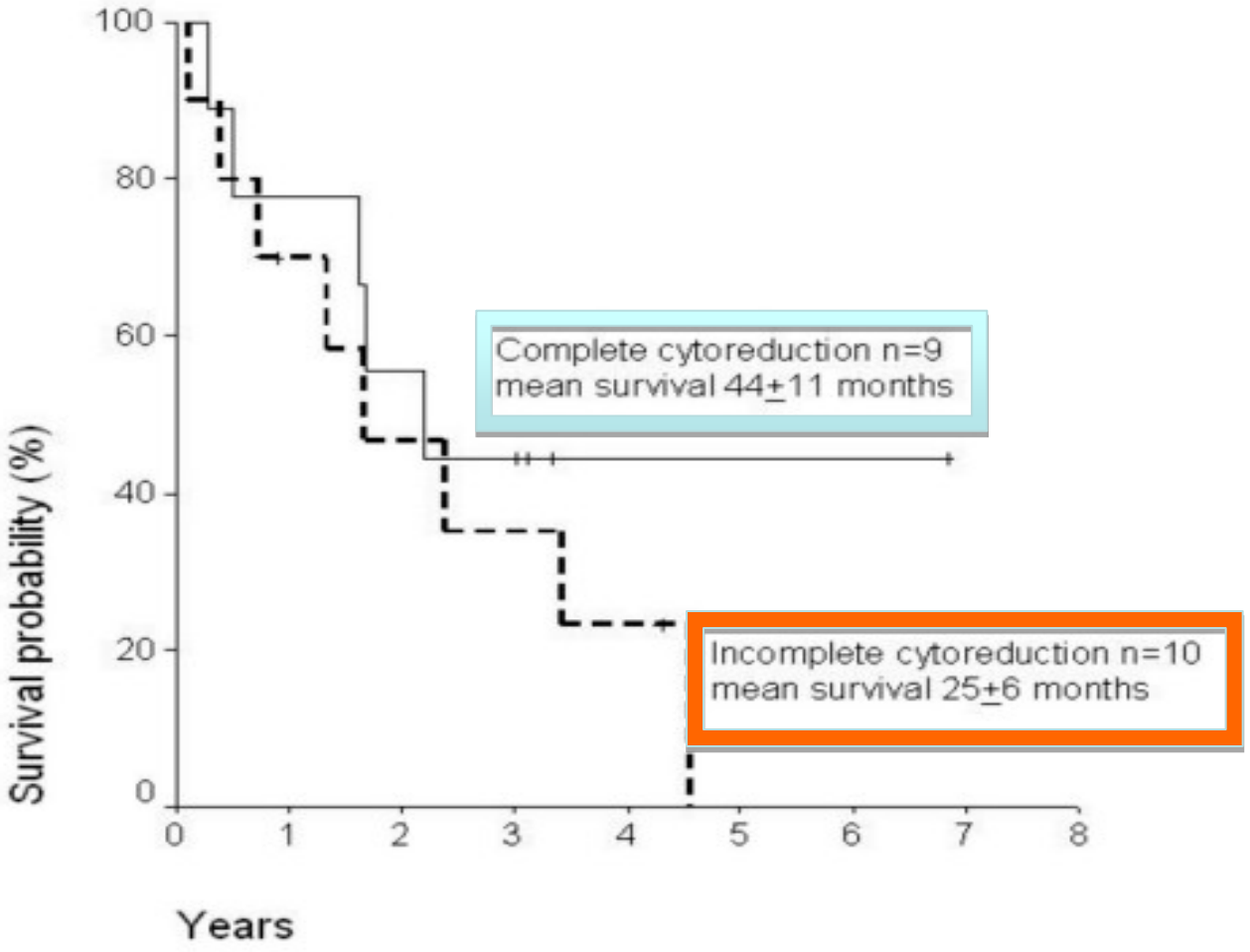
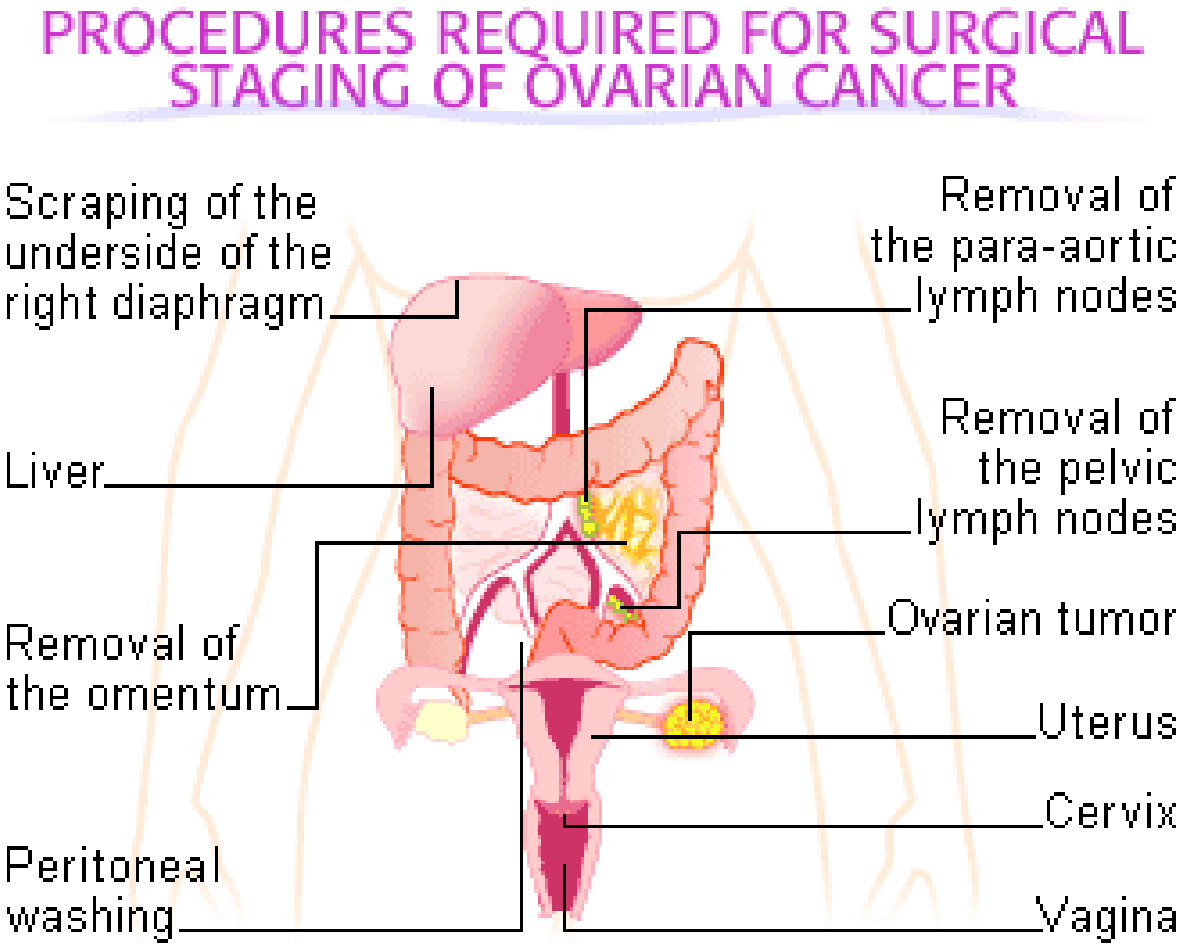
Il residuo tumorale e la prognosi



Il residuo tumorale e la prognosi

- Residuo tumorale ottimale deve essere assente
- L'intervento di prima istanza è da preferire
- Spesso sono necessarie peritonectomie multiple e resezioni intestinali: impegnativo
- Il chirurgo deve essere un ginecologo oncologo (minore sopravvivenza se operate dal chirurgo o ginecologo "generale")

L’intervento chirurgico negli stadi precoci



Stadi avanzati

Perchè iniziare dalla chirurgia negli stadi avanzati?

- diminuzione della massa tumorale su cui dovrà agire la chemioterapia
- eliminazione di popolazioni cellulari chemioresistenti

Quando dobbiamo iniziare con la chemioterapia?

- Retrazione del mesentere
- Carcinosi diffusa con masse grossolane (ca 125 molto elevato)
- Metastasi extra-addominali

- PROBABILE RESIDUO ALL'INTERVENTO

Perché iniziare dalla chemioterapia?

- Diminuzione della massa tumorale su cui dovrà agire la chirurgia, *interventi meno demolitivi*
- *Saggio di chemiosensibilità* in vivo
- obbligatoria se *inoperabilità* iniziale

Chirurgia di intervallo stadi avanzati

- Dopo 3-4 cicli di chemioterapia iniziale si esegue il trattamento chirurgico a cui seguiranno ulteriori cicli di chemioterapia

- Il trial EORTC sembra mostrare l'equivalenza di questi 2 approcci nello stadio III-IV.
- Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer.
- Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, Verheijen RH, van der Burg ME, Lacave AJ, Panici PB, Kenter GG, Casado A, Mendiola C, Coens C, Verleye L, Stuart GC, Pecorelli S, Reed NS; European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group; NCIC Clinical Trials Group.
- N Engl J Med. 2010 Sep 2;363(10):943-53.

Chemioterapia
tra vecchi farmaci e nuove speranze…

- Stadi avanzati

Ruolo del platino nel carcinoma ovarico avanzato negli anni ‘90

Chemotherapy in advanced ovarian cancer: an overview of randomised clinical trials

Advanced Ovarian Cancer Trialists Group

Abstract

***Objectives*—To consider the role of platinum and the relative merits of single agent and combination chemotherapy in the treatment of advanced ovarian cancer.**

***Design*—Formal quantitative overview using updated individual patient data from all available randomised trials (published and unpublished).**

***Subjects*—8139 patients (6408 deaths) included in 45 different trials.**

***Results*—No firm conclusions could be reached. Nevertheless, the results suggest that in terms of survival immediate platinum based treatment was better than non-platinum regimens (overall relative risk 0·93; 95% confidence interval 0·83 to 1·05); platinum in combination was better than single agent platinum when used in the same dose (overall relative risk 0·85; 0·72 to 1·00); and cisplatin and carboplatin were equally effective (overall relative risk 1·05; 0·94 to 1·18).**

***Conclusions*—In the past, randomised clinical trials of chemotherapy in advanced ovarian cancer have been much too small to detect the degree of benefit which this overview suggests is realistic for currently available chemotherapeutic regimens. Hence a new trial comparing cisplatin, doxorubicin, and cyclophosphamide (CAP) with carboplatin has been launched and plans to accrue 2000 patients.**

Introduction

Ovarian carcinoma is the seventh most common cancer of women in the world. Some 140 000 new cases are diagnosed every year and the disease is responsible for the greatest number of deaths from gynaecological malignancy in Europe and North America.[1] Despite over 50 randomised clinical trials having examined the relative efficacy of different chemotherapeutic regimens in advanced disease (FIGO (International Federation of Gynaecology and Obstetrics) stages III and IV), individually these trials have been too small to show clear benefit of one type of chemotherapy over another. Nevertheless, many of these trials have had an important influence on clinical practice, and consequently the type and intensity of chemotherapy used routinely for patients with advanced disease have fluctuated greatly.

Ovarian cancer was one of the first solid malignant tumours to be treated by chemotherapy, and the single alkylating agents that were first used over 30 years ago were considered optimal treatment until the mid-1970s. The past 15 years, however, have seen many changes in disease management. In 1978 a small randomised trial in advanced disease found that Hexa-CAF, a combination of cytotoxic drugs (hexamethylmelamine, cyclophosphamide, methotrexate, and fluorouracil), achieved higher response rates than the single alkylating agent melphalan and suggested the possibility of a corresponding improvement in survival.[2] At about the same time phase II studies suggested that cisplatin was the most promising new drug then available.[3] These results rapidly led to the standard use of cisplatin in combination with other cytotoxic drugs, usually doxorubicin and cyclophosphamide with or without hexamethylmelamine.[4,5]

When, however, doubt was cast on the effectiveness of doxorubicin by both randomised phase III trials[6-8] and phase II studies in patients not responding to cisplatin[9] several major centres adopted cisplatin plus cyclophosphamide as standard. Furthermore, when other trials failed to find significant survival differences between single agent cisplatin and cisplatin in combination with other drugs[10,11] some centres reverted to using single agent platinum as routine first line treatment. Recently a large number of trials have compared cisplatin with its less nephrotoxic and neurotoxic analogue carboplatin, and although follow up times were often short, many institutions have now adopted carboplatin as standard.

Currently it is unclear what constitutes optimal chemotherapy for advanced disease and treatment strategies vary both nationally and internationally. What is clear is that to date no individual clinical trial has been large enough to detect survival differences of the magnitude that could reasonably be expected with available treatment.[12] Consequently the inconclusive results of over 50 such trials reported could be consistent with moderate treatment benefits.[13] The British Medical Research Council Gynaecological Cancer Working Party realised the need to synthesise the information from these trials to evaluate currently used chemotherapeutic regimens. Given the problems associated with a qualitative review of published work,[13] this group initiated an overview which used formal quantitative methods to combine the results from all available randomised trials examining the role of platinum and of combination chemotherapy in the treatment of advanced ovarian cancer. At the outset the MRC overview secretariat contacted the investigators responsible for each trial, inviting their collaboration. In so doing it established the Advanced Ovarian Cancer Trialists Group, under whose auspices the overview was conducted.

Methods and data

The relative merits of single agent and combination chemotherapy and the role of platinum in disease management were sought, and five comparisons between different forms of chemotherapy were identified as being of interest. These were: (I) single non-platinum agent versus non-platinum combination; (II) single non-platinum agent versus platinum combination; (III) addition of platinum to a regimen; (IV) single agent platinum versus platinum combination; (V) cisplatin versus carboplatin.

Trials were eligible for inclusion in the overview if they examined first line treatment for advanced epithelial ovarian carcinoma and made one or more of the comparisons listed above. Each had also to be unconfounded and believed to have been randomised in a manner that precluded prior knowledge of the next treatment assignment. To avoid publication bias[14] it was essential that both published and unpublished studies were included, and various methods were employed to identify relevant trials. A bibliographic

Advanced Ovarian Cancer Trialists Group
Members of the trialists group and the organisations and groups that collaborated in the overview are listed at the end of this report.

Correspondence to: Dr L A Stewart, MRC Cancer Trials Office, 1 Brooklands Avenue, Cambridge CB2 2BB.

BMJ 1991;303:884-93

L’aggiunta del taxol

The New England
Journal of Medicine

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Volume 334 JANUARY 4, 1996 Number 1

CYCLOPHOSPHAMIDE AND CISPLATIN COMPARED WITH PACLITAXEL AND CISPLATIN IN PATIENTS WITH STAGE III AND STAGE IV OVARIAN CANCER

WILLIAM P. MCGUIRE, M.D., WILLIAM J. HOSKINS, M.D., MARK F. BRADY, B.S., PAUL R. KUCERA, M.D., EDWARD E. PARTRIDGE, M.D., KATHERINE Y. LOOK, M.D., DANIEL L. CLARKE-PEARSON, M.D., AND MARTIN DAVIDSON, M.D.

Chemiosensibilità al platino

- Pazienti platino sensibili: risposta al platino che dura > 6 mesi
- Pazienti platino resistenti: ricaduta entro 6 mesi dal trattamento
- Pazienti platino refrattarie: non risposta al platino.

nuovi farmaci chemioterapici e biologici una speranza in più…..

Seconda linea CARBOPLATINO + ADRIAMICINA LIPOSOMIALE

VOLUME 28 · NUMBER 20 · JULY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

From the University Paris Descartes, Assistance Publique-Hôpitaux de Paris, Hôpital Hôtel-Dieu; Association de Recherche sur les Cancers dont Gynécologiques Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens, Paris; Centre Catherine De Sienne, Nantes; Centre Hospitalier Universitaire-Centre François Baclesse, Caen, France; Philipps University Marburg, Marburg; University Hospital Charité/Campus Virchow-Klinikum, Berlin; Klinikum Offenbach, Offenbach; Dr Horst Schmidt Klinik, Wiesbaden, Germany; Karolinska University Hospital and Karolinska Institutet Stockholm, Sweden; NHMRC Clinical Trials Centre, Sydney, New South Wales; University of Queensland, Brisbane, Queensland, Australia; British Columbia Cancer Agency, Vancouver, British Columbia, Canada; Medical University Innsbruck, Innsbruck, Austria; University Hospital Leuven, Leuven, Belgium; National Cancer Institute, Naples; Academic Division of Gynecological Oncology, Institute for Cancer Research

Pegylated Liposomal Doxorubicin and Carboplatin Compared With Paclitaxel and Carboplatin for Patients With Platinum-Sensitive Ovarian Cancer in Late Relapse

Eric Pujade-Lauraine, Uwe Wagner, Elisabeth Aavall-Lundqvist, Val Gebski, Mark Heywood, Paul A. Vasey, Birgit Volgger, Ignace Vergote, Sandro Pignata, Annamaria Ferrero, Jalid Sehouli, Alain Lortholary, Gunnar Kristensen, Christian Jackisch, Florence Joly, Chris Brown, Nathalie Le Fur, and Andreas du Bois

A B S T R A C T

Purpose

This randomized, multicenter, phase III noninferiority trial was designed to test the efficacy and safety of the combination of pegylated liposomal doxorubicin (PLD) with carboplatin (CD) compared with standard carboplatin and paclitaxel (CP) in patients with platinum-sensitive relapsed/recurrent ovarian cancer (ROC).

Seconda linea
Ruolo di trabectidina

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Trabectedin Plus Pegylated Liposomal Doxorubicin in Recurrent Ovarian Cancer

Bradley J. Monk, Thomas J. Herzog, Stanley B. Kaye, Carolyn N. Krasner, Jan B. Vermorken, Franco M. Muggia, Eric Pujade-Lauraine, Alla S. Lisyanskaya, Anatoly N. Makhson, Janusz Rolski, Vera A. Gorbounova, Prafull Ghatage, Mariusz Bidzinski, Keng Shen, Hextan Yuen-Sheung Ngan, Ignace B. Vergote, Joo-Hyun Nam, Youn Choi Park, Claudia A. Lebedinsky, and Andrés M. Poveda

From the University of California at Irvine (UCI) and UCI Medical Center, Orange, CA; Columbia University College of Physicians and Surgeons; New York University Hospital, New York, NY; the Royal Marsden Hospital, Surrey, United Kingdom; Gillette Center for Women's Studies, Massachusetts General Hospital, Boston, MA; Antwerp University Hospital, Edegem; University Hospital, Leuven, Belgium; Université Paris Descartes, Assistance Publique

See accompanying editorial doi: 10.1200/JCO.2009.29.7077

A B S T R A C T

Purpose

The objective of this study was to compare the efficacy and safety of trabectedin plus pegylated liposomal doxorubicin (PLD) with that of PLD alone in women with recurrent ovarian cancer after failure of first-line, platinum-based chemotherapy.

Farmaci di II linea

- Topotecan
- Taxotere
- Taxol settimanale
- Adriamicina liposomiale
- Gemcitabina
- Etoposide
- Oxaliplatino
- Ifosfamide
- Tamoxifen
- Trabectidina

Farmaci di II linea

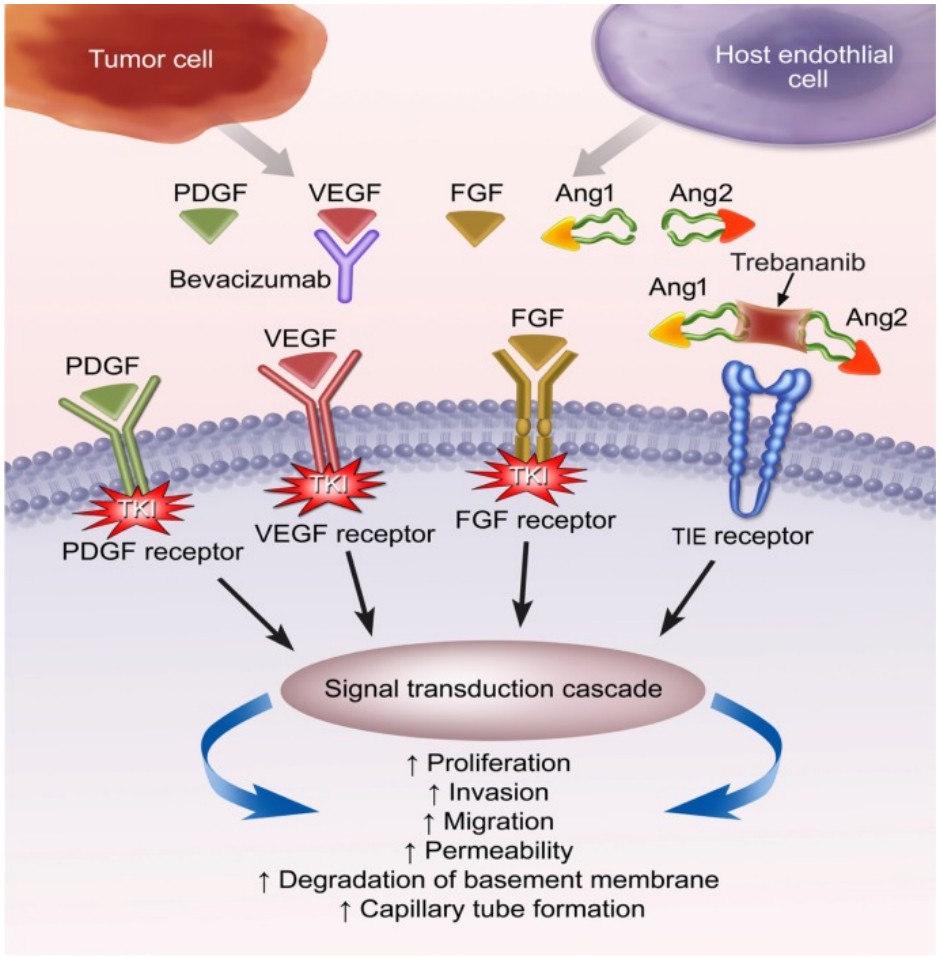
- Topotecan
- Taxotere
- Taxol settimanale
- Adriamicina liposomiale
- Gemcitabina
- Etoposide
- Oxaliplatino
- Ifosfamide
- Tamoxifen
- Trabectidina

Il trattamento del carcinoma ovarico in molti casi mira a rendere la malattia “cronica”, utilizzando tutti i farmaci a disposizione con la sequenza giusta per dare la massima efficacia e la minima tossicità

Nuovi farmaci

- Antiangiogenetici (bevacizumab, pazopanib)
- Inibitori di PARP (olaparib) per donne BRCA mutate

I farmaci angiogenetici

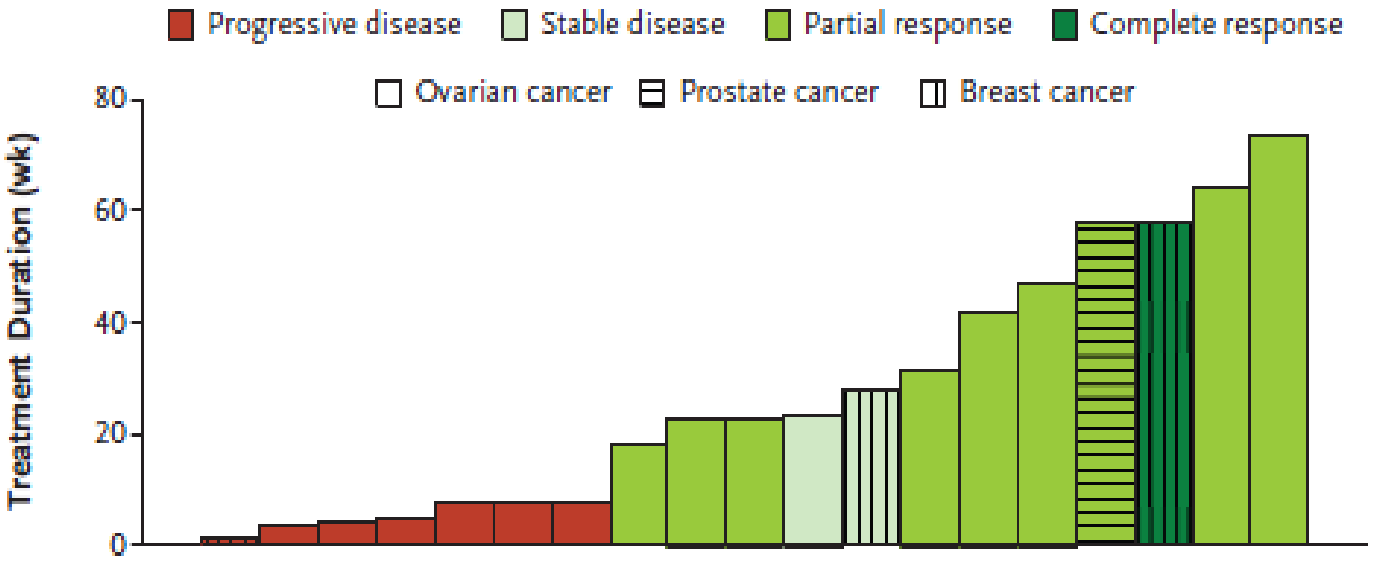


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 9, 2009 VOL. 361 NO. 2

Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from *BRCA* Mutation Carriers

Peter C. Fong, M.D., David S. Boss, M.Sc., Timothy A. Yap, M.D., Andrew Tutt, M.D., Ph.D., Peijun Wu, Ph.D., Maria Mergui-Roelvink, M.D., Peter Mortimer, Ph.D., Helen Swaisland, B.Sc., Alan Lau, Ph.D.

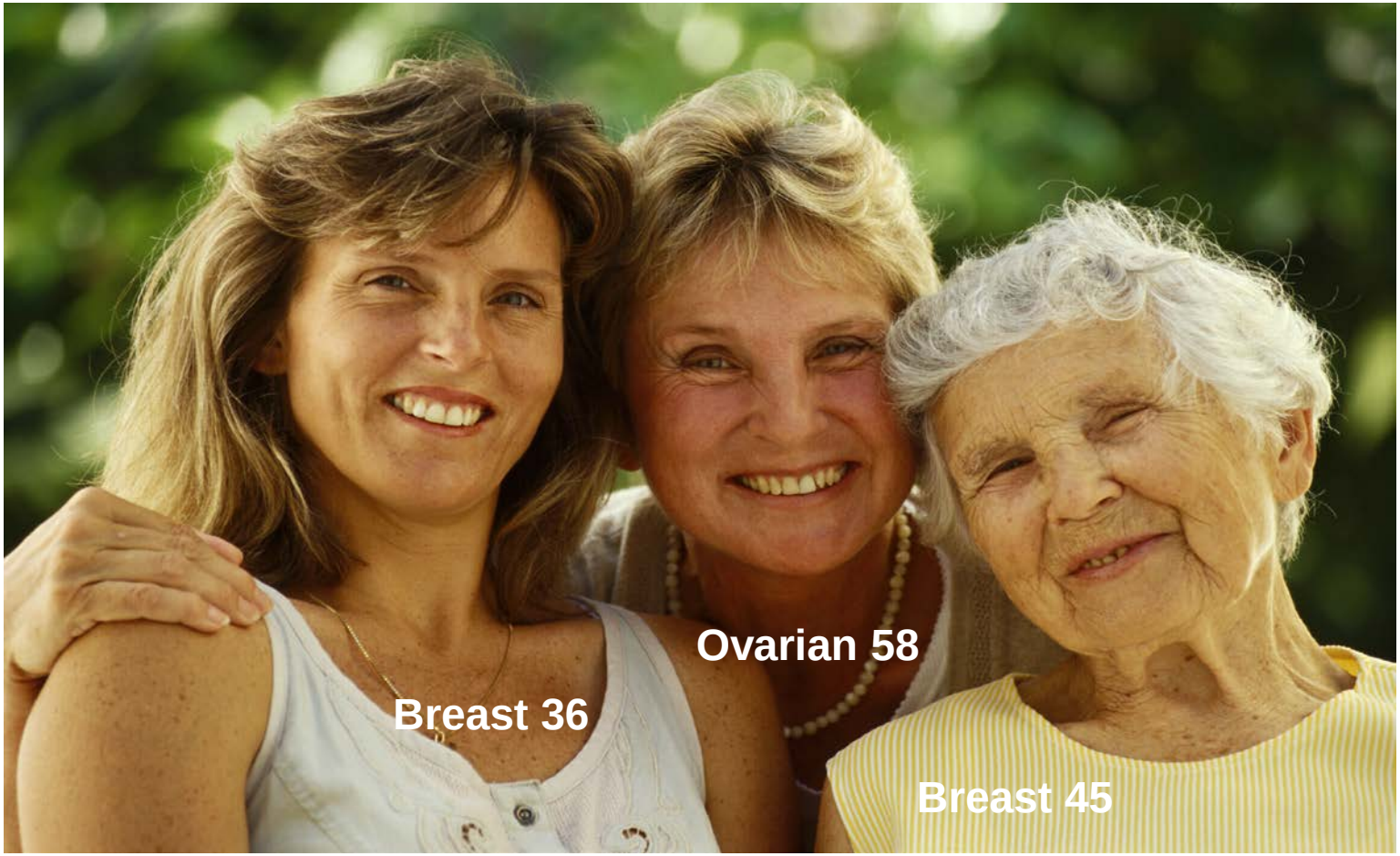


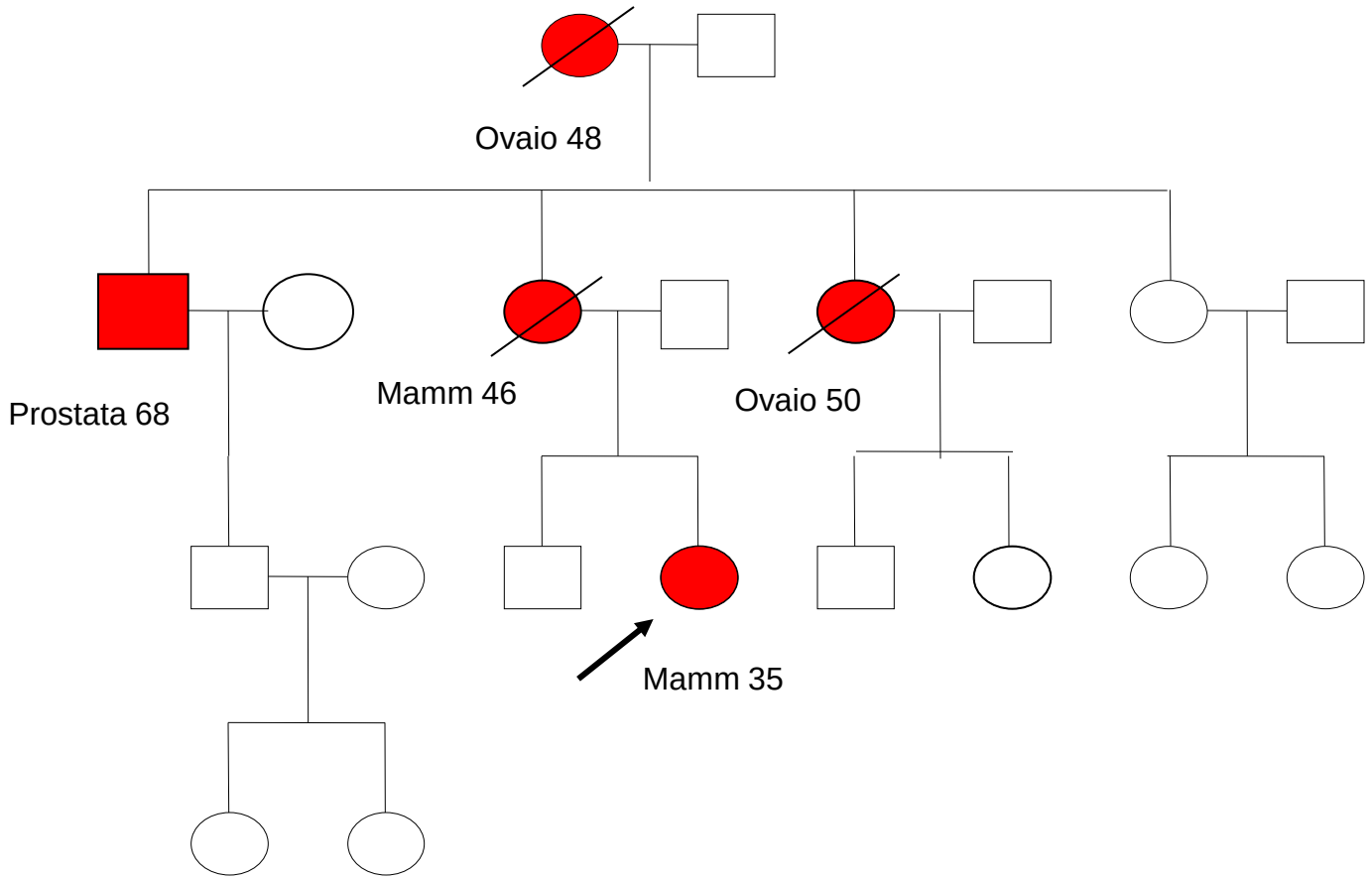
CONCLUSIONS

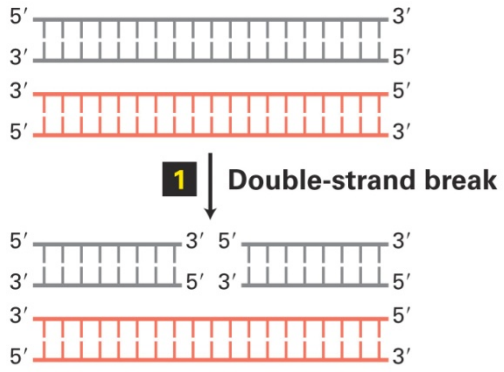
Olaparib has few of the adverse effects of conventional chemotherapy, inhibits PARP, and has antitumor activity in cancer associated with the *BRCA1* or *BRCA2* mutation.

Agire sui fattori di rischio ereditario e sulle donne ad alto rischio

Familiarità/ereditarietà




Ovaio 48
Prostata 68
Mamm 46
Ovaio 50
Mamm 35



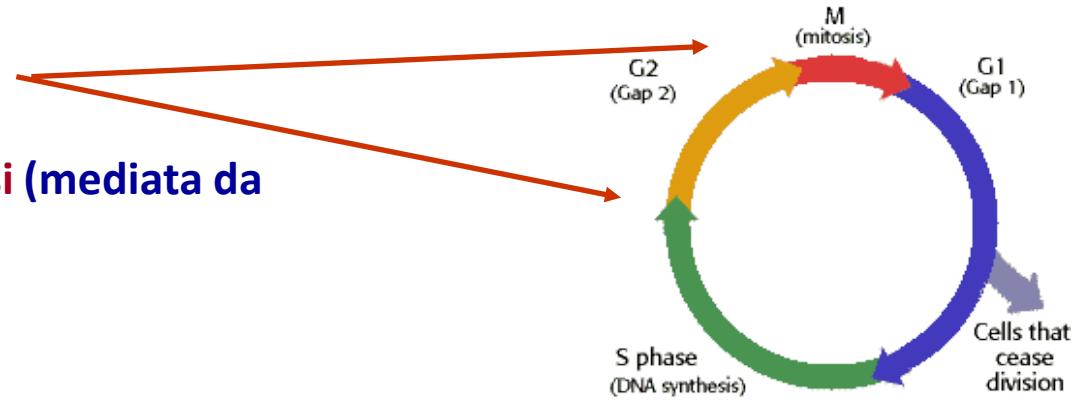
Le proteine BRCA1 & 2 sono essenziali nella riparazione del DNA (ricombinazione omologa) necessaria per la integrità del genoma

Rotture del DNA sono tipiche della azione di radiazioni e agenti chimici

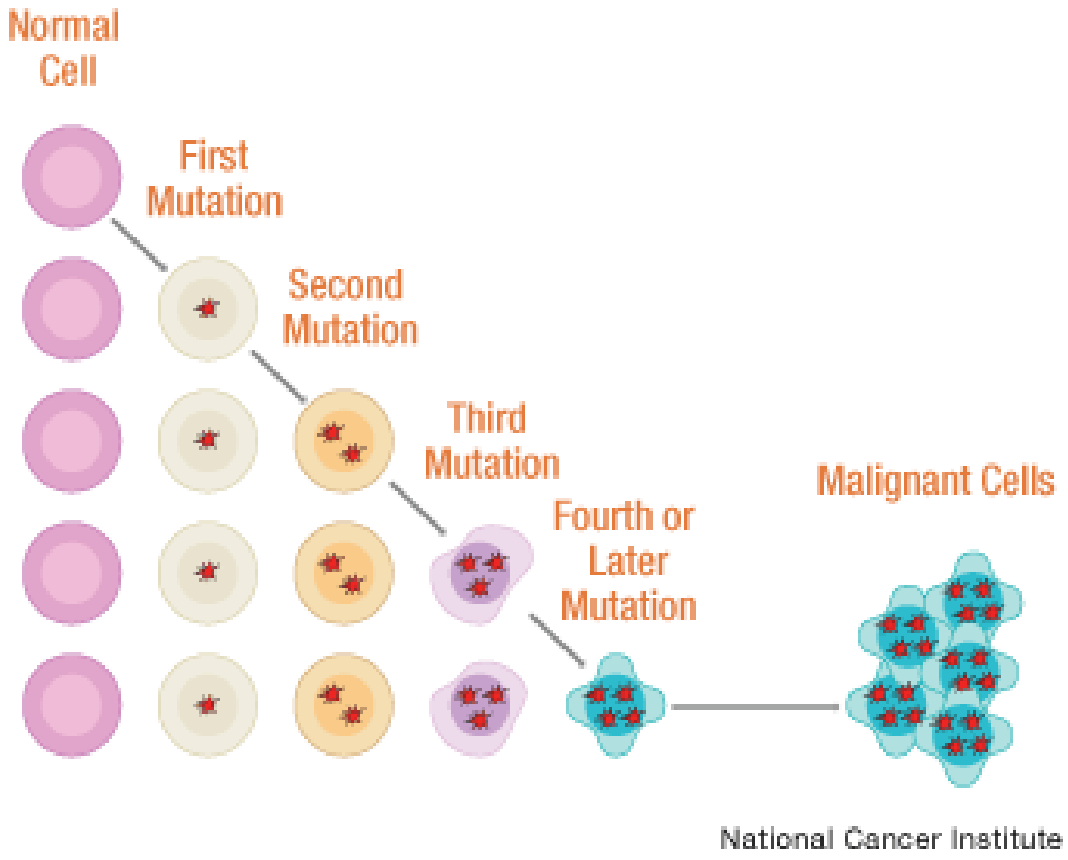
Chekpoint S-G2, G2-M:

Riparazione = OK

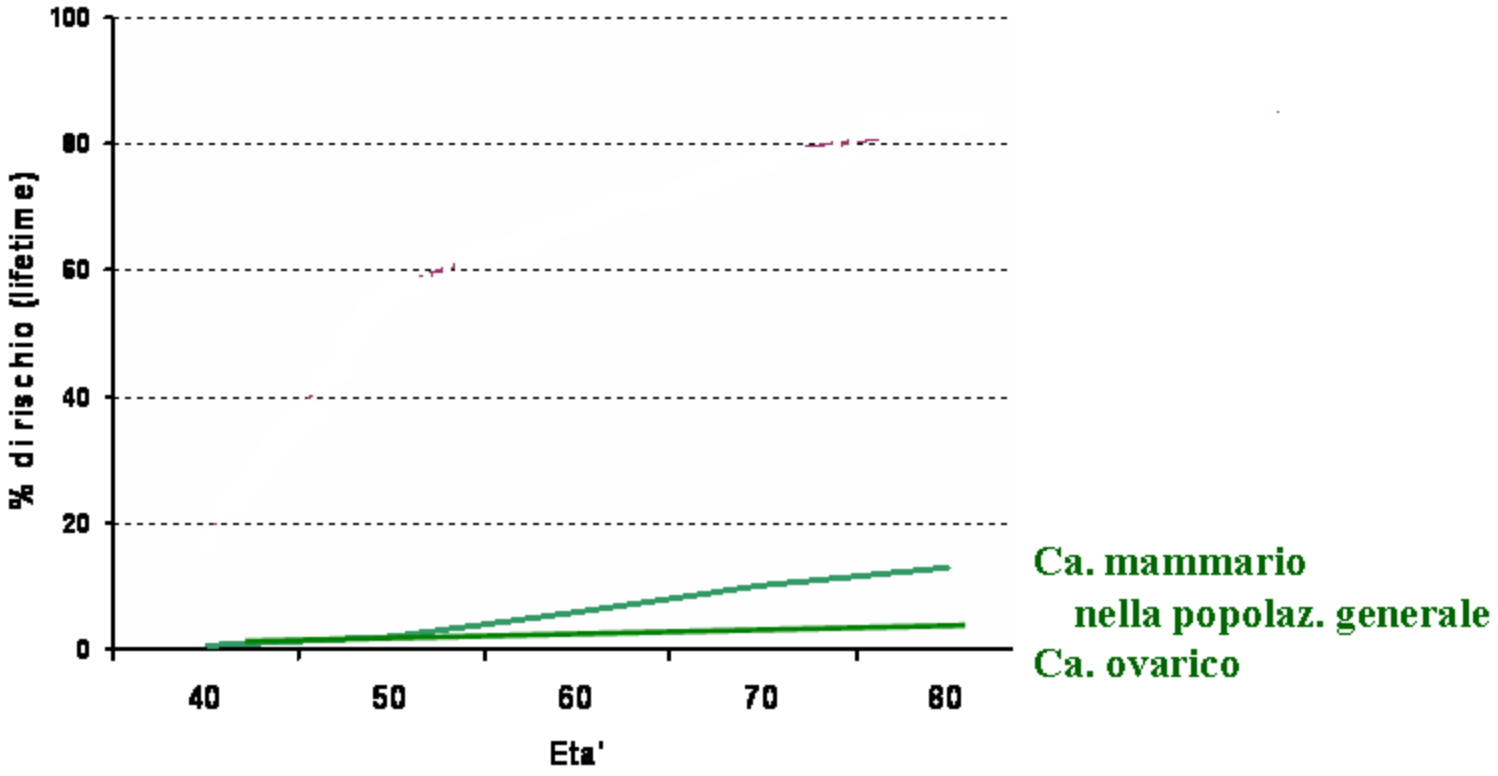
Mancata riparazione = apoptosi (mediata da p53)



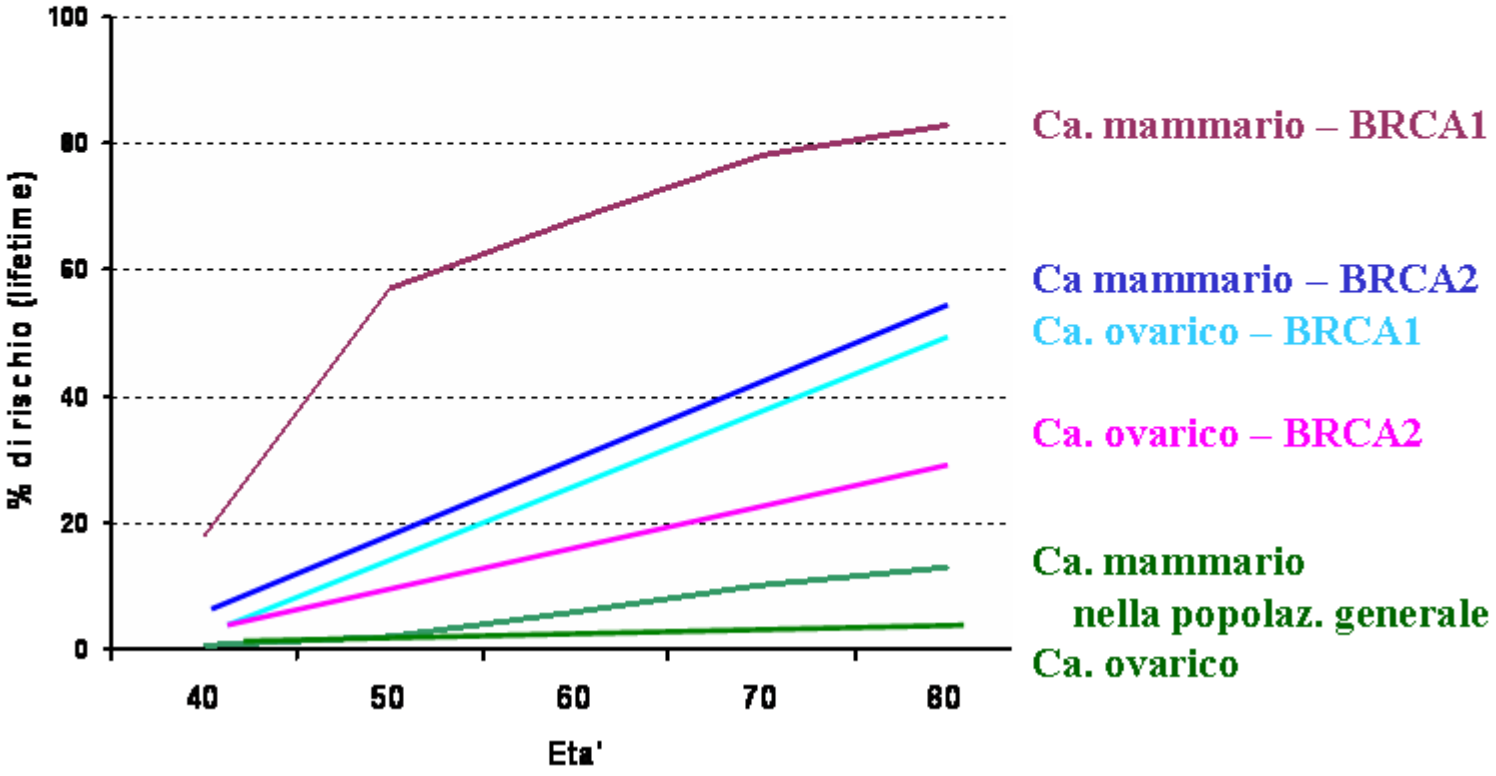
Il cancro è una malattia "genetica"



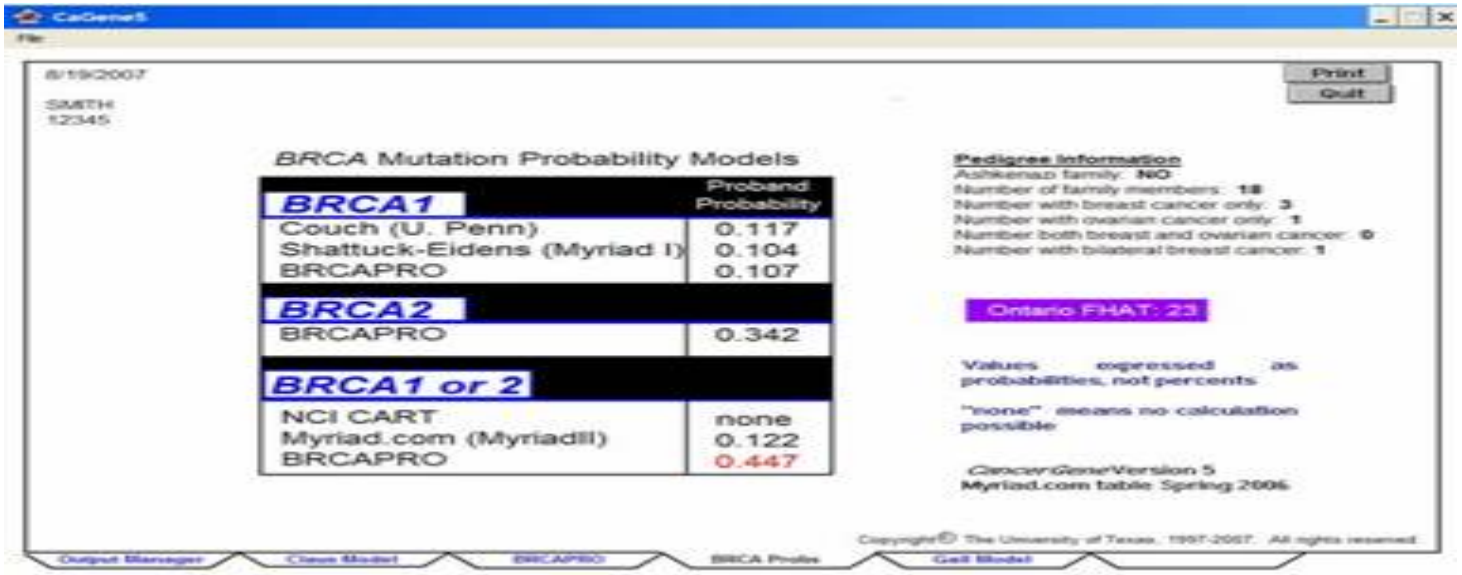
Rischio di ammalare in portatrici di mutazione di BRCA1/2



Rischio di ammalare in portatrici di mutazione di BRCA1/2

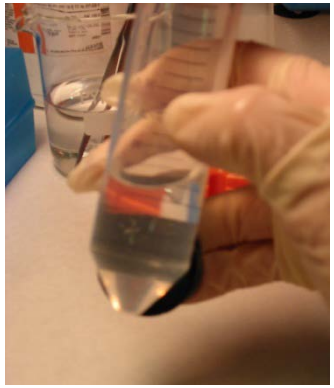


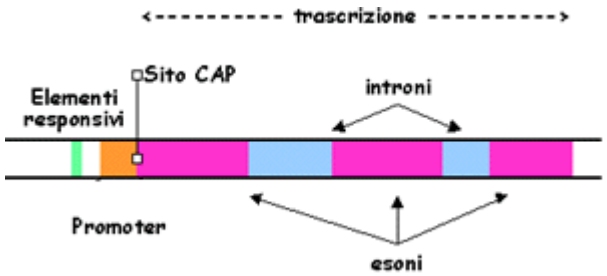
B R C A P R O



BOadiCea

Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm



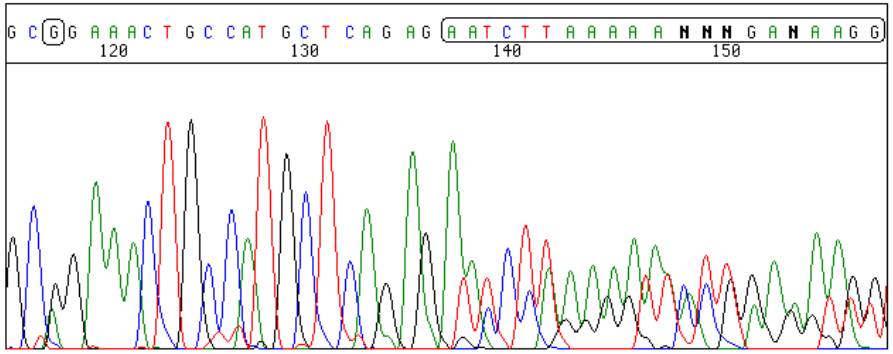


Test indiretti (PTT, SSCP): semplici, economici, bassa sensibilità e specificità

DHPLC: rapida, buona sensibilità, costosa

MLPA: evidenzia le delezioni esoniche, non mutazioni intra-esoniche.

Sequenza diretta: identifica le mutazioni di una singola base all'interno degli esoni, non le delezioni



Pazienti con mutazione di BRCA1 e 2	
Numero totale di test eseguiti e terminati dal 1996 al 2013	996
Numero totale di pazienti con mutazione BRCA1	111
Numero totale di pazienti portatori di mutazione BRCA2	132
Tipo di neoplasia	
Numero donne con carcinoma ovarico nelle famiglie	186
Donne mutate BRCA1 che hanno fatto il test per carcinoma ovarico	27
Donne mutate BRCA2 che hanno fatto il test per carcinoma ovarico	20
Età mediana di insorgenza dell'Adenocarcinoma ovarico BRCA1	53 anni (38-60)
Età mediana di insorgenza del carcinoma mammario femminile BRCA1	42 anni (24-60)
Età mediana di insorgenza dell'Adenocarcinoma ovarico BRCA2	53 anni (39-59)
Età mediana di insorgenza del carcinoma mammario femminile BRCA2	39 anni (32-73)

J Genet Counsel (2007) 16:241–260
DOI 10.1007/s10897-007-9090-7

PROFESSIONAL ISSUES

Risk Assessment and Genetic Counseling for Hereditary Breast and Ovarian Cancer: Recommendations of the National Society of Genetic Counselors

Janice L. Berliner · Angela Musial Fay

Table IV Medical Management Options for Patients after Testing

	Surveillance	Chemoprevention Options	Prophylactic Surgery Options
High Risk (Women)	Monthly breast self-exams starting at age 18; semiannual clinical breast exams, starting at age 25.	Drugs such as tamoxifen (used for 5 years) may significantly reduce the risk of breast cancer in women with BRCA mutations. Tamoxifen is estimated to reduce the risk of contralateral breast cancer by up to 60% in BRCA mutation carriers.	Prophylactic mastectomy reduces the risk of breast cancer by at least 90% in women with BRCA mutations.
	Yearly mammography beginning at age 25.	Oral contraceptives have been associated with up to a 50% reduction in the risk of ovarian cancer in women with BRCA mutations. Studies reveal that this effect can persist for up to 15 years after discontinuing their use.	Prophylactic BSO is estimated to reduce the risk of ovarian cancer by 80–96% and reduces the risk of breast cancer by up to 50% in pre-menopausal women with BRCA mutations.
	Breast ultrasound, digital mammography and MRI may also be considered, especially in younger women who may have limitations of imaging, e.g. due to increased breast density.		
	Annual or semiannual transvaginal ultrasound, pelvic exam and testing for CA-125 to screen for ovarian cancer beginning at 25 years of age or ten years younger than the earliest age at diagnosis in the family.		

Ovarian cancer surveillance is unfortunately still quite limited. Even with regular screening, the early diagnosis of ovarian cancer is rarely made (Rosenthal and Jacobs 1998), and false positive results from screening can lead to anxiety and unnecessary invasive procedures. Therefore, prophylactic bilateral salpingo-oophorectomy (BSO), with or without hysterectomy, should be done when a woman is sure she has completed childbearing, as it reduces the risk of ovarian cancer by 80–96% in BRCA1/2 carriers (Rebbeck *et al.* 2002; Finch *et al.* 2006). Women should not wait until menopause to have this surgery, especially in the setting of BRCA1, where the risk of ovarian cancer has been reported in women under the age of 40 (Antoniou *et al.* 2005). In addition, the earlier a pre-menopausal woman has BSO, the more risk reduction there is for development of a future breast cancer. Prior to BSO, screening may include annual or semi-annual recto-pelvic examination, transvaginal ultrasound with color Doppler, and CA-125 serum tumor marker testing beginning at 25–35 years of age.

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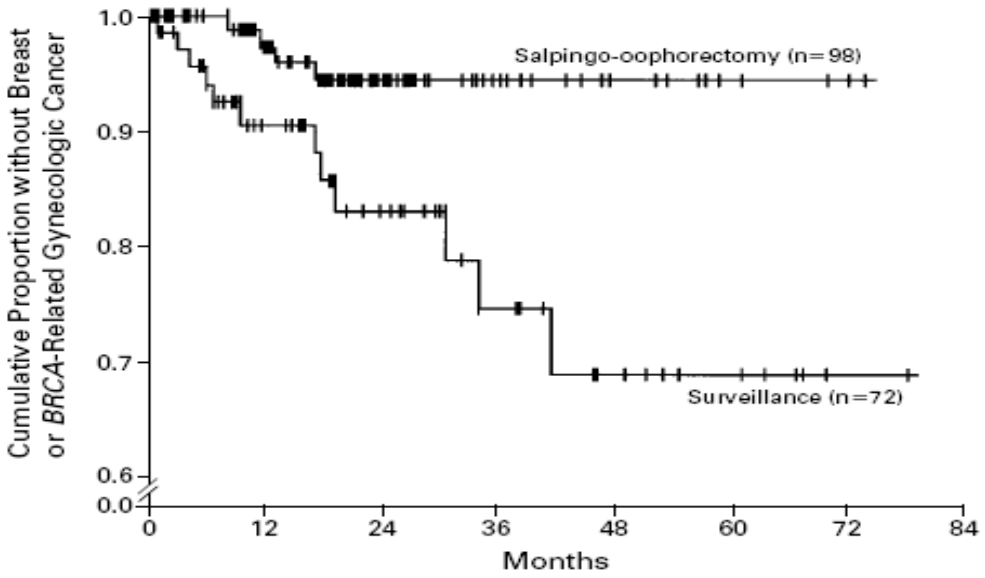
VOLUME 346 MAY 23, 2002 NUMBER 21

RISK-REDUCING SALPINGO-OOPHORECTOMY IN WOMEN WITH A *BRCA1* OR *BRCA2* MUTATION

NOAH D. KAUFF, M.D., JAYA M. SATAGOPAN, PH.D., MARK E. ROBSON, M.D., LAUREN SCHEUER, M.S., MARTEE HENSLEY, M.D., CLIFFORD A. HUDIS, M.D., NATHAN A. ELLIS, PH.D., JEFF BOYD, PH.D., PATRICK I. BORGEN, M.D., RICHARD R. BARAKAT, M.D., LARRY NORTON, M.D., AND KENNETH OFFIT, M.D., M.P.H.



No. at Risk							
Salpingo-oophorectomy	98	69	36	17	11	4	0
Surveillance	72	44	28	16	9	5	1

Figure 1. Kaplan–Meier Estimates of the Time to Breast Cancer or *BRCA*-Related Gynecologic Cancer among Women Electing Risk-Reducing Salpingo-oophorectomy and Women Electing Surveillance for Ovarian Cancer.

Titolo | 10.05.2014

Bibliografia

Centro Regionale di Genetica Oncologica

Informazioni: 071 2206151

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0715964550