Queen Mary University of London

ENGAGe
ESGO | European Network of Gynaecological Cancer Advocacy Groups

women's Precision Prevention

# Preventive operation for BRCA / Lynch mutation

8th March 2024


**Prof Ranjit Manchanda MD, MRCOG, PhD**

Professor of Gynaecological Oncology
Wolfson Institute of Population Health, Queen Mary University of London
Barts Health NHS Trust , Royal London Hospital, UK
Honorary Professor, London School of Hygiene & Tropical Medicine
NHS Innovation Accelerator (NIA) Alumnus




NHS Barts Health NHS Trust

# Disclosures……

## Research Funding

b+tlc BARTS CHARITY

Rosetrees Trust
Supporting the best in medical research

Yorkshire Cancer Research

NHS CANCER PROGRAMME

TheAHSNNetwork NHS England
NHS Innovation Accelerator

BC CANCER FOUNDATION

gsk GlaxoSmithKline

the eve appeal fighting women's cancers

China Medical Board

BRITISH GYNAECOLOGICAL CANCER SOCIETY

NHS North East London Cancer Alliance

SBRI HEALTHCARE ACCELERATED ACCESS COLLABORATIVE NHS

NHS North Central London Cancer Alliance

**Other Disclosures- Honorarium – MSD, Astrazeneca, GSK, EGL, Israel National Institute for Health Policy Research**

- BACKGROUND
- Preventive Surgery in BRCA +
- Preventive Surgery in Lynch
- SUMMARY

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GLOBOCAN 2020 ESTIMATED CANCER INCIDENCE, MORTALITY AND PREVALENCE WORLDWIDE IN 2012

International Agency for Research on Cancer

World Health Organization

GCO

CANCER TOMORROW

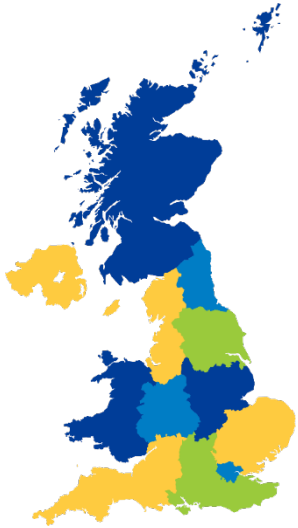
**50% women's cancers**

| Cases WORLDWIDE | Breast Cancer | Ovarian Cancer | Bowel Cancer | Womb (Endometrial) Cancer |
|---|---|---|---|---|
| Number of Cases Annually | 2,261,419 | 313,959 | 1,931,590 | 417,367 |

**WORLD**

**4.9 M cases annually**

**UK**



**116,000 cases annually**

Wolfson Institute of Population Health

NHS Barts Health NHS Trust

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GLOBOCAN 2020
ESTIMATED CANCER INCIDENCE, MORTALITY AND PREVALENCE WORLDWIDE IN 2012

International Agency for Research on Cancer

World Health Organization

GCO | CANCER TOMORROW

# Predicted Rise in Cancer Cases by 2040

**WORLD**

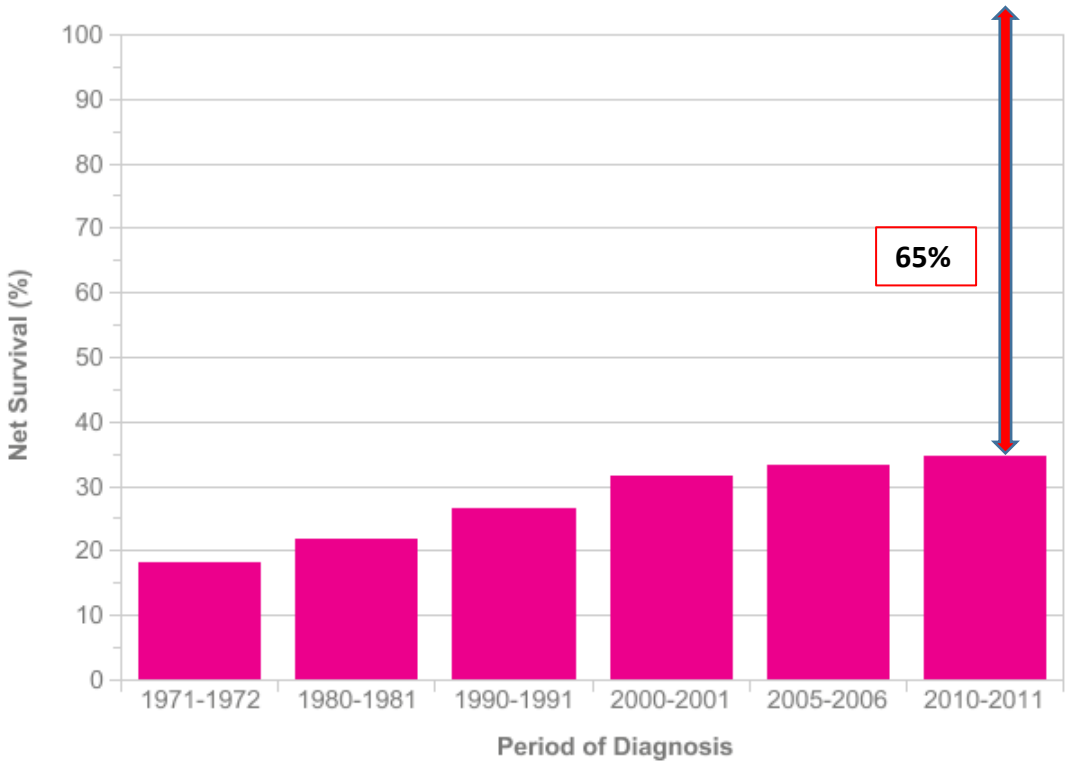
**Cases: 27-53%**
**Deaths: 49-69%**

**UK**

**Cases: 20-36%**
**Deaths: 36-47%**

# Ovarian Cancer is a horrible disease ……..

**65% patients will die from OC**
**Much higher if we look at high grade EOC**




**Ovarian Cancer (C56 C57.0-C57.7): 1971-2011**

**Age-Standardised Ten-Year Net Survival, England and Wales**

# PREVENTION STRATEGY

BETTER IDENTIFICATON OF HIGH-RISK PEOPLE

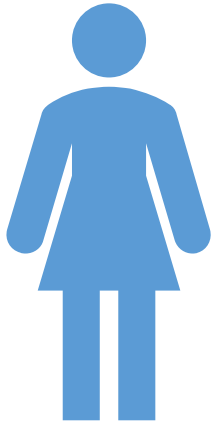
BETTER TARGETED
PREVENTION
SCREENING
RISK MANAGEMENT

FEWER CANCERS
REDUCED DEATHS

**MOST EFFECTIVE STRATEGY: SURGICAL PREVENTION**


20%

1 in 5



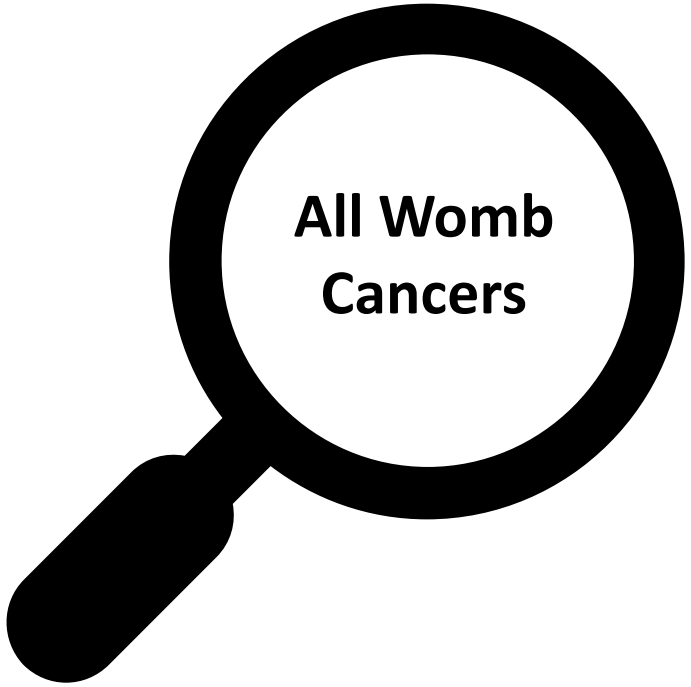
| |
|---|
| BRCA1 |
| BRCA2 |

| |
|---|
| MLH1 |
| MSH2 |
| MSH6 |
| PMS2 |

Lynch Syndrome

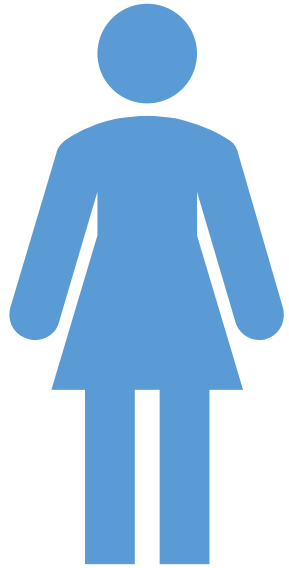
| |
|---|
| PALB2 |
| RAD51C |
| RAD51D |
| BRIP1 |

Other Genes




3%

1 in 33



**Lynch Syndrome**

20% Ovarian Cancers
4% Breast Cancers
3% Womb Cancers
4% Bowel Cancers

| Breast | Ovary | Bowel | Endometrial |
|---|---|---|---|
| BRCA1 | BRCA1 | MLH1 | MLH1 |
| BRCA2 | BRCA2 | MSH2 | MSH2 |
| PALB2 | PALB2 | MSH6 | MSH6 |
| RAD51C | RAD51C | PMS2 | PMS2 |
| RAD51D | RAD51D | EPCAM | |
| CHEK 2 | BRIP1 | | |
| ATM | MLH1 | | |
| BARD1 | MSH2 | | |
| | MSH6 | | |
| | | | |

~1% women in the general population may have one of these cancer genes

THESE CANCERS ARE POTENTIALLY PREVENTABLE

## GERMLINE

## TUMOUR (SOMATIC)

- BRCA1
- BRCA2
- HRD assay/test

## OVARIAN CANCER GENES

- BRCA1
- BRCA2
- RAD51C
- BRIP1
- PALB2
- RAD51D

MMR: Lynch Syndrome Genes
MLH1, MSH2, MSH6

## WOMB CANCER GENES

- MLH1
- MSH2
- MSH6
- PMS2

NHS
National Genomic Test Directory

Testing Criteria for Rare and Inherited Disease

V3.1 August 2022 (Official)

**GUIDELINES RECOMMEND TESTING FOR THESE GENES**

# Lynch Syndrome

| | Cancer risks (%) | | |
|---|---|---|---|
| GENE | Ovarian cancer | Colorectal cancer | Endometrial cancer |
| MLH1 | 11 | 48 | 37 |
| MSH2 | 17 | 47 | 49 |
| MSH6 | 11 | 20 | 41 |
| PMS2 | 3% | 10 | 13 |
| General population risk (no altered gene) | 2% (1 in 50) | 5.6% (1 in 18) | 2.7% (1 in 36) |

*Prospective Lynch Syndrome Database, Moller, et al. 2020*

| GENE | Ovarian Cancer Risk | Breast Cancer Risk |
|---|---|---|
| *BRCA1* | 44% | 77% |
| *BRCA2* | 17% | 69% |
| *RAD51C* | 11% | |
| *RAD51D* | 13% | |
| *BRIP1* | ~8% | |
| *PALB2* | 5% | 53% |
| *MLH1* | 11% | |
| *MSH2* | 17% | |
| *MSH6* | 11% | |
| General Population Risk | 1.3-2% | 12-15% |

RRSO: RISK REDUCING SALPINGO-OOPHORECTOMY

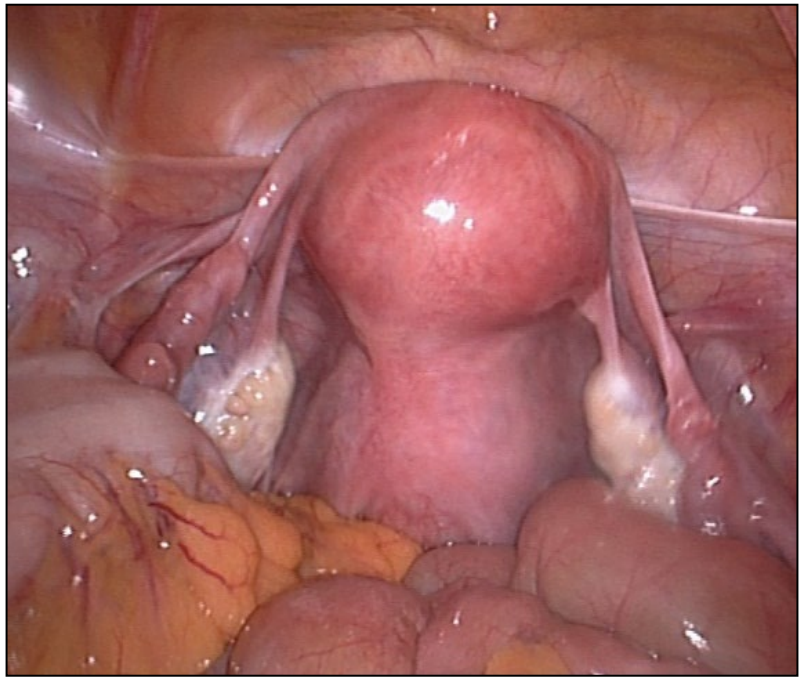
REMOVING BOTH TUBES & OVARIES

HYSTERECTOMY AND BILATERAL SALPINGO-OOPHORECTOMY

REMOVING UTERUS + BOTH TUBES & OVARIES

RRESDO: RISK REDUCING EARLY SALPINGECTOMY + DELAYED OOPHORECTOMY

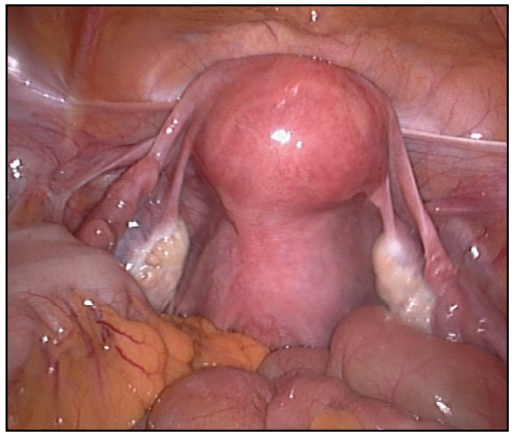
NEW 2 STAGE OPTION: BOTH TUBES FIRST BOTH OVARIES LATER



BROADENING ACCESS TO SURGICAL PREVENTION

# Removing Tubes and Ovaries:

# Most effective method to reduce Ovarian Cancer risk



**Keyhole surgery, Washings for cytology**

**~ 80-97% reduction in Ovarian Cancer Incidence**

**Reduction in Deaths from Ovarian Cancer (Mortality)**

**Reduction in deaths overall (all-cause)**

**Reduces Anxiety and Ovarian Cancer worry**

**No change in General Quality of Life**

*Wei, Manchanda 2023 AJOG*

*Finch et al, JCO 2014*

*Domchek et al, JAMA 2010, Kotsopoulos Jama Oncol 2024*

*Crosbie, Evans IJC 2020, Domchek JAMA 2010, Finch 2014 JCO, Rebbeck 2009 JNCI*

Contents lists available at ScienceDirect
Gynecologic Oncology
journal homepage: www.elsevier.com/locate/ygyno
ELSEVIER

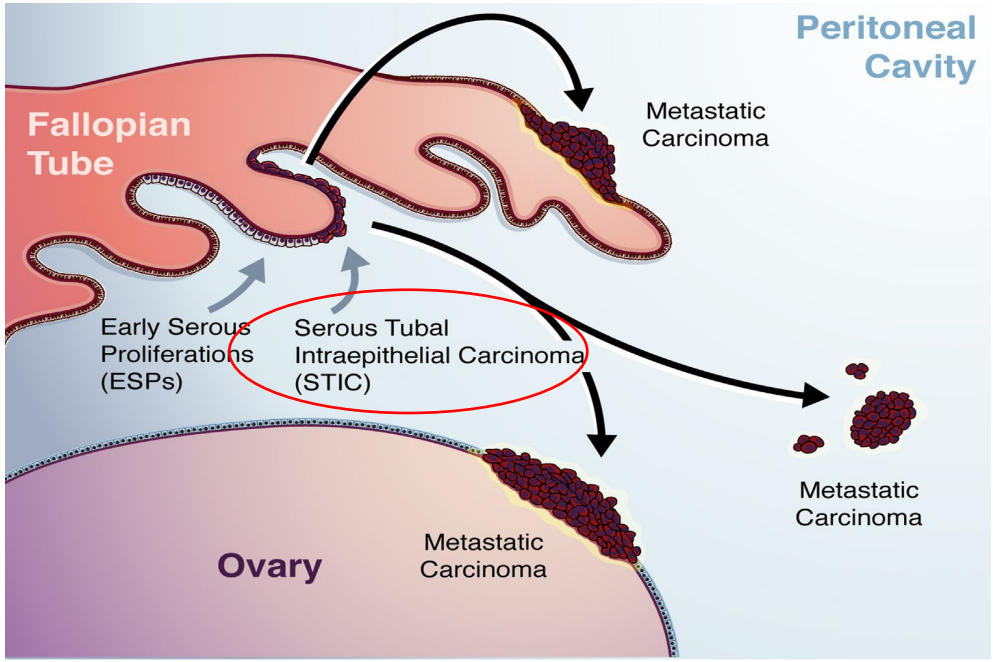
*Gynecol Oncol 2019*

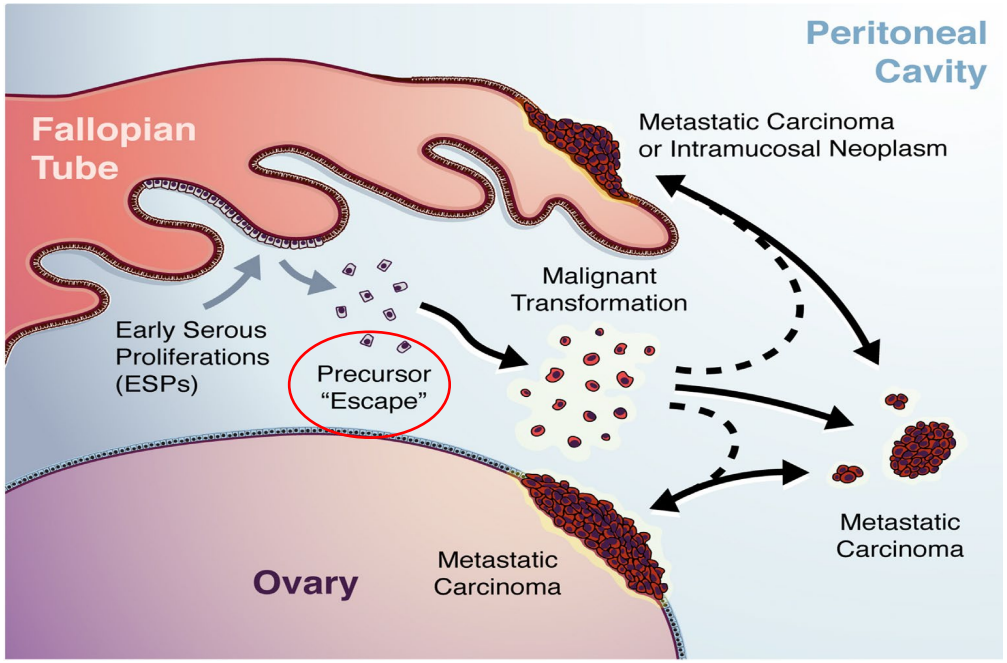
Review Article

# The fallopian tube, "precursor escape" and narrowing the knowledge gap to the origins of high-grade serous carcinoma

Thing Rinda Soong [a], Brooke E. Howitt [b], Neil Horowitz [c], Marisa R. Nucci [d], Christopher P. Crum [d,*]

## TUBAL ORIGIN OF OVARIAN CANCER

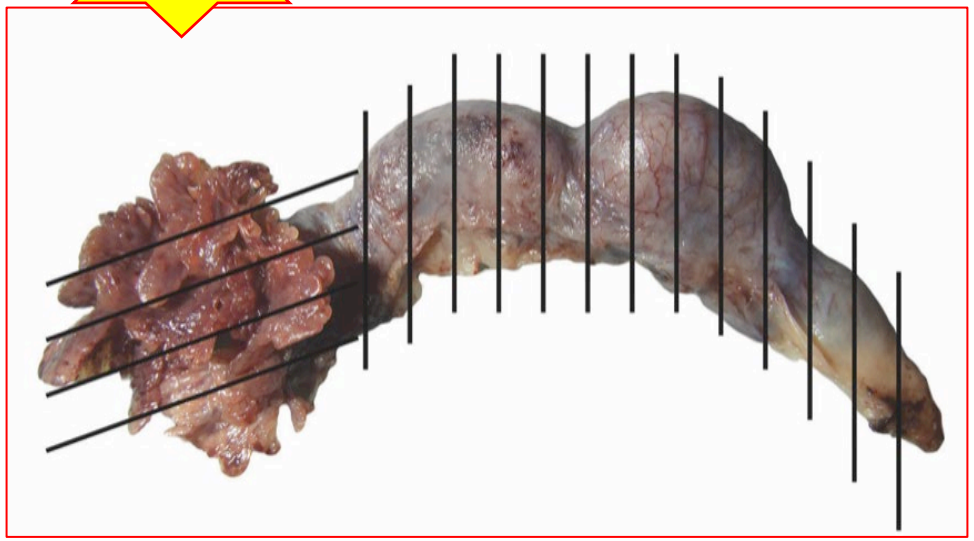


## Historical

## SPECIAL PATHOLOGY PROTOCOL

IMP

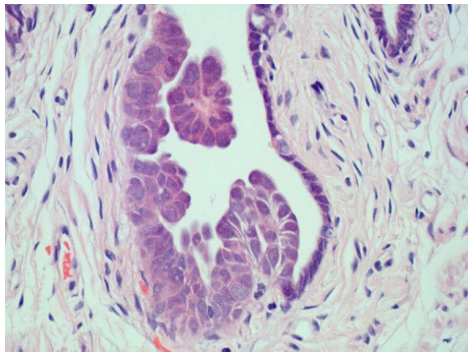


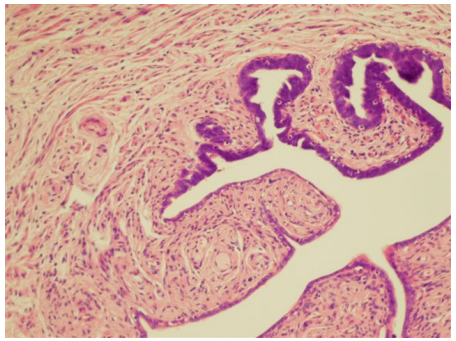
**SEEFIM PROTOCOL-**
**Sectioning and Extensively Examining the FIMbriated end of the Fallopian Tube**

**ESSENTIAL**

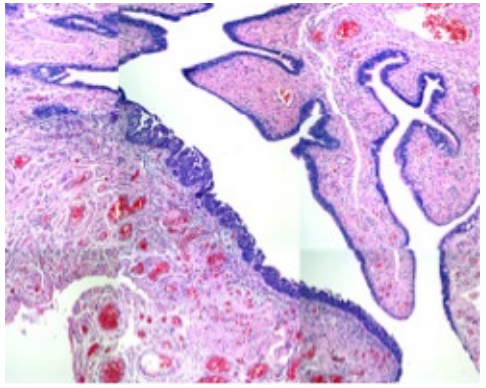
**PRE CANCER**

**S**erous **T**ubal
**I**ntraepithelial
**C**arcinoma = **STIC**





**CANCER**



**1:20 Individuals**
**Normal scan and Ca125**

**SEEFIM ESSENTIAL**

# Other Points

**70% these lesions are Tubal**

**Small residual chance of Peritoneal cancer over 20 yrs**

*2-4% Finch 2014 J Clin Oncol*
*0% Marcinkute 2021 JMG (Manchester)*

| Presence of STIC | 5 Year | 10 Year |
|---|---|---|
| STIC | 10.5% | 27.5% |
| No STIC | 0.3% | 0.9% |

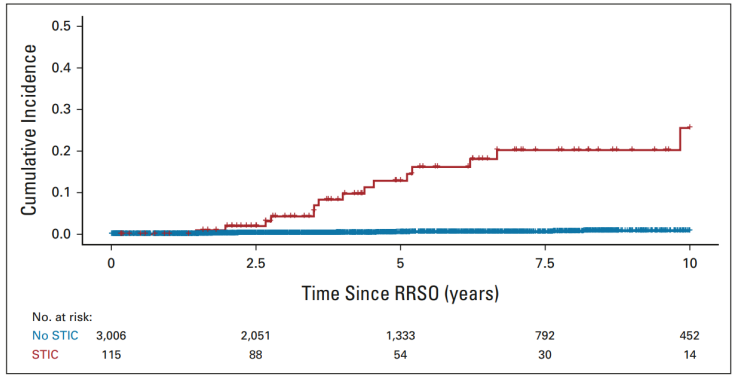



FIG 2. Kaplan-Meier plot to visualize the occurrence of peritoneal carcinomatosis after RRSO. RRSO, risk-reducing salpingo-oophorectomy, STIC, serous tubal intraepithelial carcinoma.

original reports

**Risk of Peritoneal Carcinomatosis After Risk-Reducing Salpingo-Oophorectomy: A Systematic Review and Individual Patient Data Meta-Analysis**

Miranda P. Steenbeek, MD[1]; Majke H.D. van Bommel, MD[1]; Johan Bulten, MD, PhD[2]; Julia A. Hulsmann, MD[1]; Joep Bogaerts, MD[2]; Christine Garcia, MD, PhD[3]; Han T. Cun, MD, PhD[4]; Karen H. Lu, MD, PhD[4]; Heleen J. van Beekhuizen, MD, PhD[5]; Lucas Minig, MD, PhD[6]; Katja N. Gaarenstroom, MD, PhD[7]; Marielle Nobbenhuis, MD, PhD[8]; Mateja Krajc, MD, PhD[9]; Vilius Rudaitis, MD, PhD[10]; Barbara M. Norquist, MD, PhD[11]; Elizabeth M. Swisher, MD, PhD[11]; Marian J.E. Mourits, MD, PhD[12]; Leon F.A.G. Massuger, MD, PhD[1]; Nicoline Hoogerbrugge, MD, PhD[13]; Rosella P.M.G. Hermens, PhD[14]; Joanna IntHout, PhD[15]; and Joanne A. de Hullu, MD, PhD[1]

*JCO Feb 2022*

# Important issues

- Fertility
- Age
- Gene, Cancer Risk
- Premature Surgical Menopause: implications
- HRT

# IMPACT ON BC RISK

**Initially multiple studies: Up to a 50% reduction BC incidence in premenopausal women**
**Recently become controversial: Many Studies showing no benefit**

*Systematic Review*

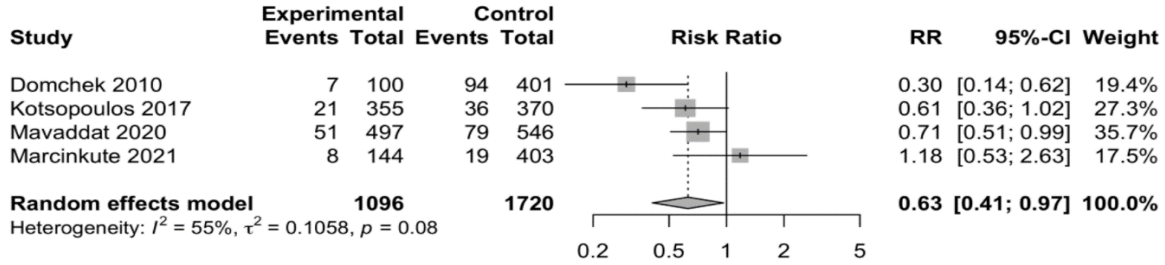
## Breast Cancer Risk and Breast-Cancer-Specific Mortality Following Risk-Reducing Salpingo-Oophorectomy in *BRCA* Carriers: A Systematic Review and Meta-Analysis

Faiza Gaba [1,2], Oleg Blyuss [3,4], Alex Tan [3], Daniel Munblit [4,5,6], Samuel Oxley [2,3], Khalid Khan [7], Rosa Legood [8] and Ranjit Manchanda [2,3,8,9,10,*]

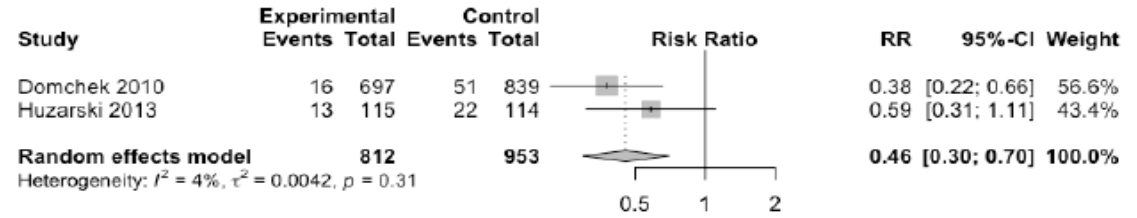
**Reduction of Breast Cancer risk in *BRCA2*-carriers alone**
**(RR=0.63, 95%CI:0.41-0.97)**

**Reduction Deaths from breast cancer in BC-affected *BRCA1* carriers**
**(RR=0.46, 95%CI:0.30-0.70)**

## META ANALYSIS




J: Breast-cancer-specific mortality following RRSO in breast-cancer-affected *BRCA1* carriers




**21 RRSOs to prevent one breast cancer in *BRCA2*-carriers**
**6 RRSOs - Prevent one BC-death in *BRCA1*-&-*BRCA2*-carriers**

# HYSTERECTOMY: YES or NO?

**OUR VIEW + TRADITIONAL VIEW: NOT ROUTINELY UNLESS OTHER INDICATION**

**PROPONENTS :**
**Avoids smears**
**Estrogen alone HRT**
**In patients on tamoxifen**

**Not a Strong enough Clinical Rationale**

**BRCA1 & Serous EC Risk? - Recent studies**

**Increased Serous EC risk** → **Small number cases 2-5, Wide CI**
**Only 7% EC**
**Overall EC risk not increased**

*Saule JNCI 2018*
*Shu, Kauff 2016 Jama Oncol*
*Laitman Cancer 2018*
*Kitson 2020 EJC*

**No increase in serous EC risk**

**More Corroboratory evidence is needed**

## CSG-specific strategies

**Screening**
**Surgery**
**Medical prevention**

JAMA Network Open.

Original Investigation | Genetics and Genomics

### Cost-Effectiveness of Gene-Specific Prevention Strategies for Ovarian and Breast Cancer

Xia Wei, MSc; Li Sun, PhD; Eric Slade, MSc; Caitlin T. Fierheller, PhD; Samuel Odey, MRCOG; Ashwin Kalra, MBBS; Jacqueline Sia, MRCOG; Michail Sideris, PhD; W. Glenn McCluggage, FRCPath; Nathan Bromham, PhD; Katharina Dworzynski, PhD; Adam N. Rosenthal, PhD; Adam Brentnall, PhD; Stephan Duffy, PhD; D. Gareth Evans, PhD; Li Yang, PhD; Rosa Legood, PhD; Ranjit Manchanda, MD, PhD

| | |
|---|---|
| **BRCA1:** | **RRSO @35 ; RRM @30** |
| **BRCA2:** | **RRSO @35-40 ; RRM @30** |
| **PALB2:** | **RRSO @45 ; RRM @40** |
| **RAD51C/RAD51D:** | **RRSO @45** |
| **BRIP1:** | **RRSO @45** |

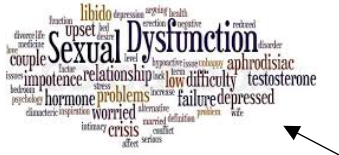
# Base case

## Population impact of risk-reducing surgery for preventing cancer (per 1,000 pathogenic variant carriers)

| Strategy | BC cases | BC deaths | OC cases | OC deaths | BC cases prevented | BC deaths prevented | OC cases prevented | OC deaths prevented |
|---|---|---|---|---|---|---|---|---|
| ***BRCA1*** | | | | | | | | |
| High-risk BC surveillance and tamoxifen from age 30* | 601 | 63 | 412 | 253 | | | | |
| RRM at age 30 | 83 | 11 | 423 | 260 | -518 | -52 | 11 | 6 |
| RRSO at age 35 with high-risk BC surveillance and tamoxifen from age 30 | 710 | 56 | 24 | 7 | 108 | -7 | -388 | -246 |
| RRM at age 30 with RRSO at age 35 | 65 | 7 | 25 | 8 | -536 | -56 | -387 | -246 |
| ***BRCA2*** | | | | | | | | |
| High-risk BC surveillance and tamoxifen from age 30* | 630 | 74 | 171 | 106 | | | | |
| RRSO at age 35 with high-risk BC surveillance and tamoxifen from age 30 | 549 | 33 | 7 | 2 | -80 | -41 | -164 | -103 |
| RRM at age 30 | 91 | 15 | 174 | 107 | -539 | -59 | 3 | 2 |
| RRM at age 30 with RRSO at age 35 | 65 | 5 | 7 | 2 | -565 | -69 | -163 | -103 |
| ***PLAB2*** | | | | | | | | |
| High-risk BC surveillance and tamoxifen from age 30* | 481 | 109 | 46 | 30 | | | | |
| RRM at age 40 | 77 | 18 | 47 | 30 | -404 | -91 | 0 | 0 |
| RRSO at age 45 with high-risk BC surveillance and tamoxifen from age 30 | 402 | 40 | 4 | 2 | -79 | -69 | -42 | -28 |
| RRM at age 40 with RRSO at age 45 | 59 | 7 | 4 | 1 | -422 | -102 | -42 | -28 |
| ***RAD51C*** | | | | | | | | |
| Moderate-risk BC surveillance and tamoxifen from age 40* | 188 | 53 | 108 | 66 | | | | |
| RRSO at age 45 with moderate-risk BC surveillance and tamoxifen from age 40 | 238 | 48 | 6 | 2 | 50 | -6 | -102 | -64 |
| ***RAD51D*** | | | | | | | | |
| Moderate-risk BC surveillance and tamoxifen from age 40* | 174 | 48 | 124 | 78 | | | | |
| RRSO at age 45 with moderate-risk BC surveillance and tamoxifen from age 40 | 220 | 43 | 6 | 2 | 46 | -5 | -118 | -76 |
| ***BRIP1*** | | | | | | | | |
| No surgery* | / | / | 63 | 40 | / | / | | |
| RRSO at age 45 | / | / | 7 | 3 | / | / | -55 | -37 |

**Inc CV risk**
**CV mortality: NNH 1:33 without HRT**

**Sexual DysFn**




**Neurocognitive problems: Parkinsons, Dementia**

**Surgical Menopause**

**VMS**



**Osteoporosis**

**HRT Until Age 51, Unless Any Contraindications**

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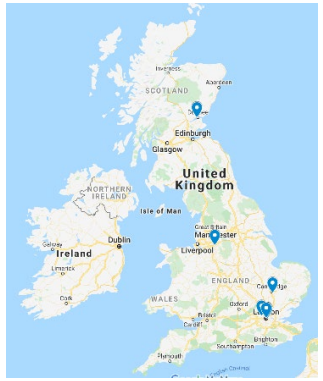
Contents lists available at ScienceDirect
Best Practice & Research Clinical Obstetrics and Gynaecology
journal homepage: www.elsevier.com/locate/bpobgyn

Systematic review of acceptability, cardiovascular, neurological, bone health and HRT outcomes following risk reducing surgery in *BRCA* carriers

Faiza Gaba [a, b], Ranjit Manchanda [a, b, c, *]

2020

**RRESDO**




**Manchester**
**Barts**
**UCLH**
**Guys**
**Cambridge**
**Dundee**

**683 BRCA women**

BJOG An International Journal of Obstetrics and Gynaecology *2020*

## Attitudes towards risk-reducing early salpingectomy with delayed oophorectomy for ovarian cancer prevention: a cohort study

F Gaba,[a,b] O Blyuss,[c,d,e] D Chandrasekaran,[a,b] M Osman,[a] S Goyal,[a] C Gan,[f] L Izatt,[g] V Tripathi,[g] I Esteban,[h] L McNicol,[h] K Ragupathy,[h] R Crawford,[i] DG Evans,[j] R Legood,[k] U Menon,[l] R Manchanda[a,b,l]

**89% premenopausal vs 95% postmenopausal**
**Satisfaction with RRSO**

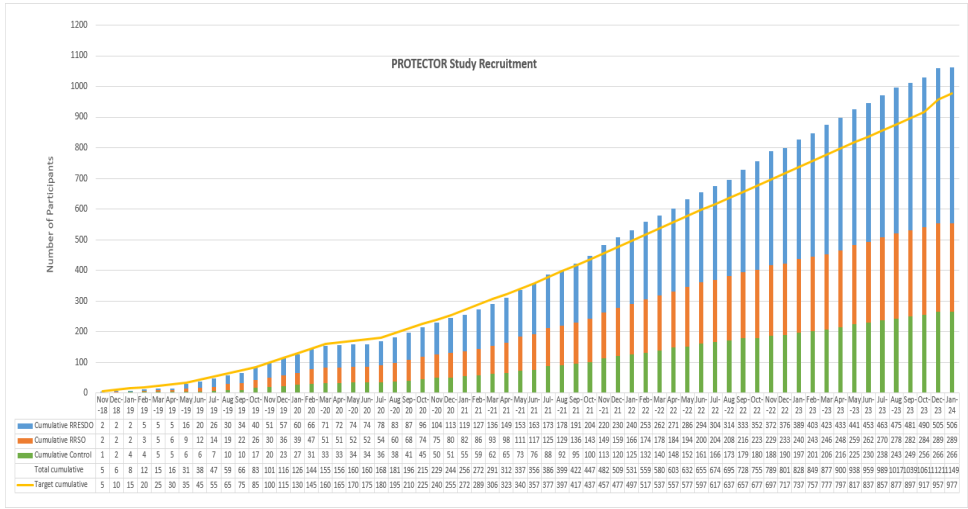
**9.4% premenopausal vs 1% postmenopausal**
**Regretted RRSO**

- **RRESDO high acceptability - 69%**
- **38% RRSO women would have opted for RRESDO in retrospect**
- **Concerned about sexual-dysfunction- RRESDO TWICE AS acceptable**
- **Women who prioritise greater reduction in OC risk: prefer RRSO**

# PROTECTOR

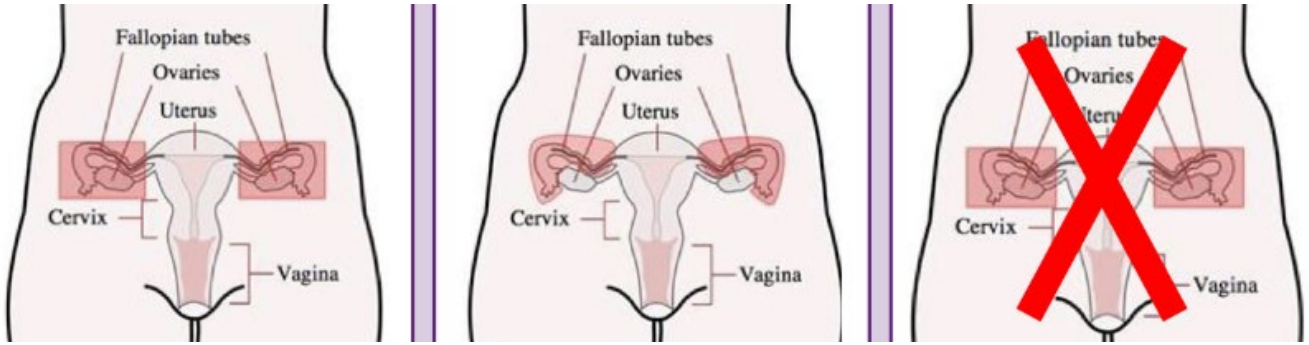
Preventing Ovarian Cancer Through early Excision of Tubes & late Ovarian Removal

- 2 step – tubes and then ovaries
- Tubes & ovaries
- Control




**N = 1250**

**Multicentre Prospective Study**




Risk reducing salpingo-oophorectomy (**RRSO**)

Risk reducing early salpingectomy followed by delayed oophorectomy (**RRESDO**)

No surgery (**Control**)


**Participants Self-Select Study Arm**

**RRESDO offers women delaying/declining premenopausal oophorectomy, particularly those concerned about menopausal effects, a degree of ovarian cancer risk reduction whilst avoiding premature menopause**

## TUBA Study

JAMA Oncology | Original Investigation

Association of Salpingectomy With Delayed Oophorectomy Versus Salpingo-oophorectomy With Quality of Life in *BRCA1/2* Pathogenic Variant Carriers
A Nonrandomized Controlled Trial

*Steenbeek et al* 2021

**EARLY SALPINGECTOMY HAS IMPROVED MENOPAUSAL SYMPTOMS & SEXUAL FUNCTION COMPARED TO RRSO**

# Experiences of women following risk-reducing early-salpingectomy and delayed-oophorectomy and salpingo-oophorectomy on the PROTECTOR trial: a qualitative study

## Decision making

- High satisfaction and low decision regret
- RRES enabled participants to benefit from risk-reduction sooner than otherwise
- Control of DO timing is essential. Patients value annual follow-up to answer concerns, discuss timing and HRT
- The decision for DO is more difficult – patients need more support

## Menopause management

- Patients desire adequate pre-op counselling and post-op management - often the major determinant of satisfaction
- Strongly prefer specialist advice

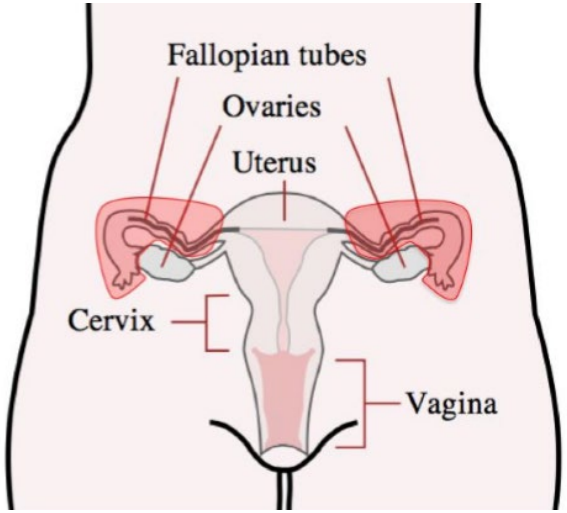
## STIC

- Uncertainty over risks, heightened cancer worry, desire for follow-up/ monitoring.
- Particularly grateful for risk-reducing surgerY

# What We Don't Know about early salpingectomy or removal of tubes

**Level of Reduction in Cancer Risk**

**How best to manage STIC?**




**Impact on long term hormonal function and menopause**

**RRESDO should only be offered in a research study (UK CGG, RCOG, NICE)**

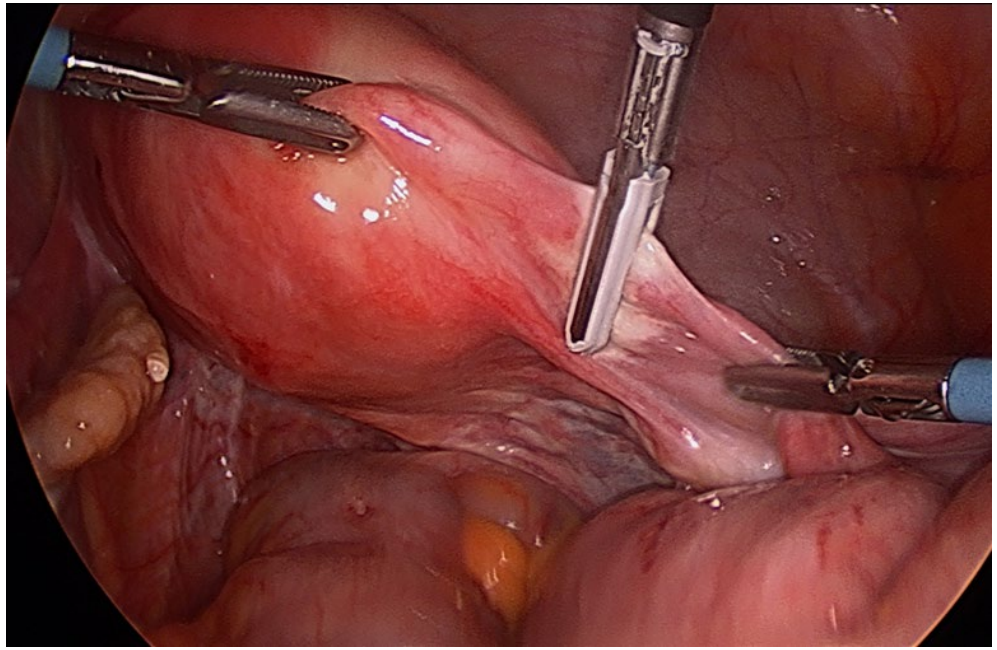
# Lynch Syndrome: Surgical Prevention

**HYSTERECTOMY + BILATERAL SALPINGO OOPHORECTOMY**

**REMOVAL OF UTERUS, TUBES AND OVARIES**

**MLH1, MSH2, MSH6** → **REMOVAL OF UTERUS, TUBES AND OVARIES**

**PMS2** → **REMOVAL OF UTERUS**



**Age of Surgery-**
**35-40 years onwards**

**Usually Minimal Access**

**As complete protection as possible**

Genetics inMedicine
www.nature.c
Check for

ARTICLE

Risk-reducing hysterectomy and bilateral salpingo-oophorectomy in female heterozygotes of pathogenic mismatch repair variants: a Prospective Lynch Syndrome Database report

Mev Dominguez-Valentin, PhD Emma J. Crosbie, PhD, MRCOG et al.#

NICE
National Institute for Health and Care Excellence

NICE National Institute for Health and Care Excellence



# Ovarian cancer: identifying and managing familial and genetic risk

In development [GID-NG10225] Expected publication date: 20 March 2024 Register as a stakeholder

Project information | Project documents

# Key Messages

Removal of tubes &ovaries  is the most effective strategy to prevent ovarian cancer

It can be offered for a number of ovarian cancer genes - >5% lifetime risk

SEEFIM special pathology protocol is essential for RRSO

HRT till 51 for premenopausal RRSO if no other contraindication

Removal of Uterus, tubes and ovaries – effective in women with Lynch Syndrome

Surgical prevention needs to be personalised depending on gene, age, risk, fertility, personal wishes, etc.

Early Salpingectomy should be undertaken in a research study only

# women's
## Precision Prevention

@womensprecisionprevention

@wpp_wiph

# THANK YOU