Pregnancy during Breast Cancer: Any News?

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Disclosures

✓ No conflicts of interest to disclose
Issues of Pregnancy during Breast Cancer

✓ The unexpected during expecting

✓ Unsolved scientific questions
  Is epidemiology the same in different countries?
  Is breast cancer in pregnant = not pregnant?
  How should we stage high-risk patients?

✓ Difficult choices for mothers-to-be and their family
  Should I interrupt the pregnancy?
  Is it safe to receive chemotherapy during pregnancy?
  When is the best time for delivery?
Any news?

1. Epidemiological data in Lombardy Region (ITA)
2. Gene expression, copy number, WGS in BCP
3. Diffusion-weighted whole body MRI
4. Sentinel node biopsy for BCP
5. Obstetrical complication after treatment of BCP
6. Long-term outcome of children after in-utero exposure to chemo

BCP= Breast Cancer during Pregnancy
1. Epidemiological data in Lombardy

We are here in Lugano!

Lombardy: 10,000,000 inhabitants

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**Original Study**

A Population Based Linkage Study in Lombardy, Italy

fabio parazzini, MD, matteo franchi, ScD; alessandra tavani, ScD; eva negri, ScD; and pedro alessandro pezzatti, MD

**Objective:** The aim of this study was to estimate the occurrence of pregnancy-associated cancer overall and by site, to evaluate if the risk increases over time, and to investigate some major determinants.

**Methods:** This is a population-based linkage study using the regional hospital discharge forms (Sistema di Dati di hospitali di Lombardia, Italy) and data from the Italian Cancer Registry. We identified all women who were pregnant between 2001 and 2012, and women who were not pregnant during pregnancy or within 12 months after pregnancy. The effect of potential predictors on the risk was estimated using a logistic regression model, and odds ratios (OR) were estimated.

**Results:** The period 2001–2012, the risk of pregnancy-related cancer was 12.9 per 100,000 pregnancies. The most common cancers were breast cancer (479 cases, 9.9/100,000 pregnancies), thyroid cancer (186 cases, 15.5/100,000), and lymphoma (117 cases, 13.4/100,000). Skin cancer accounted for 177 cases (14.4/100,000), half of which were melanomas.

**Conclusions:** This study confirms previously reported incidence estimates but does not show increases over time.

**Keywords:** Cancer, Incidence, Pregnancy, Record linkage
1. Epidemiological data in Lombardy

- Population-based linkage study with hospital discharge forms of birth or abortion (2001-2012)
- 890,595 deliveries and 309,665 abortions
- 1475 women with pregnancy-related cancer
- Risk of pregnancy related cancer 122.9/100,000 pregnancies

- Risk of breast cancer 39.9/100,000 pregnancies (479 cases)
- Most relevant risk factors:
  AGE (from 60/100,000 if <30 y/o to 265/100,000 if >40 y/o)
  BEING ITALIAN (OR 1.6; 95% CI 1.38-1.90)
2. Gene expression, copy number, WGS

ARTICLE

Breast cancer diagnosed during pregnancy is associated with enrichment of non-silent mutations, mismatch repair deficiency signature and mucin mutations

Bastien Nguyen, David Verem, Katem A. Azim Jr, David Brown, Christine Desmedt, Matteo Lamberti, Sima Majia, Giancarlo Pruneri, Felice Roccati, Martine Piccart, Françoise Rothé and Christos Sotiriou

Breast cancer diagnosed during pregnancy (BCP) is a rare and highly challenging disease. To investigate the impact of pregnancy on the biology of breast cancer, we conducted a comparative analysis of a cohort of BCP patients and non-pregnant control patients by integrating gene expression, copy number alterations and whole genome sequencing data. We showed that BCP exhibit unique molecular characteristics including an enrichment of non-silent mutations, a higher frequency of mutations in mucin-gene family and an enrichment of mismatch repair deficiency mutational signature. This provides important insights into the biology of BCP and suggests that these features may be implicated in promoting tumor progression during pregnancy. In addition, it provides an unprecedented resource for further understanding the biology of breast cancer in young women and how pregnancy could modulate tumor biology.


INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy during pregnancy, its incidence is increasing given the rising trend of delayed childbirth. Given its rarity, few dedicated studies were performed so far; hence, our understanding of these tumors remains poor. The clinical management of these patients follows standard guidelines with only minor adaptations according to gestational age, maternal wishes and fetal considerations. Therefore, the molecular characterization of BCP goes beyond academic curiosity as it is of utmost clinical interest to determine if these patients should be treated similarly to non-pregnant breast cancer patients. In this report, we aimed to identify specific molecular alterations characterizing BCP by combining whole genome sequencing, copy number alteration and gene expression data.

RESULTS

A total of 167 patients with primary breast cancer were retrospectively included in this study. 54 of whom were diagnosed during pregnancy. Detailed patient characteristics were previously published. At a median follow-up of 9 years, median disease-free survival (DFS) time of BCP was 9.6 years vs. 12.5 years in controls (P = 0.041, log rank test, Supplementary Fig. S1A). Observed 5-year overall survival (OS) rate was 83.1% vs. 85.1% in BCP and control, respectively; median OS time was not reached within the time frame of this study (Supplementary Fig. S1B). In a multivariable Cox proportional hazards regression of DFS and OS, adjusted for age at diagnosis, date of diagnosis, pathological stage and molecular subtypes by IHC, we found that BCP was associated with worse DFS (multivariable hazard ratio [mHR] 1.81; 95% CI 1.09-2.91, P = 0.024) and OS (mHR 2.13; 95% CI 1.10-4.10, P = 0.027) (detailed survival data is provided in Supplementary Table S1).

BCP and controls have similar somatic copy number alteration profiles. We first sought to investigate whether tumors from BCP patients show distinct copy number alterations (CNAs) compared to tumors from matched non-pregnant breast cancer patients (controls). Hence, we performed genome-wide copy number alterations profiling on 160 formalin-fixed paraffin-embedded (FFPE) primary tumor samples from 52 BCP patients and 50 controls. Of note, gene expression data were available for all patients as previously described. After quality control, CNAs profiles were obtained for 125 tumor samples (78% from 38 BCP and 87 controls). The main reason for exclusion was low cancer cell fraction (CCF < 10%) as estimated with the Genome Alteration Print algorithm (Supplementary Fig. S2). No differences in clinopathological features were observed between BCP and controls (Supplementary Table S2). We found no significant differences between BCP and controls in terms of cancer cell fraction, ploidy, and fraction of genome altered (Supplementary Table S3). Moreover, no significant differences were observed between the CNA profiles of the two groups neither at the segment nor at the chromosome arm levels, including the gains of 1q and 8q and loss of 17p.

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Published in partnership with the Breast Cancer Research Foundation
2. Gene expression, copy number, WGS

- 54 patients with BCP and 113 matched controls
- Median DFS in BCP was 9.8y vs 12.5y (multivariable HR 1.81, 95%CI= 1.09-3.01)
- 5-year OS was 85.1% in BCP vs 95.5% in controls (mHR 2.53, 95%CI= 1.20-5.36)
- No genome wide (GW) copy number alterations (CNA) in 38 BCP and 87 controls.

![Gene expression, copy number, WGS graph](image)
2. Gene expression, copy number, WGS

- 54 patients with BCP and 113 matched controls
- Median DFS in BCP was 9.8y vs 12.5y (multivariable HR 1.81, 95%CI= 1.09-3.01)
- 5-year OS was 85.1% in BCP vs 95.5% in controls (mHR 2.53, 95%CI= 1.20-5.36)
- No amplifications, gains, deletions or deep deletions in 35 drivers genes
2. Gene expression, copy number, WGS

- Higher number (20 vs 12) non-silent mutations as assessed by whole genome sequencing (WGS) in 35 BCP compared to 25 controls paired samples
- Higher frequency (45.7 vs 23.1%) of non-silent mutations in the mucin family
2. Gene expression, copy number, WGS

- Higher percentage (37.1 vs 11.1%) of a specific mutational signature (Sig20) associated with DNA mismatch repair deficiency, mutational load, MSH2 deletion and poorer prognosis.
3. Diffusion-weighted MRI

Original article
Whole body MRI for systemic staging of breast cancer in pregnant women

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2. Department of Medical and Surgical Specialities, University of Rome “Tor Sapienza”, Italy

ABSTRACT
When breast cancer is diagnosed during pregnancy, treatment should be as close as possible to what is used in non-pregnant patients. This requires accurate local and systemic staging: ultrasonography (US) is used for local staging and allows adequate evaluation of the breast and pelvis, but chest and bone cannot be explored and imaging techniques involving exposure to ionizing radiation would be needed. However, since imaging techniques involving ionizing radiation and the use of radiocisclides should be limited, whole-body magnetic resonance imaging (WB-MRI) without administration of contrast agents represents a very interesting alternative, but limited data is available. In this paper we describe the abdominal and oncological outcome of 14 patients in whom breast cancer was diagnosed during the second or third trimester of pregnancy and that were staged using WB-MRI. Median age of the patient at diagnosis was 35 years (range 30–36), median gestational age at MRI was 30 weeks (range 13–32) and median age at delivery was 38 weeks (range 32–38). At birth, one new born presented respiratory distress syndrome and one jaundice. We conclude that diffusion-weighted MRI is feasible accurate and safe for the mother and the fetus. It may represent the staging technique of choice in pregnant women diagnosed with breast cancer after the first trimester of pregnancy.

1. Introduction
As a consequence of the rising trend of delaying childbearing [12], more women are being diagnosed with cancer during pregnancy. It is estimated that at present 1 in every 1000 pregnancies is complicated by cancer [13], but this percentage is growing since cancer incidence increases with age [1]. Breast, melanoma and haematological malignancies are the most common malignancies diagnosed during pregnancy in Europe, even if geographical differences may occur [3,5–8]. While generally no systemic treatment is indicated in melanoma, which is usually diagnosed at early stage [9], the opposite applies to breast cancer [10] and to leukaemia/lymphoma where chemotherapy is frequently prescribed, after the first trimester. The staging procedure for pregnant women with breast cancer is challenging. Any imaging modality to be used in this condition should be carefully selected in order to limit the exposure of the fetus to ionizing x-rays [10]. Ionising radiations have been associated with abortion, stillbirth, malformations, growth retardation and carcinogenesis [11]. Abdominal plain films, calmodinice tomography (CT) scans and computerised tomography (CT) scans should therefore be avoided [11].

Tumour staging in pregnancy has been traditionally performed using chest X-rays and ultrasound scanning. Chest tomograms with appropriate abdominal shielding expose the fetus to 0.0001 Gy [11]. Ultrasonography is particularly useful for abdominal, breast and pelvic assessment, and noticeably can be safely performed [12,13]. For imaging of the brain, mediastinum or bones, and to evaluate suspicious abdominal or pelvic lesions detected by radiotherapy [18], magnetic resonance imaging (MRI) has been proposed as the
3. **Diffusion-weighted MRI**

- Exploits random motion of free water molecules within tissues
- In highly cellular tissues (cancer) water molecules movement is restricted and this can be detected in T2 sequences
- No need of contrast media/gadolinium
3. Diffusion-weighted MRI

- 14 patients diagnosed during second and third trimester
- All examinations completed and readable
- Average time from pts positioning to discharge 57 min
- 6 pts had ipsilateral lymph node mets confirmed at surgery
- 1 pt had contralateral suspicious lymph node, with negative biopsy
- 1 pt had bone mets, confirmed at later follow up
- No fetal or neonatal damage detected
Diffusion-weighted Magnetic Resonance Imaging for breast cancer staging in pregnant women

Giovanni Codacci-Pisanelli, Fedro A. Peccatori, Maria Del Grande, Giovanna Scarfone, Fabio Zugni, Giuseppe Petralia

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4. Sentinel node biopsy

Dosimetry study in non-pregnant patients (N=26)

- Median age (range): 38 (33 – 42)
- Clinical stage: T1N0 (7); T2N0 (5)
- Gestational age: 17w (5-33w)
- SLN outcome: 10 –ve; 2 +ve
- At 32 months of FU
  - Patient
  - Babies: No axillary recurrence; Normal development

Pilot study in pregnant patients (N=12)

- Median age (range): 38 (33 – 42)
- Clinical stage: T1N0 (7); T2N0 (5)
- Gestational age: 17w (5-33w)
- SLN outcome: 10 –ve; 2 +ve
- At 32 months of FU
  - Patient
  - Babies: No axillary recurrence; Normal development

12 MBq $\Rightarrow$ fetal exposure < 0.1 mGy
4. Sentinel node biopsy

**Axillary staging for breast cancer during pregnancy: feasibility and safety of sentinel lymph node biopsy**

S. N. Han1,2,3, F. Amant4,5,6,7, E. H. Cardonick1,2,8, S. Loh1,2,3, F. A. Pecatori4,5, F. O. Ghysen1,2,3, C. A. Sangalli1,2,3, V. Nekljudova1,2,3, K. Dahl Steffensen1,2,3, M. Mhallem Ghor6,7,1, C. R. Schröder1,2,3, C. A. R. Loe1,2,3, A. Verest1,2,3, P. Neven1,2,3, A. Smeets1,2,3, G. Pruner1,2,3, M. Cremonesi1,2,3, G. Gentilini2,4,5 - On behalf of the International Network on Cancer, Infertility and Pregnancy

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**Abstract**

**Background** Safety of sentinel lymph node (SLN) biopsy for breast cancer during pregnancy is insufficiently explored. We investigated efficacy and local recurrence rate in a large series of pregnant patients.

**Patients and methods** Women diagnosed with breast cancer who underwent SLN biopsy during pregnancy were identified from the International Network on Cancer, Infertility and Pregnancy, the German Breast Group, and the Cancer and Pregnancy Registry. Chart review was performed to record technique and outcome of SLN biopsy, locoregional and distant recurrence, and survival.

**Results** We identified 145 women with clinically N0 disease who underwent SLN during pregnancy. The SLN detection techniques were as follows: 99mTc-labeled albumin nanocolloid only (n = 96; 66.2%), blue dye only (n = 14; 9.7%), combined technique (n = 15; 10.3%), or unknown (n = 20; 13.8%). Mapping was unsuccessful in one patient (0.7%) and she underwent an axillary lymph node dissection (ALND). Mean number of SLNs was 3.2 (interquartile range 1-3; missing n = 15). Positive SLNs were found in 43 (29.7%) patients and 34 subsequently underwent ALND. After a median follow-up of 48 months (range 1-177), 123 (84.8%) patients were alive and free of disease. Eleven patients experienced a locoregional relapse, including one isolated ipsilateral axillary recurrence (0.7%). Eleven (7.6%) patients developed distant metastases, of whom 9 (6.2%) died of breast cancer. No neonatal adverse events related to SLN procedure during pregnancy were reported.

**Conclusions** SLN biopsy during pregnancy has a comparatively low axillary recurrence rate as in nonpregnant women. Therefore, this method can be considered during pregnancy instead of standard ALND for early-stage, clinically node-negative breast cancer.
## 4. Sentinel node biopsy

<table>
<thead>
<tr>
<th>Number</th>
<th>145</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>35 (28 – 45)</td>
</tr>
<tr>
<td><strong>Technique</strong></td>
<td></td>
</tr>
<tr>
<td>-99m TC albumin nanocolloid only</td>
<td>96 (66.2%)</td>
</tr>
<tr>
<td>-Blue dye only</td>
<td>14 (9.7%)</td>
</tr>
<tr>
<td>-Combined</td>
<td>15 (10.3%)</td>
</tr>
<tr>
<td>-Unknown</td>
<td>20 (13.8%)</td>
</tr>
<tr>
<td><strong>Successful mapping</strong></td>
<td>144 (99%)</td>
</tr>
<tr>
<td><strong>Mean N of SLN</strong></td>
<td>3.2 (0 – 7)</td>
</tr>
<tr>
<td><strong>Positive SLN</strong></td>
<td>43 (29.7%) – including 7 micromets, 2 isolated cells</td>
</tr>
<tr>
<td><strong>Loco regional events at median FU 35m</strong></td>
<td>11 (1 in axilla)</td>
</tr>
</tbody>
</table>
5. Obstetrical complications after chemotherapy

An increase in the risk of pregnancy complications “on average” in patients treated with chemo during pregnancy even if started after the 1\textsuperscript{st} trimester

<table>
<thead>
<tr>
<th></th>
<th>Obstetric complications</th>
<th>Fetal weight &lt;10\textsuperscript{th} percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemo</td>
<td>No chemo</td>
</tr>
<tr>
<td>Cardonick, 2010</td>
<td>22/104 (22%)</td>
<td>8/104 (7.5%)</td>
</tr>
<tr>
<td>Loibl, 2012</td>
<td>31/179 (17%)</td>
<td>15/149 (9%)</td>
</tr>
</tbody>
</table>
5. Obstetrical complications after chemotherapy

Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients

5. Obstetrical complications after chemotherapy

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Total</th>
<th>Miscarriage</th>
<th>Termination of pregnancy</th>
<th>Stillbirth*</th>
<th>Livebirth &lt;37 weeks</th>
<th>Livebirth ≥37 weeks</th>
<th>Livebirth gestational age unknown</th>
<th>Maternal death during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>428</td>
<td>6 (1%)</td>
<td>26 (6%)</td>
<td>1 (&lt;1%)</td>
<td>184 (43%)</td>
<td>182 (43%)</td>
<td>28 (7%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>140</td>
<td>2 (1%)</td>
<td>21 (15%)</td>
<td>2 (1%)</td>
<td>72 (51%)</td>
<td>37 (26%)</td>
<td>6 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>107</td>
<td>0</td>
<td>8 (7%)</td>
<td>3 (3%)</td>
<td>48 (45%)</td>
<td>45 (42%)</td>
<td>3 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>83</td>
<td>3 (4%)</td>
<td>3 (4%)</td>
<td>0</td>
<td>21 (25%)</td>
<td>53 (64%)</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>64</td>
<td>5 (8%)</td>
<td>6 (9%)</td>
<td>2 (3%)</td>
<td>26 (41%)</td>
<td>25 (39%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal cancer</td>
<td>47</td>
<td>2 (4%)</td>
<td>4 (9%)</td>
<td>2 (4%)</td>
<td>29 (62%)</td>
<td>8 (17%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>43</td>
<td>0</td>
<td>2 (5%)</td>
<td>0</td>
<td>3 (7%)</td>
<td>34 (79%)</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>37</td>
<td>0</td>
<td>4 (11%)</td>
<td>0</td>
<td>1 (3%)</td>
<td>37 (85%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>19</td>
<td>0</td>
<td>2 (11%)</td>
<td>0</td>
<td>9 (47%)</td>
<td>6 (32%)</td>
<td>0</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Other malignant diseases</td>
<td>121</td>
<td>2 (2%)</td>
<td>19 (16%)</td>
<td>4 (3%)</td>
<td>37 (31%)</td>
<td>36 (30%)</td>
<td>23 (19%)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1089</td>
<td>20 (2%)</td>
<td>95 (9%)</td>
<td>14 (1%)</td>
<td>430 (39%)</td>
<td>458 (42%)</td>
<td>67 (6%)</td>
<td>5 (&lt;1%)</td>
</tr>
</tbody>
</table>

Table shows data for all singleton pregnancies with known obstetric outcome (1089 (98%) of 1170). *Stillbirths consisted of seven intrauterine deaths and seven perinatal deaths.

Table 3: Obstetric outcomes, stratified by cancer type

Table A11. Neonatal outcomes stratified by different variables (singleton live births, n=955).
6. Long term outcomes after prenatal exposure to chemo

Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study

Frédéric Amant, Kristel Van Calsteren, Michael J Halaska, Mina Mhallem Gziri, Wei Hui, Lieven Lagae, Michèl A Willemsen, Livia Kapusta, Ben Van Calster, Heidi Wouters, Silen N Han, Viktor Tomek, Luc Mertens, Petronella B Ottevanger
6. Long term outcomes after prenatal exposure to chemo

✓ 70 children 18 months or older
✓ Child’s behaviour, general health, hearing and growth was reported as in a general population
✓ Most of the children have an age-adequate neurological development (intelligence, attention, memory) and cardiac function
✓ Prematurity was frequently encountered, and was associated with impairment in cognitive development

Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study

Frédéric Amant, Kristel Van Calsteren, Michiel J Haleska, Milene Mihailov Geiri, Wei Hui, Lieven Legae, Michiel A Willumsen, Livhe Kapusta, Ben Van Calster, Hélène Wouters, Liesbeth Heyse, Sifang Ni Han, Willem Tomak, Luc Mariën, Pietronella B Ottevanger
6. Long term outcomes after prenatal exposure to chemo

IQ score increases with 2.5 points (95% CI: 1.2-3.9) for each week increase in pregnancy duration (p=0.0003).
Case control study on pediatric outcome after gestational cancer (n=129)

Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy

Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy


A Cognitive Outcome According to Gestational Age

Bayley II Score vs. Gestational Age (wk)

- Prenatal-exposure group
- Control group

Cancer in Pregnancy (N=129)
- Control

All Chemotherapy (N=96)
- Control

Anthracyclines (N=78)
- Control

Taxanes (N=22)
- Control

Platinum Derivatives (N=18)
- Control

Radiotherapy (N=11)
- Control

Bayley II or III Score

P=0.08

P=0.43

P=0.43

P=0.57

P=0.95

P=0.69
Take Home messages

1. **Epidemiological data in Lombardy Region (ITA)**
   - Incidence of BCP 1/3000 pregnancies
   - Age and Italian heritage main risk factors

2. **Gene expression, copy number, WGS in BCP**
   - Similar somatic copy number alterations
   - Higher number of non silent mutations (mucin gene family)
   - Enrichment in mutational signatures related to MMR deficiency

3. **Diffusion-weighted whole body MRI**
   Feasible and safe after the first trimester
Take Home messages

4. Sentinel node biopsy for BCP
   - Feasible and safe. No false negative

5. Obstetrical complication after treatment of BCP
   - Premature delivery, small for age and NICU stay in around 20% of children

6. Long-term outcome of children after prenatal exposure to chemo
   - No behavioural, general health or growth alterations
   - Normal cardiac and neurological development
   - Small impairment due to prematurity, but the kids are all right
Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. A. Peccatori1, H. A. Azim, Jr, P. Orecchia1, H. J. Hoekstra4, N. Pavlidis5, V. Kecić6 & G. Pentheroudakis2, on behalf of the ESMO Guidelines Working Group*

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These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)

INCIP
International Network on Cancer, Infertility and Pregnancy

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