



UZ
LEUVEN



Kanker tijdens de zwangerschap

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Wat als kanker wordt vastgesteld tijdens de zwangerschap?



Midwife

Clinical geneticist

Primary care team

Physiotherapist/lymphoedema specialist

(Breast) surgeon

(Breast) nurse

Pediatrician

Medical ethicist

Pathologist

Radiologist

Psychologist

Medical oncologist

Radiotherapist

Perinatologist/obstetrician

Reconstructive/plastic surgeon

Social worker

Obstetric nurse



Take home message

- ❖ Behandeling tijdens de zwangerschap is mogelijk
 - ❖ Multidisciplinair
 - ❖ Individueel behandelingsplan
 - ❖ Opvolging in ziekenhuis met hoog-risico verloskundige en neonatale dienst
- ❖ INCIP studie



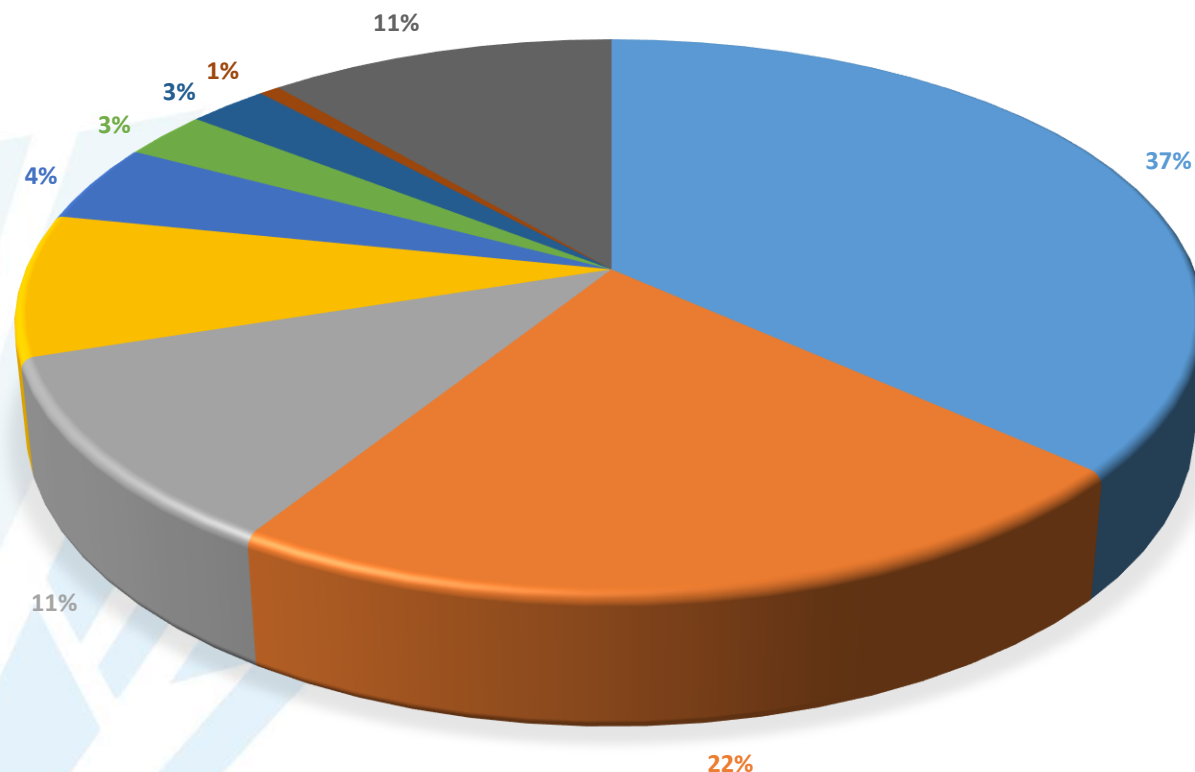
Kanker tijdens de zwangerschap

- Inleiding
- Diagnose
- Behandeling
 - Heelkunde
 - Radiotherapie
 - Chemotherapie
- Obstetrische en neonatale uitkomst
- Verloskundige opvolging en planning
- Prognose van moeder
- Emotionele impact
- Take home message

KANKER TIJDENS DE ZWANGERSCHAP

N= 1533

*Diagnose van kanker tijdens
1/1000 zwangerschappen*



■ Breast cancer

■ Haematological
malignancies

■ Cervical cancer

■ Ovarian cancer

■ Melanoma

■ Thyroid cancer

■ Brain tumor

■ Gastric cancer

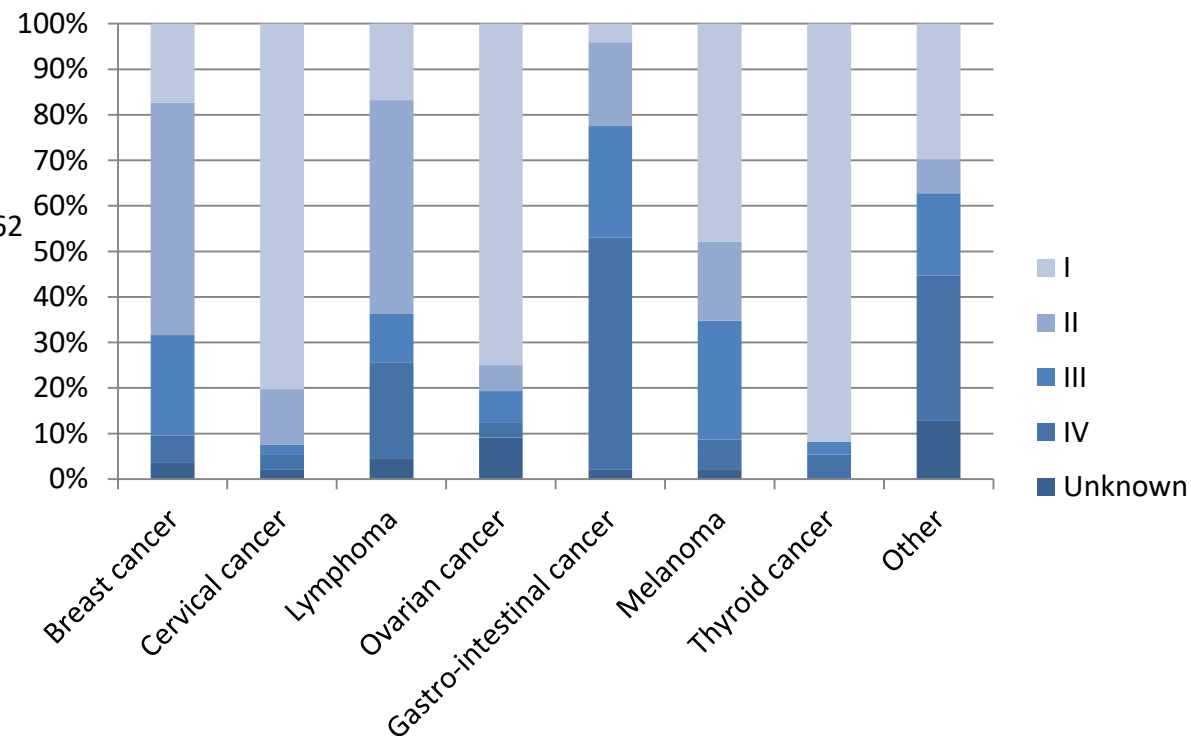
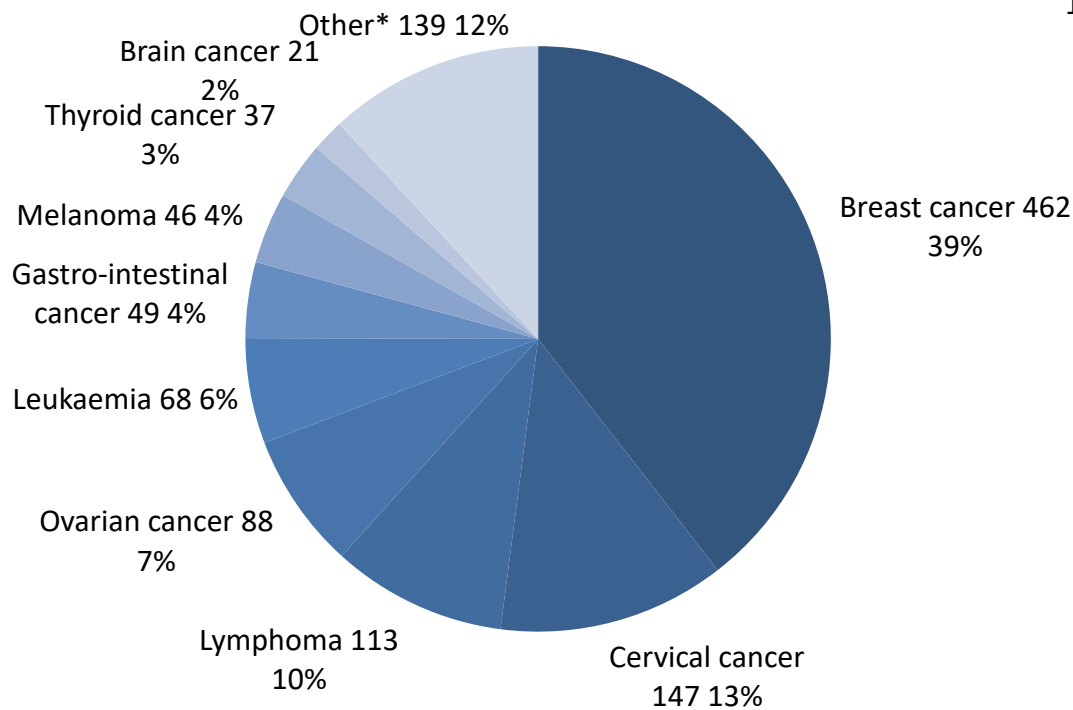
■ Other

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

J. de Haan, M. Verheecke, K. Van Calsteren, B. Van Calster, R. Shmakov, M. Mhallem Gziri, M. Halaska, R. Fruscio, C. Lok, I. Boere, P. Zola, P. Ottevanger, C. de Groot, F. Peccatori, K. Dahl Steffensen, E. Cardonick, E. Polushkina, L. Rob, L. Ceppi, G. Sukhikh, S. Han, **F. Amant**.

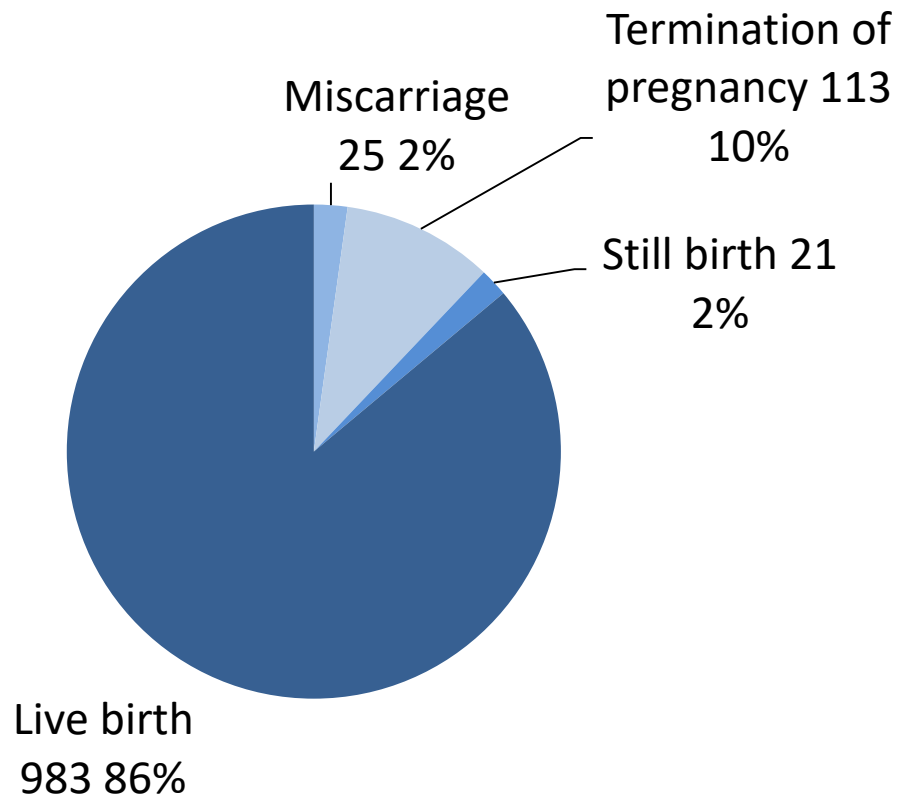
On behalf of the International Network on Cancer, Infertility and Pregnancy (INCIP). *Lancet Oncology*, 2018

- 1170 patienten:
 - 37 centra in 16 landen

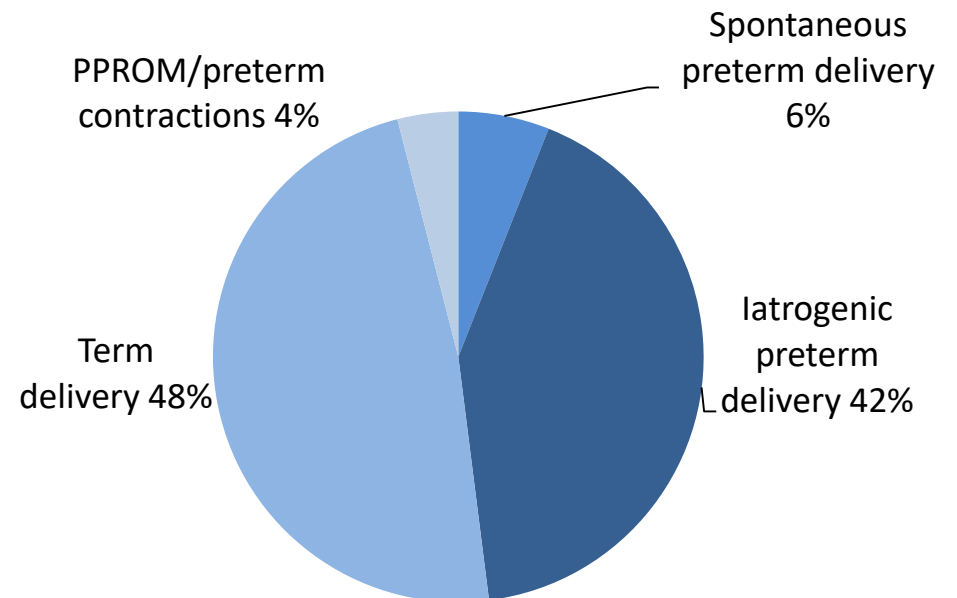


Obstetrische uitkomst

- 1142 zwangerschappen met gekende uitkomst



- 995 zwangerschappen met geboorte van kind



Neonatale uitkomst

- Laag geboortegewicht (<P10)

- 21% (167/796)

- Opname neonatologie

- 41% (298/720)
- 84% prematurity related

- Congenitale afwijkingen

- 4% (32/741)
 - 2% (17) minor malformations
 - 2% (15) major malformations

Leeftijd bij diagnose (OR 1.36 per five years, 95% CI 1.11-1.68, p=0.003)

Systemische ziekte (OR 1.86, 95% CI 1.04-3.33, p=0.04).

Chemotherapie (p<0.0001 for a joint evaluation of all 6 agents)

Platinum-bevattende

chemotherapy (OR 3.12, 95% CI 1.45-6.70)

Type maligniteit (p<0.0001)

Highest: Gastro-intestinal cancer (OR 7.13, 95% CI 2.86-17.7)

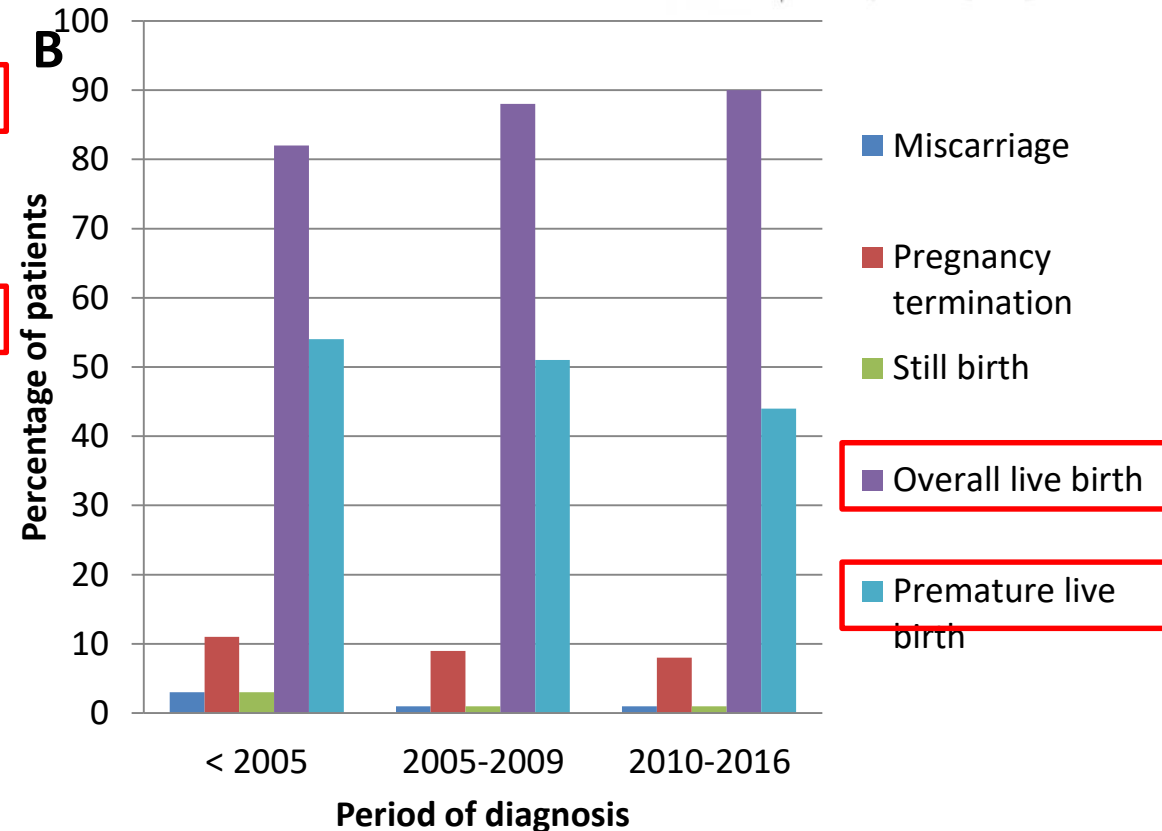
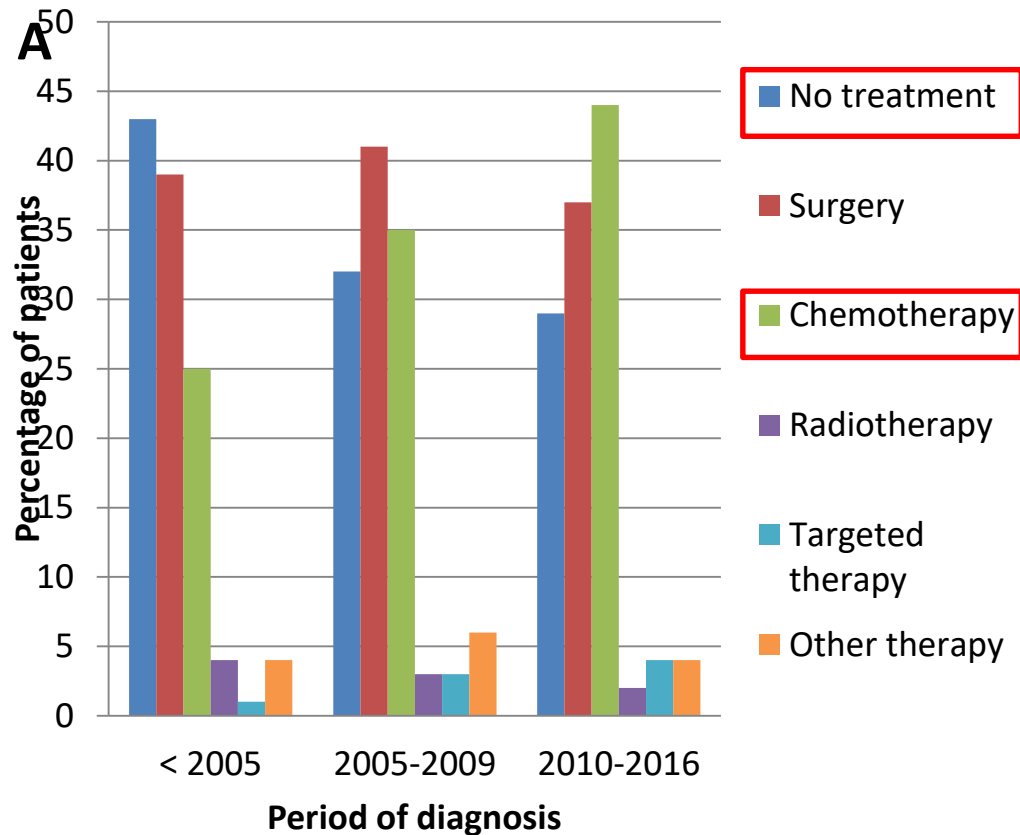
Lowest: Thyroid cancer (OR 0.14, 95% CI 0.02-0.90).

Chemotherapie (p=0.009)

Taxanes (OR 2.37, 95% CI 1.31-4.28)

Abdominale en cervicale heekunde (OR 0.30, 95% CI 0.17-0.55)

Veranderingen in management (A) en obstetrische uitkomst (B) over 20 jaren.



Management changes are shown for all 1170 patients, obstetrical outcome is shown for all singleton pregnancies.

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- Symptomen van kanker

- Abdominale pijn
- Bloedverlies
- Palpeerbaar gezwel borst
- Vermoeidheid
-



-> Deze symptomen kunnen ook zwangerschapsgerelateerd zijn -> Laattijdige diagnose!

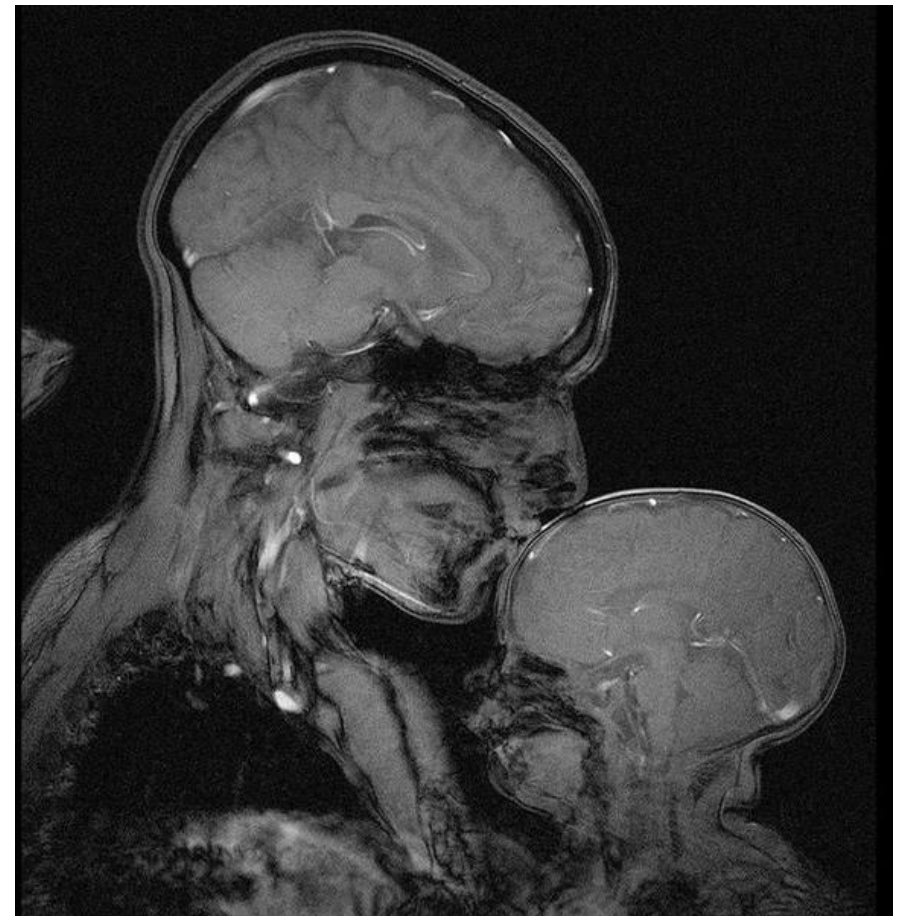
-> Nauwkeurig klinisch onderzoek en laagdrempelig aanvullend onderzoek!

Voorkeursorsonderzoeken tijdens zwangerschap



Echografie

MRI



Beeldvorming met stralingsbelasting(RX, CT)

*Approximate fetal absorbed doses during imaging studies
(Toppenberg, 1999)*

*The threshold dose for fetal damage 10 cGy
(0,1 mGy)*

Procedure	Fetal dose (cGy)	Procedure	Fetal dose (cGy)
Chest x-ray (PA & lateral)	0.00006	Lumbosacral spine	0.2 – 0.6
Abdominal x-ray	0.15 – 0.26	Mammography	0.01 – 0.04
Pelvic x-ray	0.2 – 0.35	CT thorax	0.01 – 1.3
Intravenous pyelography	0.4 – 0.9	CT abdomen	0.8 – 3
Barium enema	0.3 – 4	CT pelvis	2.5 – 8.9
Dorsal spine	< 0.001	Tc bone scan	0.15 – 0.20
Lumbar spine	0.4 – 0.6		

- Contraststoffen
 - Gadolinium
 - Teratogeen
 - Skelet malformaties
 - Iodide
 - Foetale schildklierfunctie



- Tumormerkers
 - Niet diagnostisch!
 - Verhoogde waarden tijdens zwangerschap (CA 125, CA 15,3,...)
 - LDH, AMH en inhibine B wel betrouwbaar

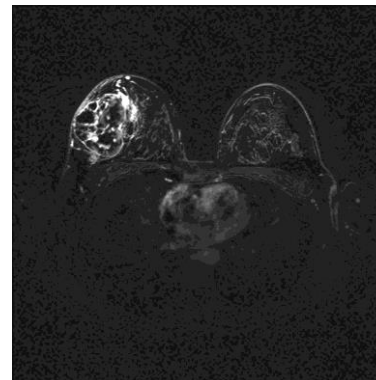
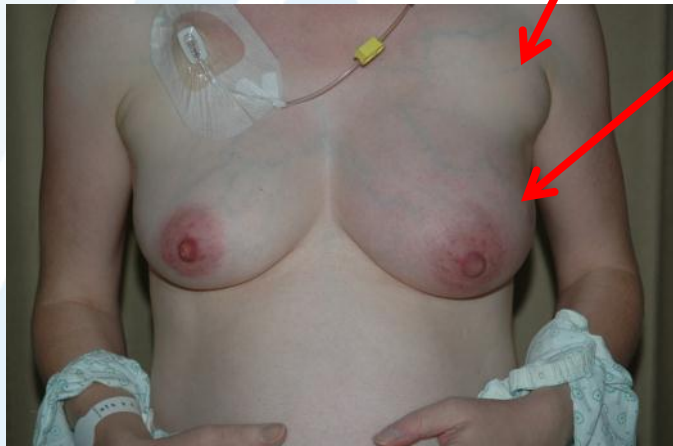
Diagnose van borstkanker tijdens de zwangerschap

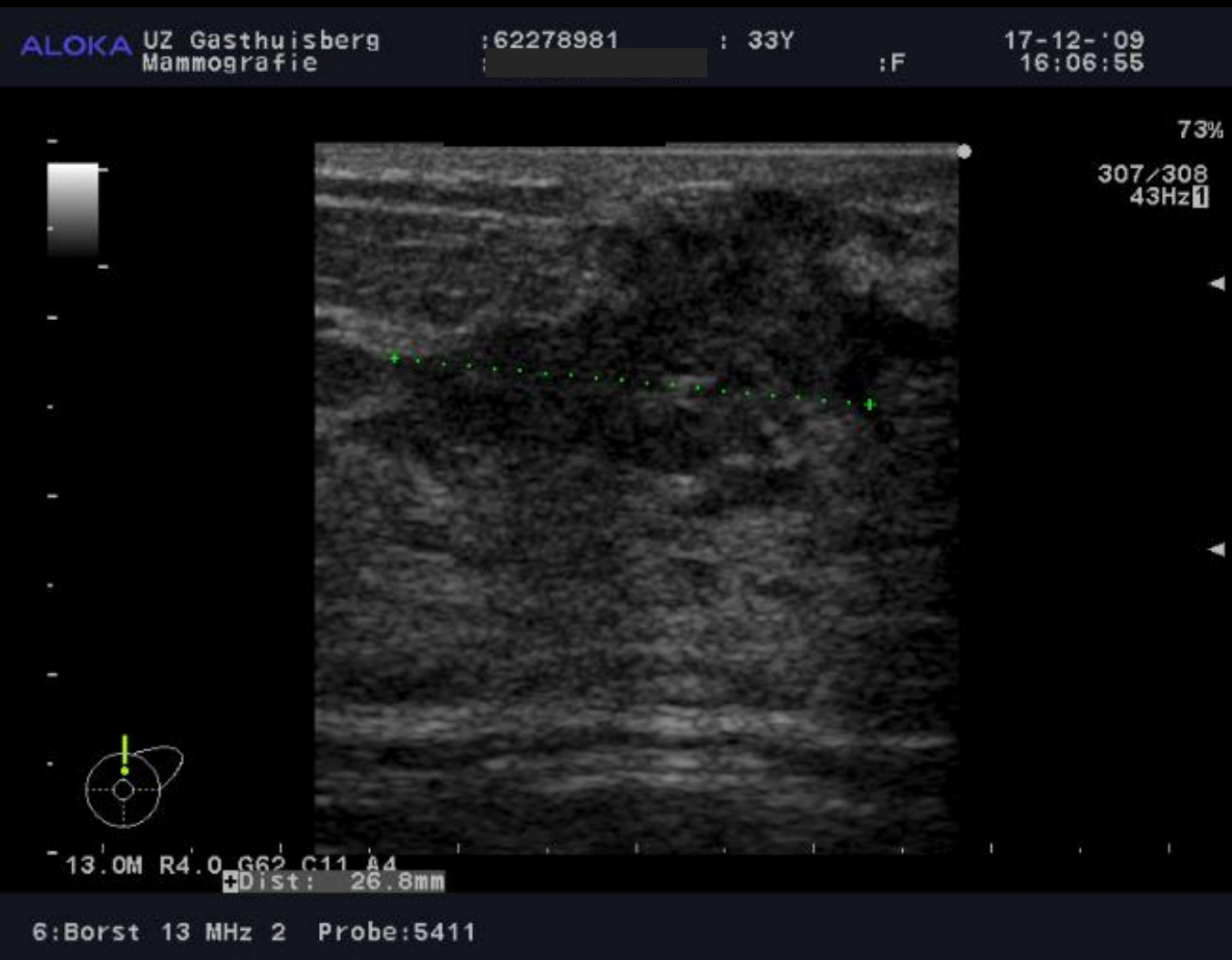
■ Voorgeschiedenis

- **BRCA mutation** (2-29% bij jonge vrouwen met borstkanker) (Samphao et al, 2009)
- Adviseer genetische counselling (jonger dan 40 jaar)

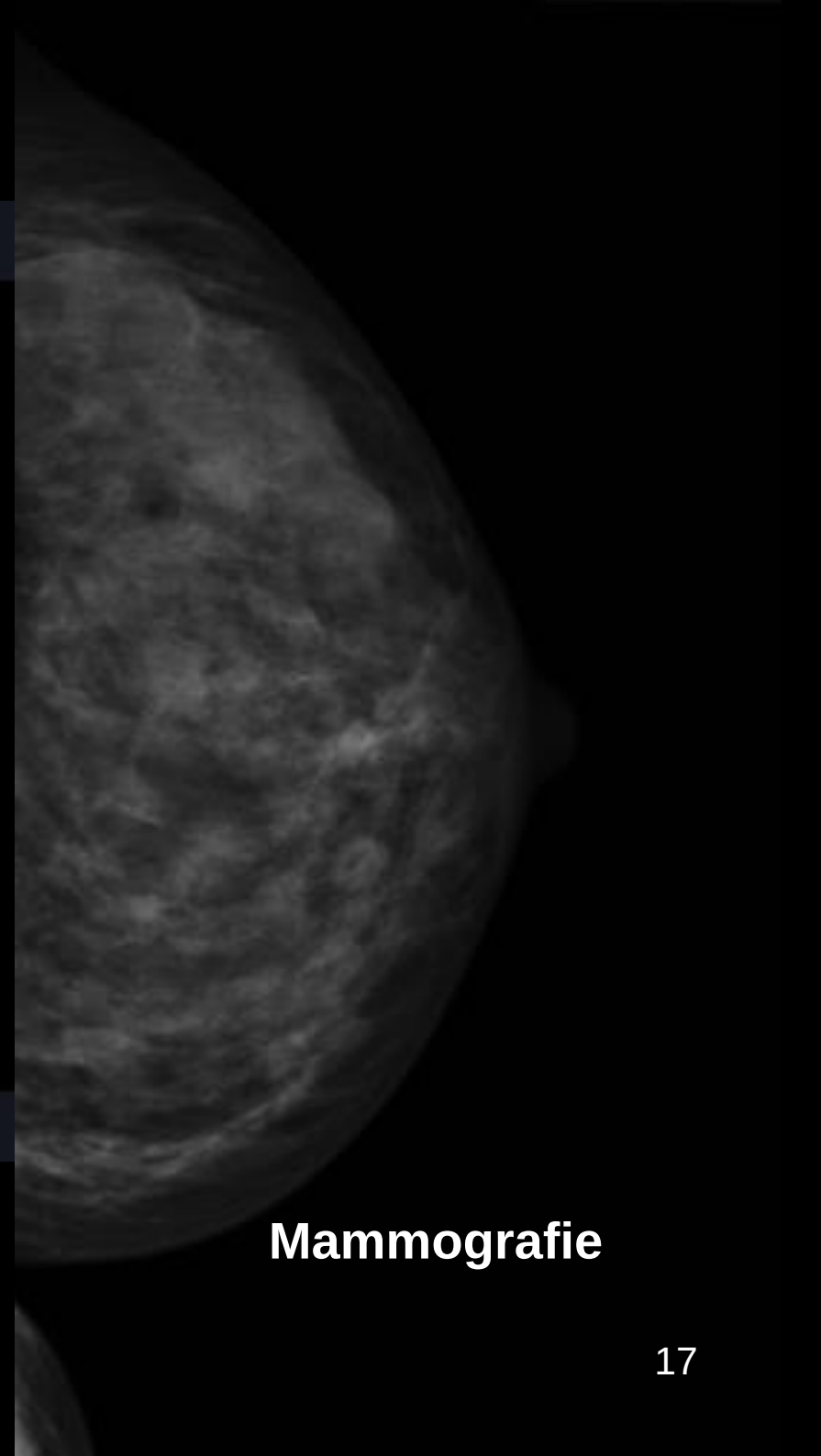
■ Klinisch onderzoek

- Meestal **symptomatisch**, meestal vastgesteld als een **pijnloze, palpabele massa**
- Moeilijk in te schatten en diagnose vaak laattijdig
- **Laagdrempelig onderzoek bij palpabele borstmassa bij zwangere vrouw!**





Echografie: letsel van 23 x 29 x12 mm



Mammografie

Staging van borstkanker tijdens zwangerschap

Diffusion weighted MRI whole body: distant (bone, liver,...) metastasis

(Han et al 2017)

Mammografie (1 opname) en **echografie** van de borst en klierstreken

Chest X-ray:
pulmonary metastasis

Liver ultrasound:
liver metastasis

Sentinel lymph node biopsy (SLNB):

(Gentilini et al., 2004; Han et al 2017)

- ! *one day protocol* (↓ dose), *no blue dye* (anaphylactic reaction) (Khera et al., 2008)

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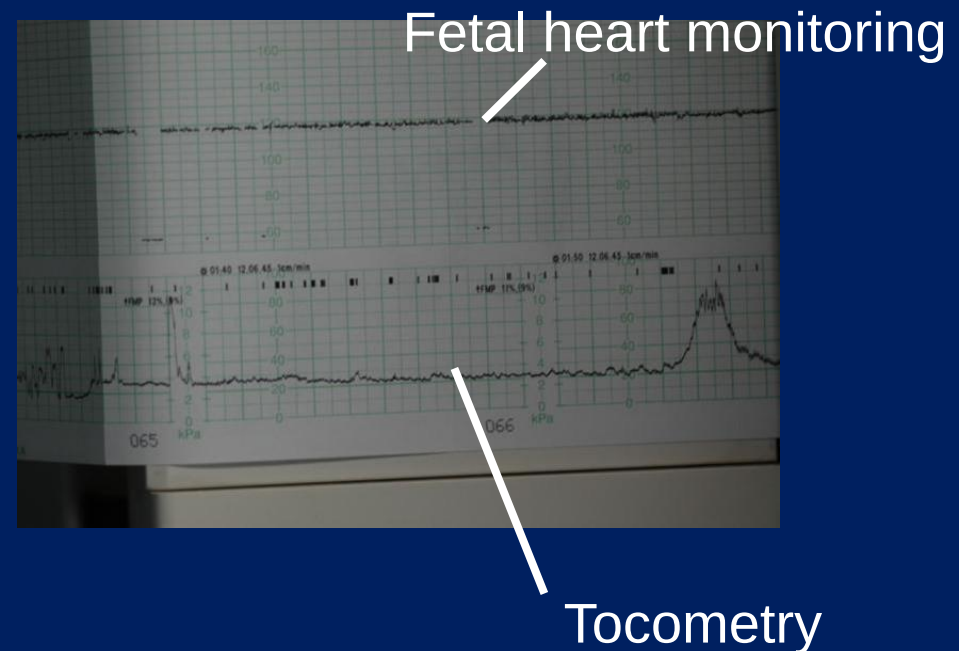
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Adequate oxygenation and left lateral tilt position



No fetal monitoring when fetus is non viable

- *Tromboprofylax*
- *Tocolytica*
- *Foetale longrijping*



Laparoscopie tijdens zwangerschap

- Tot 26-28 zwangerschapsduur
- Umbilical trocar 3-4 cm boven uterine fundus
- Intra-abdominal druk maximaal 15 mmHg
- Maximale totale operatieduur 90 minutes



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Radiotherapie (van het bovenlichaam) tijdens zwangerschap

- Verhoogd risico: > 100 mGy
- Gemiddeld risico: 50 – 100 mGy
- Laag risico: < 50 mGy

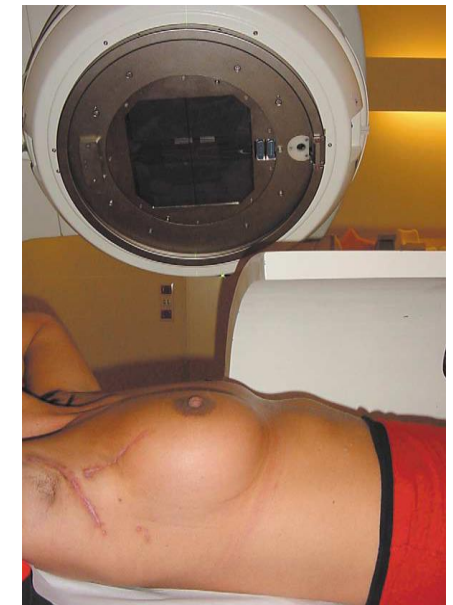
Gestational age (weeks)	Risk
Preimplantation (1)	lethality*
Organogenesis (2-7)	lethality, gross malformations*, growth retardation*, sterility, cataracts, other neuropathology, malignant disease
Early fetal (8-15)	lethality, gross malformations, growth retardation, mental retardation*, sterility, cataracts, malignant disease
Midfetal (16-25)	gross malformations, growth retardation, mental retardation, sterility, cataracts, malignant disease
Late fetal (>25)	growth retardation, , sterility, cataracts, malignant disease
* : high incidence	

Radiotherapie tijdens de zwangerschap

Veilig tijdens eerste en tweede trimester van de zwangerschap, gecontra-indiceerd in derde trimester (Mazonakis *et al.*, 2003)

met ↑ zwangerschapsduur: ↑ foetus dichterbij stralingsveld,
↑ Foetale blootstelling (grenswaarde van dosis 10 – 20 cGy)

FIELD SIZE (cm ²)	CONCEPTUS DOSE (cGy)		
	First trimester	Second trimester	Third trimester
4.5 x 11.0	2.1–2.9	2.2–7.5	2.2–16.8
6.0 x 12.5	2.8–3.9	2.9–10.4	3.3–23.8
8.0 x 14.0	3.5–5.1	3.7–13.9	4.0–34.7
10.0 x 16.0	4.4–6.2	4.7–18.2	5.0–45.2
11.5 x 18.0	5.2–7.6	5.9–24.6	6.5–58.6



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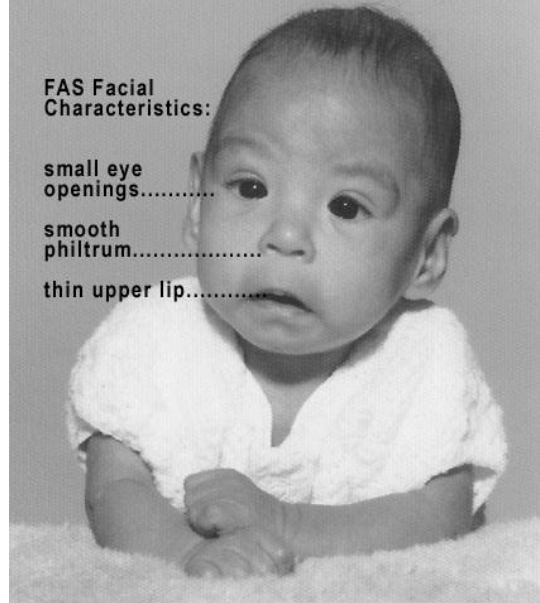
Baby with Fetal Alcohol Syndrome

FAS Facial
Characteristics:

small eye
openings.....

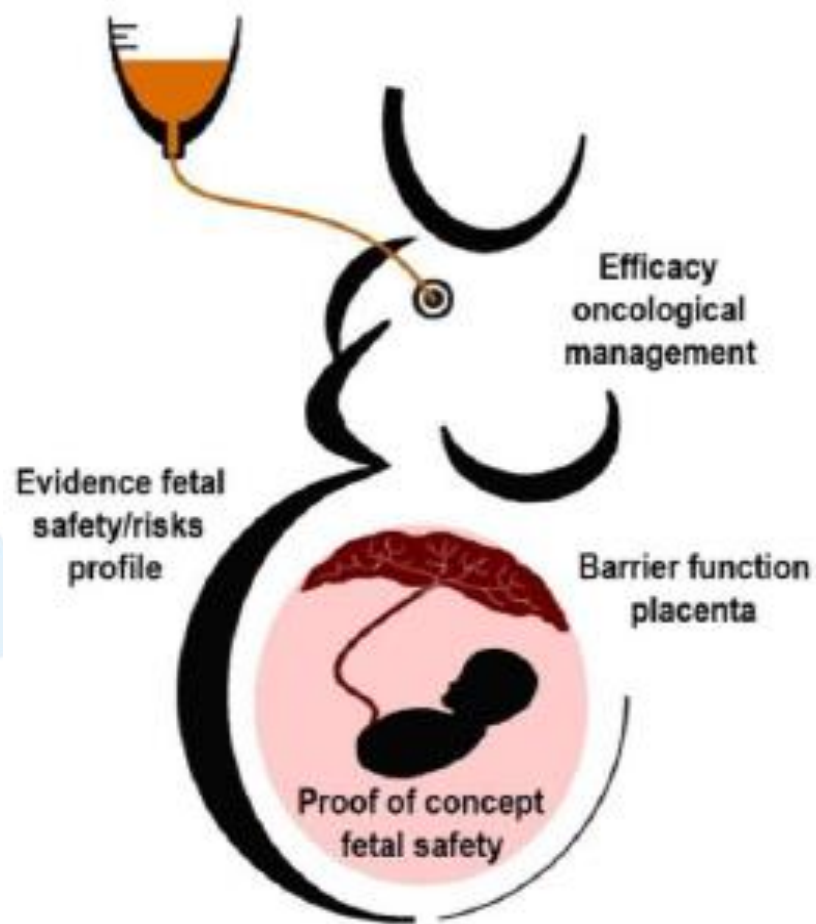
smooth
philtrum.....

thin upper lip.....



Is chemotherapie veilig?

- Transplacentair transport
- Pharmacokinetiek: fysiologische veranderingen in de zwangerschap



Results of transplacental transfer of chemotherapeutic agents in a pregnant baboon model, based on simultaneously collected maternal and foetal plasma samples.

Van Calsteren et al., IJGC 2010, Van Calsteren et al., Gynecol Oncol 2010

Drug	Baboon (%)	(Samples)
Doxorubicin	7.5 ± 3.2	(n = 6) (in 9 other fetuses <LLQ)
Epirubicin	4.0 ± 1.6	(n=8) (in 3 other fetuses <LLQ)
Carboplatin	57.5 ± 14.2	(n = 7)
Paclitaxel	1.4 ± 0.8	(n = 7) (in 4 other fetuses <LLQ)
Docetaxel	ND	(n=9 < LLQ in foetus)
4-OH-cylophosphamide	25.1 ± 6.3	(n=3) (<LLQ in 1 foetus and mother)
Vinblastine	18.5 ± 15.5	(n=9) (in 1 other fetus <LLQ).
LLQ, lower limit of quantification; ND, not detectable		



De placenta beschermt de foetus

Andere systemische behandeling tijdens zwangerschap

- **Supportieve (co-)medicatie:** anti-emetica (metoclopramide, ondansetrone), Zyrtec, Medrol ipv dexamethasone
- **Herceptine:** niet aangeraden door een verhoogd risico op oligo/anhydramnios
- **Tamoxifen:** niet aangeraden door verhoogd risico op afwijkingen

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- **Obstetrische en Neonatale uitkomst**
- Verloskundige opvolging en planning
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Cancer During Pregnancy: An Analysis of 215 Patients Emphasizing the Obstetrical and the Neonatal Outcomes

Kristel Van Calsteren, Liesbeth Heyms, Frank De Smet, Liesbet Van Eycken, Mina Mhallem Gziri, Willemijn Van Gemert, Michael Halaska, Ignace Vergote, Nelleke Ottevanger, and Frédéric Amant

From the Department of Obstetrics & Gynecology, University Hospital Gasthuisberg, Katholieke Universiteit, Leuven; National Alliance of Christian Sickness Funds; Belgian Cancer Registry, Brussels; Obstetrics and Gynecol-

A B S T R A C T

Purpose

The aim of this study was to assess the management and the obstetrical and neonatal outcomes of pregnancies complicated by cancer.

Obstetrical complications in women with early breast cancer with and without chemotherapy (n=343) (Loibl et al., Lancet Oncol 2012)

Chemotherapie tijdens zwangerschap:

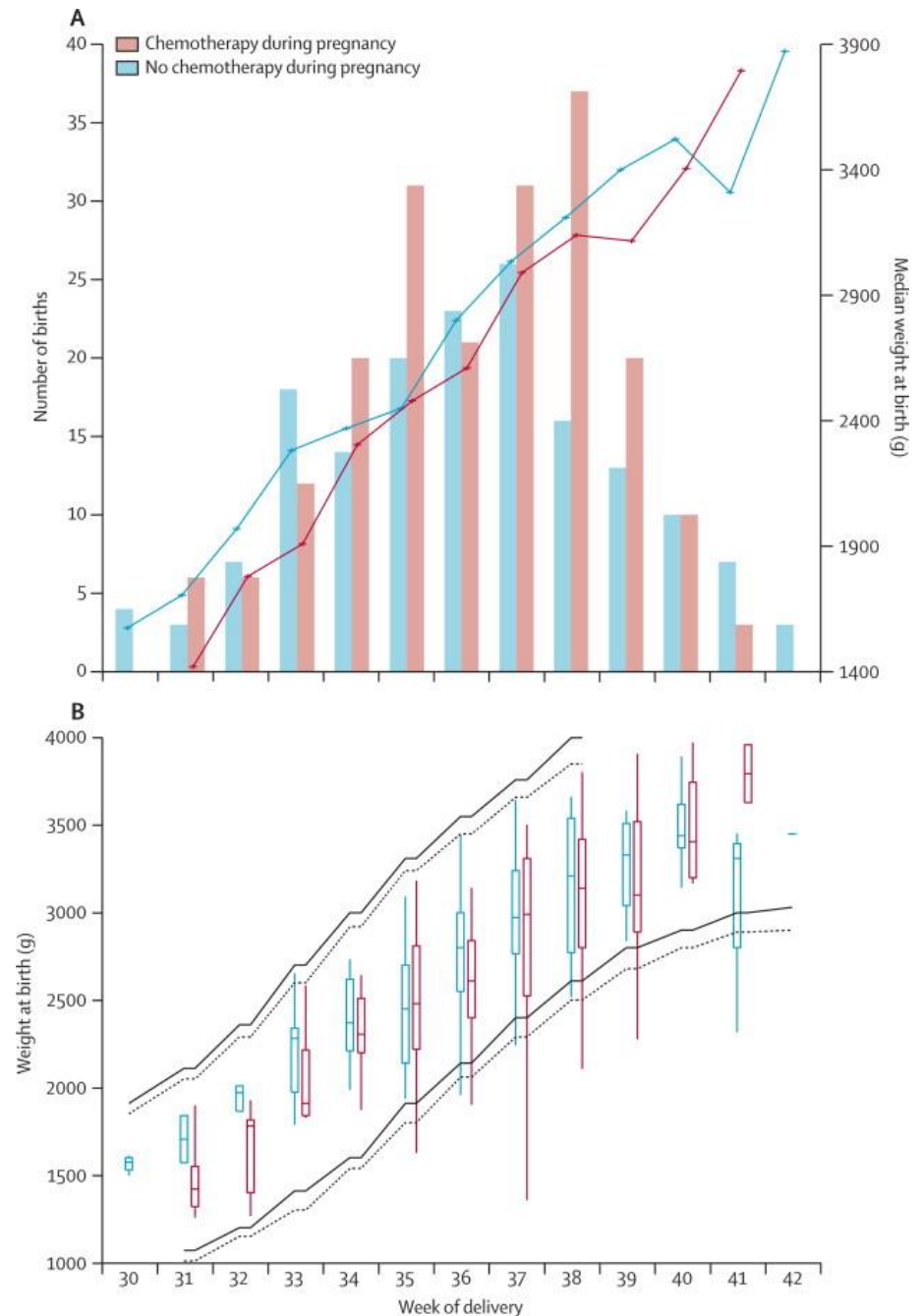
-> meer risico op:

IUGR

Premature arbeid

Prematuur gebroken vliezen

Geboortegewicht is beïnvloed door blootstelling aan chemotherapie, onafhankelijk van het aantal cycli



Lange-termijn opvolging van kinderen

General Health	Cognitive outcome	Heart morphology and functions
General pediatric and clinical neurological examination	Bayley Scales of Infant Development – second / third edition	Echocardiography
General health questionnaire		Electrocardiography



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, Michèle A Willemsen, Livia Kapusta, Ben Van Calster, Heidi Wouters, Liesbeth Heyns, Sileny N Han, Viktor Tomek, Luc Mertens, Petronella B Ottevanger

Summary

Background Chemotherapy for the treatment of maternal cancers during pregnancy has become more acceptable in the past decade; however, the effect of prenatal exposure to chemotherapy on cardiac and neurodevelopmental outcomes of the offspring is still uncertain. We aimed to record the general health, cardiac function, and neurodevelopmental outcomes of children who were prenatally exposed to chemotherapy.

Methods We did an interim analysis of a multicentre observational cohort study assessing children who were prenatally exposed to maternal cancer staging and treatment, including chemotherapy. We assessed children at birth, at age 18 months, and at age 5–6, 8–9, 11–12, 14–15, or 18 years. We did clinical neurological examinations, tests of the general level of cognitive functioning (Bayley or intelligence quotient [IQ] test), electrocardiography and echocardiography, and administered a questionnaire on general health and development. From age 5 years, we also did audiometry, the Auditory Verbal Learning Test, and subtasks of the Children's Memory Scale, and the Test of Everyday Attention for Children, and we also completed the Child Behavior Checklist. This study is registered with ClinicalTrials.gov, number NCT00330447.

Findings 236 cycles of chemotherapy were administered in 68 pregnancies. We assessed 70 children, born at a median gestational age of 35·7 weeks (range 28·3–41·0; IQR 3·3; 47 women at <37 weeks), with a median follow-up period of 33·2 months (range 16·8–311·6; IQR 54·0). Although neurocognitive outcomes were within normal ranges

Published Online

February 10, 2012

DOI:10.1016/S1470-2045(11)70363-1

See Online/Comment

DOI:10.1016/S1470-2045(11)70408-9

See *Series Lancet* 2012;

379: 558, 570, and 580

Leuven Cancer Institute,

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of Paediatrics (L Lagae PhD,

H Wouters MSc), University

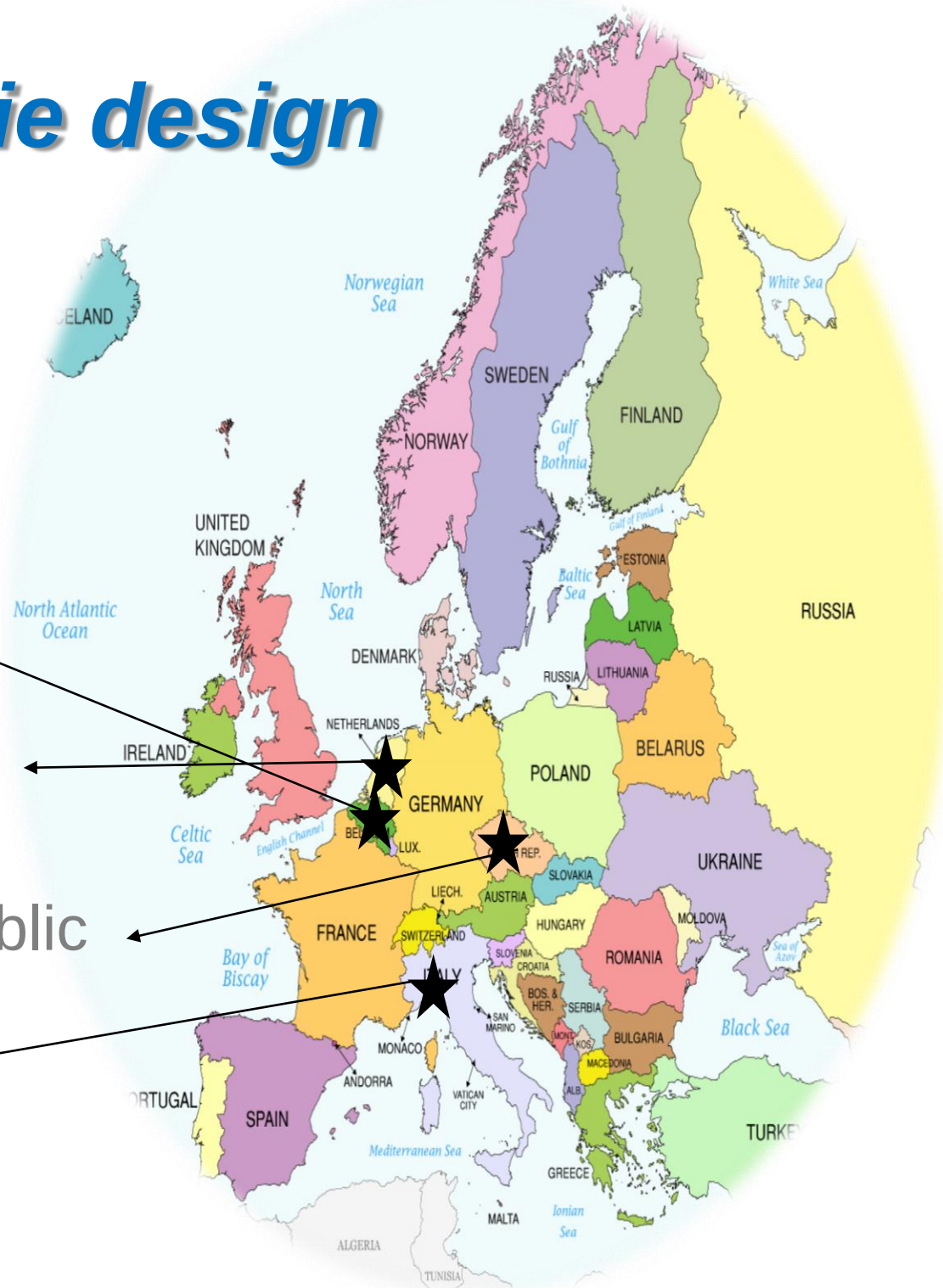
ORIGINAL ARTICLE

Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy

F. Amant, T. Vandenbroucke, M. Verheecke, M. Fumagalli, M.J. Halaska,
I. Boere, S. Han, M.M. Gziri, F. Peccatori, L. Rob, C. Lok, P. Witteveen,
J.-U. Voigt, G. Naulaers, L. Vallaey, F. Van den Heuvel, L. Lagae,
L. Mertens, L. Claes, and K. Van Calsteren, for the International Network
on Cancer, Infertility, and Pregnancy (INCIP)

Studie design

- Belgium
- Netherlands
- Czech Republic
- Italy



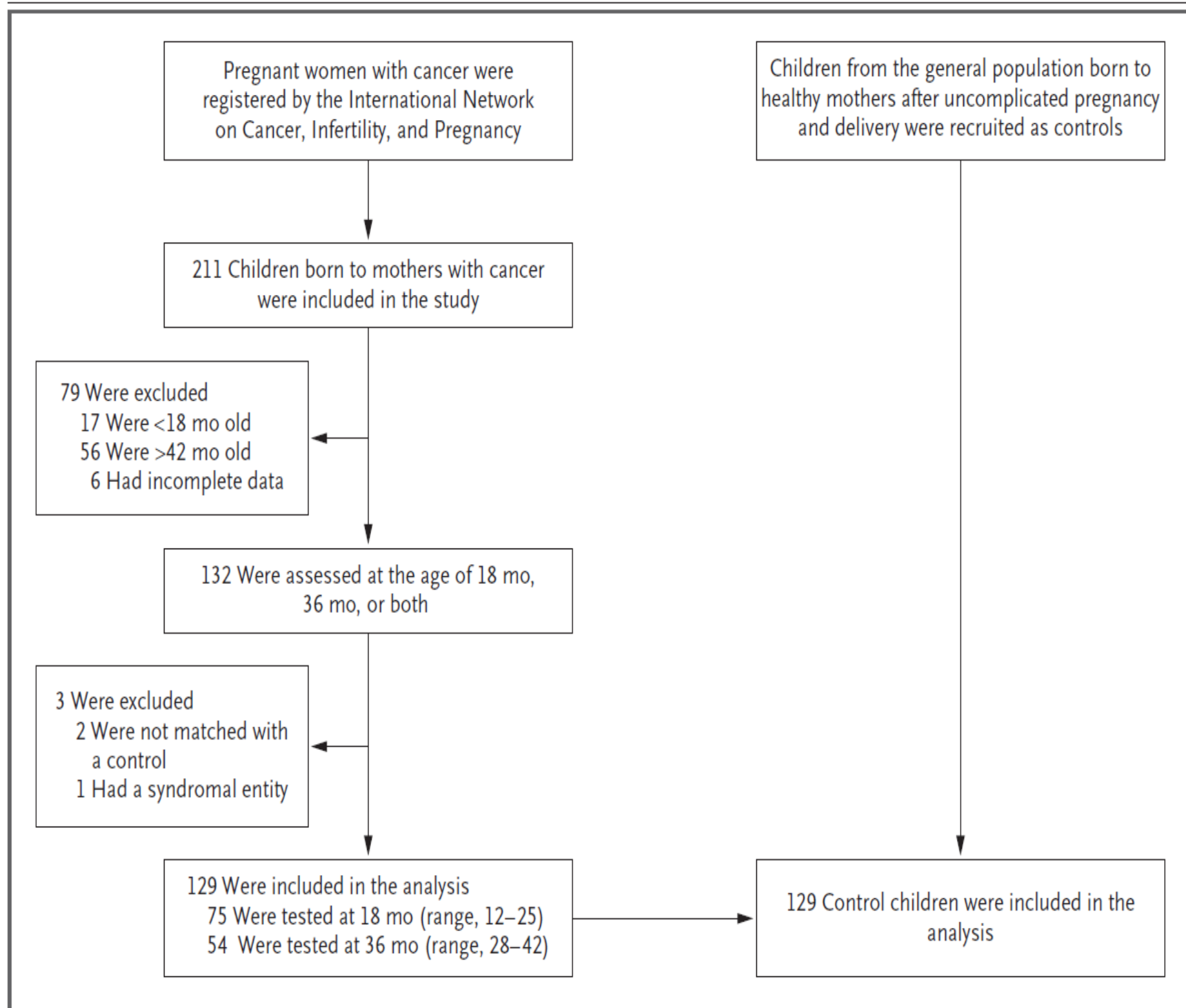


Table 2. Cancer Treatment during Pregnancy for All Children and Those Categorized as Small for Gestational Age.

Cancer Treatment	All Children (N= 129)	Small for Gestational Age (N= 28)*
	no. (%)	no. (% of children with treatment)
Surgery	13 (10.1)†	2 (15.4)
Chemotherapy	41 (31.8)	11 (27.5)
Radiotherapy	1 (0.8)	0
Surgery and chemotherapy	48 (37.2)†	10 (20.8)
Surgery and radiotherapy	3 (2.3)	1 (33.3)
Chemotherapy and radiotherapy	3 (2.3)†	2 (66.7)
Surgery, chemotherapy, and radiotherapy	4 (3.1)	1 (25.0)
Trastuzumab	1 (0.8)	0
Interferon β	1 (0.8)	1 (100.0)
No treatment	14 (10.9)	0

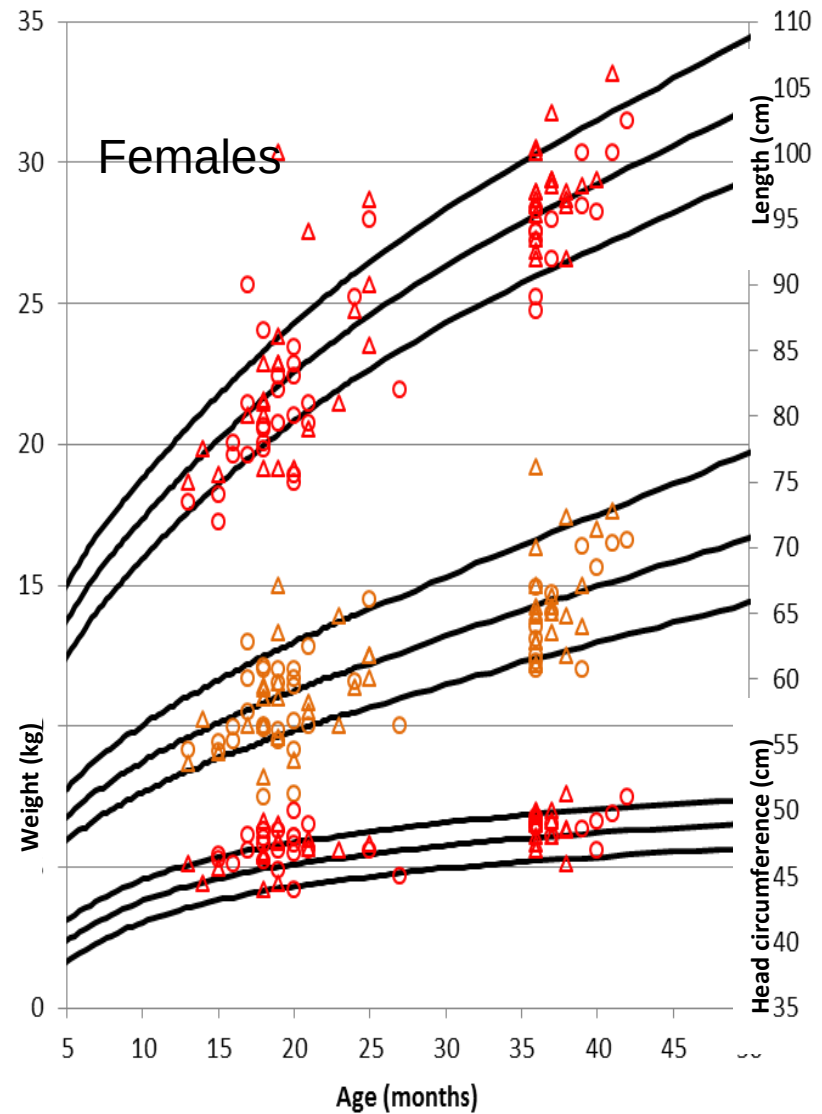
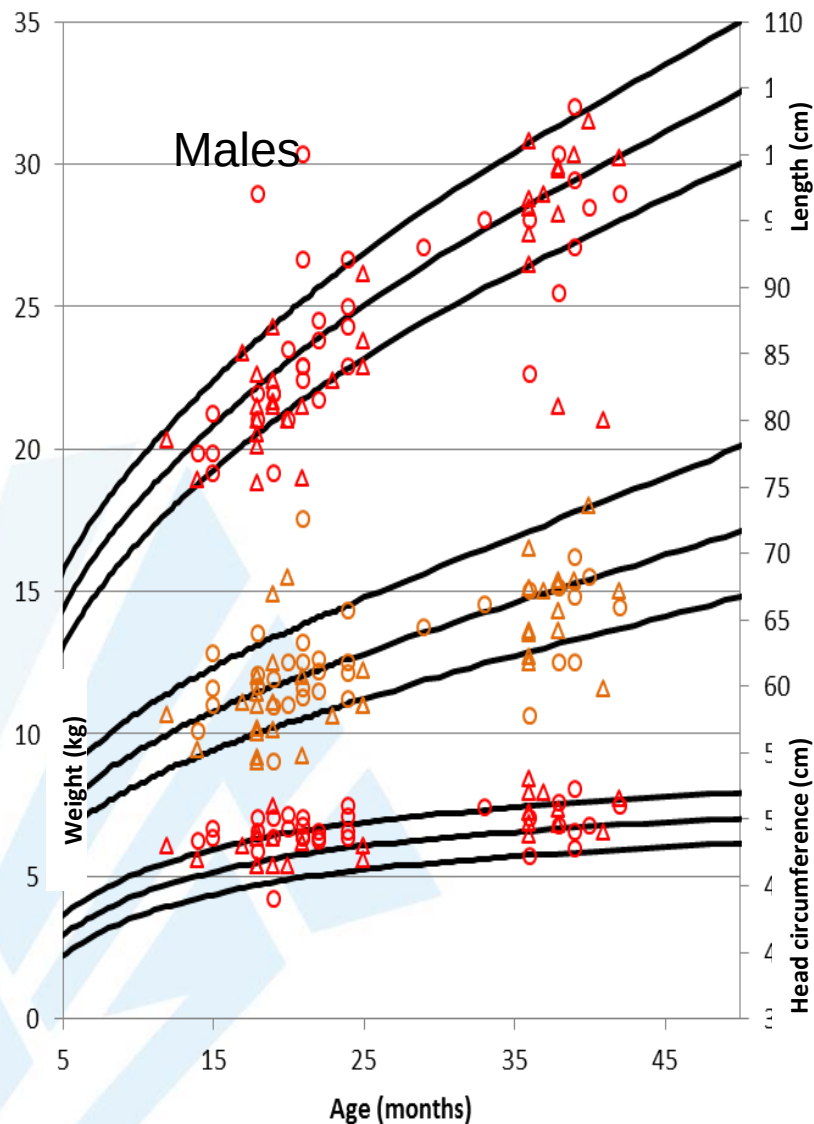
Resultaten

Table 1. Characteristics of the Children at Baseline.

Characteristic	Prenatal-Exposure Group (N=129)	Control Group (N=129)*	P Value
Median age (range) — mo	22 (12–42)	22 (12–42)	0.15
Median gestational age (range) — wk	36 (27–41)	36 (27–41)	1.00
Median birth weight (range) — g	2705 (720–4690)	2755 (1100–4905)	0.50
Median maternal age (range) — yr	33.4 (19.6–43.5)	31.0 (20.6–40.2)	0.001

Perinatale uitkomst: 61,2% preterm geboren

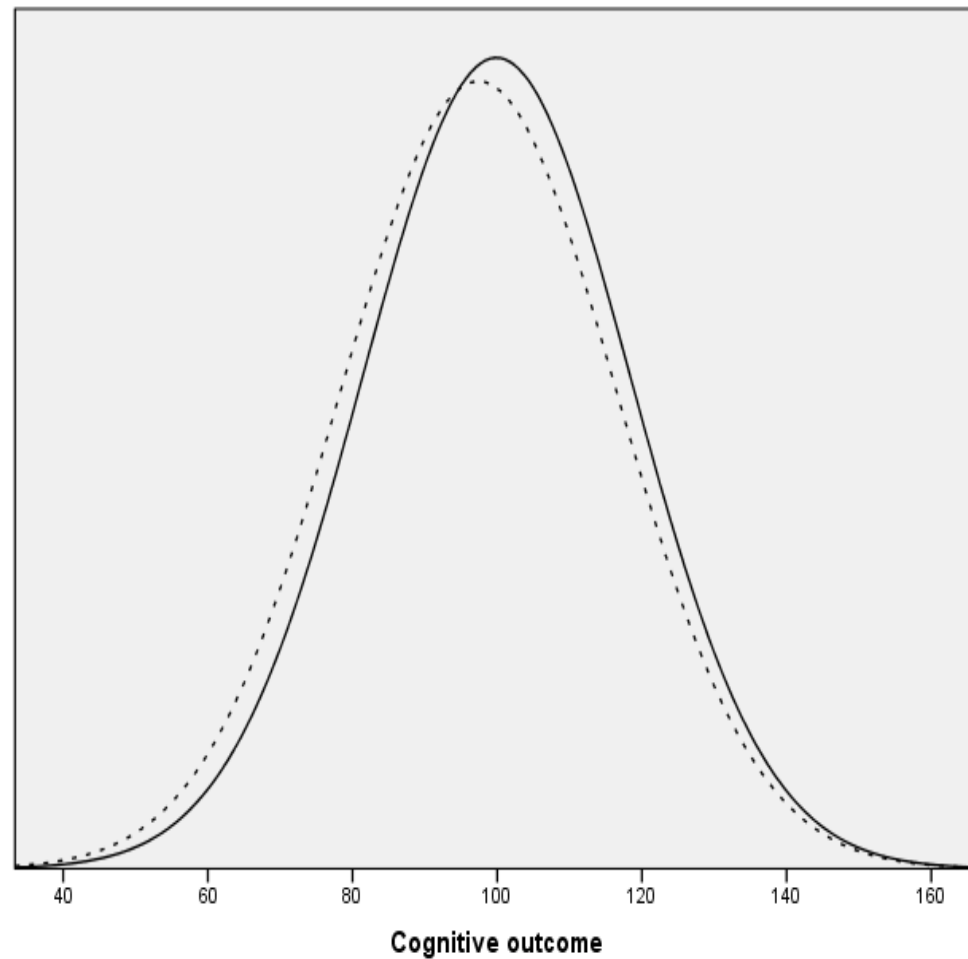
Postnatale groei



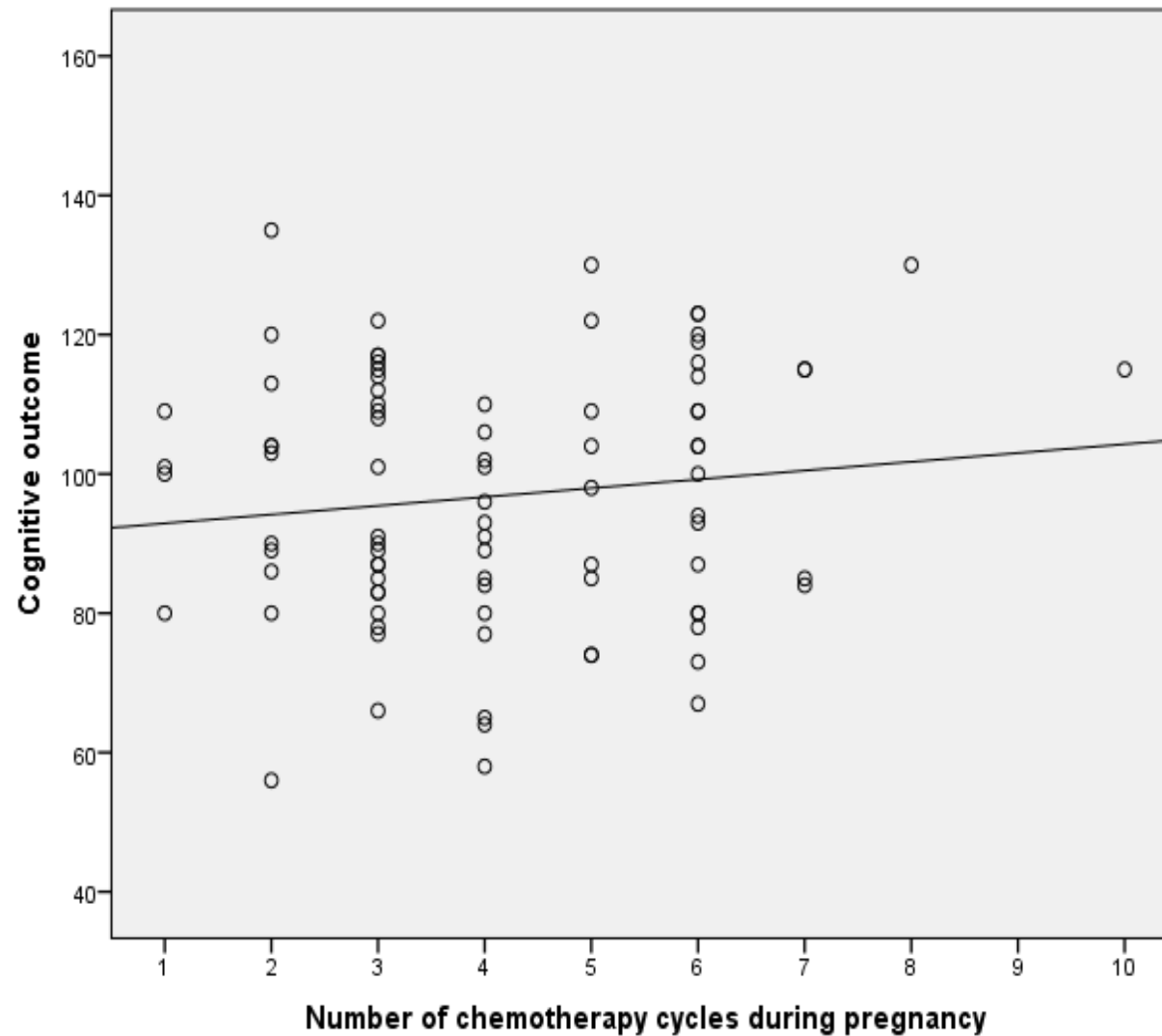
○ Study group △ Control group

Cognitieve uitkomst

— Study group
----- Control group

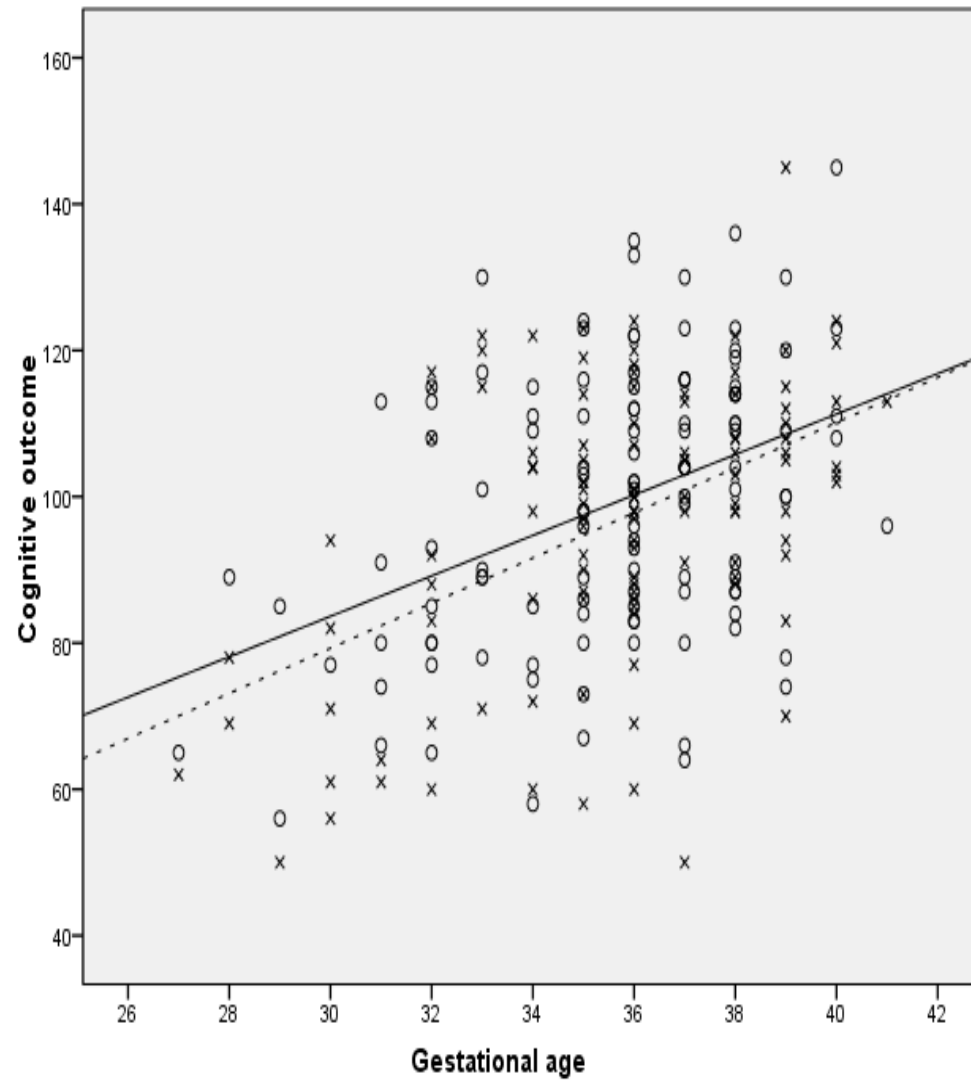


Cognitieve uitkomst en aantal chemo cycli



Cognitieve uitkomst en prematuriteit

○ } Study group
X } Control group



Besluit

- ❖ **Prenatale blootstelling** aan kanker of kankerbehandeling heeft **geen effect** op
 - ❖ Cognitieve functie
 - ❖ cardiale functie
 - ❖ Algemene ontwikkeling
- ❖ **Prematuriteit** is gecorreleerd aan een verminderde cognitieve uitkomst, onafhankelijk van een blootstelling aan kanker of kankerbehandeling

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Check list when prenatal care in breast cancer patients

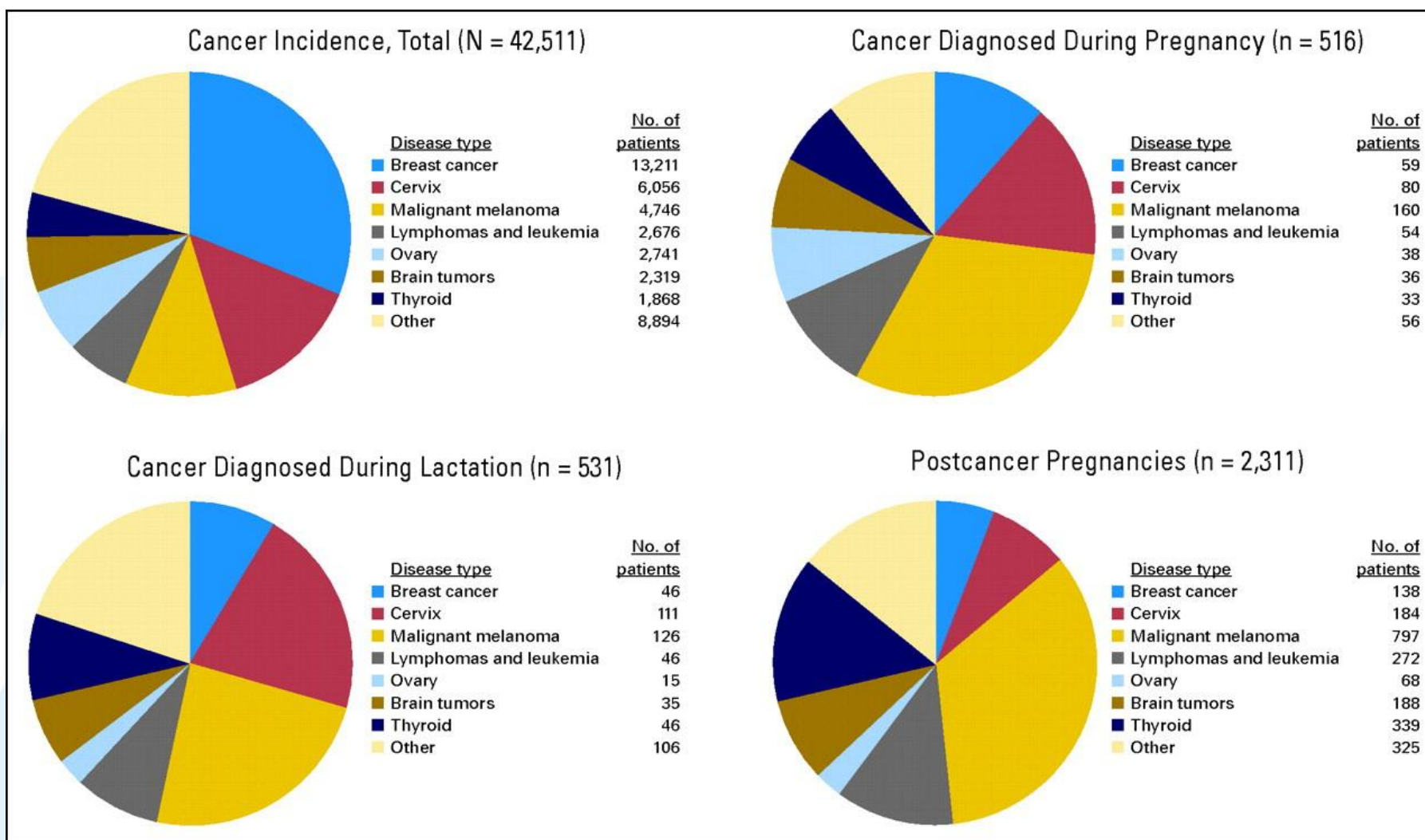
Amant et al., Lancet 2012

At diagnosis	- Confirm evolutionary pregnancy and determine gestational age - Exclude preexisting fetal anomalies by ultrasonography before examinations or interventions are performed
Obstetrical follow up during oncological treatment	- Consider intraoperative foetal monitoring from 24-26 weeks onwards according to local policy - Chemotherapy is possible during 2nd or 3rd trimester *check for fetal wellbeing and general development *check for preterm contractions *check for intrauterine growth restriction *no chemotherapy after 35 weeks of gestation - Radiotherapy is possible during 1st or 2nd trimester *check for preterm contractions *check for intrauterine growth restriction *after every cycle, check foetal wellbeing, growth and morphology
Delivery	- Mode of delivery is determined by obstetrical indications - Timing of delivery: * preferable after 35-37 weeks * at least 3 weeks after chemotherapy * in case preterm delivery is inevitable fetal lung maturation is mandatory
Postpartum	- Examine placenta for metastatic disease - Breast feeding * if physiologically possible e.g. after radiotherapy * contraindicated in case of recent chemotherapy - Oncological treatment can be continued immediately after vaginal delivery, and one week after uncomplicated c-section

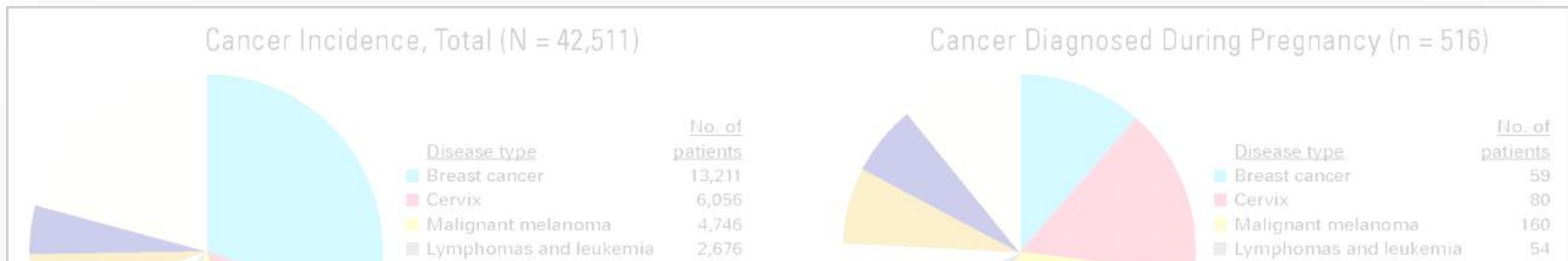
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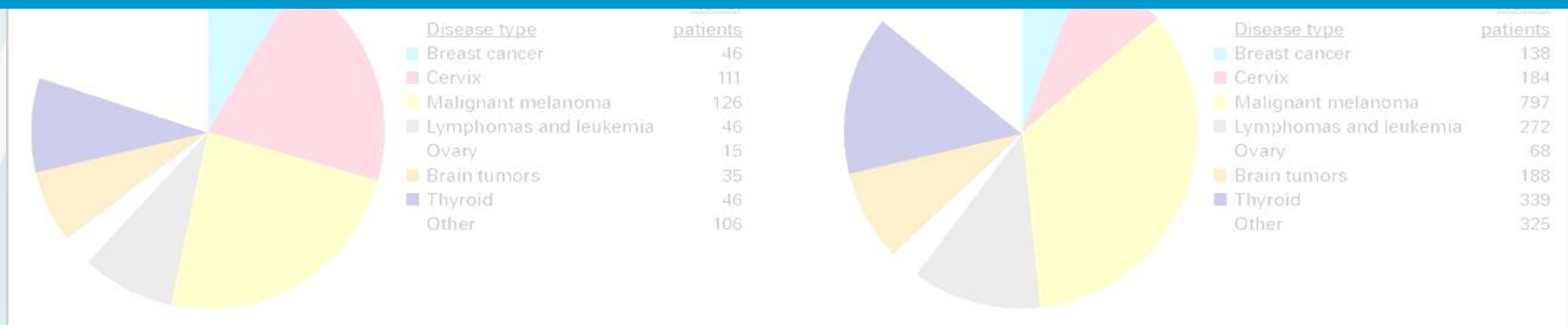
Population-based cohort study data van national kankerregister en geboorteregister van Noorwegen, 42,511 vrouwen, leeftijd 16 to 49 jaar



Population-based cohort study: data van national kankerregister en geboorteregister van Noorwegen, 42,511 vrouwen, leeftijd 16 to 49 jaar



Diagnose van kanker tijdens zwangerschap of lactatie, **verhoogt het risico op sterfte niet.**
Uitzondering voor borstkanker en ovariumkanker dat in de lactatieperiode gediagnosticeerd werd.



Prognosis of women with primary breast cancer during pregnancy: Results from an international collaborative study.

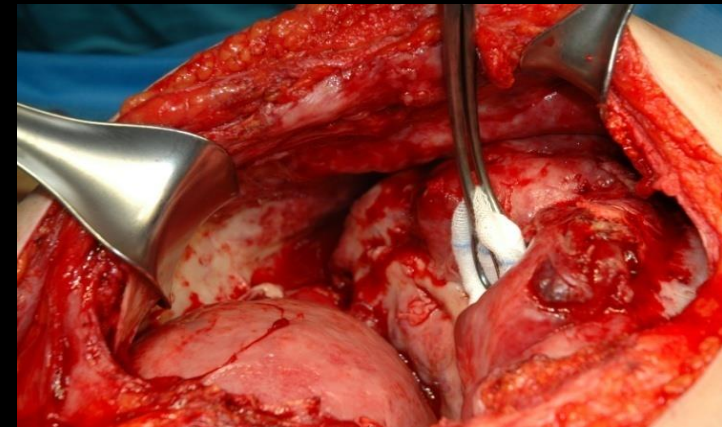
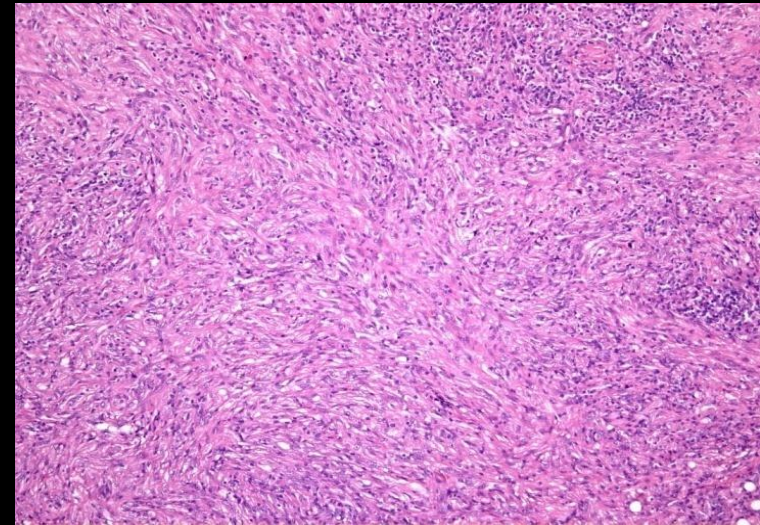
Amant et al , J Clin Oncol 2013

Table 3. Cox Proportional Hazards Regression of DFS and OS				
Outcome		HR	95% CI	P
DFS				
Main analysis: IPW for age		1.34	0.93 to 1.91	.14
Sensitivity analysis: stratification for age		1.31	0.92 to 1.85	.15
OS				
Main analysis: IPW for age		1.19	0.73 to 1.93	.51
Sensitivity analysis: stratification for age		1.06	0.66 to 1.68	.80
NOTE. To account for clustering in data obtained by IPW or stratification, we used robust sandwich variance estimator when fitting Cox proportional hazards model. Age groups used for stratification: ≤ 30 , 31 to 35, 36 to 40, and 41 to 45 years. Abbreviations: DFS, disease-free survival; HR, hazard ratio; IPW, inverse probability weighting; OS, overall survival.				

5-year DFS would have increased from 65% to 71% if these patients had not been pregnant
5-year OS would have increased from 78% to 81% if these patients had not been pregnant

MAAR....Ongedifferentieerd hooggradig sarcoma tijdens zwangerschap: een dubbele bedreiging

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Kanker tijdens de zwangerschap

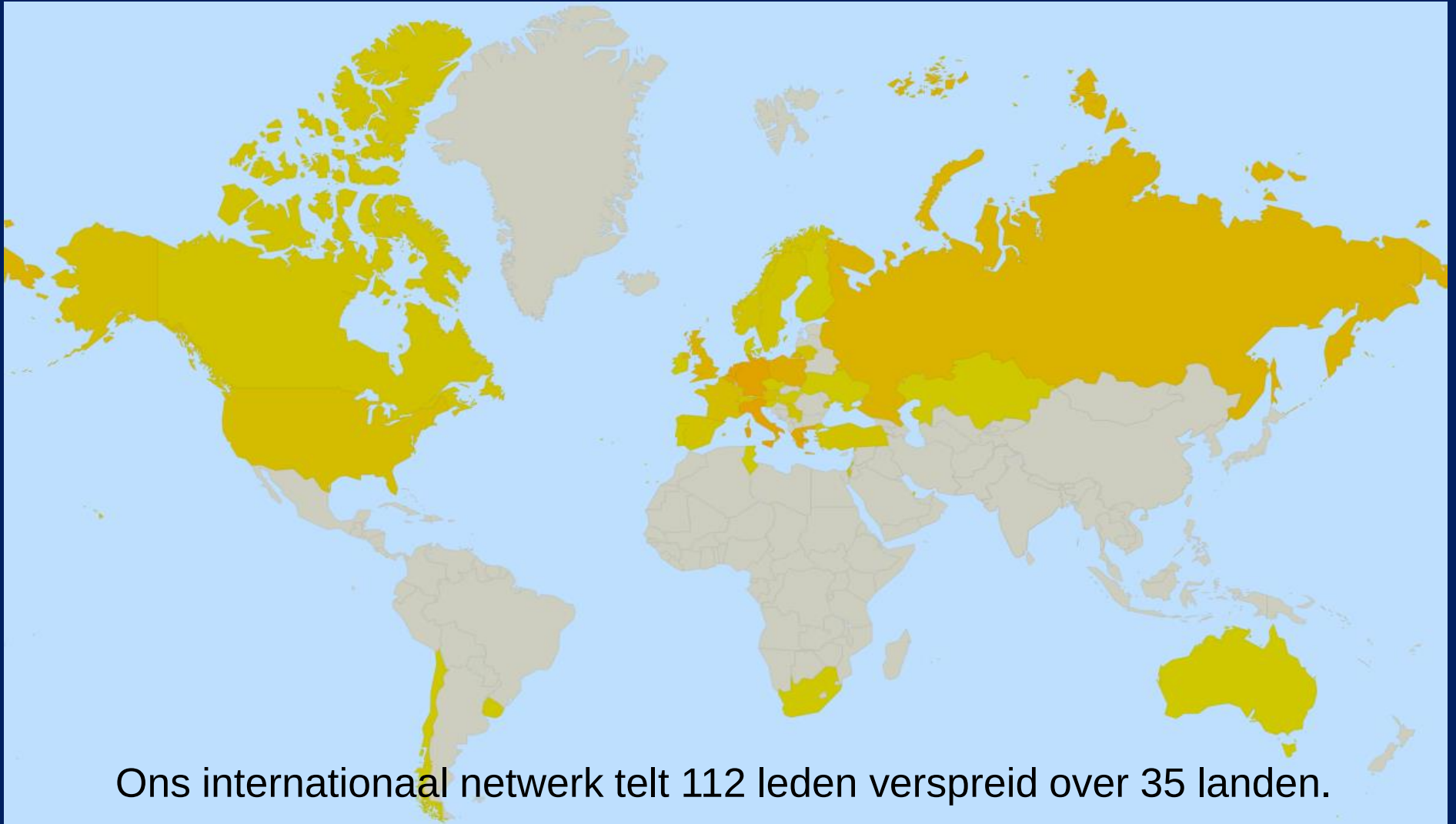
- Inleiding
- Diagnose
- Behandeling
 - Heelkunde
 - Radiotherapie
 - Chemotherapie
- Obstetrische en neonatale uitkomst
- Verloskundige opvolging en planning
- Prognose van moeder
- Take home message

Take home message

- ❖ Behandeling tijdens de zwangerschap is mogelijk
 - ❖ Multidisciplinair
 - ❖ Individueel behandelingsplan
 - ❖ Opvolging in ziekenhuis met hoog-risico verloskundige en neonatale dienst
- ❖ INCIP studie



INCIP



Europe					Other continents		
Austria: 4	Belgium: 8	Czech Republic: 1	Denmark: 1	Finland: 1	Australia: 1	Kazakhstan: 1	Turkey: 2
France: 3	Germany: 8	Greece: 7	Hungary: 1	Ireland: 1	Canada: 2	Qatar: 1	Ukrain: 1
Italy: 8	Lithuania: 2	Norway: 3	Poland: 6	Portugal: 3	Chile: 1	Russia: 5	Uruguay: 1
Serbia: 2	Slovenia: 1	Spain: 5	Sweden: 2	Switzerland: 2	Israel: 3	Tunisia: 1	United States: 3
The Netherlands: 9	United Kingdom: 5				South-Africa: 1		



International Network of Cancer,
Infertility and Pregnancy

www.cancerinpregnancy.org

www.kankerenzwangerschap.be

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Bedankt voor uw aandacht!



Fund for Cancer in
Pregnancy