UZ LEUVEN | GYNAECOLOGIE EN VERLOSKUNDE

INCIP ESGO International Network on Cancer, Infertility and Pregnancy

S59981

Study Protocol

Fertility preservation in young women with cancer

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Version 2.1

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Multicenter research	
Coordinating centers per country:	
The Netherlands	**Prof. dr. Frédéric Amant** **Dr. C.A.R. Lok** Center Gynaecologic Oncology Amsterdam Netherlands Cancer Institute (NKI) Antoni van Leeuwenhoek Hospital **Dr. I.A. Boere** Department of Medical Oncology Erasmus Medical Center, Rotterdam **Dr. P.B. Ottevanger** Department of Medical Oncology University Medical Center St Radboud, Nijmegen **Dr. P.O. Witteveen** Department of Medical Oncology University Medical Center Utrecht **Prof. Dr. V.A.C. Tjan-Heijnen** Department of Medical Oncology Maastricht University Medical Center **Dr. C.P. Schröder** Department of Medical Oncology University Medical Center Groningen **Dr. J. Kroep** Department of Medical Oncology Leiden University Medical Center
Other	Members from INCIP will in addition be invited and facilitated to participate to this substudy.
Sponsor	UZ Leuven

PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
Coordinating Investigator/Project leader/Principal Investigators: Prof. dr. F. Amant Dr. C. Tomassetti		

PROTOCOL SIGNATURE SHEET PARTICIPATING SITE

Authorization of Ethical Committee/IRB	**Authorization of Competent Authority**	**Insurance**	**Informed consent form**
○ Not required ○ Required	○ Not required ○ Required	○ Not required ○ Certificate available	○ Not required ○ Required

Name Participating Site & Investigator	***Declaration***	***Signature and Date***
_____ _____	I hereby agree (1) with this protocol version (2) to submit this protocol version to the Ethical Committee (EC)/IRB or Competent authority, if required (3) to provide access to Prof. Amant upon his request, to the supporting documentation relating to EC/CA approval(s), ICF and insurance, where required.	_____ _____

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CRF	**Case Report Form**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
GCP	**Good Clinical Practice**
IC	**Informed Consent**
n.a.	**Not applicable**
(S)AE	**(Serious) Adverse Event**
WMO	**Medical Research Involving Human Subjects Act**

1. SUMMARY

Rationale:

Cancer is the second leading cause of death during the reproductive years. The long term survival improves for most cancers, reaching 80% for pediatric cancer and more than 70% for cancers in adults between 20 and 49 years of age. Early detection and improvements in cancer treatment contribute to these figures. As a result, quality of life of which preservation of fertility is one aspect, becomes more important. Fertility may however be influenced by surgery and by the gonadotoxic effects of chemo and/or radiotherapy. Therefore, fertility sparing treatments are offered to young patients in order to maintain the wish to conceive after cancer treatment. This however is associated with deviation of standard treatment and many different strategies are applied among different centers. In addition, there is a lack of studies investigating the oncological safety of these fertility sparing treatment protocols. The results of this study will enable us to better inform clinicians and patients on the efficacy of fertility sparing cancer treatment.

Objective:

To record the incidence, treatment and long term follow up of fertility preserving cancer treatment. Both the oncological and fertility outcome are recorded.

Study design: International multicentre prospective observational trial

Study population: All female adults with a cancer for whom a fertility preserving cancer treatment is applied. The results of the study population are compared to young women undergoing standard cancer treatment.

Intervention (if applicable): n.a.

Main study parameters/endpoints:

Registration of cancer diagnosis, treatment and outcome. Both the oncologic and fertility outcome is registered.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

All patients receive fertility sparing cancer treatment on their specific request. Participation in this observational registration study is not associated with burdens or risks, since participation will not alter the treatment regimens.

2. INTRODUCTION AND RATIONALE

Never ending research in cancer treatment and optimization of prevention methods have led to increased survival rates in people diagnosed with cancer. The long term survival improves for most cancers, reaching 80% for pediatric cancers and more than 70% for cancers in adults between 20 and 49 years of age (1). As the prognosis for malignancies improves, the long-term side effects become more important. The focus has switched from a purely oncology point of view towards oncofertility, in which fertility, as one of the major factors for a good quality of life, becomes substantially more important (2).

Decreased ovarian reserve, premature ovarian insufficiency and premature menopause due to surgery and the gonadotoxic effects of chemotherapy and radiotherapy may however result in fertility impairment. As more than 60% of patients with cancer is most concerned about the impact of the treatment on their fertility, fertility sparing treatments should be offered to young patients in order to maintain the wish to conceive after cancer treatment (5).

Counselling and referring patients, who wish to safeguard their reproductive potential, to a fertility center is of great importance as up to 75% of young cancer survivors want to have children (4).

Embryo cryopreservation is the most frequently used intervention to preserve fertility, for patients undergoing a gonadotoxic treatment. Oocyte cryopreservation is less frequently used, but has a similar outcome and could be a good alternative for single women.

Other more experimental alternatives are cryopreservation of ovarian tissue, temporary translocation of the ovaries when pelvic radiotherapy is needed and ovarian function suppression with GnRH-analogues during chemotherapy (5).

Regarding cancer of the female genital tract, in which radical surgery is mostly the standard, alternatives are being investigated to preserve fertility. There are still a lot of gaps in research regarding these fertility sparing surgical treatments and the interventions are often experimental, as there is no standardized technique available due to lack of data. This leads to many different strategies being applied among different centers. In addition, there is a lack of studies investigating the oncological safety and obstetric outcome of these fertility sparing treatment protocols. Another major consequence of the absence of a standard technique is the difficulty to inform patients about the best treatment.

It is important to obtain a significant amount of cases in order to make a thorough study especially since several types of cancer do not occur regularly. It is in this respect that this study aims to fill the gap in current research.

The purpose is to enable us to obtain a significant amount of data to create more standardized fertility sparing treatment protocols and to better inform clinicians and patients on the efficacy of fertility sparing cancer treatment.

3. STUDY DESIGN

The proposed research concerns a multicenter prospective observational cohort study. European collaboration is utilized in order to include sufficient number of patients.

This is a study, for which primary approval was granted by UZ Leuven. UZ Leuven is the initiator of the study and the ethical committee of UZ Leuven is the central ethical committee. The UZ Leuven protocol is used in all centers, including the international collaborators.

3.1 Objectives

Primary Objective:

To record the incidence and oncological outcome when a fertility preserving cancer treatment is applied in young women and compare the oncological outcome with a control group.

Secondary Objective(s):

To record the incidence and fertility outcome when a fertility preserving cancer treatment is applied in young women and compare the obstetrical and neonatal outcome with the general population.

3.2 Inclusion criteria

Histological proven cancer in young women over 18 years of age for whom a fertility preserving cancer treatment is applied. For the control group, patients are eligible when they are in the fertile age but over 18 years of age and undergoing standard cancer treatment.

3.3 Sample size

We aim for at least 500 cases per tumour type + 1 control patient per study patients (resulting in 500 control patients per tumour type). This is a minimum that allows us to calculate the oncological prognosis (secondary objective).

3.4 Study procedures

In women over 18 years of age with a cancer diagnosis for whom a fertility preserving treatment is applied, the most important oncological data will be registered, as well as information on the fertility and oncological outcome. Control patients are women who are 18 years of older but younger than 40 years of age diagnosed with cancer and who receive standard treatment. All types of cancer and all types of treatment will be registered. Patients can be included both prospectively and retrospectively. For every study patients, we include one control patient.

Recruitment of patients:

Because information on pregnant state is not available in most cancer registries prospective recruitment of patients is done as follows: networking (e.g. INCIP), newsletters, presentation at conferences for obstetricians, oncologists, haematologists, and also a website for professionals (www.cancerinpregnancy.org) and for patients (http://www.uzleuven.be/kanker-en-zwangerschap).

We will collect the following data:

<u>At baseline:</u>

Oncological data include type of cancer, the date of diagnosis, tumour histology, stage of the disease, the type of treatment, the recurrence of the cancer and the cancer survival.

Fertility data include gravidity and parity, menstrual pattern after cancer treatment, conception (artificial of natural), obstetrical complications, gestational age at delivery and mode of delivery (induction, caesarean section, spontaneous labour).

Paediatric data that are collected include birth weight, gender, congenital malformations, admission to neonatal care unit and reason of admission.

<u>Annually until end of study:</u>

We will request information from the treating physician regarding patient's health status (pregnant yes/no, relapse yes/no, site of relapse, treatment of relapse, date of relapse, date of death if applicable).

This study does not involve any direct input or effort from the patient. Only the collection of existing information through the medical records is aimed for.

4. STUDY POPULATION

4.1 Population (base)

All women over 18 years of age diagnosed with cancer for whom a fertility preserving cancer treatment is applied will be eligible for inclusion.

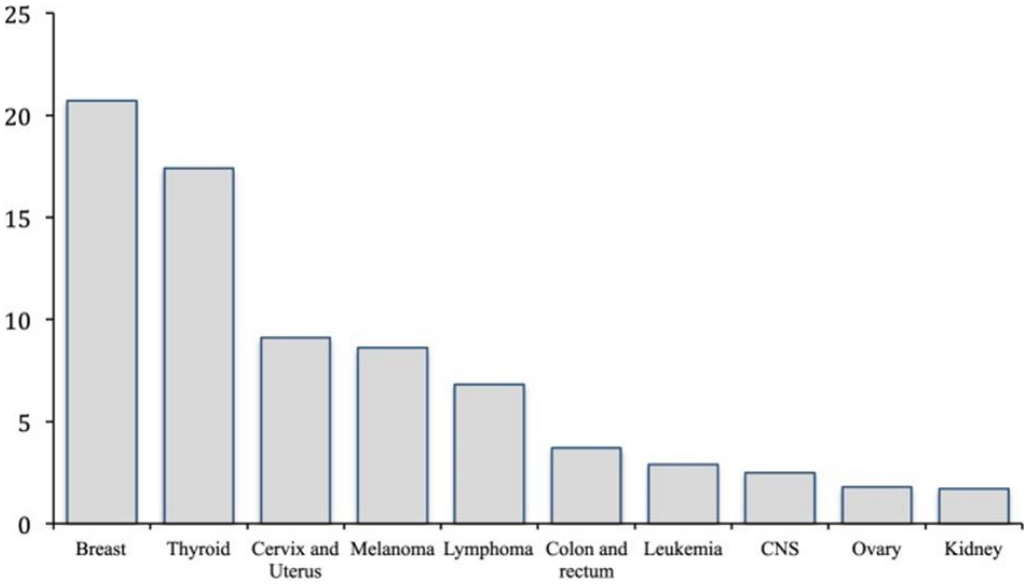

Fig. 1: Most common cancer in women 15–39 years old. *Incidence rates per 100,000.(6,7)

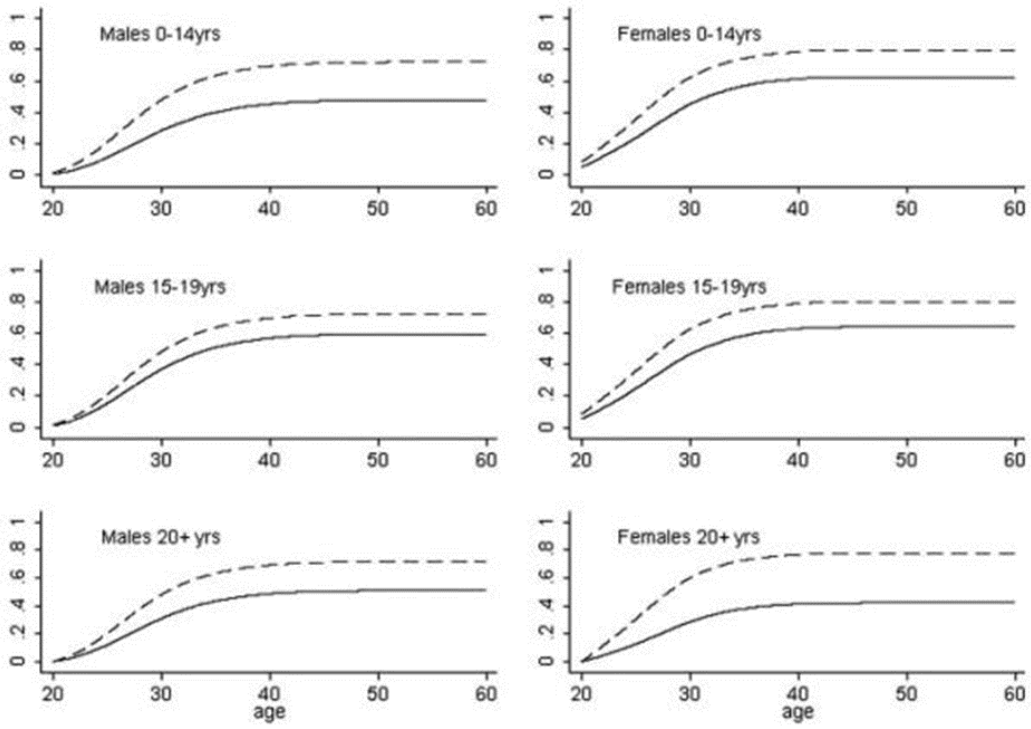

Fig. 2: Model-based cumulative probabilities of first postdiagnosis parenthood. For the young adult diagnostic age group, the curves represent conditional cumulative probability of parenthood

given the patient had no children at age 20. The dashed line represents siblings and the solid line represents cancer patients.(8)

4.2 Inclusion criteria

Histological proven cancer in women of 18 years of age but in their fertility years with a wish to preserve their fertility by undergoing fertility preserving cancer treatment.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Mentally disabled or significantly altered mental status that would prohibit the understanding and giving of informed consent.
- Age below 18 years

5. METHODS

5.1 Randomisation, blinding and treatment allocation

n.a.

5.2 Study procedures

For this study, it will not be necessary to postpone diagnostic procedures or treatment. Participation in this study does not influence normal treatment.

5.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

5.4 Replacement of individual subjects after withdrawal

n.a.

5.5 Follow-up of subjects withdrawn from treatment

n.a.

5.6 Premature termination of the study

No reasons for premature termination of the study are anticipated.

6. STATISTICAL ANALYSIS

We plan to use descriptive statistics (mean +/- standard deviation), two-sided tests, and wilcoxon rank sum test to compare continuous variables in two groups, for more than two groups, the Kruskal-Wallis exact test will be used. For comparing a proportion with an expected value, a binominal exact test will be used. Results are considered significant at P<.05.

Analysis will be performed with SAS (version 9.2) and Statistical Package for Social Sciences for Windows (version 16). Statistical analysis will be performed under supervision of Prof. B. Van Calster (Leuven Cancer Institute, Belgium).

7. SAFETY REPORTING

7.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited ethical committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

Definitions in Law of May 7, 2004 concerning experiment on the human person

Adverse event (AE): any untoward medical occurrence in a patient or subject of the treated group during an experiment, and which does not necessarily have a causal relationship with this treatment

Serious adverse event (SAE): any untoward medical occurrence or effect that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;

Suspected unexpected serious adverse reaction (SUSAR): is an AR that is serious and unexpected (meaning that nature or severity of the AR is not consistent with the Investigational Medicinal Product reference safety information, which is the Investigator's Brochure) and is judged by either

the investigator or the sponsor as having a reasonable suspected causal relationship with the investigational medicinal product.

7.2.1 Adverse events (AEs)

All adverse events caused by study interventions reported spontaneously by the subject or observed by the investigator or his staff will be recorded. We do not expect any study related adverse events for this study.

7.2.2 Serious adverse events (SAEs) expected

The investigator shall report all study intervention-related serious adverse events immediately, after first knowledge, to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by code numbers. For reported study intervention related deaths of a subject, the investigator shall supply the sponsor and the accredited ethics committee with any additional information requested.

The sponsor shall keep detailed records of all study intervention-related adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the minister if the experiment is being conducted in Belgium, if he so requests. Regarding those study intervention-related serious adverse events the Principal Investigator will take all reasonable measures, in consultation with Sponsor, to protect subjects at risk following the occurrence of such events.

Participation in this study holds an extremely low risk of AEs and study intervention-related SAEs since no invasive interventions are performed, except for venous punctures (for which also no SAE’s are expected). Since this study holds an extremely low risk of a study intervention-related SAE and no invasive interventions are performed, this present study is relieved of reporting non study related SAEs.

7.3 Data Safety Monitoring Board (DSMB)

Data safety monitoring board is not needed. As this study is a study with extremely low risks and does not falls under the scope of the WMO, no monitoring is needed.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI) Ethical Principles for Medical Research Involving Human Subjects Version Edinburgh, Scotland, October 2000, with Note of Clarification on paragraph 29 added by the WMA General Assembly, Washington 2002 end note of clarification on paragraph 30 added by the WMA General Assembly, Tokyo 2004 and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

8.2 Recruitment and consent

Eligible patients will be informed about the study by the supervising physician (e.g. gynaecologist, surgeon or medical oncologist) primarily treating the malignancy. The patient will also obtain written information about the study. The patient can think about participation and discuss the study with her family. They will be given enough time to consider their decision and are free to reconsider their decision at any moment during the trial. In case of participation the informed consent should be signed prior to registration of patient data. This is applicable for the prospective part of this study. An exception is made for the retrospective part of this registration study; retrospective data without the need for follow-up may be collected anonymously without a signed consent form for evaluation of quality of care since it does not fall under the scope of the WMO.

8.3 Objection by incapacitated subjects (if applicable)

No incapacitated subjects will be included in the study.

8.4 Benefits and risks assessment, group relatedness

As this study will not change treatment nor randomize patients, participation in this study will not affect patients' outcomes. As this is an observational study, no additional risks from the study are expected.

8.5 Compensation for injury

Participation in this study does not imply any study related actions and only carries negligible risks for the research subjects. However, the sponsor shall be liable, even without fault, for any damages incurred by a study subject and linked directly or indirectly to the participation to the study.

Sponsor shall enter into an insurance agreement in order to cover the liability for any damages incurred by a study subject from a Belgian participating site. See paragraph 9.4 for further information.

8.6 Incentives

Eligible participants do not receive any special incentives that may encourage participation in this study.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

The investigator records clinical data, using a paper or electronic case report form (CRF), all data is collected in an online database that is available through www.cancerinpregnancy.org, such database being the ownership of Sponsor. Participating physicians have a personal account to log in to the registration page and access the electronic CRF. They will have permanent access only to their own series of patients. The participating physician ensures the confidentiality, accuracy, completeness, legibility and timeliness of the data recorded. Data handling and statistical analysis will be done anonymously by the investigator, with the subject identification code list only available to the local investigator (and research nurse if applicable) working in the local center. The code will be based on the birth date and center abbreviation (and not patient initials). The investigator will be the owner of the data. The investigator will be the owner of its recorded data. Data will be kept for 20 years.

Sponsor, participating physicians and sites agree and commit to handle and protect the data in accordance with the terms and provisions of all applicable data protection rules and legislation including the Belgian law of 08 December 1992 on Privacy Protection in relation to the Processing of Personal Data and the Belgian law of 22 August 2002 relating to patient's rights.

9.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited ethical committee has been given. All amendments will be notified to the ethical committee that gave a favourable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the ethical committee application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the ethical committee and to the competent authority. Non-substantial amendments will not be notified to the accredited ethical committee and the competent authority, but will be recorded and filed by the sponsor.

9.3 Public disclosure and publication policy

This study is registered with ClinicalTrials.gov, number NCT02878434.

All publications from this study will be done by the principle investigators and other investigators according to their contribution to this study.

9.4 Insurance

Sponsor shall be liable, even without fault, for any damages incurred by a study subject and linked directly or indirectly to the participation to the study.

Sponsor shall enter into an insurance agreement in order to cover the liability for any damages incurred by a study subject from a Belgian participating site.

If an insurance coverage is required by local laws of non-Belgian participating sites, such participating sites shall have and maintain in full force and effect during the term of this Agreement (and following termination of the study to cover any claims arising from the study) adequate insurance coverage for any damages linked directly or indirectly to the subjects' participation to the study at participating sites. Participating sites shall provide a corresponding insurance certificate to Sponsor.

10. COMPENSATION

Participating Site shall receive a reasonable compensation for the work performed: €50 (per new completed case, including yearly update)

The above mentioned amounts are exclusive of VAT and inclusive of Participating Site's overhead.

Payments will be made by Sponsor in euro via bank transfer once a year upon receipt of correct, accurate and complete dataset (including follow-up data) from Participating Site and upon receipt of a valid VAT invoice.

VAT will be regulated in accordance with the provisions foreseen in the European Directives of 2008/8/EC and 2006/112/EC. The regulations valid at the time of invoicing will be applicable.
In case services provided under this Agreement should be subject to VAT, the Participating Site shall be entitled to charge VAT at the legal rate in addition to the fees stated in this Agreement, provided the VAT is stated separately on the invoice made out to Sponsor.
Under the current provisions stated in the Directives mentioned above; reverse charges will be applicable; this last sentence does not apply in case invoices come from Belgian Participating Sites.

Sponsor VAT number: BE0419 052 173

Invoices will be sent to:
UZ Leuven
Clinical Trial Center (finance department)
Herestraat 49
3000 Leuven
Belgium

Invoices will contain the following payment details:

- Name Participating Site
- VAT ID number of Participating Site
- Address of Participating Site
- Payment currency: EUR
- Bank account holder name
- Bank account number
- IBAN
- Bank identifier code (SWIFT)
- Bank Name
- Bank Address
- Reference: S59981

Participating Site acknowledges the fact that Sponsor received a limited ERC grant to finance this Study and Participating Site hereby agrees that if the limited grant is fully spent, Sponsor shall be under no obligation to reimburse Participating Site according to the above agreed payment schedule. As a consequence, Participating Site agrees to finance its own Study related costs.

11. REFERENCES

1) National Cancer Institute. SEER cancer statistics review 1975-2011. 2011, last update 2014 [cited 19/09/2016]. Available from: http://seer.cancer.gov/archive/csr/1975_2011/
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8) Madanat LM1, Malila N, Dyba T, Hakulinen T, Sankila R, Boice JD Jr, Lähteenmäki PM. Probability of parenthood after early onset cancer: a population-based study. Int J Cancer. 2008 Dec 15;123(12):2891-8. doi: 10.1002/ijc.23842.