Cancer and pregnancy, French and International registers

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for the French pregnancy-associated cancer network [3]

Abstract

Aim: the association of cancer and pregnancy is defined as cancer occurring during pregnancy and up to 1 year after delivery of review register. Such an event is rare and the best way to learn what treatments are safe in pregnancy, and to learn how these women do compared to non-pregnant women, is to collect the cases from women into larger series. We review aims and motivations of existing registers in this paper.

Materials and methods: a literature review was performed with the use of a MedLine search strategy. A search was also performed on the web and in ClinicalTrials.gov, a registry and results database of publicly and privately supported clinical studies.

Results: national cancer databases provide exhaustive results at the population level but few individual details such as treatment and toxicities. Registers have been created

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to learn what anti-cancer treatments are possible in pregnancy and establish recommendations. Teratogen information services also provide information regarding all types of exposures during pregnancy, including chemotherapy.

Conclusion: national cancer databases, registers and networks all provide information that can help physician facing the situation of cancer during pregnancy.

Keywords: cancer, pregnancy, register, database, recommendation

Public declaration of interest

I hereby, Roman Rouzier, acknowledge do not have direct or indirect interest (financial or in kind) with a private organization, industrial or commercial in connection with the subject presented.

Cancer is the second leading cause of death in women aged 25-44 [1], which makes the association of cancer and pregnancy rare but not uncommon. Indeed, this disease affects between 1/1,000 and 1/6,000 pregnant women [2, 3]. The association of cancer and pregnancy is expected to increase as more women delay child-bearing over the age of 30. Few physicians have treated more than 1 or 2 pregnant patients with cancer. Therefore, the best way, to learn what treatments are safe in pregnancy, and to learn how these women do compared to non-pregnant women, is to collect the cases from women into larger series to establish recommendations.

Diagnosing cancer during pregnancy is a very stressful situation for the patient, her family as well as for the medical team. If termination of pregnancy has sometimes been considered, this option is generally not justified, firstly because it doesn't improve prognosis and also because most initial cancer treatments are not contraindicated according to available data. Nonetheless, religious, social, medical and personal considerations may also influence the decision making

process. Meticulous biological and staging evaluations are necessary for the optimal management of patients. This complex clinical situation requires a multidisciplinary approach in a cancer centre which should involve the patient and her partner. Data from national cancer database that estimate incidence and outcome and dedicated networks/registers that monitors the clinical course, treatment, and disease outcome of women diagnosed with cancer during pregnancy and the perinatal and neonatal outcomes of their children help physicians.

I. NATIONAL CANCER REGISTERS

Accurate reporting of the incidence of pregnancy-associated cancer and pregnancy outcomes are important for informing treatment and counseling for women. However, estimates of the incidence of pregnancy-associated cancer have been imprecise. In fact, the majority of published incidence estimates of pregnancy-associated cancer have relied on data collected before the year 2000 and have come from case reports or small case studies.

Four large studies reporting data from cancer registers have been published and provide interesting data.

A population-based Californian study identified pregnancy-associated cancers with hospital data, and was then repeated with linked hospital and cancer registry data [5]. This study provides revised population-based measurements for the occurrence rates of cancer associated with obstetric delivery and examines perinatal and cancer-related outcomes within the group of women with 4,846,505 obstetric deliveries in California, inclusive of the years 1991 through 1999. This observational study used a population-based retrospective review of cases identified as a result of computer linkage of maternal/neonatal hospital discharge and birth/death records with case files in the California Cancer Registry (CCR). The effect of timing of cancer diagnosis on clinical outcomes was studied by dividing the cases into three groups as follows: « prenatal » for cancer diagnosis within 9 months before delivery, « at delivery » for cancer diagnosis during delivery hospitalization, and « post partum » for cancer diagnosis within 12 months after delivery. Computerized records for 4,846,505 obstetric patients and 4,906,920 newborn infants comprising the linked vital statistics birth/patient discharge database (VS/PDD) were used to identity-match cases within the CCR case files. Among 4,846,505

obstetric deliveries, 4,539 cases of invasive malignancy were identified for an observed occurrence rate of 0.94 per 1,000 births. Sixty-four percent of the cases occurred post partum; cancers of the breast, thyroid, cervix, along with malignant melanoma, and Hodgkin's disease accounted for 64% of the cases. The timing of cancer diagnosis affected clinical outcomes: for all cancer cases as a group, the most favorable perinatal and cancer outcomes occurred in women whose cancer diagnosis was made 6 to 9 months before delivery (6% of cases). The most unfavorable perinatal and cancer outcomes were associated with cancer diagnosis made 0 to 3 months before delivery (14% of cases). For women whose cancer was diagnosed post partum, perinatal outcomes were minimally affected by the presumed existence of occult cancer at the time of obstetric delivery.

A large Australian study looked at 781,907 women who gave birth in New South Wales (NSW) between 1994 and 2008 which corresponds to 1,309,501 maternities [4]. Women with pregnancy-associated cancer, where the initial diagnosis of cancer is made during pregnancy or within 12 months of delivery, are compared to women without cancer. A total of 1,798 pregnancy-associated cancers were identified from the total number of maternities corresponding to an overall incidence rate of 137.3 per 100,000 maternities. The research found that between 1994 and 2008 the incidence rate of pregnancy-associated cancer increased from 112.3 to 191.5 per 100,000 maternities. During this period maternal age also increased. The percentage of women aged 35 years and over increased from 13.2% to 23.6% in New South Wales. Despite this the research found that only 14% of the increase was explained by increasing maternal age. The research looked at independent risk factors for pregnancy-associated cancer including older maternal age, Australian-born, socio-economic status, multiparity, multiple pregnancy and prior diagnosis of cancer. The authors state that improved diagnostic techniques, detection and increased interaction with health services during pregnancy may contribute to higher incidence rates of pregnancy-associated cancer. They also say that the genetic and environmental origins of pregnancy-associated cancers are likely to pre-date the pregnancy, however the hormones and growth factors necessary for fetal growth may accelerate tumour growth. The most common cancers were melanoma of skin, breast cancer, thyroid and other endocrine cancers, gynaecological and lymphohaematopoeitic cancers. However it must be noted that Australia has the highest incidence of melanoma in the world. In addition the study looked at pregnancy outcomes and found that cancer during pregnancy was associated with a significantly increased

risk of caesarean section, planned preterm birth and large-for-gestational-age infants.

Andersson *et al.* estimated the incidence of pregnancy-associated breast cancer during different calendar periods and when pregnancy-associated breast cancer was diagnosed in relation to delivery [6]. They performed a population-based cohort study using data from Swedish registers between 1963 and 2002, encompassing women aged 15-44 years at the date of breast cancer diagnosis. Outcome measures included incidence of pregnancy-associated breast cancer per 100,000 deliveries, the proportion of pregnancy-associated breast cancer among all breast cancers, and observed-to-expected rates. Between 1963 and 2002, 1,161 cases of pregnancy-associated breast cancer among a total of 16,620 breast cancers were identified in women aged 15 to 44 years. The incidence of pregnancy-associated breast cancer increased from 16.0 to 37.4 per 100,000 deliveries comparing the first and last calendar periods under study. During pregnancy, the overall incidence was 2.4 per 100,000 deliveries; the incidence during the first and second year after delivery was 10.6 and 15.0 per 100,000 deliveries, respectively. Fewer pregnancy-associated breast cancers than expected were diagnosed during pregnancy and the first 6 months after delivery. Thereafter, there was no difference between observed compared with expected number of breast cancers. The authors concluded that the incidence of pregnancy-associated breast cancer increased during the study period, partly caused by a trend of postponement of childbearing to an older age. The present findings suggest that breast cancer is underdiagnosed during pregnancy and lactation.

Stensheim *et al.* assessed if cancers diagnosed during pregnancy or lactation are associated with increased risk of cause-specific death [7]. In this population-based cohort study using data from the Cancer Registry and the Medical Birth Registry of Norway, 42,511 women, age 16 to 49 years and diagnosed with cancer from 1967 to 2002, were eligible. They were grouped as not pregnant (reference), pregnant, or lactating at diagnosis. Cause-specific survival for all sites combined, and for the most frequent malignancies, was investigated using a Cox proportional hazards model. An additional analysis with time-dependent covariates was performed for comparison of women with and without a postcancer pregnancy. The multivariate analyses were adjusted for age at diagnosis, extent of disease, and diagnostic periods. For all sites combined, no intergroup differences in cause-specific death were seen, with hazard ratio (HR) of 1.03 (95% CI, 0.86 to 1.22) and HR 1.02 (95% CI, 0.86 to 1.22) for the pregnant and lactating groups, respectively. Patients with breast (HR, 1.95; 95% CI, 1.36 to 2.78) and

ovarian cancer (HR, 2.23; 95% CI, 1.05 to 4.73) diagnosed during lactation had an increased risk of cause-specific death. Diagnosis of malignant melanoma during pregnancy slightly increased this risk. For all sites combined, the risk of cause-specific death was significantly decreased for women who had postcancer pregnancies. Authors concluded that in general, the diagnosis of most cancer types during pregnancy or lactation does not increase the risk of cause-specific death. Breast and ovarian cancer diagnosed during lactation represents an exception.

Therefore, National Cancer databases provided important information in terms of incdence and outcome. However, several limitations of the National Cancer database approach warrant consideration. First, as early pregnancy loss (miscarriage or abortion) are not registered in the birth data, the number of pregnancy-associated cancers is somewhat underestimated, and the average gestational age at diagnosis is over-estimated. Second, cancer treatment cannot be examined, as chemotherapy and radiotherapy are primarily provided in outpatient clinics. Third, history of smoking, alcohol consumption and maternal obesity are not available to provide adjustment for the potential confounding of pregnancy outcomes.

II. NATIONAL OR INTERNATIONAL SPECIFIC NETWORKS

The aims and expected outputs of registers and networks on cancer in pregnancy are: to provide an operational definition of the cancer in pregnancy (delay after delivery); to estimate the burden of this situation; to improve the quality of data; and, to develop strategies and mechanisms for the diffusion of information among all the key players involved in surveillance on and treatment of this situation.

Ideally, registers results in precise information for all cancers in pregnancy. Data quality should be analyzed for a subset of cancers, by confirming the diagnostic data and, if possible, analyzing additional data on stage and treatment. Websites on cancers in pregnancy have been designed to disseminate the results of the project, and in particular, to inform clinicians, patients and health planners.

Several networks have been set-up. Some networks encompass all cancers while others focus on Breast cancer.

In the USA, a dedicated network has been created: the Pregnant with Cancer Network (*http://www.hopefortwo.org/*). It is a national non-

profit organization for women diagnosed with cancer during pregnancy. This network maintains a cancer and childbirth registry/data base of all pregnant women diagnosed with cancer and with each patient's permission, reviews their cancer treatment and pregnancy outcomes. In this Cancer and Pregnancy Registry, children are not only followed up until birth, but on an ongoing yearly basis. Pregnant women diagnosed with cancer find the registry helpful in learning how many other pregnant women were diagnosed and treated for the same cancer during pregnancy. Patient data is kept confidential. It is a valuable contribution to the oncological and obstetrical knowledge base for pregnant women with cancer. The database is listed on the FDA website as a recognized pregnancy registry. The mission is to connect women who are pregnant with cancer with other women who have been pregnant with the same type of cancer. These women are here to lend support, offer hope and share their experiences with one another through phone and e-mail conversation.

In Europe, France, Belgium, Netherlands, Germany, and others have also constituted networks.

In France, the network has been created in 2008 (*www.cancer-et-grossesse.fr/*). It consists in providing answers to physicians if necessary. Three tumor boards have been set up: breast cancer, gynecological cancer and other malignancies. Patient cases are discussed during these tumor boards and recommendations are made. This network also collects patient cases to answer specific questions. For example, a study has been conducted to determine the chemosensitivity of pregnancy-associated breast cancer (PABC) in the neoadjuvant setting by comparing the observed pathological complete response (pCR) rate with the rate predicted by a validated nomogram [8]. Through the use of nomograms, this study demonstrates that PABC is as chemosensitive as non-PABC and suggests that taxanes should be part of the NACT regimen for PABC. Further studies are warranted to increase the power of the presented data. The French network has also reported the possibility of using Epirubicin and Taxanes during pregnancy [9, 10].

In Germany, the network has launched a trial: *http://clinicaltrials.gov/ct2/show/ NCT00196833?term=pregnancy+breast+cancer&rank=3.* Women who are diagnosed with breast cancer during their pregnancy may be registered in this trial. Data is collected on the foetal outcome 4 weeks after delivery, maternal outcome of pregnancy as well as the breast cancer therapy applied (treatment, response to chemotherapy, type of surgery), diagnostic procedures applied (palpation, US, mammogram) and the outcome of mother and child after 5 years of therapy. Details about this trial are reported in table 1.

Table 1 - Breast Cancer in Pregnancy - German Trial
http://clinicaltrials.gov/ct2/show/record/NCT00196833

Brief title	Breast Cancer in Pregnancy
Official title	Prospective and Retrospective Register Study of the German Breast Group (GBG) for Diagnosis and Treatment of Breast Cancer in Pregnancy
Brief summary	Women who were diagnosed with breast cancer during their pregnancy may be registered in this trial. Data is collected on the fetal outcome 4 weeks after delivery, maternal outcome of pregnancy as well as the breast cancer therapy applied (treatment, response to chemotherapy, type of surgery), diagnostic procedures applied (palpation, US, mammogram) and the outcome of mother and child after 5 years of therapy.
Detailed description	Breast cancer is the most common cancer malignancy in women of childbearing age after the age of 25 years. Since the incidence of breast cancer under the age of 40 is increasing, and women tend to delay pregnancy into later reproductive years, the coincidence of pregnancy and breast cancer is increasing. About 1 in 1,000 pregnancies is complicated by breast cancer. Nevertheless, little is known about the right therapy for the mother and the unborn child. We are therefore carrying out a trial, collecting prospective and retrospective data about pregnant women, with histological confirmed breast cancer. Data on the biology of the tumour and placenta tissues is also collected. The anonymous data is collected in a database.
Study type	Observational
Biospecimen	Retention: samples With DNA Description: tumour and placenta specimens are collected
Sampling method	Non-probability sample
Study population	Women with histologically confirmed breast cancer during pregnancy
Condition	Breast cancer
Recruitment information	
Recruitment status	Recruiting
Estimated enrollment	500
Estimated completion date	April 2014
Estimated primary completion date	April 2013 (final data collection date for primary outcome measure)
Eligibility criteria	Inclusion criteria: – women with histologically confirmed breast cancer during pregnancy – informed consent for data and specimen collection Exclusion criteria: – diagnosis of breast cancer outside the period of pregnancy
Gender	Female

All European networks are collaborating into a task force: Cancer and Pregnancy (*http://www.cancerinpregnancy.org/*). This multidisciplinary team consisting of obstetricians, pediatricians, hematologists, medical oncologists, pharmacologists and gynaecological oncologists focus on the problem of cancer during pregnancy. Using a multicentric and international approach, this team aims to obtain scientific data in order to inform and guide our patients as good as possible in this complex matter.

This task force has published recommendations for management of breast cancer in pregnancy [11]. In most circumstances, serious consideration should be given to the option of treating breast cancer whilst continuing with the pregnancy. Each woman should ideally be referred to a centre with sufficient expertise, given a clear explanation of treatment options. Most diagnostic and staging examinations can be performed adequately and safely during pregnancy. Treatment should however be adapted to the clinical presentation and the trimester of the pregnancy: surgery can be performed during all trimesters of pregnancy; radiotherapy can be considered during the first and second trimester but should be postponed during the third trimester; and standard chemotherapies can be used during the second and third trimester. Since neonatal morbidity mainly appears to be related to prematurity, delivery should not be induced before 37 weeks, if at all possible. Therefore, the treatment of breast cancer in pregnancy should be executed by experienced specialists in a multidisciplinary setting and should adhere as closely as possible to standard protocols.

These networks are helped by teratogen information services that provide information regarding all types of exposures during pregnancy, including chemotherapy.

CONCLUSION

National cancer registers and specific cancer during pregnancy registers/networks provide complementary information. Incidence and outcome data are more accurate on a national basis while specific networks collect management information and establish recommendations.

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