Birth outcome in Danish women with breast cancer, cutaneous malignant melanoma, and Hodgkin's disease

PhD thesis

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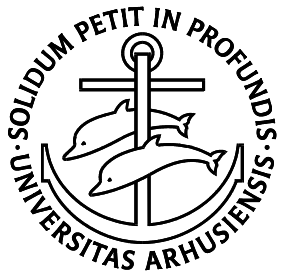

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Preface

This PhD thesis was carried out during my employment at the Department of Clinical Epidemiology, Aarhus University Hospital and the Department of Epidemiology, Institute of Public Health, University of Aarhus.

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III. Langagergaard V, Puho EH, Nørgaard M, Nørgård B, Sørensen HT. Hodgkin's disease and birth outcome: A Danish nationwide cohort study (submitted).

Contents

Abbreviations

ABVD	Adriamycin, bleomycine, vinblastine, dacarbazine
CEF	Cyclophosphamide, epirubicine, 5-fluorouracil
CI	Confidence Interval
CMF	Cyclophosphamide, methotrexate, 5-fluorouracil
DBCG	Danish Breast Cancer Cooperative Group
ICD	International Classification of Diseases
IUGR	Intrauterine growth retardation
LBW	Low birth weight
LBW at term	Low birth weight at term
MOPP	Mechlorethamine, vincristine, procarbazine and prednisone
OR	Odds ratio
POR	Prevalence odds ratio
RR	Relative risk
SGA	Small for gestational age

1. Introduction

In Western countries women often postpone childbearing for personal or professional reasons (1). The average age of Danish women at their first delivery has gradually increased from 23 years in the 1960s to 29 years in 2005 (2). Since the incidence rates of most cancers increase with advancing age (3), more women can be expected to be diagnosed with cancer before childbearing, during pregnancy or shortly after giving birth.

In Denmark, the most common malignancy affecting women of childbearing age is breast cancer, and the second most common one is cutaneous malignant melanoma (excluding non-melanoma skin cancer) (3). Hodgkin's disease, whose incidence peaks in early adulthood and thus also affects women of childbearing age, belongs to cancers with a good prognosis (4). While in previous decades pregnancy in patients with a history of cancer was discouraged (5), presently such pregnancies are treated with more optimism (5), partly owing to the improved prognosis for several cancers (6), and partly because pregnancies subsequent to breast cancer, for example, do not seem to adversely effect maternal life expectancy (7;8). However, with a growing population of young cancer survivors, concerns have been raised regarding the adverse effects of cancer and cancer therapy on the offspring of the treated individuals (9). That includes offspring conceived after completion of treatment, and fetuses exposed to cancer therapy *in utero*. Data on birth outcome in women diagnosed with cancer before, during, or shortly after pregnancy are very sparse. This thesis examines birth outcome in Danish women who were diagnosed with breast cancer, cutaneous malignant melanoma, or Hodgkin's disease before or during pregnancy, or within two years after giving birth.

1.1. The burden of breast cancer, cutaneous malignant melanoma, and Hodgkin's disease in women of childbearing age

Breast cancer - incidence and prognosis

Breast cancer is the most common female cancer in Denmark with more than 4,000 women diagnosed every year (approximately 375 are younger than 45 years of age at the time of diagnosis) (3). The age-standardized incidence rate of breast cancer has almost doubled

over the last four decades, but this increase is mainly confined to women aged between 45 and 75 years (2). The incidence of breast cancer in pregnancy is unknown, but is estimated to range from one in 3,000 to one in 10,000 pregnancies (10).

The overall 5-year relative survival for Danish women with breast cancer is almost 80% (11). Women diagnosed with breast cancer *during* pregnancy often present with an advanced disease, but pregnancy itself does not seem to be a prognostic factor (12). However, women diagnosed with breast cancer in the first few years after childbirth have a worse survival, which is ascribed to the induction of tumor growth at the preclinical stage by physiological changes during pregnancy (12). In contrast, there is no evidence of a negative prognostic effect of pregnancy *subsequent* to breast cancer treatment (12) (7) (8).

Cutaneous malignant melanoma – incidence and prognosis

For decades, the incidence of cutaneous malignant melanoma has been rising in most white populations around the world (13). In Denmark, the incidence of melanoma for women aged 15 to 34 years increased, on average, by 4.3% annually from 1970 to 1999 (14), and in the recent years, approximately 200 Danish women younger than 45 years have been annually diagnosed with melanoma (3). It has been estimated that melanoma represents approximately 8% of malignancies diagnosed during pregnancy (15).

The overall 5-year relative survival for Danish women with melanoma is 91% (11). The effect of pregnancy on melanoma prognosis has been discussed in the medical literature for years (15). Two recent cohort studies did not find a worsened survival for women diagnosed with an early stage melanoma *during* pregnancy (16;17), or within one year following delivery (16), compared to non-pregnant controls. Furthermore, pregnancy *subsequent* to the diagnosis of an early stage melanoma was not associated with increased mortality (17).

Hodgkin's disease – incidence and prognosis

Hodgkin's disease is characterized by a bimodal age incidence curve, with the first peak in young adults and the second, in old age groups (18). While age standardized incidence of Hodgkin's disease has been slightly declining over time, the true incidence in older age groups has in fact decreased substantially,

whilst among young adults in industrialized countries increases have been documented (18). In 2000, 29 women younger than 45 years of age were diagnosed with Hodgkin's disease in Denmark (19). Hodgkin's disease during pregnancy has a reported incidence ranging from 1 per 100,000 to 1 per 6,000 deliveries (20;21).

Hodgkin's disease is a cancer with one of the higest curability rates. The 5-year relative survival has improved from 40% in the beginning of the 1960s to more than 80% in the 1990s (18). Studies have reported that pregnancy at the time of Hodgkin's disease diagnosis does not adversely affect survival (21-23).

1.2. Treatment of breast cancer, cutaneous malignant melanoma, and Hodgkin's disease in a historical view

For decades, cancer has been treated with different combinations of surgery, radiotherapy, chemotherapy, and endocrine therapy. These treatments may diminish fertility, cause teratogenesis, or adversely affect future offspring of treated individuals (9). Since we had limited data concerning the treatment of women with cancer in our studies, below we have outlined the standards for treatment of breast cancer, melanoma, and Hodgkin's disease that were in effect in Denmark from 1970 to 2002 (the period of cancer diagnosis in our studies):

Breast cancer

Since 1977, the Danish Breast Cancer Cooperative Group (DBCG) has worked out uniform guidelines for breast cancer treatment, aiming to ensure optimal handling of operable primary breast cancer nationwide (24). Below, we focus on the guidelines concerning treatment of premenopausal women.

Between 1977 and 2002, DBCG has initiated several generations of treatment programs (1977, 1982, 1989, 1999, and 2001). In DBCG-protocol 1982TM, breast conserving therapy versus mastectomy was evaluated in a randomized trial. As a result, in 1989 breast conserving surgery with postoperative radiotherapy became the standard treatment for women with tumors suitable for this procedure.

Since 1977, breast cancer patients have been classified as low- or high-risk, depending on their prognostic factors (*i.e.* size and histological grade of the tumor, hormonal receptor status, presence of regional metastases, and age). Low-risk patients did not receive adjuvant systemic treatment, while high-risk patients were randomized into specific treatment protocols. From 1977 to 2002, the proportion of premenopausal women receiving adjuvant chemotherapy has increased, since a stricter definition of low-risk was adopted. In our study period, systemic adjuvant therapy for premenopausal women has included treatment regimens of cyclophosphamide, levamisole, CMF (cyclophosphamide, methotrexate, and 5-fluorouracil), CEF (cyclophosphamide, epirubicine, and 5-fluorouracil), pamidronate, tamoxifen, and oophorectomy. From 1999 to 2001 some women in trials also received adjuvant taxanes. In DBCG-1989, the effect of CEF was tested against CMF, and in 1998 CEF became the standard chemotherapeutic regimen for premenopausal women.

Though the indications for radiotherapy in premenopausal breast cancer patients have changed over the years as well, during the large part of our study period, the indications for radiotherapy were breast-conserving therapy, non-radical mastectomy, local advanced disease, or regional metastases.

Cutaneous malignant melanoma

Surgery is the primary treatment for localized melanoma (stages I and II) and melanoma spreading to regional lymph nodes (stage III). Since the mid-1980s several attempts have been made to decrease the risk of recurrence among high risk patients by administering adjuvant treatment such as Interferon or vaccination treatment (with ganglioside) in protocol settings, neither with convincing benefit.

Metastatic melanoma (stage IV) is highly resistant to most treatment modalities, including radiotherapy. In the 1970s, the treatment of choice was chemotherapy. Due to low response rates, this treatment strategy has widely been abandoned, and first line therapies now usually consist of immunomodulatory regimens (including Interferon-α2b). Because treatment remains unsatisfactory, melanoma is a disease in which experimental treatments are widely tested.

Hodgkin's disease

In the 1970s, Hodgkin's disease was treated with MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) and wide radiation fields. Later, the less toxic ABVD (adriamycine, bleomycine, vinblastine and dacarbazine) chemotherapeutic regimen became standard, while radiation fields became more restricted in the form of "involved field radiotherapy".

In the 1990s, treatment of patients with relapse has included high dose chemotherapy and autologous hematopoietic cell transplantation. The typical treatment of early-stage disease in our study period was either radiation alone (with minimal effect on the gonads in case of supradiaphragmatic location), or a few series of combination chemotherapy followed by radiation. In contrast, later stages of Hodgkin's disease were typically treated with six series of combination chemotherapy and only rarely with radiotherapy.

1.3. Possible adverse effects of cancer and cancer therapy on birth outcome

When cancer is diagnosed in pregnancy, there is often a conflict between optimal maternal therapy and fetal well-being (5). Thus, the benefit of the diagnostic work-up, surgery, radiotherapy and chemotherapy must be weighed carefully against the risk to the fetus (10). Under these circumstances, preterm labor is often induced as soon as the fetus becomes viable, in order to allow amplification of therapy (10).

The rationale for examining birth outcome in women diagnosed with cancer within two years after delivery is that pregnancies starting before the diagnosis may be affected by the preclinical cancer. A Swedish study, which compared observed to expected rates of cancer during pregnancy and during the first year following delivery, suggested that diagnosis is often delayed to the postpartum period (25). A possible explanation for this delay could be that unusual signs and symptoms may be ascribed to the pregnancy instead of the cancer.

For women who retain or regain fertility after cancer treatment, an issue of great importance is their ability to carry a pregnancy to term and give birth to a normal child. Chemotherapy and radiotherapy may affect future pregnancies in cancer survivors by directly affecting the reproductive tract or by causing mutations in germ cells (26). It is

therefore important to establish the magnitude of an increased risk (if any) of adverse birth outcomes such as preterm birth, low birth weight at term (LBW at term), stillbirth and congenital abnormalities.

1.3.1. Possible adverse effects of the cancer itself on birth outcome

Little is known about exact mechanisms whereby maternal cancer may pose risk to a developing fetus. In theory, several factors might influence the fetus in a woman with a malignant disease:

- It has been proposed that the cancer may alter metabolism and distribution of hormones and vitamins, some of which are determinants for certain congenital abnormalities (27).
- Cancer patients have an increased tendency to suffer from febrile illness (5), and maternal fever in early pregnancy has been associated with stillbirth (28) and congenital abnormalities (28) (29).
- Malnutrition is more frequent in the cancer patients. Maternal undernutrition during pregnancy resulting in reduced transfer of nutrients to fetus may cause fetal undernutrition and intrauterine growth retardation (IUGR) (30). Impaired fetal growth is strongly associated with neonatal morbidity and mortality (31), and may also be associated with diseases later in life (32). DJ Barker and colleagues have suggested that several of the major diseases of adult life, including coronary heart disease, hypertension, and type 2 diabetes originate from impaired intrauterine growth and development (33). According to this hypothesis, these diseases are consequences of "programming", whereby an insult at a critical, sensitive period of early life permanently affects structure, physiology, and metabolism.
- Psychological stress (caused by a diagnosis of cancer) around the time of conception may reduce the male proportion of newborns, partly because of differential abortion of male embryos (34). Likewise, some studies have reported associations of stress in pregnancy with preterm delivery (35;36), and congenital abnormalities (37).

1.3.2. Possible adverse effects of specific cancer therapy on birth outcome

Surgery

If a cancer surgery is conducted during pregnancy, the fetus may potentially suffer from the transplancental effects of anesthetic agents, and from potential complications of maternal surgery. According to a recent review of the risks of anesthesia in non-obstetric surgery during pregnancy, no anesthetic agent has yet been proven teratogenic in humans (38). However, intraoperative complications, such as hypoxia, hypotension, hypovolemia, and decreased utero-placental perfusion secondary to prolonged maintenance in the supine position may threaten fetal well-being (5).

Radiation

Radiation is commonly used for cancer diagnosis and treatment.The fetus is sensitive to ionizing radiation, with the brain being the most sensitive organ (39). During the peri-implantation and immediate post-implantation periods, radiation has an all-or none effect, resulting in either embryonic death or further normal development. Later in pregnancy, radiation may cause congenital abnormalities, IUGR, mental retardation, or childhood cancer (39).

According to Kal *et al.* (40), congenital abnormalities might occur above a threshold dose of 0.1 to 0.2 Gy during organogenesis (weeks 2-8 after conception). The fetal brain is most susceptible to ionizing radiation during weeks 8-15 after conception, and to a lesser extent during weeks 16-25, and least susceptible prior to the 8^{th} week and after the 25^{th} week (10). The threshold dose for mental retardation appears to be higher than 0.18 Gy between 8 and 15 weeks gestation, and higher than 0.5 Gy during the latter part of pregnancy (10). Most diagnostic procedures expose the fetus to much smaller doses (40). There is, however, some concern that *in utero* exposure even to low doses of radiation may increase the risk of childhood cancer, though the magnitude of the increase is unclear (41). As a result, the recommended maximum fetal dose is 0.05-0.1 Gy (10) and the general recommendation is to postpone radiotherapy until after delivery if possible (10). At the same time, several studies reported births of healthy children after radiotherapy of pregnant women for breast cancers and supradiaphragmatic Hodgkin's disease (with appropriate shielding of the fetus) (21;22;40;42).

In non-pregnant women of childbearing age ionizing radiation may damage ovarian function, cause premature ovarian failure, or trigger germ cell mutations, which can lead to congenital abnormalities in future offspring (26).

Studies of women exposed to the atomic-bomb radiation and their subsequently conceived offspring have indicated a higher rate of spontaneous abortion, but showed no increase in the risk of major congenital abnormalities compared with the children of women from the general population (9). These results corroborate studies of childhood cancer survivors reporting no increased risk of congenital abnormalities or genetic diseases in the offspring of women exposed to pre-gestational radiotherapy (43-45).

It has also been postulated that maternal gonadal exposure to radiation would decrease the male proportion of newborns by inducing recessive sex-linked lethal mutations (46). In addition, women previously treated with high-dose abdominal radiotherapy have – during subsequent pregnancies – an increased risk of spontaneous abortions (47;48), preterm deliveries (49), and LBW infants (43;44;47-49). These effects are most likely due to radiation-induced damage to the women's abdominopelvic structures (9;44).

Traditional ways of protecting the ovaries against the radiation damage are shielding of the ovaries, and, in case of pelvic lymph node irradiation, repositioning of the ovaries out of the irradiation field (oopheropexy) (50). Today, many young patients needing radiotherapy (or chemotherapy) are offered the option of cryopreservation of their ovarian tissue (51), while recent studies of ovarian tissue autotransplantation offer promising results (51). So far, however, only one Danish woman has become pregnant as a result of this method.

Chemotherapy

For decades, physicians believed that placenta shielded the fetus from the external environment. This belief was questioned in 1941 after the Australian physician, N. M. Gregg, observed that women who contracted rubella during the first trimester of pregnancy frequently gave birth to children with abnormalities of the heart, eyes and ears (52). Furthermore, the "thalidomide-disaster" of the late 1950s and early 1960s made it clear that maternal drug exposure in critical periods of pregnancy could result in congenital abnormalities (52). Thalidomide caused congenital abnormalities (*i.e.* phocomelia, spine

and central nervous system defects) in about 20-50% of newborns exposed *in utero* (53). By the time thalidomide was withdrawn from the market, the drug had caused more than 10,000 cases of congenital abnormalities worldwide (54). As a result, it is now generally accepted that the developing fetus may be adversely affected by exposure to drugs, especially when the exposure coincides with the organogenesis (52).

A potential teratogenic effect of chemotherapy during pregnancy depends on the agent used, the timing of exposure, the dose, and the characteristics affecting placental transfer. Use of chemotherapy during the first trimester increases the risk of miscarriage and congenital abnormalities (55). A review of 139 cases of first-trimester exposure to chemotherapy reported a total of 24 (17%) infants with congenital abnormalities after a single agent exposure, and a prevalence of 25% after combination-agent exposure (56).

Chemotherapy during the second and third trimesters may increase the risk of preterm birth, IUGR and stillbirth (10). Furthermore, the central nervous system continues to develop after the first trimester, which makes it sensitive to insults during the entire pregnancy (10). While exposure to chemotherapy after the first trimester does not cause macroscopic anatomical defects, it may have long-term subanatomical consequences, for example, by interfering with the neuronal proliferation and migration (10). However, a study of late side effects among 84 children whose mothers received chemotherapy, during pregnancy, for haematological malignancies did not show impairments in learning behaviour, or neurological abnormalities after a median follow-up of 18 years (57). Other potential risks of *in utero* chemotherapy exposure include childhood malignancy and long-term infertility (10). However, the knowledge regarding these issues is limited (10). Given all the evidence, it is generally recommended that chemotherapy is delayed until after the first trimester (10).

In non-pregnant women of childbearing age, chemotherapy can adversely affect fertility (58;59). The damage to the ovarian tissue depends on the agent used, the dose, and the age of the patient at treatment (60). Alkylating agents are particularly gonadotoxic with a high risk of inducing premature ovarian failure (50). In addition, women older than 35 years of age are more sensitive than younger women to the adverse effects of cytotoxic agents on reproductive function (50).

Chemotherapy is potentially mutagenic (9), with animal studies showing that it can cause mutations in oocytes and increase the risk of fetal abnormalities (50). However, human studies that examined the offspring of treated individuals did not report an increased risk of congenital abnormalities or genetic diseases (61-63).

Endocrine therapy

The use of anti-estrogenic therapy, such as tamoxifen, in pregnant breast cancer patients has been discouraged because of teratogenic effects seen in animal models (10). Direct evidence for teratogenesis in humans is very limited, with only isolated reports of rare forms of congenital abnormalities associated with tamoxifen use (64). Furthermore, uneventful use has been reported in pregnant patients with metastatic breast cancer (65).

1.4. Measuring birth outcome

Problems that arise during the course of the reproductive process define adverse outcomes in epidemiologic studies of pregnancy (66). As described above, cancer and cancer treatment may affect the risk of several adverse outcomes of pregnancy as well as the risk of diseases in offspring later in life. This thesis focuses on the prevalence of specific birth outcomes for children of cancer patients. It does not examine the risk of spontaneous or induced abortions, or diseases diagnosed later in life.

The birth outcomes examined are discussed in detail below:

Preterm birth

Preterm birth (defined as delivery before 37 completed weeks of gestation) is an important contributor to neonatal morbidity (67), and perinatal and neonatal mortality (68;69). Usually gestational age is calculated from the date of the last menstrual period or from a combination of that and ultrasound (66). A recent study found that the prevalence of preterm births in Denmark rose from 5.2% in 1995 to 6.3% in 2004, and that primiparity and multiple births were the most important contributing factors (70). The time of delivery depends both on the natural course of the pregnancy and on clinical interventions, which

may either shorten or prolong gestation. Given this mixture of spontaneous events and effects of medical interventions, the outcome of preterm birth itself is heterogeneous (66).

LBW at term

IUGR indicates failure by the fetus to reach its growth potential. Since the growth potential is unknown in most situations, it is difficult to define pathological intra-uterine growth. LBW (defined as birth weight less than 2,500 g) as a definition for pathological growth is not useful, because children in this group represent a mix of newborns whose growth is suboptimal, newborns delivered early, and newborns who are small for genetic reasons (66). As an alternative, many studies define IUGR as birth weight below the 10^{th} percentile or as two birth weight standard deviations below the mean birth weight for a given gestational age. However, children with a birth weight below the 10^{th} percentile are not always growth retarded, while some children with a birth weight above the 10^{th} percentile may be growth retarded if they fail to reach their genetically determined optimal weight.

We used the measure "LBW at term", which suggests that the child remains small despite having had adequate time for growth (66). The presumption is that a child with LBW at term is likely to be growth retarded.

Stillbirth

Stillbirth is one of the major causes of perinatal mortality. From 1973 to 2003 the prevalence of stillbirths in Denmark has declined from approximately 0.73% to 0.38% (71). Etiologic determinants of stillbirth differ markedly depending on whether it occurs antepartum or intrapartum. In developed countries the vast majority of stillbirths (85-90%) occur antepartum (72). Antepartum stillbirths are often caused by severe maternal, placental or fetal abnormalities, including preeclampsia, umbilical cord complications, IUGR, abruptio placentae, or infection (72). Maternal smoking, advanced age, multiparity and obesity are also widely recognized determinants of antepartum stillbirths; still about one fourth of them occur without a known cause (72).

Intrapartum fetal deaths usually results from fetal distress and/or obstructed labor and thus they often reflect poor access to or quality of clinical care during delivery (72).

Congenital abnormalities

Congenital abnormalities occur in 3-5% of all live-births (66). However, each individual type of congenital abnormality is rare, with the most common occurring in about 1/1000 live births (66). The etiologic events that generate structural abnormalities typically occur within the first 2-8 weeks post-conception, but the recognition of the abnormality may not occur until later in pregnancy (during ultrasound evaluation), at birth, in early childhood or in adulthood, or the abnormality may never be recognized (66). Because of the early-gestation onset of abnormalities, subsequent events, including spontaneous abortion, prenatal diagnosis and subsequent induced abortion, or survival of the fetus to birth, affect the degree to which prevalence of congenital abnormalities at birth differs from their incidence.

Male proportion of newborns

Approximately 51.3% of live-born children in Denmark are boys. There are at least two hypotheses concerning the effect of cancer on male proportion of newborns. First, it has been proposed that psychological stress related to severe life events around the time of conception (such as severe illness in a partner or death of a child) may reduce the male proportion of newborns through differential conception or differential abortion of male embryos (34). Thus, psychological stress, caused by a cancer diagnosis, may also increase rate of early male-fetus abortion.

Furthermore, alterations in the sex ratio of the offspring of cancer survivors have been suggested to be an indicator of germ-cell mutations (26). It has been proposed that mutagenic exposure (radiotherapy or chemotherapy) would increase the male-to-female ratio in newborns of male cancer survivors and decrease the male-to-female ratio in newborns of female survivors due to sex-linked lethal mutations (26). In 1958, Schull *et al.* described an altered sex-ratio in the expected direction for offspring of survivors of the atomic bombings of Hiroshima and Nagasaki (46), but this finding was refuted by further studies of the atomic bomb exposure victims in Japan (73). In addition, several studies that have examined the sex-ratio for offspring of childhood cancer survivors likewise failed to find significant alterations (63;74;75).

1.5. Review of the literature on birth outcome in women with breast cancer, cutaneous malignant melanoma, and Hodgkin's disease

With few exceptions, almost all prior studies among women with previous cancer that included control groups for birth outcome have been restricted to birth outcome among women diagnosed in childhood or adolesence. The majority of these studies found no increased prevalence of congenital abnormalities or genetic disease in offspring of survivors compared with the general population (61) or with offspring of siblings (45;62;63). In addition, offspring of childhood cancer survivors treated with potentially mutagenic therapy (abdominal radiotherapy and/or alkylating chemotherapy) were not reported to have an increased risk of congenital abnormalities or genetic disease compared with offspring of survivors not so treated (44;63). Moreover, a case-control study based on 50,032 children with congenital abnormalities found that the parents of these children were not more likely to have been treated for cancer than parents of controls (76).

However, late effects of treatment for female childhood cancer patients may include an increased risk of preterm birth and/or low birth weight among their offspring, with risks concentrated among women who received pelvic irradiation (43;44;47-49). Mulvihill *et al.* (77) in a study of 58 pregnancies occurring after treatment of adult women for various malignancies, found an increase in LBW (mainly due to preterm birth) and stillbirth, but no excess of congenital abnormalities, during the first year after cancer treatment.

Despite the overall reassuring results from these studies of birth outcome in women with a history of cancer, their conclusions were, for the most part, based on combined results for many different types of tumors and, with few exceptions (76;77), only women with childhood or adolescent cancers were included. Therefore, the results from these studies may not apply to adult women treated for specific cancers, such as breast cancer, melanoma or Hodgkin's disease. As described in the following literature search, data concerning birth outcome in women diagnosed with these three cancers before, during or shortly after pregnancy are very limited.

Literature search

Below is a summary of the existing epidemiologic evidence of the adverse effect of maternal breast cancer, melanoma, and Hodgkin's disease. We classified

studies as case-series if they reported birth outcome in a cohort of women with cancer without comparing it with the outcome of a control group. However, if the authors computed risk estimates for adverse birth outcome in comparison with the general population, the study was classified as a cohort study.

Tables I, II and III show selected studies of birth outcome in women with, respectively, breast cancer, melanoma and Hodgkin's disease. The studies listed in the tables were selected based on the following criteria: We selected only studies that examined the same outcomes as in this thesis (*i.e.* preterm birth, LBW at term (or LBW), stillbirths, congenital abnormalities, male proportion of newborns, mean birth weight). We excluded studies that reported overall risks of adverse birth outcome for survivors of different cancers combined (*i.e.* (44;45;61-63;76;77). In addition, we excluded case-reports, case-series, comments and reviews.

Studies on breast cancer and birth outcome

To review the literature, we searched the MEDLINE database and used a combination of the MeSH (Medical Subject Heading) terms "Breast Neoplasms" [MAJR] (Major Topic headings only), and "Pregnancy" [MAJR], limiting the search to include only studies on human females, in English language, and with an abstract. This search strategy yielded 212 studies. Several more studies were identified through communication with other researchers and by reviewing the reference lists of relevant articles. We found that nearly all studies of women diagnosed with breast cancer before pregnancy had maternal prognosis as the main outcome (1;7;8;78-81). None of these studies included a control group for birth outcome and several of them lacked information on birth weight (7;8;78-81), stillbirths (7;8;81), and congenital abnormalities (1;7;8;78;81).

At the time the search was conducted, it did not reveal any cohort studies addressing birth outcome in women with previous breast cancer. However, a population-based cohort study from Sweden was published nine months after our study (82); its main results appear in Table I.

Case-series ranging from four to 121 women, have shown that the majority of women diagnosed with breast cancer during or shortly after pregnancy give birth to healthy children (55;78;83-88). Table I shows the main results of the two studies with control groups for birth outcome. In these studies, however, no distinction was made of whether the women had been diagnosed with breast cancer during or shortly after pregnancy, nor was parity or calendar time of birth adjusted for (20;89). Only one study (20) reported risk estimates for birth outcome – and only for preterm birth and very LBW. Thus, no prior cohort study has computed risk estimates of LBW at term, stillbirth or congenital abnormalities, or estimated the male proportion of offspring for newborns of breast cancer patients diagnosed during or shortly after pregnancy.

Studies of cutaneous malignant melanoma and birth outcome

To review the literature, we searched the MEDLINE using the MeSH terms "Melanoma" [MAJR] and "Pregnancy" (Limits: Only items on human females, in English language, and with abstracts). In addition, the reference lists of relevant articles as well as the book "Cancer in pregnancy: Maternal and fetal risks" (90) were reviewed.

No cohort study of birth outcome in women diagnosed with melanoma before pregnancy has been published, and only two cohort studies (16;91) examined birth outcome in women diagnosed with melanoma during or shortly after pregnancy (Table II). Of those, only O'Meara *et al.* (16) computed risk estimates. None of the studies computed risk estimates for LBW at term, stillbirth, or congenital abnormalities, or reported the male proportion of offspring.

Studies of Hodgkin's disease and birth outcome

Through a regular search in the MEDLINE using the MeSH terms "Hodgkin disease" [MAJR] and "Pregnancy" combined with manual searches and communication with other researchers, several case-series reporting birth outcome in women diagnosed with Hodgkin's disease before pregnancy were identified (23;92-103). A few of these case-series, which included birth outcome of 8 to 54 women with previous Hodgkin's disease, found a high prevalence of stillbirths

(92), congenital abnormalities, preterm birth and LBW among newborns (93). The remaining studies reported little, if any, detrimental effect of a preceding Hodgkin's disease on birth outcome among women capable of becoming pregnant. Likewise, several case-series found normal birth outcome for women diagnosed with Hodgkin's disease during or shortly after pregnancy (22;42;57;104-109).

Table III shows the results of seven studies with control groups for birth outcome, only three of which adjusted for potential confounding factors (20;21;48). Although there seems to be a high – relative to sibling controls - proportion of preterm deliveries among survivors of childhood Hodgkin's disease (49), the overall outcomes reported in these studies are reassuring. However, with two exceptions (48;49), the results for birth outcome in women with previous Hodgkin's disease are based on small number of observations, and no study has computed risk estimates for LBW at term or for congenital abnormalities among newborns of women diagnosed with Hodgkin's disease before, during or shortly after pregnancy.

Conclusion

Few data exist on birth outcome in women with breast cancer, cutaneous malignant melanoma or Hodgkin's disease. Important limitations in the existing studies are summarized below:

- Only one other study of women with previous breast cancer has computed relative risk estimates for adverse birth outcome (published nine months after our study). No study has computed relative risk estimates for adverse birth outcome in women with previous melanoma.
- None of the existing cohort studies of birth outcome in women diagnosed with breast cancer or with melanoma during or shortly after pregnancy computed relative risk estimates for LBW at term, stillbirth, or congenital abnormalities, none has estimated the male proportion of newborns or controlled the analyses for parity or calendar time of birth.

- The existing cohort studies of birth outcome in women with previous Hodgkin's disease were (with two exceptions) based on small study samples and did not control for potential confounders (with one exception). No study computed relative risk estimates for congenital abnormalities.
- None of the existing studies of birth outcome in women diagnosed with Hodgkin's disease during or shortly after pregnancy computed relative risk estimates for LBW at term, stillbirth or congenital abnormalities, or estimated the male proportion of newborns, or controlled the analyses for parity or calendar time of birth.

Table I. Studies of birth outcome in women with breast cancer.

Breast cancer diagnosed before pregnancy						
Author Country, year	Period of cancer diagnosis	Design	Number	Adjustment	Relative effect estimates	Results for birth outcome
Dalberg *et al.* Sweden 2006 (82)	Not stated	Cohort study Comparison: Birth outcome in the general population	331 births by women with previous breast cancer	Yes, maternal age, parity, and year of delivery	OR for preterm birth (<32 wk and 32-36 wk), stillbirth, LBW (<1,500 g and 1,500-2,499 g) CAs, and SGA	$OR_{<32\ wk}$ = 3.2 (95% CI: 1.7-6.0) $OR_{32\text{-}36wk}$ = 1.5 (95% CI: 1.0-2.3) $OR_{stillbirth}$ = 1.2 (95% CI: 0.3-4.7) $OR_{<1,500\ g}$ = 2.9 (95% CI: 1.4-5.8) $OR_{1,500\ g\text{-}2,499\ g}$ = 1.0 (95% CI: 0.6-1.8) OR_{CAs} = 1.7 (95% CI: 1.1-2.5) OR_{SGA} = 1.2 (95% CI: 0.9-1.4)
Breast cancer diagnosed during or shortly after pregnancy						
Author Country, year	Period of cancer diagnosis	Design	Number	Adjustment	Relative effect estimates	Results for birth outcome
Smith *et al.* USA, 2001 (20)	1992-97	Cohort study Comparison: Control group not specified	Births by 423 women who were diagnosed from 9 months preceding delivery until 12 months after delivery	Yes, maternal age	OR for preterm birth and very LBW	$OR_{very\ LBW}$= 2.0 (95% CI: 1.0-4.1) $OR_{preterm\ birth}$=2.2 (95% CI: 1.7-2.8)
Zemlickis *et al.* Canada 1992 (89)	1958-87	Cohort study Comparison: Births of age-matched controls exposed to non-teratogenic drugs in pregnancy	85 births by 118 women who were pregnant no earlier than 9 months before and no later than 3 months after their first treatment	Yes, maternal age (by matching) and mean BW was adjusted for GA.	No	Lower mean birth weight (p=0.02) Shorter mean GA (p=0.01) Higher proportion of preterm births (p=0.003) Mean birth weight=3010 g vs. 3451 g in controls Mean GA=38.3 wk. vs. 39.4 wk. in controls Preterm births=26.7% Stillbirths=2.4% CAs=0.0%

OR = Odds ratio, LBW = Low birth weight, GA = Gestational age, CAs = Congenital abnormalities, SGA = Small for GA

Table II. Studies of birth outcome in women with cutaneous malignant melanoma.

Cutaneous malignant melanoma (CMM) diagnosed during or shortly after pregnancy						
Author Country, year	Period of cancer diagnosis	Design	Number	Adjustment	Relative effect estimates	Results for birth outcome
O'Meara *et al.* USA, 2005 (16)	1991-99	Cohort study Comparison: Births by melanoma free women	149 births by women diagnosed during pregnancy and 263 births by women diagnosed within 12 months of delivery	Yes, maternal age and race	OR for preterm birth and LBW	Women diagnosed during pregnancy: OR_{LBW}=0.8 (95% CI: 0.3-1.8) $OR_{preterm\ birth}$=0.9 (95% CI: 0.5-1.6) Stillbirths=0%. Women diagnosed within 12 months after delivery: No increased risk of LBW and preterm birth Stillbirths=0%
Ravid *et al*. Canada, 1996 (91)	Not stated, but over a period of 30 years	Cohort study Comparison: Births by age-matched controls	18 births of women diagnosed during pregnancy	Yes, maternal age (by matching)	No	Lower mean birth weight (*p*=0.15) No difference in mean GA (P=0.53) Mean birth weight = 3036 g vs. 3392 g in controls Mean GA=39.5 wk. vs. 40.1 wk. in controls Stillbirths=5.6% CAs=5.6%

OR = Odds ratio, LBW = Low birth weight, CAs = Congenital abnormalities, GA = Gestational age, SGA = Small for GA

Table III. Studies of birth outcome in women with Hodgkin's disease.

Hodgkin's disease diagnosed before pregnancy						
Author Country, year	Period of cancer diagnosis	Design	Number	Adjustment	Relative effect estimates	Results for birth outcome
Janov *et al.* USA, 1992 (110)	1966-86	Cohort study Comparison: Birth outcome in the general population	15 births by women with previous HD	No	RR for LBW	RR_{LBW}=2.5 (95% CI: 0.3-9.0) CAs=0.0%
Swerdlow *et al.* UK, 1996 (111)	1970-91	Cohort study Comparison: Birth outcome in the general population	49 births by 16 women with previous HD and by wives of 11 men with a history of HD	No	RR for preterm birth, LBW, and male sex in newborn	$RR_{preterm}$=0.88 (95% CI: 0.32-2.46) RR_{LBW}=1.58 (95% CI: 0.52-4.26) $RR_{male\ sex}$=0.91 (95% CI: 0.52-1.59) Stillbirths=0.0% Minor/major CAs=8.2% (not different from general population) Chromosomal abnormalities=0.0%
Holmes & Holmes USA, 1978 (112)	1944-75	Cohort study Comparison: Birth outcome in siblings	52 births by 29 women with a history of HD	No	No	No overall increase in risk of abnormal birth outcome (stillbirth and CA combined) (p=1.00). No increased risk associated with radiotherapy alone (p=0.25). Increased risk of abnormal birth outcome associated with radiotherapy and chemotherapy combined (p=0.047).
Green *et al.* USA, 2002 (48)	1970-86	Cohort study Comparison: Birth outcome in siblings	729 births by women with childhood HD	Yes, maternal age, smoking, alcohol use and education	RR for stillbirth	$RR_{stillbirth}$=1.6 (95% CI: 0.64-4.03)

Signorello *et al.* USA, 2006 (49)	1970-86	Cohort study Comparison: Birth outcome in siblings	337 births by women with childhood HD	No	No	$Proportion_{preterm\ birth}$=19.2% vs. 12.5% in controls $Proportion_{LBW}$=5.9% vs. 4.2% in controls $Proportion_{SGA}$=9.0% vs. 9.2 in controls
Hodgkin's disease diagnosed during or shortly after pregnancy						
Author Country, year	Period of cancer diagnosis	Design	Number	Adjustment	Relative effect estimates	Results for birth outcome
Janov *et al.* USA, 1992 (110)	1966-86	Cohort study Comparison: Birth outcome in the general population	10 births by women who were pregnant from 12 months before diagnosis until end of treatment	No	RR for LBW	3 premature children with LBW (1 induced preterm delivery) RR_{LBW}=5.6 (95% CI: 1.2-17.5) CAs=0.0%
Smith *et al.* USA, 2001 (20)	1992-97	Cohort study Comparison: Control group not specified	Births by172 women who were diagnosed from 9 months before until 12 months after delivery	Yes, maternal age	OR for prematurity and very LBW	$OR_{very\ LBW}$=3.6 (95% CI: 1.5-8.9) $OR_{prematurity}$=2.4 (95% CI: 1.6-3.5)
Lishner *et al.* Canada, 1992 (21)	1958-84	Cohort study Comparison: Births of age-matched controls exposed to non-teratogenic drugs in pregnancy	40 births by 48 women who were pregnant no earlier than 9 months before and no later than 3 months after their first treatment	Yes, maternal age (by matching)	No	No difference in mean birth weight (p=0.7), mean GA (p=0.3), or stillbirths (p=0.08). Mean birth weight = 3325 g vs. 3371 g in controls Mean GA = 39.7 wk vs. 40.0 in controls Preterm births=3.4% Stillbirths=5.0% CAs=3.2%

HD = Hodgkin's disease, RR = Relative risk, OR = Odds ratio, LBW = Low birth weight, CAs = Congenital abnormalities, GA = Gestational age

1.6. Considerations for choice of study design

In order to better understand the effect of cancer and its treatment on birth outcome we need large and valid sources of information with prospective data collection and complete and accurate registration of birth outcome. Properly designed population-based observational studies take into consideration potential confounding factors, such as maternal age, parity, calendar time of birth, and gestational age.

In a cohort study, women exposed to cancer/cancer therapy and a group of unexposed women can be followed forward in time to directly measure and compare the incidence (or prevalence for birth outcome) of the outcome in question between the groups (113). Measuring exposure before the outcome has occurred is expected to reduce differential misclassification. A further advantage of a cohort study is the ability to study several outcomes in relation to the same exposure. However, cohort studies of rare outcomes, such as LBW at term, stillbirth, and congenital abnormalities may be inefficient. This obstacle may be circumvented by conducting a historical cohort study, where the cohort is identified from past records and then followed to the present time.

Most adverse birth outcomes have low prevalence, and because the statistical precision of the effect estimates is mainly determined by the number of adverse birth outcomes, the sample size becomes an issue of special interest (114). This is particularly relevant for congenital abnormalities, because each known teratogen increases the risk of a selected congenital abnormality, rather than uniformly affecting the rates of all abnormalities (53). However, it would require a sample of over 20,000 exposed pregnancies to detect a doubling of the risk for a relatively common specific congenital abnormality (*e.g.* 1/1000 live-births) (53). Thus, small cohort studies can detect only large increases in the risk of specific congenital abnormalities, and absence of observed effect in such studies cannot serve as an assurance of safety.

Arguably, identical research questions can be addressed in a case-control study, with markedly smaller sample sizes. Odds ratios, obtainable in case-control studies, are reasonable estimators of the relative risk, particularly when a birth outcome under study is rare (114). At the same time, the case-control design is unsuitable for examining several

outcomes in relation to a rare exposure. Such is the situation with a specific cancer type diagnosed before, during, or shortly after pregnancy, which requires identification of several cases of different birth outcomes, only few of which would have mothers with the specific cancer of interest. Moreover, in a case-control study incidence rates (or- in this case- prevalence proportions) and absolute risks cannot be calculated.

In this thesis, we conducted historical cohort studies of existing population-based records, enabling us to examine six different birth outcomes (preterm birth, LBW at term, stillbirth, and congenital abnormalities, mean birth weight and the male proportion of newborns) among children of women who had been diagnosed with breast cancer, melanoma, or Hodgkin's disease before, during, or shortly after pregnancy.

1.7. Hypothesis of the thesis

Because of the possible adverse effects of cancer and cancer treatment on birth outcome, we hypothesized that newborns of women with breast cancer, melanoma, or Hodgkin's disease have higher than the general population risks of

- preterm birth
- LBW at term
- stillbirth
- congenital abnormalities

We further hypothesized that newborns of these women may have lower than that of population controls

- mean birth weight
- male proportion of newborns

1.8. Specific aims

Study I. Women with breast cancer

- To examine risks of preterm birth, LBW at term, stillbirth, and congenital abnormalities as well as mean birth weight and male proportion of newborns in cohorts of women diagnosed with breast cancer before or during pregnancy, or within two years after delivery. The comparison cohorts comprised newborns of women without cancer.
- To examine the association of newborn's sex and maternal pre-gestational treatment (surgery alone or other) with the birth outcome.

Study II. Women with cutaneous malignant melanoma

- To examine risks of preterm birth, LBW at term, stillbirth, and congenital abnormalities as well as mean birth weight and male proportion of newborns in cohorts of women diagnosed with melanoma before or during pregnancy, or within two years after delivery. The comparison cohorts comprised newborns of cancer-free women.
- To examine the association between child's sex and birth outcome.

Study III. Women with Hodgkin's disease

- To examine risks of preterm birth, LBW at term, stillbirth and congenital abnormalities as well as mean birth weight and male proportion of newborns in cohorts of women diagnosed with Hodgkin's disease before or during pregnancy, or within two years after delivery. The comparison cohorts comprised newborns of women without cancer.
- To examine the association of child's sex, maternal radiotherapy, or calendar time of Hodgkin's disease diagnosis with birth outcome in women diagnosed with Hodgkin's disease before pregnancy.

2. Material and methods

2.1. Data sources

All studies are historical cohort studies based on data from Danish administrative registries with nationwide coverage.

The Danish Cancer Registry

The Danish Cancer Registry is a population-based nationwide registry with data on incident cases of cancer in Denmark since 1943 (115). Until 1987, reporting to the Registry was voluntary, and a small fee was paid for each notification form received. In 1987, reporting became mandatory for all medical doctors. Each individual record includes civil registration number, diagnosis with the date, method of verification, spread of the tumor at time of diagnosis (local, regional, distant metastases), and treatment administered within four months after the diagnosis (*i.e.* surgery (yes/no), radiotherapy (yes/no), chemotherapy (yes/no)). All available data are reclassified to the modified International Classification of Diseases, 7th revision (ICD-7) (115). The registry receives information from hospital departments (including departments of pathology and forensic medicine), general practitioners, and practicing specialists. Annual links to the National Hospital Discharge Registry and the National Death Certificate Files ensure inclusion of the under-reported cases to the Cancer Registry (115).

The Danish Medical Birth Registry

Since 1973, the Danish Medical Birth Registry has kept records of all births in Denmark, including home births. Data in this registry are obtained from birth notifications, filled in by midwives. The variables include the civil registration number of the mother and child (for live-born children), date and place of birth, maternal age at the time of delivery, stillbirth, gestational age, birth weight, parity, whether the birth was medically induced, whether elective section was performed, and whether a congenital abnormality was present at time of birth (there are no data on the specific type of abnormality) (116). Since 1991, mother's self-reported smoking status at the first visit to the midwife has also been recorded.

The National Hospital Discharge Registry

The National Hospital Discharge Registry has collected nationwide data on 99.4% of all discharges from Danish somatic hospitals since 1977 (117). Since 1995, data on outpatients have been included as well. The recorded information includes the civil registration number, dates of admission and discharge, the surgical procedure(s) performed, and up to 20 physician-given discharge diagnoses classified according to the Danish version of the International Classification of Diseases (ICD-8 before 1994 and ICD-10 from 1994 onward, since ICD-9 was never used in Denmark).

The Civil Registration System

Unambiguous linkage of records from the different registries is possible via the unique 10-digit civil registration number that has been assigned, since 1968, to all permanent and temporary Danish residents, by the Central Office of Civil Registration. The civil registration number is stored in the Danish Civil Registration System together with information on vital status, emigration, address, and nuclear family members' civil registration numbers.

2.2. Study population and comparison cohorts

Table IV summarizes, for the three thesis studies, periods of cancer diagnoses and pregnancy, and describes study population and birth outcomes.

Study population (Study I, II, and III)

We used the Danish Cancer Registry to trace all women who were diagnosed with breast cancer (ICD-7 codes 170.0-170.5) between January 1, 1943 and December 31, 2002. We excluded all cases of carcinoma *in situ.* We linked the data from the Cancer Registry with the Danish Medical Birth registry to establish a cohort of all Danish women with a record of breast cancer diagnosis who gave birth between January 1, 1973 and December 31, 2002 (Study I). The first breast cancer in the study population was diagnosed in 1970.

Likewise, we established cohorts for all Danish women who were recorded with a diagnosis of cutaneous malignant melanoma (ICD-7 codes 190.0-190.9) or Hodgkin's disease (ICD-7 code 201) recorded between January 1, 1970 and December 31, 2002, who

gave birth between January 1, 1973 and December 31, 2002 (Study II and III). In the melanoma cohort we excluded all cases of carcinoma *in situ.* Births were included in the respective studies if the mothers were diagnosed with breast cancer, melanoma, or Hodgkin's disease before or during pregnancy, or up to two years post partum. Since multiple births have been associated with an increased risk of adverse birth outcome (118), we restricted all analyses to singleton births to avoid potential confounding.

Comparison birth cohorts

For each birth by a woman with breast cancer, melanoma, or Hodgkin's disease, we randomly selected from the Birth Registry, 50 singleton comparison births by 50 different cancer-free women, matched to the exposed newborns on month and year of the birth and maternal county of residence. If fewer than 50 births fulfilled the matching criteria, we used all the available births. On average, 48 comparison births were selected for each exposed birth.

There is usually little point in expending resources to achieve a ratio between the exposed cohort and the comparison cohort above 4 or 5, since nearly all the information achievable is already extracted from the exposed cohort using a comparison cohort four or five times as big (119). However, in our registry based studies the cost of obtaining the additional information was negligible. Furthermore, a larger comparison cohort facilitates stratified analyses.

2.3. Data on birth outcomes

We examined the following birth outcomes in all three studies:

1. Preterm birth: delivery before 37 completed weeks of gestation.
2. LBW at term: birth weight less than 2,500g in those born with at least 37 completed weeks of gestation.
3. Stillbirth: delivery of a dead fetus at 28 or more completed weeks of pregnancy.
4. Congenital abnormalities (including chromosomal abnormalities) diagnosed during the first year of life: ICD-8 codes: 740.00 to 759.99 and ICD-10 codes: Q0.00 to Q99.9.
5. Mean birth weight.
6. Male proportion of newborns.

Except for congenital abnormalities, data on all these outcomes were obtained from the Medical Birth Registry. For live-born children, data on congenital abnormalities (including chromosomal abnormalities) diagnosed during the first year of life were collected from the National Hospital Discharge Registry. Thus, data on congenital abnormalities applied to births from 1977 to 2002. Diagnoses of congenital dislocation of the hip and undescended testis were excluded because of their poor validity (120).

2.4. Data on potential confounders

A confounder is a factor which is 1) a risk factor for the outcome, 2) associated with the exposure, and 3) not a consequence of the exposure. Some of the potential confounding factors in studies of birth outcome in women with cancer include maternal age (since high maternal age is both associated with cancer and poor birth outcome (121-123)).

Furthermore, parity, calendar time of birth, and gestational age may be associated with cancer and are related to birth outcome. Data on these potential confounding factors were collected from the Medical Birth Registry. Other potential confounders are discussed under "Methodological considerations."

2.5. Statistical Analysis

Birth weights of 7,000 g or greater were assumed to be coding errors and such newborns were excluded (124). Similarly, we excluded births with a recorded GA of less than 20 weeks or more than 44 weeks and births with missing GA data (Study I: N = 21 in the exposed cohort and N = 969 in the comparison cohort, Study II: N = 29 in the exposed cohort and N = 1,868 in the comparison cohort, Study III: N = 20 in the exposed cohort and N = 698 in the comparison cohort).

We classified the births of women with breast cancer (Study I), melanoma (Study II), and Hodgkin's disease (Study III) into three subgroups according to the time of cancer diagnosis in relation to pregnancy. Each birth was treated as an independent event. **Group 1** included births of women who were diagnosed with cancer before pregnancy. (We only included the *first birth after* the cancer diagnosis, since we assumed that any adverse effects of the cancer or its therapies would be more likely to affect the birth closest to the

time of diagnosis). **Group 2** included the births by women who were diagnosed with the cancer *during pregnancy* (*i.e.* between the first day of the last menstruation and the date of birth). **Group 3** included births by women who were diagnosed with the cancer *after delivery* (*i.e.* between the day following the delivery up to two years thereafter). For women giving birth more than once in this two-year period, only the last birth before the cancer diagnosis was included based on the assumption that the preclinical cancer would be more likely to affect the birth closest to the time of diagnosis.

In all three studies, we computed prevalence odds ratios (POR) as estimates of the relative risks for preterm birth, LBW at term, stillbirth, and congenital abnormalities. The PORs had been adjusted for month and year of birth and maternal county of residence by matching. We used unconditional logistic regression analysis to further adjust for maternal age and parity. We also included the calendar period of the birth (1973-1986, 1987-1994, 1995-2002) , as an independent variable in the model, which did not change the risk estimates in any of the three studies. Since the aim of the studies was to examine the risk of adverse birth outcomes among live-born children, stillbirths were excluded from the analyses of preterm birth, LBW at term, mean birth weight, and congenital abnormalities (the latter were not recorded for stillbirths).

For each type of cancer defining a study's exposure, we computed the difference between proportions of male newborns of mothers with cancer and that of comparison mothers. We used linear regression to model mean birth weight and to estimate differences in mean birth weight between children of exposed and unexposed mothers. We adjusted the models for maternal age, parity, gestational age, and calendar period of the birth.

In **study I**, we additionally stratified the analyses by sex of the newborn for births in exposure Groups 1 and 3, thus evaluating any gender differences in the putative association between breast cancer and birth outcome. (The small number of outcome events precluded such stratified analyses in Group 2). For births in Group 1, we also examined whether treatment of the mother modified the POR estimates by repeating the analyses in strata of births of women treated with surgery alone and births of women who received other treatment (*i.e.* radiotherapy, chemotherapy, or endocrine therapy).

In **study II**, we conducted analyses analogous to those in study I to examine the effect modification by child's sex in Groups 1 and 3; Group 2 had too few events. Since cardiovascular congenital abnormalities are more frequent relative to other types (125), we computed separate POR for cardiovascular (codes: 746.09 to 747.99 in ICD-8 and Q20.0 to Q28.9 in ICD-10) and all other abnormalities in Groups 1 and 3.

In **study III**, we examined whether sex of the child or maternal radiotherapy modified the POR estimates for births in Group 1, by repeating the analyses in strata of boys and girls and strata of births of women who were treated with radiotherapy and women who were not. In order to examine potential modification by calendar period of Hodgkin's disease diagnosis, we additionally stratified the analyses in Group 1, by calendar period of Hodgkin's disease diagnosis (1970-1980 (reference), 1981-1990, 1991-2000). We used Wald chi-square statistics to test the hypothesis of homogeneity of the POR estimates for congenital abnormalities in 1981-1990 and 1991-2000. The low count of outcome events in Group 2 and 3 precluded stratified analyses in these groups.

All estimates were presented with 95% confidence intervals (95% CI). We analyzed the data with SAS software, version 8.2

Table IV. Summary of studies I to III.

Study	Period of cancer diagnosis	Period of delivery	Study population	Birth outcomes
I. Birth outcome in women with breast cancer	1943-2002	1973-2002	All women diagnosed with breast cancer: a) before pregnancy, b) during pregnancy, or c) within 2 years after delivery	Preterm birth, LBW at term, stillbirth, and congenital abnormalities (overall and according to sex of the child and maternal treatment before pregnancy). Mean birth weight and male proportion of newborns.
II. Birth outcome in Danish women with cutaneous malignant melanoma	1970-2002	1973-2002	All women diagnosed with melanoma: a) before pregnancy, b) during pregnancy, or c) within 2 years after delivery	Preterm birth, LBW at term, stillbirth, and congenital abnormalities (overall and according to sex of the child). Mean birth weight and male proportion of newborns.
III. Hodgkin's disease and birth outcome: A Danish nationwide cohort study	1970-2002	1973-2002	All women diagnosed with Hodgkin's disease: a) before pregnancy, b) during pregnancy, or c) within 2 years after delivery	Preterm birth, LBW at term, stillbirth, and congenital abnormalities (overall and according to sex of the child, maternal radiotherapy, and time of Hodgkin's disease diagnosis in women diagnosed before pregnancy). Mean birth weight and male proportion of newborns.

3. Results

The main results of the three studies are summarized below along with some additional data that were not reported in the papers.

3.1. Study I. Birth outcome in women with breast cancer

Altogether there were 695 singleton births delivered by women with breast cancer. Of these, 216 births occurred in Group 1 (breast cancer diagnosed before pregnancy), 37 occurred in Group 2 (breast cancer diagnosed during pregnancy), and 442 occurred in Group 3 (breast cancer diagnosed within two years of delivery).

Birth outcome

The prevalence of male newborns of women with breast cancer in Group 1 was 50.0%, compared with 52.2% among the matched comparison mothers, difference = -2.2%, (95% CI: -8.9; 4.5). The corresponding findings were 48.6% versus 52.0% (difference = -3.4%, 95% CI: -20; 13) for Group 2, and 53.4% versus 50.9% (difference = 2.5%, 95% CI: -2.2; 7.2) for Group 3.

No stillbirth to a mother with breast cancer was observed. For births in Group 1, we found no substantial increase in the risk of any of the examined birth outcomes (Table V). For births in Group 2, the risk of preterm birth increased eight-fold (POR = 8.1, 95% CI: 3.8-17), although 10 of the 12 preterm deliveries among the women with breast cancer were elective. For Group 3, the POR was 1.4 (95% CI: 1.0-2.0) for preterm birth, and 1.4 (95% CI: 0.7-2.8) for LBW at term. The prevalence of congenital abnormalities was not increased.

Stratification according to sex of the newborns had no substantial effect on the estimates in Group 1. In Group 3, boys had an increased risk of LBW at term (POR = 2.9; 95% CI: 1.3-6.3), and girls had a decreased risk (PR = 0.3; 95% CI: 0.03-2.0), when compared to children of cancer-free mothers. Stratification according to mother's treatment in Group I (surgery alone or other treatment) did not change the overall results (Table VI).

It was estimated by multiple linear regression that newborns of women in Group 2 had, on average, birth weight 240 g (95% CI: -404; -76) less than newborns of matched comparison mothers. Mean birth weight of the newborns of women in Groups 1 and 3 was nearly the same as that of matched unexposed newborns.

Table V. Prevalence odds ratios of birth outcome in women with breast cancer

Group 1: Birth outcome in women diagnosed with breast cancer before pregnancy.

Group 2: Birth outcome in women diagnosed with breast cancer during pregnancy.

Group 3: Birth outcome in women diagnosed with breast cancer within two years after delivery.

	Breast Cancer Cohort Outcome/Total (%)		Comparison Cohort Outcome/Total (%)		Prevalence odds ratio* (95 % CI)	Prevalence odds ratio† (95 % CI)
Births in Group 1	(N=216)		(N=10,453)			
Preterm birth‡	14/216	(6.5)	507/10,414	(4.9)	1.4 (0.8-2.3)	1.3 (0.7-2.2)
LBW at term‡	3/202	(1.5)	137/9,885	(1.4)	1.1 (0.3-3.4)	1.2 (0.4-3.8)
Stillbirth	0/216	(0.0)	39/10,453	(0.4)	-	-
Abnormalities‡§	7/203	(3.4)	369/9,775	(3.8)	0.9 (0.4-1.9)	0.9 (0.4-1.9)
Births in Group 2	(N=37)		(N=1,795)			
Pretem birth‡	12/37	(32)	102/1,785	(5.7)	7.9 (3.9-16)	8.1 (3.8-17)
LBW at tem‡	1/25	(4.0)	19/1,679	(1.1)	3.6 (0.5-28)	5.3 (0.6-51)
Stillbirth	0/37	(0.0)	10/1,795	(0.6)	-	-
Abnormalities‡§	1/35	(2.9)	53/1,685	(3.1)	0.9 (0.1-6.7)	0.5 (0.1-3.6)
Births in Group 3	(N=442)		(N=21,195)			
Pretem birth‡	33/442	(7.5)	1,143/21,120	(5.4)	1.4 (1.0-2.0)	1.4 (1.0-2.0)
LBW at term‡	9/408	(2.2)	329/19,917	(1.7)	1.3 (0.7-2.6)	1.4 (0.7-2.8)
Stillbirth	0/442	(0.0)	75/21,195	(0.4)	-	-
Abnormalities‡§	16/389	(4.1)	685/18,519	(3.7)	1.1 (0.7-1.9)	1.1 (0.6-1.8)

* Adjusted for month and year of the birth and maternal county of residence (by matching).

† Further adjusted for maternal age and parity. Prevalence odds ratios for congenital abnormalities were additionally adjusted for gestational age.

‡ Stillborn babies were excluded from the analyses of preterm birth, low birth weight at term and congenital abnormalities

§ Data on congenital abnormalities included births from 1977 to 2002.

Table VI. Birth outcome stratified according to maternal treatment.

Group 1 (N=216)*	Surgery alone Outcome/total (%)	Adjusted prevalence odds ratio (95% CI)†	Other treatment Outcome/total (%)	Adjusted prevalence odds ratio (95% CI)†
	N = 99		N = 112	
Preterm birth	6/99 (6.1)	1.2 (0.5-2.8)	8/112 (7.1)	1.3 (0.6-2.8)
LBW at term	2/93 (2.2)	1.4 (0.3-6.3)	1/104 (1.0)	0.8 (0.1-6.2)
Stillbirth	0/99 (0.0)	-	0/112 (0.0)	-
Abnormalities	3/97 (3.1)	0.8 (0.2-2.6)	4/101 (4.0)	1.1 (0.4-3.0)

* Five births were excluded because of missing data on treatment.

† Controlled for month and year of the birth and county of mother's residence by matching, and adjusted for maternal age and parity. Prevalence odds ratios for congenital abnormalities

3.2. Study II. Birth outcome in Danish women with cutaneous malignant melanoma

Of the 1,059 singleton births delivered by women with melanoma, 620 occurred in Group 1 (melanoma diagnosed before pregnancy), 88 occurred in Group 2 (melanoma diagnosed during pregnancy), and 351 occurred in Group 3 (melanoma diagnosed within two years after delivery). The proportion of melanomas registered as localized at time of diagnosis was 95% for women in Group 1, 93% for women in Group 2 and 92% for women in Group 3. This information was missing for 5%, 1% and 4% in Groups 1 to 3, respectively.

Birth outcome

The proportion of male newborns of women with melanoma consistently exceeded the proportion of male newborns of the matched comparison mothers (53.2% versus 51.7%, difference = 1.5%, (95% CI: -2.5; 5.5) for Group 1, 56.8% versus 51.9%, difference = 4.9%, (95% CI: -5.5; 15) for Group 2, and 58.4% versus 51.9%, difference = 6.5%, (95% CI: 1.3; 12) for Group 3.

There was no stillbirth among the births delivered by mothers with melanoma in Groups 1 and 2, and no substantially increased risk of preterm birth, LBW at term, or congenital abnormalities compared with the matched comparison cohort. For newborns of mothers in Group 3, the POR of stillbirth was 4.6 (95% CI: 1.7-12.3). We did not identify any

characteristics consistently in common to all of the stillborn children in Group 3. There was no increased risk of preterm birth, LBW at term or congenital abnormalities in this group (Table VII).

The POR for cardiovascular congenital abnormalities and other abnormalities were 1.2 (95% CI: 0.6-2.5) and 1.1 (95% CI: 0.7-1.7), respectively, in Group 1 and 0.7 (95% CI: 0.2-2.7) and 1.2 (95% CI: 0.6-2.2), respectively, in Group 3. Stratification according to sex of the newborn in Groups 1 and 3 did not change the overall risk estimates substantially. Newborns in Groups 1 and 3 had nearly the same mean birth weight as newborns in the comparison cohort, while mean adjusted birth weight of newborns in Group 2 was 88 g (95% CI: -18; 194) higher than newborns of comparison mothers (Table VIII)

Table VII. Prevalence odds ratios of birth outcome in women with cutaneous malignant melanoma

Group 1: Birth outcome in women diagnosed with melanoma before pregnancy.

Group 2: Birth outcome in women diagnosed with melanoma during pregnancy.

Group 3: Birth outcome in women diagnosed with melanoma within two years after delivery.

	Melanoma Cohort Outcome/Total (%)		Comparison Cohort Outcome/Total (%)		Prevalence odds ratio* (95 % CI)	Prevalence odds ratio† (95 % CI)
Births in Group 1	(N=620)		(N=29,788)			
Preterm birth‡	36/620	(5.8)	1,510/29,685	(5.1)	1.2 (0.8-1.6)	1.1 (0.8-1.6)
LBW at term‡	10/583	(1.7)	436/28,075	(1.6)	1.1 (0.6-2.1)	1.1 (0.6-2.0)
Stillbirth	0/620	(0.0)	103/29,788	(0.3)	-	-
Abnormalities‡§	29/593	(4.9)	1,105/28,353	(3.9)	1.3 (0.9-1.9)	1.2 (0.8-1.8)
Births in Group 2	(N=88)		(N=4,180)			
Pretem birth‡	1/88	(1.1)	214/4,158	(5.1)	0.2 (0.03-1.5)	0.2 (0.03-1.5)
LBW at tem‡	1/87	(1.1)	65/3,936	(1.7)	0.7 (0.1-5.0)	0.6 (0.1-4.5)
Stillbirth	0/88	(0.0)	22/4,180	(0.5)	-	-
Abnormalities‡§	2/80	(2.5)	148/3,768	(3.9)	0.6 (0.2-2.6)	0.6 (0.2-2.7)
Births in Group 3	(N=351)		(N=16,826)			
Pretem birth‡	16/346	(4.6)	852/16,546	(5.1)	0.9 (0.5-1.5)	0.9 (0.5-1.5)
LBW at term‡	5/330	(1.5)	264/15,648	(1.7)	0.9 (0.4-2.2)	0.9 (0.4-2.2)
Stillbirth	5/351	(1.4)	65/16,826	(0.4)	3.7 (1.5-9.3)	4.6 (1.7-12.3)
Abnormalities‡§	13/314	(4.1)	557/14,977	(3.7)	1.1 (0.6-2.0)	1.1 (0.6-2.0)

* Adjusted for month and year of the birth and maternal county of residence (by matching).

† Further adjusted for maternal age and parity. Prevalence odds ratios for stillbirth were additionally adjusted for gestational age.

‡ Stillborn babies were excluded from the analyses of preterm birth, low birth weight at term and congenital abnormalities.

§ Data on congenital abnormalities included births from 1977 to 2002.

Table VIII. Mean birth weight for newborns of women with cutaneous malignant melanoma and for the comparison cohort.

Group 1: Mean birth weight for newborns of women diagnosed with melanoma before pregnancy.
Group 2: Mean birth weight for newborns of women diagnosed with melanoma during pregnancy.
Group 3: Mean birth weight for newborns of women diagnosed with melanoma from the day after giving birth until two years post partum.

	Melanoma		Comparison Cohort		Mean difference in birth weight (g)	
	Mean birth weight (g)		Mean birth weight (g)		Difference*	Adjusted difference† (95% CI)
Group 1	N=619	3,459	N=29,568	3,486	- 27	-18 (-58; 21)
Missing	1		117			
Group 2	N= 88	3,604	N= 4,147	3,468	136	88 (-18; 194)
Missing	0		11			
Group 3	N=346	3,502	N= 16,491	3,472	30	4 (-49; 58)
Missing	0		55			

* After matching for month and year of the birth and maternal county of residence.

† Further adjusted for gestational age, mother's age, and parity.

Stillborn babies were excluded from the analysis.

3.3. Study III. Hodgkin's disease and birth outcome: A Danish nationwide cohort study

We identified 292 singleton births by women with Hodgkin's disease. There were 192 births by women with Hodgkin's disease in Group 1 (Hodgkin's disease diagnosed before pregnancy). The majority of these women (76%) were 20 years or older at the time of Hodgkin's disease diagnosis. Group 2 (Hodgkin's disease diagnosed during pregnancy) included 15 and Group 3 (Hodgkin's disease diagnosed within two years of delivery), 85 births.

Birth outcome

The prevalence of boys born to women with Hodgkin's disease in Group 1 was 50.0%, compared with 51.3 % among the matched comparison mothers, difference = -1.3%, (95% CI: -8.4-5.8). The corresponding findings were 73.3% versus 50.1% (difference = 23.2%, 95% CI: 5.1-45.6) for Group 2, and 62.2% versus 51.4% (difference = 9.8%, 95% CI: -0.7-20.3) for Group 3.

In Group 1, there was no increased risk of preterm birth or low birth weight at term (Table IX). There was one stillbirth among 192 births, corresponding to an adjusted POR of 2.0 (95% CI: 0.3-15.4). The POR for congenital abnormalities was 1.7 (95% CI: 0.9-3.1). In Groups 2 and 3, there were no children with low birth weight at term and no stillbirths. The POR of preterm birth in Group 2 was 26.6 (95% CI: 8.5-83.0), but five of the eight preterm deliveries among women with Hodgkin's disease had been elective. There was one child with a congenital abnormality among 13 births in Group 2 (POR = 2.7; 95% CI: 0.3-22.8) and four children with congenital abnormalities among 78 births in Group 3 (POR = 1.6; 95% CI: 0.6-4.5). The specific types of congenital abnormalities identified in children of women with Hodgkin's disease in Groups 1, 2 and 3 are listed according to affected organ system in Table X.

Stratification of the analysis in Group 1 according to radiation treatment suggested a slightly lower risk (except for stillbirths) of adverse birth outcomes in women who had received radiotherapy (Table XI). In addition, the POR for congenital abnormalities

increased with calendar time of Hodgkin's disease diagnosis (Table XI). Stratification according to sex of the newborn did not substantially change the risk estimates. Multiple linear regression analyses indicated that newborns in all three groups had nearly the same adjusted mean birth weight as newborns in the matched comparison cohort.

Table IX. Prevalence odds ratios of birth outcome in women with Hodgkin's disease

Group 1: Birth outcome in women diagnosed with Hodgkin's disease before pregnancy.

Group 2: Birth outcome in women diagnosed with Hodgkin's disease during pregnancy.

Group 3: Birth outcome in women diagnosed with Hodgkin's disease within two years after delivery.

	Hodgkin's disease Cohort Outcome/Total (%)		Comparison Cohort Outcome/Total (%)		Prevalence odds ratio* (95 % CI)	Prevalence odds ratio† (95 % CI)
Births in Group 1	(N=192)		(N=9,247)			
Preterm birth‡	12/191	(6.3)	479/9,162	(5.2)	1.2 (0.7-2.2)	1.1 (0.6-2.0)
LBW at term‡	2/177	(1.1)	145/8,649	(1.6)	0.7 (0.2-2.7)	0.6 (0.2-2.6)
Stillbirth	1/192	(0.5)	35/9,247	(0.4)	1.4 (0.2-10.1)	2.0 (0.3-15.4)
Abnormalities‡§	11/181	(6.1)	323/8,673	(3.7)	1.7 (0.9-3.1)	1.7 (0.9-3.1)
Births in Group 2	(N=15)		(N=706)			
Pretem birth‡	8/15	(53.3)	30/704	(4.3)	25.7 (8.7-75.4)	26.6 (8.5-83.0)
LBW at term‡	0/7	(0.0)	9/674	(1.3)	-	-
Stillbirth	0/15	(0.0)	2/706	(0.3)	-	-
Abnormalities‡§	1/13	(7.7)	18/606	(3.0)	2.7 (0.3-22.1)	2.7 (0.3-22.8)
Births in Group 3	(N=85)		(N=4,089)			
Pretem birth‡	5/85	(5.9)	205/4,080	(5.0)	1.2 (0.5-2.9)	1.2 (0.5-2.9)
LBW at term‡	0/80	(0.0)	48/3,866	(1.2)	-	-
Stillbirth	0/85	(0.0)	9/4,089	(0.2)	-	-
Abnormalities‡§	4/78	(5.1)	124/3,742	(3.3)	1.6 (0.6-4.4)	1.6 (0.6-4.5)

* Adjusted for month and year of the birth and maternal county of residence (by matching).

† Further adjusted for maternal age and parity.

‡ Stillborn babies were excluded from the analyses of preterm birth, low birth weight at term and congenital abnormalities.

§ Data on congenital abnormalities included births from 1977 to 2002.

Table X. Congenital abnormalities (CA) diagnosed during the first year of life in children of Hodgkin's disease patients.

Congenital abnormalities according to organ system	Children	Type of congenital abnormalities according to ICD-8/ICD-10
Group 1	(N = 11)	(N = 13)
CA in cardiovascular organs	Child 1	Defectus septi atriorum cordis (Q21.1)
CA in respiratory organs	Child 2	CA in larynx (not specified) (Q31.8)
CA in urologic organs	Child 3	Polycystic, dysplastic kidney (Q61.4)
CA in bones and muscles		
foot	Child 4	Pes planus congenitus (Q66.5)
head, spine, and chest	Child 5 (1st CA)	Pectus excavatum (Q67.6)
other CA in bones and muscles	Child 6	Torticollis congenita (756.81)
other CA in limbs	Child 7, 8, 9	CA in limb (not specified) (Q74.9) (755.99)
other CA in bones of skull and face	Child 10	CA in bone of skull and face (not specified) (Q75.9)
CA in muscle and bones, not otherwise classified	Child 5 (2nd CA)	Hernia diaphragmatica congenita (Q79.0)
	Child 11 (1st CA)	CA in muscle and bone (not specified) (Q79.8)
Other CA	Child 11 (2nd CA)	CA (not specified) (Q89.9)
Group 2	(N=1)	(N=2)
CA in cardiovascular organs	Child 1 (1st CA)	Defectus septi atriorum cordis (Q21.1)
Chromosomal abnormality	Child 1 (2nd CA)	Down's syndrome (Q90.9)
Group 3	(N=4)	(N=11)
CA in cardiovascular organs	Child 1 (1st CA)	Tetralogia Steno-Fallot (74.629)
	Child 1 (2nd CA)	CA in heart (not specified) (74.699)
	Child 2 (1st CA)	Tetralogia Steno-Fallot (74.629)
	Child 2 (2nd CA)	CA in heart (not specified) (74.699)
	Child 3 (1st CA)	Defectus congenitus septi ventricolorum (74.639)
	Child 3 (2nd CA)	Defectus congenitus septi atriorum (74.641)
	Child 3 (3rd CA)	Other specified CA in heart (74.689)
	Child 3 (4th CA)	Coarctatio aortae (74.719)
	Child 3 (5th CA)	Transpositio vasorum (74.619)
CA in bones and muscles		
foot	Child 1 (3rd CA)	Pes equino-varus (75.400)
	Child 4	Pes calcaneo-valgus (75.402)

Table XI. Birth outcome stratified by treatment with radiotherapy and calendar period of Hodgkin's disease diagnosis for women diagnosed with Hodgkin's disease before pregnancy (Group 1).

N=192	Preterm birth		LBW at term		Stillbirth		Abnormalities*	
	Outcome/Total (%)	Adjusted POR† (95% CI)	Outcome/Total (%)	Adjusted POR† (95% CI)	Outcome/Total (%)	Adjusted POR† (95% CI)	Outcome/Total (%)	Adjusted POR† (95% CI)
Radiotherapy ‡								
Yes (N=100)	4/99 (4.0)	0.7 (0.2-1.8)	1/93 (1.1)	0.5 (0.1-3.6)	1/100 (1.0)	4.6 (0.5-38.5)	4/90 (4.4)	1.2 (0.4-3.3)
No (N=88)	8/88 (9.1)	1.8 (0.8-3.7)	1/80 (1.3)	0.9 (0.1-6.5)	0/88 (0.0)	-	6/87 (6.9)	1.9 (0.8-4.4)
Time of diagnosis								
1970-1980 (N=66)	4/65 (6.1)	1.0 (reference)	0/60 (0.0)	1.0 (reference)	1/66 (1.5)	1.0 (reference)	1/55 (1.8)	1.0 (reference)
1981-1990 (N=64)	2/64 (3.1)	0.6 (0.1-2.4)	2/62 (3.2)	1.9 (0.5-8.1)	0/64 (0.0)	-	3/64 (4.7)	1.4 (0.4-4.4)§
1991-2000 (N=62)	6/62 (9.7)	1.8 (0.8-4.1)	0/55 (0.0)	-	0/62 (0.0)	-	7/62 (11.3)	3.1 (1.4-6.9)§

* Data on abnormalities included births from 1977-2002

† Adjusted for month and year of birth and maternal county of residence by matching and further adjusted for maternal age and parity. Stillborn children were excluded from the analyses of preterm birth, LBW at term, and congenital abnormalities

‡ Data on radiotherapy were missing for 4 women.

§ Wald chi-square test, $p = 0.25$.

4. Methodological considerations

Two types of error may influence the accuracy of estimates obtained in observational epidemiologic studies: systematic error and random error (113). Systematic errors result from selection bias, information bias, and confounding, whereas random error or chance pertains to the statistical precision of the estimates. Below, we discuss these potential errors in relation to our studies.

4.1. Selection bias

Selection bias stems from the procedures used to select subjects and from factors that influence study participation. It arises when the association between exposure and outcome differs between participants and non-participants of a study (113).

In cohort studies, selection bias may be caused by lack of inclusion in the cohort at the recruitment stage or by loss to follow-up at the disease measurement stage. In the studies of this thesis, selection into the cancer cohorts was based on information on cancer diagnoses from the Danish Cancer Registry. The completeness of the cancer diagnoses in the Cancer Registry has been shown to be 95-98% (115;126). The highly efficient Civil Registration System ensured negligible loss to follow-up on the women with cancer (127). Thus, typical causes of selection bias were absent in our studies.

Some selection problems are still possible, however. Because of the Birth Registry structure, fetal abnormalities leading to spontaneous or induced abortions are not observable. Selection bias could arise if women with cancer diagnosed before (Group 1) or during pregnancy (Group 2) had greater than the unexposed mothers risks of spontaneous or induced abortions related to fetal abnormalities. Such bias would cause underestimation of the risk of congenital abnormalities in newborns of women with cancer. A study by Velentgas *et al.* reported that spontaneous abortions occurred in 24% of women who became pregnant after breast cancer compared with 18% of controls (81). In a Danish study, only 10% of pregnancies in women with previous breast cancer resulted in spontaneous abortions while 44% ended in induced abortions (7). The authors suggested

that women may have chosen induced abortion out of fear of adverse effects of a pregnancy on the course of their treated breast cancer.

Since the late 1980s, prenatal ultrasound examinations, aiming at accurate pregnancy dating, have been offered to all pregnant women in most Danish counties. These examinations, usually conducted around the 18th week of gestation, would reveal obvious fetal abnormalities, such as *i.e.* anencephaly, and - in most cases - lead to late induced abortion. However, less obvious abnormalities which may not lead to induced abortions, are more likely to be diagnosed in ultrasound examinations specifically aimed at detecting fetal abnormalities. Some hospitals in Denmark have offered these examinations to all pregnant women since the late 1990s, their availability varies throughout the country. Moreover, there were no guidelines regarding pregnancy ultrasound examinations for women previously treated for cancer in our study period. However, we cannot rule out the possibility of selection bias caused by greater risk of fetal abnormality-related induced abortions in women with previous cancer.

4.2. Information bias

Information bias can arise from inaccurate data collection (113). The errors may result in misclassification of the exposure (such as the treatment variable), the outcome, or the confounders.

The quality of most outcome variables in the Medical Birth Registry is high, but data on gestational age are subject to some misclassification, since the gestational age recorded in the Medical Birth Registry is a week longer in some cases than that recorded in the medical records (128). If non-differential, this misclassification would cause bias towards the null.

The predictive value and completeness of data on congenital abnormalities in the Hospital Discharge Registry have been reported to be 88.2% (95% CI: 85.9-90.5) and 89.9% (87.7-92.1) (120). However, differential misclassification of congenital abnormalities diagnosed during the first year of life might occur if women with a history of cancer had more frequent than comparison mother's prenatal ultrasound examinations to detect congenital abnormalities. Likewise, differential misclassification could ensue if newborns of women

with previous cancer were examined more thoroughly during the first year of life, since a minor abnormality would be more likely to be detected in children of women with previous cancer than in children of cancer-free mothers. Thus, the higher prevalence of congenital abnormalities among newborns of women diagnosed with Hodgkin's disease from 1991 to 2000 in **study III** may be partially explained by diagnostic bias caused by a recently increased interest in congenital abnormalities after maternal cancer treatment.

The information on treatment obtained from the Cancer Registry is crude (there are no clinical details on radiation fields, doses, specific chemotherapy, or duration of treatment) and may be inaccurate. Only treatment given within four months of diagnosis is reported and since notification forms are often filled in the early period of treatment planning, they may not reflect changes in treatment plans. Such changes are rarely reported to the registry (126).

In **study I** we examined birth outcome in women with previous breast cancer, stratified according to whether the woman had been treated with surgery alone or any other treatment (combined). Since treatment data were recorded prospectively and before the pregnancy, any misclassification of treatment in our study would be non-differential. With pronounced misclassification of the treatment variable the risk estimates for women who were treated with surgery alone and women who had other treatment would not be expected to differ. However, a recent study found that although overall treatment data on breast cancer patients recorded in the Danish Cancer Registry are of varying quality, surgery alone was correctly registered for 95.4% of cases (126).

In **study III** we examined birth outcome in women with previous Hodgkin's disease, stratified according to radiotherapy (yes/no). Since treatment data were recorded prospectively before the pregnancy, any misclassification of treatment would be non-differential. A study of childhood cancer survivors reported that 97 of 110 patients treated with radiotherapy (88%) and 78 of 79 patients not treated with radiotherapy (99%) were correctly coded in the Danish Cancer Registry (129).

The Cancer Registry contains no detailed information on tumor stage. In **study III**, the distribution of Hodgkin's disease stage could bias the estimates of the radiotherapy-stratified analyses. Women with early-stage Hodgkin's disease, which is often located

above the diaphragm, were probably more likely than women with more advanced stages to receive radiotherapy, since during our study period the typical treatment of early-stage disease was either radiation alone (with minimal effect on the gonads in case of supradiaphragmatic location), or a few series of combination chemotherapy followed by radiation. In contrast, later stages of Hodgkin's disease have typically been treated with six series of combination chemotherapy and only rarely with radiotherapy. Thus, women not receiving radiotherapy were more likely to have advanced disease and to receive several series of chemotherapy. This may help explain our finding of a lower risk of adverse birth outcomes for women who were treated with radiotherapy compared with women who were not

4.3. Confounding

Calendar time of birth, maternal county of residence, maternal age, parity, and gestational age were the potential confounders accounted for in our studies. Still, the estimates could be affected by residual or unmeasured confounding.

Residual confounding results from improper categorization or misclassification of one or more confounding variables such as *i.e.* maternal age or parity. The quality of the data on these variables in the Medical Birth Registry, however, is reportedly good (116;130). Moreover, in all three studies, the relative estimates (calculated after matching for calendar time of birth and maternal county of residence) were virtually unchanged after adjustment for maternal age and parity, speaking against substantial residual confounding by these factors.

Unmeasured confounding by the factors discussed below may have influenced our results:

Socioeconomic status

It has been reported that women with high socioeconomic status have a higher incidence of breast cancer and melanoma (131;132). Likewise, Hodgkin's disease in young adults has been associated with a higher social class (18), while low socioeconomic status has been associated with adverse birth outcomes (133). Absence of adjustment for socioeconomic status may have caused us to underestimate the effect of cancer on birth outcome.

Smoking and alcohol consumption

Maternal smoking during pregnancy has been associated with increased risks of preterm birth, LBW, IUGR, and stillbirth (134;135). Similarly, moderate alcohol consumption during pregnancy has been associated with reduced birth weight (136) and increased risks of preterm birth (137) and stillbirth (138).

Whether maternal smoking or moderate alcohol consumption in pregnancy causes congenital abnormalities is controversial. Smoking in early pregnancy has been reported to cause no overall increase in risk of congenital abnormalities, but possibly a slightly increased risk of certain specific abnormalities (cleft lip and palate and abnormalities of the circulatory and digestive system) (139). Another study reported no overall increased risk of congenital abnormalities for women consuming 1-2 drinks daily in early pregnancy compared with non-drinkers, but a greater alcohol consumption was associated with an increasing risk of abnormalities in the genitourinary system (140).

Although some studies have reported an increased risk of melanoma associated with alcohol use (141;142), the existing evidence of a positive association of either melanoma or Hodgkin's disease with smoking or alcohol consumption is not convincing (18;141-143). Concerning breast cancer, a meta-analysis found that women consuming two drinks per day had a 20% increase in breast cancer risk compared with non-drinkers (144). Smoking at an early age has been reported to be a risk factor for premenopausal breast cancer (145). However, since our studies showed no substantially increased risk of adverse birth outcomes for women with breast cancer, it is unlikely that maternal smoking or alcohol consumption have confounded our results.

Infertility treatment

At least three studies have reported modest increases in melanoma incidence among infertile women (146-148), while singleton pregnancies from assisted reproduction have been associated with increased risk of adverse birth outcomes, including preterm birth, LBW, perinatal mortality (149), and congenital abnormalities (150). If women with melanoma were more likely to have received infertility treatment than cancer-free women, the association of melanoma with stillbirth among women who were diagnosed with melanoma within two years after delivery, reported in **study II**, may be confounded by infertility treatment.

There is no clear evidence that fertility treatment increases the risk of breast cancer although there may be an increased risk in the first year after treatment (151). However, our data did not suggest any substantial increased risk of adverse birth outcome for women with breast cancer.

4.4. Statistical precision

Random error is the component of overall error that cannot be predicted, but can be quantified using statistical distributions (152). The widths of the 95% confidence intervals express the precision of our estimates. Although our study populations were large compared with most other studies, the number of adverse birth outcomes available for analyses was often small. Thus, the wide confidence intervals of several estimates complicate their interpretation.

Estimating of a large number of epidemiologic effects (multiple comparisons (153)) increases the risk that some associations are observed by chance.

5. Main conclusions

5.1. Study I. Birth outcome in women with breast cancer

We found no substantially increased risk of adverse birth outcome among newborns of women diagnosed with breast cancer before becoming pregnant. This was unaltered after stratification by mother's treatment. The eight-fold increased risk of preterm delivery for women diagnosed during pregnancy reflected a high rate of elective early delivery, probably to allow an earlier start of cancer therapy. After adjustment for gestational age, there was a 240 g reduction in the mean birth weight for newborns in this group. The weak association of preterm birth with maternal breast cancer diagnosed within two years of delivery may be explained by suboptimal intrauterine conditions caused by a preclinical cancer disease. In this group, only boys had an increased risk of LBW at term. The main limitations of study I were lack of treatment details and low statistical precision, especially for women diagnosed with breast cancer during their pregnancy.

5.2. Study II. Birth outcome in Danish women with cutaneous malignant melanoma

We found no evidence of increased risk of adverse birth outcome in newborns of women diagnosed with melanoma before or during pregnancy. The finding of a four-fold increased risk of stillbirth for newborns of women diagnosed with melanoma within two years after delivery was unexpected. From the available data we cannot determine whether the factors underlying the association may be causal, unmeasured confounding (*i.e.* infertility treatment) or chance. The main limitation of study II was the low statistical precision, particularly for the estimates pertaining to women diagnosed with melanoma during their pregnancy.

5.3. Study III. Hodgkin's disease and birth outcome: A Danish nationwide cohort study

Pre-pregnancy Hodgkin's disease was not associated with a substantially increased risk of preterm birth, LBW at term, or stillbirth, but we cannot rule out the possibility of an increased risk of congenital abnormalities among newborns of these women. We found a lower risk of adverse birth outcomes among children of women treated with radiotherapy

before pregnancy, compared with women who did not receive radiotherapy. This finding may be due to women with advanced Hodgkin's disease typically receiving intensive chemotherapy and only rarely radiotherapy. Higher risk of congenital abnormalities among children of women diagnosed with Hodgkin's disease between 1991 and 2000 may be due to a diagnostic bias. The 26-fold increase in risk of a preterm delivery among women diagnosed during pregnancy mainly reflected a higher rate of elective early delivery. We found no substantially increased risk of adverse birth outcome among women diagnosed within two years post partum. The main limitations of study III were lack of clinical detail on treatment and low statistical precision, especially concerning the risk of congenital abnormalities for women diagnosed with Hodgkin's disease during or shortly after pregnancy.

6. Discussion in relation to the existing literature

6.1. Birth outcome in women with breast cancer

To the best of our knowledge, this is the first cohort study of birth outcome in women diagnosed with breast cancer before pregnancy. Earlier, small case series have reported births of healthy children to women who became pregnant after being diagnosed with breast cancer (79;80).

In a recently published registry-based cohort study from Sweden, Dalberg *et al.* examined 331 births from 1973 to 2002 to women with previous breast cancer (82). They found a large majority of births to these women to be free of adverse events, and reported no increased risk of stillbirth or SGA. These findings are similar to those in our study. The Swedish study, however, also reported an increased risk of very preterm birth (<32 wk) (OR = 3.2; 95% CI: 1.7-6.0) and LBW (<1500 g) (OR = 2.9; 95% CI: 1.4-5.8) and an increased risk of congenital abnormalities (OR = 1.7; 95% CI: 1.1-2.5) among children of breast cancer survivors, compared with the general population. The increased risk of congenital abnormalities was seen especially in the births occurring in 1988-2002 (OR = 2.1; 95% CI: 1.2-3.7), which the authors explained by an increased use of chemotherapy in younger patients. The study, however, had no data on the treatment of women with breast cancer.

In contrast to the Swedish study, we found no increased risk of preterm birth or congenital abnormalities among newborns of women with previous breast cancer, with results unaltered by stratification by a treatment variable. As suggested by Dalberg *et al.* the different results in the Swedish and the Danish cohorts may be caused by different degrees of misclassification of the outcome variables between the registries or differences in the usage of adjuvant radiotherapy or systemic treatments after breast cancer (82).

The increased observed risk of preterm delivery among women diagnosed with breast cancer during pregnancy reflected a higher rate of elective early delivery, probably to allow an early start of cancer therapy. Our data also showed a tendency towards an increased risk of preterm birth for women diagnosed with breast cancer within two years after delivery. These findings corroborate the results of two earlier cohort studies of birth outcome in women with breast cancer diagnosed during or shortly after pregnancy (20;89).

In these studies, however, the authors did not distinguish between birth outcome in women diagnosed with breast cancer during pregnancy and women diagnosed shortly after pregnancy. Smith *et al.* identified 423 cases of breast cancer diagnosed from nine months preceding delivery until 12 months after delivery over a period of six years in California (20). After adjusting the analyses for maternal age, the authors reported an odds ratio of 2.2 (95% CI: 1.7-2.8) for preterm birth, and an odds ratio of 2.0 (95% CI: 1.0-4.1) for very low birth weight.The study concluded that the data were consistent with an obstetric practice involving elective early delivery for cancer patients. Likewise, a historical cohort study of 118 women, who were pregnant within nine months before or three months after their first treatment for breast cancer, reported a higher proportion of preterm births among offspring of women with breast cancer compared with controls, mainly because elective caesarean sections were done more often to allow earlier start of cancer therapy (89). In that study, only two stillbirths and no congenital abnormalities were observed. However, no children were exposed to chemotherapy during embryogenesis. The authors also reported a lower mean birth weight after adjustment for gestational age. In our study this effect was to newborns of women diagnosed during pregnancy.

Three case-series of 24, 28, and 29 pregnant breast cancer patients, respectively, have reported that chemotherapeutic treatment in the second and third trimester caused no congenital abnormalities or other complications, except for IUGR in one case (55;84;87).

Our data did not show substantial differences in proportions of boys born to breast cancer patients compared with cancer-free mothers.Thus, our findings did not corroborate the theory of psychological stress (caused by a cancer diagnosis) or potential mutagenic exposure (from chemotherapy or radiation) reducing the male proportion of newborns. This is in line with earlier studies that examined the sex-ratio for newborns of childhood cancer survivors and found no significant alterations (63;74;75).

The overall results of this study regarding the birth outcome among women with breast cancer are reassuring.

6.2. Birth outcome in Danish women with cutaneous malignant melanoma

Two cohort studies have examined birth outcome in offspring of women diagnosed during or shortly after pregnancy (16;91). In the hospital-based cohort study of 18 deliveries by women diagnosed with melanoma during pregnancy over a period of 30 years (91), there were 17 live births and one anencephalic stillbirth. The newborns of women with melanoma had a lower mean birth weight than newborns of women without cancer, and there was no difference in mean gestational age. The authors suggested that the differences in birth weight were due to IUGR secondary to the melanoma, its therapies, or its complications. In that study, however, mean birth weights were based on only nine melanoma-exposed newborns and nine newborns of age-matched comparison mothers. Based on many more population-based observations, our study found no important difference in mean birth weight between newborns of women with melanoma and newborns of comparison mothers.

In the population-based cohort study, O'Meara *et al.* identified 149 women diagnosed with melanoma during pregnancy and 263 women diagnosed within 12 months after delivery over a period of 9 years in California (16). That study and our study were in agreement with respect to the findings of no increased risk of preterm birth or low birth weight among newborns of mothers with melanoma. For women diagnosed during pregnancy, O'Meara and colleagues reported and odds ratio of 0.9 (95% CI: 0.5-1.6) for prematurity and an odds ratio of 0.8 (95% CI: 0.3-1.8) for LBW, adjusted for age and race. They found no fetal deaths in the exposed group and no increased risk of adverse birth outcome in women diagnosed with melanoma in the first post partum year. The study did not examine the risk of congenital abnormalities among newborns.

Our data showed an unsubstantial increase in the male proportion of newborns born to women with melanoma compared with newborns of comparison mothers and thus did not support the hypothesis of psychological stress (caused by a cancer diagnosis) reducing the male proportion of newborns.

Our finding of a four-fold increased risk of stillbirth for newborns of women diagnosed with melanoma within two years after delivery has not been shown by other studies. We cannot determine from the data at hand whether this association is causal, a result of

unmeasured confounding, or a chance finding. With this possible exception, our results suggest no substantially increased risk of adverse birth outcome for women with melanoma.

6.3. Hodgkin's disease and birth outcome: A Danish nationwide cohort study

On the whole, our findings are in line with the existing studies. Janov *et al.* did not find any substantial increased risk of LBW and no congenital abnormalities among newborns of 15 women with pre-pregnancy Hodgkin's disease compared with the general population (110). Likewise, Swerdlow *et al.* reported no increased risk of preterm birth, LBW, stillbirth, congenital abnormalities or chromosomal abnormalities among 49 children of 16 women and 11 men who had previously been treated for Hodgkin's disease compared with the general population (111). Another study, which compared 52 births by 29 women previously treated for Hodgkin's disease with births by the women's siblings (112), found no overall increased risk of congenital abnormalities and stillbirths combined among children of Hodgkin's disease patients. The study also found no association of birth outcome with radiotherapy alone (supra- or infradiaphragmatic), whereas women treated with both chemotherapy and radiation were more likely to give birth to an abnormal child ($p = 0.047$). The three studies, however, were all based on small study populations and did not control for potential confounders.

A large multicenter cohort study of childhood cancer survivors (the Childhood Cancer Survivor Study) reported 11 stillbirths among 729 births of female survivors of childhood Hodgkin's disease, corresponding to an adjusted RR of 1.6 (95% CI: 0.64-4.03) (48). We found only one stillbirth among 192 women, of whom more than 75% had been diagnosed with Hodgkin's disease in adulthood (≥20 years of age at diagnosis).

Another recent study, based on data from the Childhood Cancer Survivor Study, reported a moderately increased risk of preterm deliveries among 1,264 female survivors of childhood cancer (including 337 survivors of Hodgkin's disease), with risks concentrated among women who received pelvic irradiation (49). Among women with childhood Hodgkin's disease, 19.2% had a preterm birth compared with 12.5% among sibling controls. There

was no increased risk of SGA. In the specific analyses of birth outcome among women with previous Hodgkin's disease, the authors did not compute risk estimates, control for potential confounders, or evaluate the effect of specific treatment.

We found no overall increased risk of preterm birth among women with previous Hodgkin's disease. Nor did women who received radiotherapy have an increased risk of preterm birth, probably because they were likely to have received supradiaphragmatic radiation.

Our finding of an increased risk of preterm delivery for women diagnosed with Hodgkin's disease during pregnancy mainly reflected a high rate of elective early delivery. This finding is consistent with other studies on pregnant cancer patients (20;89). Smith *et al.* identified 172 cases of Hodgkin's disease diagnosed from 9 months preceding until 12 months following the delivery and estimated relative risks to be 2.4 (95% CI: 1.6-3.5) for preterm birth and 3.6 (95% CI: 1.5-8.9) for very LBW (20). The authors suggested that these findings reflected a higher rate of elective early deliveries among women with Hodgkin's disease, performed in order to initiate therapy. In contrast, a historical cohort study by Lishner *et al,* which included 40 births by women who were pregnant between 9 months before and three months after their first treatment for Hodgkin's disease, reported no increased risk of preterm birth or induced deliveries (21). Furthermore, the study indicated no difference in mean birth weight compared with controls, while the proportion of stillbirths was not statistically different from that of the general population. The study reported one child with a congenital abnormality born to the only patient treated with chemotherapy in the first trimester. Overall, the findings of Lishner *et al.* corroborate our data, with the exception of their result for preterm births.

In a small cohort study, Janov *et al.* found an increased risk of LBW (RR = 5.6; 95% CI: 1.2-17.5) for 10 newborns of women who were pregnant from 12 months before diagnosis to the end of treatment (110). This finding was based on only three preterm newborns with LBW (one of the preterm deliveries was induced). There were no congenital abnormalities among the newborns.

Our estimates of increased risk of congenital abnormalities among newborns of women diagnosed with Hodgkin's disease during or shortly after pregnancy were based on few outcomes and are therefore imprecise. However, it is important to emphasize that teratogens increase the rate of specific, rather than all abnormalities, and we were unable to evaluate those in our study.

We found no substantial decrease in the male proportion of newborns of women with previous Hodgkin's disease, indicating that earlier treatment for Hodgkin's disease is not a risk factor for early male abortion. For newborns of women diagnosed with Hodgkin's disease during pregnancy, the male proportion, compared with newborns of comparison mothers, was *increased,* which is surprising and could be a chance finding. Thus, our findings offered no evidence of psychological stress (caused by a cancer diagnosis) or potential mutagenic exposure (from chemotherapy or radiation) reduction of male proportion of newborns, which is in line with earlier studies of the sex-ratio for newborns of childhood cancer survivors (63;74;75).

In conclusion, our overall results are reassuring regarding the risks of adverse birth outcome for women with Hodgkin's disease. However, we cannot rule out the possibility of an increased risk of congenital abnormalities in newborns of women diagnosed with Hodgkin's disease before pregnancy.

7. Perspectives

On the whole, our studies offer reassuring results concerning the risks of adverse birth outcome for women diagnosed with breast cancer, melanoma, or Hodgkin's disease before, during or shortly after pregnancy. We found the Danish population-based registries to be valuable data sources for such studies. The major strength of these registries is the longitudinal data collection and essentially complete registration of cancers and births. The shortcomings of the registries include lack of clinical detail on treatment and stage of disease. In addition, a limitation of our studies was the imprecise risk estimates caused by the small number of adverse birth outcomes.

Since even countrywide data may be sparse, an international collaboration is required in order to assemble data on the sufficient number of births by women with cancer in order to obtain more precise risk estimates for adverse birth outcomes. Moreover, a larger number of birth outcomes would allow stratified analyses according to *i.e.* different treatment regimens and stages. Information on these clinical details could be obtained from hospital medical records and clinical databases.

International collaboration has produced large cohort studies of birth outcome of childhood cancer survivors (the Childhood Cancer Survivor Study), where *i.e.* radiotherapy records have been examined to determine absorbed doses to the ovaries and uterus for survivors before pregnancy. Recently, a large-scale cohort study, based on collaboration between several countries, including research groups from Denmark and Finland, has been started with the aim of examining genetic consequences of cancer treatment. This study will examine risks of such adverse outcomes as congenital abnormalities, neonatal death, and cancer in the offspring of survivors of childhood and early-onset cancer.

Very few studies document the long-term follow-up of children exposed to maternal cancer and cancer treatment *in utero* (57). Maternal cancer may affect not only birth outcome, but also long-term health, as a consequence of intra-uterine programming. Likewise, fetal exposure to *i.e.* chemotherapy may lead to gonadal damage and later problems with fertility or cause organ damage that may not manifest itself as physical or neurological impairment until later in life (154) . Thus, cohort studies with long term follow-up are

needed to evaluate the entire spectrum of adverse effects of cancer or cancer treatment on offspring of the patients.

8. Summary

In western countries many women postpone childbearing for personal or professional reasons. Since the incidence rates of most cancers increase with age, in the future more women can be expected to receive a cancer diagnosis before, during, or shortly after pregnancy.

Because of the possible adverse effects of cancer and cancer treatment on birth outcome, we hypothesized that newborns of women with breast cancer, melanoma, or Hodgkin's disease may have a higher, compared with the general population, risk of adverse birth outcomes. The thesis includes three observational studies, based on nationwide data from the Danish Cancer Registry, the Medical Birth Registry, and the National Hospital Discharge Registry and covers births occurring from 1973 to 2002.

In this thesis we aimed 1) to examine the risk of adverse birth outcomes in women diagnosed with breast cancer before, during, or shortly after pregnancy, and to examine if maternal treatment before pregnancy or sex of the child affected any outcome, 2) to examine the risk of adverse birth outcomes in women diagnosed with melanoma before, during, or shortly after pregnancy, and to examine an effect of child's sex, and 3) to examine the risk of adverse birth outcomes in women diagnosed with Hodgkin's disease before, during, or shortly after pregnancy, and to examine if maternal radiotherapy, calendar time of Hodgkin's disease diagnosis, or sex of the child affected birth outcome in women diagnosed with Hodgkin's disease before pregnancy.

In **study I**, we found no substantially increased risk of preterm birth, low birth weight at term, stillbirth, or congenital abnormalities among 216 newborns of women diagnosed with breast cancer before pregnancy. Stratification by mother's treatment did not change the results. Among the 37 newborns of women diagnosed with breast cancer during pregnancy, there was an increased risk of preterm birth which reflected a higher rate of elective early delivery. Among 442 births of women diagnosed within two years after delivery, we found a slightly increased risk of preterm birth (POR=1.4; 95% CI: 1.0-2.0) which could be caused by suboptimal intrauterine conditions secondary to preclinical cancer. In this group, only boys had increased risk of low birth weight at term (POR=2.9; 95% CI: 1.3-6.3).

In **study II**, we did not observe an increased risk of preterm birth, low birth weight at term, stillbirth, or congenital abnormalities among 620 newborns of women diagnosed

with melanoma before pregnancy or among 88 newborns of women diagnosed during pregnancy. We found an increased risk of stillbirth among 351 newborns of women diagnosed within two years after delivery (POR=4.6; 95% CI: 1.7-12). This unexpected result was, however, based on only 5 stillbirths in the exposed group. Stratification according to sex of the child did not substantially change the relative estimates.

In **study III**, we found no increased risk of preterm birth, low birth weight at term, or stillbirth among 192 newborns of women diagnosed with Hodgkin's disease before pregnancy. However, we cannot rule out the possibility of an increased risk of congenital abnormalities among the children of these women (POR=1.7; 95% CI: 0.9-3.1). We found a lower risk of adverse birth outcomes among women treated with radiotherapy before pregnancy compared with women who were not, which could be due to an uneven distribution of cancer stage in these groups. Women diagnosed with Hodgkin's disease between 1991 and 2000 had a higher risk of giving birth to children with congenital abnormalities; this finding could have resulted from a diagnostic bias. Among 15 newborns of women diagnosed during pregnancy, we found an increased risk of preterm deliveries, which reflected a higher rate of elective early deliveries. We found no substantially increased risk of adverse birth outcomes for women diagnosed with Hodgkin's disease within two years after delivery, but the risk estimates were imprecise.

Overall, our results regarding the risks of adverse birth outcomes for women with breast cancer, melanoma, and Hodgkin's disease are reassuring. Our studies have also shown that the Danish population-based registries are suitable data sources for studying the associations between cancer and birth outcomes. Still, our risk estimates were based on few adverse birth outcomes, indicating the need for international collaboration in future studies on this topic, if a higher statistical precision is to be achieved.

9. Danish summary

I Danmark, såvel som i andre vestlige lande, har kvinders gennemsnitlige alder ved den første fødsel været stigende igennem de sidste årtier. Da forekomsten af de fleste kræftsygdomme stiger med alderen, kan det således forventes, at flere kvinder i fremtiden vil få diagnosticeret kræft enten inden de har fået børn, under graviditeten eller kort tid efter de har født.

Hypotesen i denne afhandling har været, at kvinder med brystkræft, malignt melanom eller Hodgkin's sygdom har større risiko for unormale fødselsudfald på grund af konsekvenser af selve kræftsygdommen og/eller på grund af bivirkninger af kræftbehandlingen. Afhandlingen er baseret på tre studier med landsdækkende data fra Cancerregisteret, det Medicinske Fødselsregister og Landspatientregisteret. Vi inkluderede fødsler fra 1973 til 2002.

Formålet med afhandlingen var at 1) analysere fødselsudfald hos danske kvinder som blev diagnosticeret med brystkræft før graviditeten, under graviditeten eller op til to år efter fødslen samt at undersøge om behandling før graviditeten (operation alene/anden behandling) eller barnets køn influerede på fødselsudfaldet, 2) analysere fødselsudfald hos danske kvinder diagnosticeret med malignt melanom før eller under graviditeten eller op til to år efter fødslen samt at undersøge om barnets køn influerede på fødselsudfaldet, 3) analysere fødselsudfald hos danske kvinder diagnosticeret med Hodgkin's sygdom før eller under graviditeten eller op til to år efter fødslen samt at undersøge om stråleterapi af moderen, kalendertid for diagnosen eller barnets køn påvirkede fødselsudfald hos kvinder diagnosticeret med Hodgkin's sygdom før graviditeten.

I **studie I** fandt vi ingen væsentlig øget risiko for præterm fødsel, lav fødselsvægt til terminen, dødfødsel eller misdannelser blandt 216 fødsler af kvinder med brystkræft før graviditeten. Stratifikation på moderens behandling ændrede ikke resultaterne. Blandt 37 fødsler af kvinder diagnosticeret under graviditeten var der en øget risiko for præterm fødsel på grund af en høj proportion af inducerede præterme fødsler. Blandt 442 kvinder, der fik diagnosticeret brystkræft op til to år efter fødslen, fandt vi en let øget risiko for præterm fødsel (POR=1.4; 95% CI: 1.0-2.0), der muligvis kan tilskrives suboptimale intrauterine forhold forårsaget af den prækliniske kræftsygdom. Endvidere havde kun drengebørn af disse kvinder en øget risiko for lav fødselsvægt til terminen (POR=2.9; 95% CI: 1.3-6.3).

I **studie II** var der ingen øget risiko for præterm fødsel, lav fødselsvægt til terminen, dødfødsel eller misdannelser blandt 620 fødsler af kvinder med malignt melanom før graviditeten eller blandt 88 fødsler af kvinder diagnosticeret under graviditeten. Vi fandt en højere risiko for dødfødsel blandt 351 fødsler af kvinder, der blev diagnosticeret indenfor to år efter fødslen i forhold til kontrolgruppen (POR=4.6; 95% CI: 1.7-12). Dette estimat var baseret på kun fem dødfødsler og var et uventet fund. Stratifikation på barnets køn ændrede ikke resultaterne i nogen af de tre grupper væsentligt.

I **studie III** fandt vi ingen forhøjet risiko for præterm fødsel, lav fødselsvægt til terminen eller dødfødsel blandt 192 fødsler af kvinder med tidligere Hodgkin's sygdom, men vi kunne ikke udelukke en øget risiko for misdannelser blandt børn af disse kvinder (POR=1.7; 95% CI: 0.9-3.1). Kvinder der tidligere havde fået stråleterapi havde generelt set lavere risiko for unormale fødselsudfald, hvilket muligvis skyldes en skæv fordeling af stadie og dermed kemoterapeutisk behandling blandt kvinder behandlet med stråleterapi og kvinder der ikke fik stråleterapi. Blandt 15 fødsler af kvinder, der fik diagnosticeret Hodgkin's sygdom under graviditeten, var der en øget risiko for præterm fødsel, som primært skyldtes mange inducerede præterme fødsler. Vi fandt ingen væsentlig øget risiko for unormale fødselsudfald blandt 85 kvinder, der blev diagnosticeret med Hodgkin's sygdom op til to år efter fødslen, men risikoestimaterne var upræcise.

Sammenfattende tyder vores studier på, at kvinder med brystkræft, malignt melanom eller Hodgkin's sygdom ikke har væsentligt forhøjet risiko for unormale fødselsudfald sammenlignet med kvinder der ikke har kræft. De danske populations-baserede registre er med deres høje komplethedsgrad og longitudinelle perspektiv velegnede til at studere sammenhænge mellem kræft og fødselsudfald. Men da vores resultater var baseret på få unormale fødselsudfald, er det nødvendigt fremover at samarbejde med andre lande for at kunne opnå større statistisk præcision angående risikoen for de enkelte fødselsudfald og for at kunne undersøge effekten af specifik kræftbehandling.

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11. Appendices (Study I-III)

I

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Birth outcome in women with breast cancer

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We investigated whether maternal breast cancer affects birth outcome in a nationwide cohort study of 695 births from 1973 to 2002 of women with breast cancer with respect to preterm birth, low birth weight at term, stillbirth and congenital abnormalities as well as mean birth weight, compared with the outcomes of 33 443 births from unaffected mothers. There was no excess risk of adverse birth outcome for the 216 newborns of women with breast cancer before pregnancy. Stratification by mother's treatment did not change the results. For 37 newborns of women diagnosed during pregnancy, the prevalence ratio (PR) of preterm birth was 8.1 (95% confidence interval (CI): 3.8–17). However, 10 of the 12 preterm deliveries among these women were elective early deliveries. Among 442 births of women diagnosed in the 2 years from time of delivery, the PR of preterm birth was 1.4 (95% CI: 1.0–2.0), and the PR of low birth weight at term for boys was 2.9 (95% CI: 1.3–6.3). Overall, our results are reassuring regarding the risks of adverse birth outcome for breast cancer patients.
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In western countries many women postpone childbearing for personal or professional reasons (Dow *et al*, 1994), which both increases their risk for breast cancer (Kelsey *et al*, 1993) and reduces the period between giving birth and breast cancer diagnosis. In the future, therefore, more breast cancer patients will have recently given birth, been pregnant concurrent with their diagnosis, or not yet started their childbearing at the time of their diagnosis.

Biological mechanisms related to the cancer or its treatment may impact foetal growth, development, and teratogenesis (Zemlickis *et al*, 1992; Zhu *et al*, 2002). However, the epidemiologic evidence of the effect of breast cancer on birth outcome is limited. The few studies of women who were diagnosed with breast cancer before pregnancy have focused on maternal prognosis (Ribeiro *et al*, 1986; Sutton *et al*, 1990; Dow *et al*, 1994; Malamos *et al*, 1996; Kroman *et al*, 1997; Velentgas *et al*, 1999; Blakely *et al*, 2003). Thus, no population-based cohort study of birth outcome in women diagnosed with breast cancer before pregnancy has been published. Cohorts without control groups including between four and 121 women (Ribeiro *et al*, 1986; Daly and Donnellan, 1992; Berry *et al*, 1999; Giacalone *et al*, 1999; Kuerer *et al*, 2002; Ring *et al*, 2005) have shown that the majority of women who are diagnosed with breast cancer during or shortly after pregnancy give birth to healthy children. Two controlled studies, however, suggested an increased risk of preterm birth and low birth weight for offspring of these women (Zemlickis *et al*, 1992; Smith *et al*, 2001). Therefore, within a cohort study, we examined birth outcome in all women diagnosed with breast cancer in Denmark from 1943 to 2002, compared with women without cancer.

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MATERIAL AND METHODS

Study population

We conducted this nationwide cohort study based on all Danish women who were diagnosed with breast cancer from January 1, 1943 through December 31, 2002, and who gave birth from January 1, 1973 through December 31, 2002. Women were included if they were diagnosed at any time before pregnancy, during the pregnancy, or until 2 years post partum. Their birth outcome was compared with the outcome in a comparison cohort selected from other births in Denmark. We restricted all analyses to singleton births only, and each pregnancy was included in the analyses as an independent event.

Breast cancer cohort Women with breast cancer were identified from the Danish Cancer Registry, which has kept records of all incident cases of cancer in Denmark since 1943, classified according to the International Classification of Diseases (ICD-7) (Storm *et al*, 1997). The records include the civil registration number, diagnosis, date of diagnosis, method of verification, extent of spread of the tumour at time of diagnosis, and treatment given within 4 months after diagnosis. We identified all women with a diagnosis of breast cancer (ICD-7 codes 170.0–170.5). We excluded all cases of 'Carcinoma *in situ*' and six cases of sarcoma involving the breast. Women with breast cancer were linked to the Danish Medical Birth Registry with data on all births in Denmark since January 1, 1973 (Kristensen *et al*, 1996) obtained from birth notifications, filled in by midwives (in Denmark all births,

including home births, are attended by midwives). The main variables are the civil registration number of the mother and child, date and place of birth, gestational age, birth weight, and parity. Birth weights $\geqslant 7000$ g probably reflected coding errors and were excluded from the analyses. Likewise, we excluded births registered without a gestational age or when this was less than 20 weeks or more than 44 weeks. Owing to a change in classification procedures in the Birth Registry in 1978, there was more missing data on gestational age for the years 1978–1981 than for other years (mean missing proportion, 21.7% for 1978–1981, compared with 2.4% for the years 1973–1977, and 0.7% for the years 1982–2002). We identified 695 singleton births delivered by women in the breast cancer cohort.

Comparison cohort For each birth by a woman with breast cancer, 50 comparison births matched by month and year of birth, by county of mother's residence, and born to 50 different women, who were not diagnosed with any cancer before or during the pregnancy or until 2 years after the birth were selected from the Birth Registry. If fewer than 50 comparison births fulfilled the criteria, we used the available number of births. If more than 50 comparison births were eligible after matching, the subset of 50 was randomly selected. On average, 48 comparison births were selected for each exposed birth. Altogether, 33 443 single births were selected for the comparison cohort.

Outcome data The data collected from the Birth Registry included preterm birth (birth before 37 completed weeks of pregnancy), low birth weight at term (birth weight <2500 g with a gestational age $\geqslant 37$ completed weeks of pregnancy), stillbirth (delivery of a dead foetus at 28 completed weeks of gestation or later in pregnancy), male proportion of newborns, and birth weight. Data on potential confounders included maternal age, parity, gestational age, and calendar period of the birth. Data about congenital abnormalities (including chromosomal abnormalities) diagnosed during the first year after the birth were collected from the Danish Hospital Discharge Registry, established in 1977, with records of all discharges from Danish hospitals. The recorded information includes the civil registration number, dates of admission and discharge, and up to 20 discharge diagnoses, using the International Classification of Diseases (ICD-8 before 1994 and ICD-10 from 1994 onward (Andersen *et al*, 1999)). The codes for congenital abnormalities (including chromosomal abnormalities) were 740.00–759.99 in ICD-8 and Q0.00–Q99.9 in ICD-10. Diagnoses of congenital dislocation of the hip and undescended testis were excluded because of their poor validity (Larsen *et al*, 2003).

Record linkage

Linkage between registries was made by the civil registration number stored in the Danish Civil Registration System together with information on vital status, emigration, address, and nuclear family members' civil registration number since 1968 (Frank, 2000).

Data analysis

We classified the births of women with breast cancer according to time of cancer diagnosis in relation to pregnancy. **Group 1** included the first birth after breast cancer delivered by women who were diagnosed at any time before pregnancy. **Group 2** included the births delivered by women with a diagnosis of breast cancer during their pregnancy (i.e., diagnosed between the first day in the last menstruation until the date of birth). **Group 3** included births delivered by women who were diagnosed with breast cancer after delivery (i.e., diagnosed between the day after the date of birth until 2 years later). If a woman gave birth more than once in this 2-year period, only the last birth before the cancer diagnosis was included. We computed the difference between the male proportion of newborns of women with breast cancer and that of newborns of matched comparison mothers with 95% confidence intervals (95% CI) for these differences. We estimated the prevalence ratios (PR) using prevalence odds ratios and 95% CI for preterm birth, low birth weight at term, stillbirth, and congenital abnormalities by logistic regression modelling. Stillborn children were excluded from the analyses of preterm birth, low birth weight at term, and congenital abnormalities. We adjusted for maternal age, parity, and calendar period of the birth. PRs for congenital abnormalities were additionally adjusted for gestational age. For births in Groups 1 and 3, we repeated the analyses in strata of boys and girls to examine if sex of the child modified the PR estimates. For births in Group 1, we evaluated whether treatment of the mother modified the PR estimates by repeating the analyses in strata of births of women treated with surgery alone and births of women who received other treatment (i.e., radiotherapy, chemotherapy, or endocrine therapy).

We used multivariate regression analysis to estimate differences in mean birth weight adjusted for maternal age, parity, gestational age, and calendar period of the birth. Stillborn children were excluded from this analysis.

All analyses used SAS software, version 8.2.

The study was approved by the Danish Data Protection Agency (record no. 2003-41-2833).

RESULTS

Descriptive data on Groups 1, 2 and 3 and their matched comparison births are shown in Table 1. Of the 695 single births delivered by women with BC, 216 occurred in Group 1, 37 occurred in Group 2, and 442 occurred in Group 3. For Group 1, the median number of days from the time of diagnosis until pregnancy (i.e., the first day in the last menstruation) was 753 days (range: 3–5965 days). Of the 37 births in Group 2, one woman was diagnosed in the first trimester, five in the second, and 31 women were diagnosed in the third.

For births delivered by women in Group 3, the median number of days from date of the birth until date of cancer diagnosis was 417 days (range: 1–729 days).

We evaluated the proportion of male newborns of women with breast cancer compared with that of newborns of unaffected mothers (50 *vs* 52%, difference $=-2.2$%, (95% CI $=-8.9$; 4.5) for Group 1, 49 *vs* 52%, difference $=-3.4$%, (95% CI $=-20$; 13) for Group 2, and 53 *vs* 51%, difference $=2.5$%, (95% CI $=-2.2$; 7.2) for Group 3).

Table 2 shows the PRs for preterm birth, low birth weight at term, stillbirth and congenital abnormalities for newborns in Groups 1–3. There was no stillborn child among the births delivered by mothers with breast cancer. For births in Group 1, we found no increased odds of low birth weight at term or congenital abnormalities and no substantial increased odds of preterm birth. For births in Group 2, the odds of preterm birth increased by eight-fold (PR $=8.1$, 95% CI $=3.8$–17). However, 10 of the 12 preterm deliveries among the women with breast cancer were elective preterm deliveries. As a result of the small number of outcome events, effect estimates for Group 2 were imprecise. For Group 3 the PR of preterm birth was 1.4 (95% CI $=1.0$–2.0). For low birth weight at term the PR was 1.4 (95% CI $=0.7$–2.8). There was no increased prevalence of congenital abnormalities. We found no clusters of congenital abnormalities in any specific organ system and there was only one case with a chromosomal abnormality (data not shown). Stratification according to sex of the offspring in Groups 1 and 3 did not change the overall effect estimates substantially (data not shown), except for low birth weight at term in Group 3, in which boys had almost three-fold increased odds (PR $=2.9$; 95% CI: 1.3–6.3), and girls had decreased odds (PR $=0.3$; 95% CI: 0.03–2.0). For

Table 1 Characteristics of births of women with breast cancer and of the comparison cohort

	Births in group 1 ($N=216$)	Births in comparison cohort ($N=10\,453$)	Births in group 2 ($N=37$)	Births in comparison cohort ($N=1795$)	Births in group 3 ($N=442$)	Births in comparison cohort ($N=21\,195$)
Maternal age at delivery, number (%)						
<25 years	5 (2.3)	2441 (23.4)	1 (2.7)	419 (23)	18 (4.1)	5517 (26.0)
25–29 years	29 (13)	4054 (38.8)	8 (22)	693 (39)	104 (24)	8256 (39.0)
30–34 years	76 (35)	2853 (27.3)	13 (35)	486 (27)	184 (42)	5383 (25.4)
⩾35 years	106 (49)	1105 (10.6)	15 (41)	197 (11)	136 (31)	2039 (9.6)
Data missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age at delivery (years)						
Mean (±s.d.)	34.4 (±4.8)	28.2 (±4.9)	33.3 (±4.8)	28.3 (±5.0)	32.2 (±4.4)	27.8 (±4.9)
Min/max	21–46	15–50	24–44	15–43	20–44	14–47
Parity, number (%)						
1	92 (43)	4778 (45.8)	11 (30)	849 (47)	116 (26)	9514 (44.9)
⩾2	124 (57)	5665 (54.2)	26 (70)	946 (53)	326 (74)	11 665 (55.1)
Data missing	0 (0.0)	10 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	16 (<0.1)
Offspring (sex), number (%)						
Male	108 (50)	5454 (52.2)	18 (49)	934 (52)	236 (53)	10 782 (50.9)
Female	108 (50)	4989 (47.8)	19 (51)	861 (48)	206 (47)	10 397 (49.1)
Data missing	0 (0.0)	10 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)	16 (<0.1)
Gestational age (weeks)[a]						
Mean (±s.d.)	39.2 (±2.4)	39.6 (±1.8)	37.2 (±3.8)	39.5 (±1.9)	39.3 (±2.0)	39.6 (±1.9)
Min/max	25–43	20–44	24–42	26–43	25–43	23–44

[a]Stillborn babies were excluded from the analyses of mean gestational age. Group 1: Births of women diagnosed with breast cancer before pregnancy. Group 2: Births of women diagnosed with breast cancer during pregnancy. Group 3: Births of women diagnosed with breast cancer from the day after giving birth and until 2 years later.

Table 2 Crude and adjusted prevalence odds ratios of birth outcome in women with breast cancer

	Breast cancer cohort outcome/total (%)	Comparison cohort outcome/total (%)	Crude prevalence odds ratio (95 % ci)	Adjusted prevalence odds ratio[a] (95 % CI)
Births in group 1	($N=216$)	($N=10\,453$)		
Preterm birth[b]	14/216 (6.5)	507/10 414 (4.9)	1.4 (0.8–2.3)	1.3 (0.7–2.2)
Low birth weight[b]	3/202 (1.5)	137/9885 (1.4)	1.1 (0.3–3.4)	1.2 (0.4–3.8)
Stillbirth	0/216 (0.0)	39/10 453 (0.4)	—	—
Abnormalities[b,c]	7/203 (3.4)	369/9775 (3.8)	0.9 (0.4–1.9)	0.9 (0.4–1.9)
Births in group 2	($N=37$)	($N=1795$)		
Pretem birth[b]	12/37 (32)	102/1785 (5.7)	7.9 (3.9–16)	8.1 (3.8–17)
Low birth weight[b]	1/25 (4.0)	19/1679 (1.1)	3.6 (0.5–28)	5.3 (0.6–51)
Stillbirth	0/37 (0.0)	10/1795 (0.6)	—	—
Abnormalities[b,c]	1/35 (2.9)	53/1685 (3.1)	0.9 (0.1–6.7)	0.5 (0.1- 3.6)
Births in group 3	($N=442$)	($N=21\,195$)		
Pretem birth[b]	33/442 (7.5)	1143/21 120 (5.4)	1.4 (1.0–2.0)	1.4 (1.0–2.0)
Low birth weight[b]	9/408 (2.2)	329/19 917 (1.7)	1.3 (0.7–2.6)	1.4 (0.7–2.8)
Stillbirth	0/442 (0.0)	75/21 195 (0.4)	—	—
Abnormalities[b,c]	16/389 (4.1)	685/18 519 (3.7)	1.1 (0.7–1.9)	1.1 (0.6–1.8)

Group 1: Birth outcome in women diagnosed with breast cancer before pregnancy. Group 2: Birth outcome in women diagnosed with breast cancer during pregnancy. Group 3: Birth outcome in women diagnosed with breast cancer from the day after giving birth and until 2 years post partum. [a]Prevalence odds ratios for preterm birth and low birth weight at term were adjusted for maternal age (<25 year, 25–29 year, 30–34 year and ⩾35 year), parity (1, 2+) and calendar period of birth (73–86, 87–94, 95–02). Prevalence odds ratios for congenital abnormalities were additionally adjusted for gestational age (20–33 week, 34–36 week and ⩾37 week). [b]Stillborn babies were excluded from the analyses of preterm birth, low birth weight at term and congenital abnormalities. [c]Data on congenital abnormalities included births from 1977 to 2002.

births in Group 1, stratification according to mother's treatment (surgery alone or other treatment) did not change the overall results (data not shown).

Table 3 shows the adjusted mean differences in birth weight between babies born to women with breast cancer and babies born to comparison mothers. Newborns of women in Groups 1 and 3 had nearly the same mean birth weights as newborns of comparison mothers, whereas newborns of women in Group 2 had a mean birth weight 240 g (95% CI = −404; −76) less than newborns of comparison mothers.

DISCUSSION

We examined the association between maternal breast cancer and adverse birth outcome in a nationwide cohort and found little difference in the occurrence of preterm birth, low birth weight at term, stillbirth, or congenital abnormalities, compared with the comparison cohort, among newborns of women who were diagnosed with breast cancer before pregnancy.

The eight-fold increased odds of preterm birth for newborns of women who were diagnosed with breast cancer during their

Table 3 Mean birth weight for newborns of women with breast cancer and for the comparison cohort

	Breast cancer		Comparison cohort		Mean difference in birth weight (g)	
		Mean birth weight (g)		Mean birth weight (g)	Crude	Adjusted (95% confidence limits)[a,b]
Births in group 1	$N=216$	3411	$N=10\,388$	3474	−63	−54 (−122; 13)
Data missing	0		26			
Births in group 2	$N=37$	2948	$N=1781$	3472	−524	−240 (−404; −76)
Data missing	0		4			
Births in group 3	$N=441$	3471	$N=21\,054$	3466	5	−5 (−52; 42)
Data missing	1		66			

Group 1: Mean birth weight for newborns of women with breast cancer before pregnancy. Group 2: Mean birth weight for newborns of women diagnosed with breast cancer during pregnancy. Group 3: Mean birth weight for newborns of women with breast cancer from the day after giving birth until 2 years post partum. [a]Adjusted for gestational age (20–33 week, 34–36 week and ⩾37 week), mother's age (<25 year, 25–29 year, 30–34 year, ⩾35 year), parity (1, 2+) and calendar period for birth (73–86, 87–94, 95–02) in a multivariate regression model. [b]Stillborn babies were excluded from the analysis.

pregnancy reflected a higher rate of elective early delivery, probably to allow an earlier start of cancer therapy. After adjustment for gestational age, there was a 240 g reduction in mean birth weight for newborns in this group. The association with preterm birth in Group 3 may be explained by suboptimal intrauterine conditions caused by a preclinical cancer. In this group, only boys had increased odds of low birth weight at term, suggesting that male foetuses are more vulnerable than female.

Our data are derived from a uniformly organized health care system with complete cancer and birth registration. Some selection problems are possible, however. If women with breast cancer had more miscarriages or induced abortions caused by foetal abnormalities than comparison mothers, this phenomenon could explain why we found no increased risk of congenital abnormalities. It has been suggested that exposure to severe periconceptional life events might reduce the male proportion of offspring, partly because of differential abortion of male embryos (Hansen *et al*, 1999). Thus, a lower proportion of males for offspring of the patients could be an indicator of miscarriages. Another study has indicated an increased risk of miscarriage among women with breast cancer (Velentgas *et al*, 1999). Our data, however, did not show any important difference in male proportions between the offspring of breast cancer women and offspring of comparison mothers. It has been reported that women with high socioeconomic status have a higher incidence of breast cancer (Danø *et al*, 2004), while low socioeconomic status has been associated with adverse birth outcome (Luo *et al*, 2004). We were unable to adjust for socioeconomic status and therefore we may have underestimated the effect of the disease.

A recent study found that treatment data recorded in the Cancer Register are of varying quality (Jensen *et al*, 2002). However, breast cancer treatment with surgery alone was correctly registered for 95.4% (Jensen *et al*, 2002). Coding mistakes are infrequent in the Birth Registry, but data have some misclassifications of gestational age (Kristensen *et al*, 1996). Our data did not suggest any differential misclassification of preterm birth between women with breast cancer and comparison mothers.

Hospital discharge data are not always coded correctly (Larsen *et al*, 2003), but Danish data on congenital abnormalities are of high quality compared with other countries, with 80–85% coded correctly (Larsen *et al*, 2003). We did not find any clusters of congenital abnormalities in any specific organ system.

Our finding of an increased risk of giving birth preterm for women who were diagnosed with breast cancer during or shortly after pregnancy corroborates the results of two earlier studies (Zemlickis *et al*, 1992; Smith *et al*, 2001). In a hospital-based study, Smith *et al* (2001) identified 423 cases of breast cancer diagnosed from 9 months preceding delivery until 12 months after delivery over a period of 6 years in California. They reported an odds ratio of 2.2 (95% CI = 1.7–2.8) for prematurity, and an odds ratio of 2.0 (95% CI = 1.0–4.1) for very low birth weight. They adjusted only for maternal age. A hospital-based historical cohort study from 1992 of 118 women, who were pregnant within 9 months before or 3 months after their first treatment for breast cancer, reported a lower mean birth weight after adjustment for gestational age and a higher proportion of preterm births among offspring of women with breast cancer compared with controls (Zemlickis *et al*, 1992). In these studies, however, the authors did not distinguish between birth outcome of women diagnosed with breast cancer during their pregnancy and women diagnosed shortly after pregnancy. We found a lower mean birth weight limited to newborns of women diagnosed during their pregnancy.

In conclusion, this is the first population-based cohort study of birth outcome in women diagnosed with breast cancer before pregnancy, and the largest cohort study to date of birth outcome in women diagnosed with breast cancer during or shortly after pregnancy. Overall, our results are reassuring regarding the risks of adverse birth outcome for women with breast cancer.

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II

Birth outcome in Danish Women with Cutaneous Malignant Melanoma

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ABSTRACT

Several factors may affect birth outcome in women with cutaneous malignant melanoma. We examined whether maternal cutaneous malignant melanoma affects birth outcome (preterm birth, low birth weight at term, stillbirth, congenital abnormalities, mean birth weight, and male proportion of newborns) in a nationwide cohort study of 1,059 births from 1973 to 2002 borne to women with cutaneous melanoma, compared with 50,794 births from a cohort of mothers without cancer. We found no increased risk of adverse birth outcome for the 620 newborns borne to women with a diagnosis of melanoma before pregnancy or the 88 newborns borne to women diagnosed during pregnancy. Among 351 births of women diagnosed with melanoma within two years from the time of delivery, the prevalence odds ratio (POR) of stillbirth was 4.6 (95% CI: 1.7; 12). This estimate was, however, based on only five stillbirths in the exposed group and was an unexpected finding. With this exception, our data suggest no substantially increased risk of adverse birth outcome for women with melanoma.

Keywords: Epidemiology, melanoma, birth outcome, cohort study

INTRODUCTION

The incidence of cutaneous malignant melanoma (CMM) has been rising in most white populations around the world for decades [1]. In Denmark, the incidence of CMM for women aged 15-34 years increased with an average of 4.3% annually from 1970 to 1999 [2]. Internationally, it has been estimated that about 35% of women with CMM are of childbearing age [3] and that CMM represents approximately 8% of malignancies diagnosed during pregnancy [4].

Several factors may affect pregnancy outcome in women with CMM. A diagnosis of cancer is a stressful event, and several studies have shown associations between stress and adverse pregnancy outcome such as an increased risk of preterm delivery [5;6] and congenital abnormalities [7]. It has also been suggested that psychological stress around the time of conception may reduce the male proportion of newborns [8]. In addition, three small studies have reported an increased incidence of CMM among infertile women [9-11], and pregnancies from assisted reproduction have been associated with adverse birth outcome, such as preterm birth, low birth weight, and perinatal mortality [12].

Despite these reasons to suspect that CMM diagnosis may be related to birth outcomes, the epidemiologic evidence on the topic is limited. No population-based cohort study of birth outcome in women diagnosed with CMM before pregnancy has been published. A recent cohort study, based on 412 women who were diagnosed with CMM during or shortly after pregnancy focused on the effect of pregnancy on maternal survival [13]. In a subanalysis, the authors examined the birth outcome of these women and found no increased risk of low birth weight, preterm birth or

stillbirth, compared with unaffected women. A smaller cohort study, however, has reported a lower mean birth weight for newborns of 21 women who were diagnosed with CMM during pregnancy compared with newborns borne to women without CMM [14].

Therefore, we examined the risk of preterm birth, low birth weight at term, stillbirth, and congenital abnormalities as well as mean birth weight and male proportion of newborns in a Danish cohort of women with CMM, compared with the outcome of births from a cohort of women without cancer.

MATERIALS AND METHODS

Study population

Information on women with CMM was collected from the Danish Cancer Registry, which has kept records of all incident cases of cancer in Denmark since 1943, classified according to the International Classification of Diseases (ICD-7) [15]. The records include the civil registration number, which is assigned to all Danes at birth, diagnosis, date of diagnosis, method of verification, extent of disease at diagnosis (localized, with regional spread or with metastasis to distant organs), and treatment given within four months after diagnosis. We traced all women with a diagnosis of CMM (ICD-7 codes 190.0-190.9) and excluded all cases with carcinoma *in situ*.

Since 1 January 1973 all births in Denmark have been registered in the Danish Medical Birth Registry (MBR) [16]. Data are obtained from birth notifications, which are completed by midwives (in Denmark all births, including home births, are attended by midwives). The main variables in the MBR are the civil registration number of the mother and the child (except for stillborn children), date and place of birth, gestational age, birth weight, parity, and whether a congenital abnormality is present at the time of birth (no data on the specific type of abnormality are available).

We linked the Danish Cancer Registry data with the MBR by civil registration number [17] to establish a cohort of all Danish women who were recorded with a diagnosis of CMM between January 1, 1970 and December 31, 2002, and who gave birth between January 1, 1973 and December 31, 2002. Women were included if they were diagnosed with CMM before the pregnancy, during the pregnancy, or until

two years post partum. We restricted all analyses to singleton births to avoid potential confounding of multiple births, since these have been associated with an increased risk of adverse birth outcome [18].

Comparison cohort

The prevalence of adverse birth outcomes was compared with the prevalence in a comparison cohort selected from other births in Denmark. For each birth by a woman with CMM, 50 comparison births were selected from the MBR. These births were matched to the CMM cohort members' births by month and year of birth, county of mother's residence, and borne to 50 different women who were not diagnosed with any cancer before or during the pregnancy or until two years after the birth. If fewer than 50 births fulfilled the matching criteria, we used all the available births. If more than 50 comparison births were eligible after matching, we selected a random subset of 50 births. On average, 48 comparison births were selected for each exposed birth.

Birth outcome data and potential confounders

The outcome data collected from the MBR included preterm birth (birth before 37 completed weeks of pregnancy), low birth weight at term (birth weight <2500 g with ≥37 completed weeks of pregnancy), stillbirth (delivery of a dead fetus at ≥28 completed weeks of pregnancy), male proportion of newborns, birth weight, and for stillbirths of women with CMM, whether a congenital abnormality was present at birth. Data on potential confounders included maternal age, parity, gestational age and calendar period of the birth. For live born babies, outcome data on congenital abnormalities (including chromosomal abnormalities) diagnosed during the first year of life were collected from the National Hospital Discharge Registry, with records of

all discharge diagnoses from Danish hospitals since 1977 and outpatient visits since 1995. The variables include the civil registration number, dates of admission and discharge, and up to 20 discharge diagnoses, using the International Classification of Diseases (ICD-8 before 1994 and ICD-10 from 1994 onward [19]). The codes for congenital abnormalities (including chromosomal abnormalities) were 740.00 to 759.99 in ICD-8 and Q0.00 to Q99.9 in ICD-10. Diagnoses of congenital dislocation of the hip and undescended testis were excluded because of their poor validity [20].

Statistical analysis

Birth weights ≥7000 g probably reflected coding errors and were excluded from the analyses. We also excluded births registered with a gestational age of less than 20 weeks or more than 44 weeks. Owing to a change in coding procedures in the MBR in 1978, there were more missing data on gestational age for the years 1978-1981 than for other years (mean missing proportion, 25.0% for 1978-1981, compared with 1.2% in 1973-1977, and 0.8% in 1982-2002). Births without data on gestational age were excluded from the study (N=29 in the exposed cohort and N=1,868 in the comparison cohort). In total, we identified 1,059 singleton births delivered by women with CMM and selected 50,794 singleton births for the comparison cohort.

We classified the births of women with CMM into three groups according to time of cancer diagnosis in relation to pregnancy. **Group 1** included the first birth after a CMM diagnosis (*i.e.* women who were diagnosed before pregnancy). **Group 2** included the births by women who were diagnosed with CMM during pregnancy (*i.e.* diagnosed between the first day in the last menstruation until the date of birth). **Group 3** included births by women who were diagnosed with CMM after delivery (*i.e.*

diagnosed between the day after the date of birth until two years later). If a woman gave birth more than once in this two-year period, only the last birth before the cancer diagnosis was included, based on the assumption that the preclinical cancer would be more likely to affect the birth closest to the time of cancer diagnosis.

We calculated the prevalence of births in the cohorts within the categories of each of the independent variables, stratified by cancer diagnosis group for the CMM cohort and by the matched woman's cancer diagnosis group for the comparison cohort.

We computed crude and adjusted prevalence odds ratios (POR), as an estimate of the risk ratio, and associated 95% confidence interval (CI) for preterm birth, low birth weight at term, stillbirth, and congenital abnormalities. Adjusted PORs were estimated by unconditional logistic regression analysis. We adjusted for maternal age (<25 yr, 25-29 yr, 30-34 yr, ≥35 yr), parity (1, 2+), and calendar period of the birth (1973-86, 1987-94, 1995-2002). PORs for stillbirth were also adjusted for gestational age (20-33 wk, 34-36 wk, and ≥37 wk). Stillborn children were excluded from the analyses of preterm birth, low birth weight at term, and congenital abnormalities. For births in Group 1 and Group 3 we repeated the analyses in strata of boys and girls to examine whether sex of the child modified the POR estimates. The small number of outcome events in Group 2 precluded stratified analyses. As cardiovascular abnormalities are among the most common congenital abnormalities [21], we examined whether there was a cluster of these abnormalities by segregating the POR estimates into those for all cardiovascular abnormalities (codes: 746.09 to 747.99 in ICD-8 and Q20.0 to Q28.9 in ICD-10) and all other abnormalities in Groups 1 and 3.

We also computed the difference between the male proportion of newborns of women with CMM and that of newborns of matched comparison mothers with 95% CI.

We used linear regression analysis to estimate differences in mean birth weight adjusted for maternal age (<25 yr, 25-29 yr, 30-34 yr, ≥35 yr), parity (1, 2+), gestational age (20-33 wk, 34-36 wk, and ≥37 wk), and calendar period of the birth (1973-86, 1987-94, 1995-2002). Stillborn children were excluded from these analyses.

The study was approved by the Danish Data Protection Agency (record no. 2003- 41- 2833). As the study was based on routinely registered data, informed consent from the patients involved was not necessary. All analyses used SAS software, version 8.2.

RESULTS

Descriptive data

Descriptive data on Groups 1 to 3 and their matched comparison cohort are shown in Table 1. Of the 1,059 single births delivered by women with CMM, 620 occurred in Group 1. The median number of days from the time of diagnosis until pregnancy (*i.e.* the first day in the last menstruation) was 934 days (range: 11-8025 days). Eighty-eight births in Group 2 were found (19 women were diagnosed in the first trimester, 39 in the second, and 30 in the third). In Group 3, 351 births occurred. The median number of days from date of the birth until date of cancer diagnosis was 330 days (range: 13-729 days).

The proportion of melanomas registered as localized at time of diagnosis was 95% for women in Group 1, 93% in Group 2, and 92% in Group 3. This information was missing for 5%, 1% and 4%, in Groups 1, 2 and 3, respectively.

Birth outcome

The proportion of male newborns of women with CMM consistently exceeded the proportion of male newborns of the matched comparison mothers (53.2% versus 51.7%, difference = 1.5%, (95% CI = -2.5; 5.5) for Group 1, 56.8% versus 51.9%, difference = 4.9%, (95% CI = -5.5; 15) for Group 2, and 58.4% versus 51.9%, difference = 6.5%, (95% CI = 1.3; 12) for Group 3).

Table 2 shows the crude and adjusted prevalence odds ratios (POR) for preterm birth, low birth weight at term, stillbirth, and congenital abnormalities for newborns in Groups 1 to 3 and the matched comparison cohort stratified by the matched CMM woman's group. For births in Group 1 and 2, there was no stillborn

child among the births delivered by mothers with CMM, and we found no substantially different risks of preterm birth, low birth weight at term, or congenital abnormalities, compared with the matched comparison cohort. For births in Group 3, the POR of stillbirth was 4.6 (95% CI = 1.7; 12.3). No increased risk of preterm birth, low birth weight at term, or congenital abnormalities was observed in this group. We did not identify any characteristics consistently in common to all of the stillborn children in Group 3 (Table 3).

The POR estimates for cardiovascular abnormalities and other abnormalities were 1.2 (95% CI=0.6; 2.5) and 1.1 (95% CI=0.7; 1.7), respectively, in Group 1 and 0.7 (95% CI=0.2; 2.7) and 1.2 (95% CI =0.6; 2.2), respectively, in Group 3. We found only one case with a chromosomal abnormality. Stratification according to sex of the offspring in Groups 1 and 3 did not change the overall effect estimates substantially (data not shown).

Newborns in Group 1 and Group 3 had nearly the same mean birth weights as newborns in the comparison cohort, while newborns in Group 2 had an adjusted mean birth weight 88 g (95 % CI=-18;194) higher than newborns of comparison mothers.

DISCUSSION

In this nationwide cohort study of birth outcome in women with CMM, we found no increased risk of preterm birth, low birth weight at term, stillbirth, or congenital abnormalities among newborns of women who were diagnosed with CMM before or during pregnancy, compared with newborns of mothers without cancer. The more than four-fold increased risk of stillbirth for newborns of women who were diagnosed with CMM within two years after the time of delivery was an unexpected finding.

Our data derive from a uniformly organized health care system with complete nationwide cancer and birth registration allowing for a population-based design and complete follow-up on congenital abnormalities diagnosed during the first year of life. Several factors affect the accuracy of our risk estimates and the interpretation of our data. Because of the small number of outcome events, the effect estimates in Group 2 were imprecise. We did not have data on spontaneous or induced abortions. If women with CMM had more miscarriages or induced abortions related to fetal abnormalities than comparison mothers, this difference could introduce a selection bias and explain why we found no increased risk of congenital abnormalities. We examined the male proportion of newborns, since it has been suggested that exposure to psychological stress related to severe life events (such as severe illness in a partner) around the time of conception may reduce the male proportion of newborns, partly because of differential abortion of male embryos [8]. Thus, psychological stress, caused by CMM, may cause an increased rate of early male abortion. Our data, however, showed a small but not substantial increase in the male proportion of newborns borne to

women with CMM compared with newborns borne to the matched cohort of mothers without cancer.

Coding errors are infrequent in the Medical Birth Registry (MBR) but gestational age does have some misclassifications errors [22]. Our POR estimates for preterm birth that were close to one did not suggest any differential misclassification of preterm birth between women with CMM and comparison mothers.

Data on congenital abnormalities were obtained from the National Hospital discharge registry, which may not always be coded correctly, but are of generally high quality with 85% correct coding [20]. It is important to consider that teratogens do not uniformly increase the rate of all congenital abnormalities, but rather increase the rates of selected abnormalities [23]. Therefore, we examined the risk of cardiovascular outcomes that belong to the most common congenital abnormalities [21], but we found no cluster of these specific abnormalities.

We were unable to adjust for socioeconomic status and therefore we may have underestimated the impact of CMM on birth outcome, since it has been reported that women with high socioeconomic status have a higher incidence of CMM [24], and low socioeconomic status has been associated with a moderately increased risk of adverse birth outcomes [25]. It is unlikely, however, that disparities in socioeconomic conditions between women with CMM and the comparison cohort would cause major confounding of birth outcome [25].

A hospital-based study evaluated 18 deliveries of women who were diagnosed with CMM during pregnancy over a period of 30 years [14]. The authors reported 17 live births, one anencephalic stillbirth, a lower mean birth weight for

newborns of women with CMM, as compared to women without CMM, and no difference in mean gestational age. The authors suggested that the differences in birth weight were due to intrauterine growth retardation secondary to the melanoma, its therapies, or its complications. In that study, however, mean birth weights were based on only nine melanoma exposed newborns and nine newborns born to matched mothers. Our study found no important difference in mean birth weight between newborns of women with CMM and newborns of comparison mothers, based on a substantially larger sample and nested in an unselected population. In a population-based cohort study, O'Meara *et al*. identified 149 women diagnosed with CMM during pregnancy and 263 women diagnosed within 12 months after delivery over a period of 9 years in California [13]. Our results corroborate their study with respect to the low relative risk of preterm birth and low birth weight. For women diagnosed during pregnancy, O'Meara and colleagues reported an odds ratio of 0.9 (95% CI=0.5-1.6) for prematurity and an odds ratio of 0.8 (95% CI=0.3-1.8) for low birth weight, adjusted for age and race. They found no fetal deaths in the exposed group and no increased risk of adverse birth outcome in women who were diagnosed with CMM in the first post partum year (no data were shown).

Our finding of a four-fold increased risk of stillbirth for newborns of women who were diagnosed with CMM within two years after delivery was unexpected. The five stillbirths were not caused by maternal disseminated cancer, since these children all were borne to mothers who were registered with localized disease at diagnosis. Unfortunately, our data cannot determine whether the factors behind the association may be causal, unmeasured confounding, or chance. With this exception, our results

suggest no substantially increased risk of adverse birth outcome for women with CMM.

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Table 1. Characteristics of births to Danish women diagnosed with cutaneous malignant melanoma (CMM) 1970-2002 and giving birth 1973-2002 and to a matched comparison cohort.

Group 1: Births of women diagnosed with CMM before pregnancy.

Group 2: Births of women diagnosed with CMM during pregnancy.

Group 3: Births of women diagnosed with CMM from the day after giving birth and until two years later.

	Births in Group 1 (N=620)	Births in Comparison Cohort (N=29,788)	Births in Group 2 (N=88)	Births in Comparison Cohort (N=4,180)	Births in Group 3 (N=351)	Births in Comparison Cohort (N=16,826)
Age at delivery, number (%)						
<25 years	26 (4.2)	5,642 (18.9)	8 (9.1)	902 (21.6)	23 (6.6)	3,449 (20.5)
25-29 years	202 (32.5)	11,106 (37.3)	35 (39.8)	1,628 (38.9)	147 (41.9)	6,628 (39.4)
30-34 years	251 (40.3)	9,173 (30.8)	25 (28.4)	1,149 (27.5)	121 (34.5)	4,788 (28.5)
≥ 35 years	141 (22.7)	3,867 (13.0)	20 (22.7)	501 (12.0)	60 (17.1)	1,961 (11.7)
Age at delivery (years)						
Mean (+/- SD)	31.3 (+/- 4.4)	28.9 (+/- 4.8)	30.3 (+/- 4.9)	28.5 (+/- 4.9)	30.2 (+/- 4.3)	28.6 (+/- 4.8)
Min/max	20-47	15-48	20-44	16-45	20-44	14-58
Parity, number (%)						

1	346 (55.8)	13,358 (44.9)	42 (47.7)	1,835 (44.0)	144 (41.0)	7,674 (45.7)
≥ 2	274 (44.2)	16,398 (55.1)	46 (52.3)	2,338 (56.0)	207 (59.0)	9,136 (54.3)
Calendar period of birth, number (%)						
1973-1986	131 (21.1)	5,979 (20.1)	31 (35.2)	1,391 (33.3)	101 (28.8)	4,676 (27.8)
1987-1994	170 (27.4)	8,312 (27.9)	28 (31.8)	1,370 (32.8)	122 (34.8)	5,901 (35.1)
1995-2002	319 (51.5)	15,497 (52.0)	29 (33.0)	1,419 (33.9)	128 (36.5)	6,249 (37.1)
Offspring (sex), number (%)						
Male	330 (53.2)	15,396 (51.7)	50 (56.8)	2,166 (51.9)	205 (58.4)	8,719 (51.9)
Female	290 (46.8)	14,360 (48.3)	38 (43.1)	2,007 (48.1)	146 (41.6)	8,091 (48.1)
Gestational age (weeks)*						
Mean (+/- SD)	39.5 (+/- 2.0)	39.5 (+/- 1.8)	39.9 (+/- 1.2)	39.5 (+/-1.9)	39.6 (+/- 1.7)	39.6 (+/- 1.9)
Min/max	26-43	20-44	35-42	25-44	30-44	20-44
Birth weight (g)*						
Mean (+/- SD)	3,459 (+/-581)	3,486 (+/- 569)	3,604 (+/- 522)	3,468 (+/- 575)	3,502 (+/- 543)	3,472 (+/- 570)
Min/max	850-5,100	300-5,900	2,430-5,220	520-5,800	1,515-5,070	555-6,000

*Stillborn babies were excluded from the analyses of mean gestational age and mean birth weight.

Table 2. **Crude and adjusted prevalence odds ratios of birth outcome in Danish women diagnosed with cutaneous malignant melanoma (CMM) 1970-2002 and giving birth 1973-2002 compared to a matched cohort.**

Group 1: Birth outcome in women diagnosed with CMM before pregnancy.

Group 2: Birth outcome in women diagnosed with CMM during pregnancy.

Group 3: Birth outcome in women diagnosed with CMM within two years after giving birth

	CMM Cohort Outcome/Total (%)	Comparison Cohort Outcome/Total (%)	Crude Prevalence odds ratio (95 % CI)	Adjusted Prevalence odds ratio* (95 % CI)
Births in Group 1	(N=620)	(N=29,788)		
Preterm Birth†	36/620 (5.8)	1,510/29,685 (5.1)	1.2 (0.8 - 1.6)	1.1 (0.8 - 1.6)
Low birth weight at term†	10/583 (1.7)	436/28,075 (1.6)	1.1 (0.6 - 2.1)	1.1 (0.6 - 2.0)
Stillbirth	0/620 (0.0)	103/29,788 (0.3)	-	-
Abnormalities†,‡	29/593 (4.9)	1,105/28,353 (3.9)	1.3 (0.9 - 1.9)	1.2 (0.8 - 1.8)
Births in Group 2	(N=88)	(N=4,180)		
Pretem Birth†	1/ 88 (1.1)	214/ 4,158 (5.1)	0.2 (0.03- 1.5)	0.2 (0.03- 1.5)
Low birth weight at term†	1/ 87 (1.1)	65/ 3,936 (1.7)	0.7 (0.1 - 5.0)	0.6 (0.1 - 4.5)
Stillbirth	0/ 88 (0.0)	22/ 4,180 (0.5)	-	-
Abnormalities†,‡	2/ 80 (2.5)	148/ 3,768 (3.9)	0.6 (0.2 - 2.6)	0.6 (0.2 - 2.7)
Births in Group 3	(N=351)	(N=16,826)		
Pretem Birth†	16/346 (4.6)	852/16,546 (5.1)	0.9 (0.5 - 1.5)	0.9 (0.5 - 1.5)
Low birth weight at term†	5/330 (1.5)	264/15,648 (1.7)	0.9 (0.4 - 2.2)	0.9 (0.4 - 2.2)
Stillbirth	5/351 (1.4)	65/16,826 (0.4)	3.7 (1.5 - 9.3)	4.6 (1.7 - 12.3)
Abnormalities†,‡	13/314 (4.1)	557/14,977 (3.7)	1.1 (0.6 - 2.0)	1.1 (0.6 - 2.0)

[*] Prevalence odds ratios for preterm birth, low birth weight at term, stillbirth and congenital abnormalities were adjusted for maternal age (<25 yr, 25-29 yr, 30-34 yr and ≥35 yr), parity (1, 2+) and calendar period of birth (73-86, 87-94, 95-02). Prevalence odds ratios for stillbirth were additionally adjusted for gestational age (20-33 wk, 34-36 wk and ≥37 wk).

[†] Stillborn babies were excluded from the analyses of preterm birth, low birth weight at term and congenital abnormalities.

[†] Data on congenital abnormalities included births from 1977 to 2002.

Table 3. Characteristics of the five stillborn children of women diagnosed with cutaneous malignant melanoma (CMM) within two years after the delivery (Group 3).

	Year of birth	Maternal age at delivery	Spread of the tumor at time of diagnosis*	Parity	Sex	Gestational age	Birth weight	Congenital abnormality
1.	1979	25 yr	localized	1	girl	31 weeks	1000 g	present
2.	1981	34 yr	localized	1	boy	40 weeks	2650 g	absent
3.	1987	34 yr	localized	2+	girl	30 weeks	1200 g	absent
4.	1991	28 yr	localized	1	girl	30 weeks	780 g	present
5.	1994	25 yr	localized	1	girl	31 weeks	1300 g	absent

* Extent of disease at diagnosis is registered in the Danish Cancer Registry as localized, with regional spread or with metastasis to distant organs

III

Hodgkin's disease and birth outcome: A Danish nationwide cohort study.

Short title: Hodgkin's disease and birth outcome.

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Abstract

We examined whether maternal Hodgkin's disease affects birth outcome (preterm birth, low birth weight at term, stillbirth, congenital abnormalities, mean birth weight, and male proportion of newborns) in a Danish nationwide cohort study of 292 births from 1973 to 2002 to women with Hodgkin's disease, compared with 14042 births from a cohort of mothers without cancer. We computed prevalence odds ratios (POR) as estimates of the relative risks for preterm birth, low birth weight at term, stillbirth, and congenital abnormalities. We found no substantially increased risk of preterm birth, low birth weight at term, or stillbirth, and no difference in proportion of male newborns for 192 children of women with Hogkin's disease diagnosed before pregnancy. The PORs for congenital abnormalities was 1.7 (95% confidence interval (CI): 0.9-3.1). Among 15 newborns of mothers diagnosed during pregnancy, the POR of preterm birth was 26.6 (95% CI: 8.5-83.0). However, among eight preterm deliveries, five were elective. Moreover, we found no substantially increased risk of adverse birth outcome among 85 newborns of women diagnosed within two years postpartum, though effect estimates were imprecise. Despite overall reassuring findings, we cannot rule out the possibility of an increased risk of congenital abnormalities for newborns of women with Hodgkin's disease diagnosed before pregnancy.

Keywords: Hodgkin's disease, epidemiology, pregnancy, birth outcome, cohort study

Introduction

Hodgkin's disease belongs to cancers that affect women of childbearing age [1]. Advances in the treatment of Hodgkin's disease have led to an overall 5-year relative survival of more than 80% [2]. However, this success is accompanied by concerns for adverse effects of treatment [3]. Radiotherapy and/or chemotherapy may affect future pregnancies in women with Hodgkin's disease by direct effects on the reproductive tract or by causing mutations in germ cells [4]. Furthermore, cancer treatment administered in the first trimester may be teratogenic [1], while detriments in maternal well-being may impact pregnancies in women who have preclinical Hodgkin's disease or are diagnosed with Hodgkin's disease during pregnancy [5].

Nevertheless, data concerning birth outcome in women with previous Hodgkin's disease are sparse and consist mainly of case-series [6-11]. A few of these case-series, which included birth outcome of 15 to 54 women with previous Hodgkin's disease, found a high prevalence of stillbirths [6], congenital abnormalities (CAs), preterm birth, and low birth weight among newborns [7]. The majority of studies, however, have reported that, among women who are able to become pregnant, previous Hodgkin's disease has little if any detrimental effect on birth outcome [8-11]. Likewise, several case-series found normal birth outcome for women diagnosed with Hodgkin's disease during or shortly after pregnancy [12-15].

We examined the risk of adverse birth outcomes in a Danish nationwide cohort of women who were diagnosed with Hodgkin's disease before or during pregnancy, or within two years after delivery and compared with the outcome of births from a cohort of pregnant women without cancer.

Methods

Study population

We used the Danish Cancer Registry (CR), which has kept records of all incident cases of cancer in Denmark since 1943, classified according to the International Classification of Diseases (ICD-7) [16], to trace all women with a diagnosis of Hodgkin's disease (ICD-7 code 201). Information included the civil registration number of the woman, date of diagnosis, and radiation treatment administered within four months of diagnosis.

Since January 1, 1973, all births in Denmark have been registered in the Danish Medical Birth Registry (MBR) [17]. Data are obtained from birth notifications, which are completed by midwives (in Denmark all births, including home births, are attended by midwives). The main variables in the MBR are gestational age, birth weight, parity, stillbirth, place of birth, and the civil registration number of the mother and child (which encodes sex and date of birth and is assigned to all live-born children and new residents in Denmark [18]).

Using the civil registration number, we linked the CR data with the MBR to establish a cohort of all Danish women who were recorded with a diagnosis of Hodgkin's disease between January 1, 1970 and December 31, 2002, and who gave birth between January 1, 1973 and December 31, 2002. Women were included if they were diagnosed with Hodgkin's disease before pregnancy, during the pregnancy, or until two years postpartum. We restricted all analyses to singleton births to avoid potential confounding by multiple births, since these have been associated with an increased risk of adverse birth outcome [19].

Comparison cohort

For each birth by a woman with Hodgkin's disease, 50 comparison births matched by month and year of the birth, by county of mother's residence, and born to 50 different cancer-free

women were selected from the MBR. If fewer than 50 births fulfilled the matching criteria, we used all the available births. If more than 50 comparison births were eligible after matching, we selected a random subset of 50 births. On average, 48 comparison births were selected for each exposed birth.

Birth outcome data and potential confounders

The outcome data included preterm birth (birth before 37 completed weeks of pregnancy), low birth weight at term (birth weight <2500 g with ≥37 completed weeks of pregnancy), stillbirth (delivery of a dead fetus at ≥28 completed weeks of pregnancy), male proportion of newborns, and birth weight. The potential confounders included maternal age, parity, gestational age, and calendar period of the birth. For live-born children, data on CAs (including chromosomal abnormalities) diagnosed during the first year of life were collected from the National Hospital Discharge Registry, which contains records of all discharge diagnoses from Danish hospitals since 1977 and outpatient visits since 1995 [20]. The data include the civil registration number, dates of admission and discharge, and up to 20 discharge diagnoses, coded according to the International Classification of Diseases (ICD-8 before 1994 and ICD-10 from 1994 onward [20]). The codes for CAs (including chromosomal abnormalities) were 740.00 to 759.99 in ICD-8 and Q0.00 to Q99.9 in ICD-10. Diagnoses of congenital dislocation of the hip and undescended testis were excluded because of their poor validity [21].

Statistical analysis

Birth weights ≥7000 g probably reflected coding errors and were excluded from the analyses [22]. We also excluded births registered with a gestational age of less than 20 weeks or more

than 44 weeks. Owing to a change in coding procedures in the MBR in 1978, there were more missing data on gestational age for the years 1978-1981 than for other years (mean missing proportion, 22.6 % for 1978-1981, compared with 0.8 % in 1973-1977, and 1.2 % in 1982-2002). Births without data on gestational age were excluded from the study (N=20 in the exposed cohort and N=698 in the comparison cohort).

We classified the births of women with Hodgkin's disease into three groups according to the time of diagnosis in relation to pregnancy. **Group 1** included the first birth after a Hodgkin's disease diagnosis (*i.e.* women who were diagnosed before pregnancy). **Group 2** included the births by women who were diagnosed with Hodgkin's disease during pregnancy (*i.e.* diagnosed between the first day in the last menstruation until the date of birth). **Group 3** included births by women who were diagnosed with Hodgkin's disease after delivery (*i.e.* diagnosed between the day after the delivery until two years later). If a woman gave birth more than once in this two-year period, only the last birth before the Hodgkin's disease diagnosis was included, based on the assumption that the preclinical cancer would be more likely to affect the birth closest to the time of diagnosis.

For all three groups, we computed the difference between proportions of male newborns of mothers with Hodgkin's disease and comparison mothers.

We computed prevalence odds ratios (POR) as estimates of the relative risks with associated 95% confidence intervals (95% CI) for preterm birth, low birth weight at term, stillbirth, and CAs. The PORs were controlled for month and year of birth and county of mother's residence by matching. We used unconditional logistic regression analysis to further adjust for maternal age and parity. We also included the calendar period of the birth (1973-1986, 1987-1994, 1995-2002), as an independent variable in the model, which did not change

the risk estimates. Stillborn children were excluded from the analyses of preterm birth, low birth weight at term, and CAs.

In order to examine whether sex of the child or maternal radiotherapy modified the POR estimates for births in Group 1, we repeated the analyses in strata of boys and girls and strata of births of women who were treated with radiotherapy and women who were not. Furthermore, to examine whether calendar period of Hodgkin's disease diagnosis modified the POR estimates for births in Group 1, we repeated the analyses in different calendar periods of Hodgkin's disease diagnosis (1981-1990, 1991-2000), using 1970-1980 as reference. We used the Wald test to evaluate the homogeneity of the POR estimates for CAs in 1981-1990 and 1991-2000. The low count of outcome events in Group 2 and 3 precluded stratified analyses.

We used linear regression to estimate differences in mean birth weight, while controlling for maternal age, parity, gestational age, and calendar period of birth. Stillborn children were excluded from these analyses.

The study was approved by the Danish Data Protection Agency (record no. 2003-41-2833). All analyses used SAS software, version 8.2.

Results

Descriptive data

In total, we identified 292 singleton births delivered by women with Hodgkin's disease and selected 14,042 singleton births for the comparison cohort. Characteristics of births in the three groups and their comparison births are shown in Table I. Of the 292 births by women with Hodgkin's disease, 192 occurred in Group 1. The median number of days from the time of diagnosis until pregnancy (*i.e.* the first day in the last menstruation) was 1824 days (range: 279-7877 days). The majority of women (76%) in Group 1 were ≥20 years of age at time of Hodgkin's disease diagnosis (data not shown). Group 2 included 15 births (eight women were diagnosed in the second trimester and seven, in the third). Group 3 included 85 births. The median number of days from date of giving birth until date of cancer diagnosis was 321 days (range: 6-709 days).

Birth outcome

The prevalence of male newborns of women with Hodgkin's disease in Group 1 was 50.0%, compared with 51.3% among the matched comparison mothers, difference = -1.3%, (95% CI = -8.4-5.8). The corresponding findings were 73.3% versus 50.1% (difference = 23.2%, 95% CI = 5.1-45.6) for Group 2, and 61.2% versus 51.4% (difference = 9.8%, 95% CI = -0.7-20.3) for Group 3.

Table II shows PORs for preterm birth, low birth weight at term, stillbirth, and CAs for newborns in all three groups. For births in Group 1, there was no increased risk of preterm birth or low birth weight at term. We found only one stillbirth among 192 births, corresponding to a POR of 2.0 (95% CI = 0.3-15.4). The

POR for CAs was 1.7 (95% CI = 0.9-3.1). In Groups 2 and 3, there were no children with low birth weight at term and no stillbirths. The POR of preterm birth in Group 2 was 26.6 (95% CI: 8.5-83.0). However, five of the eight preterm deliveries among women with Hodgkin's disease were elective preterm deliveries. There was one child with a CA among 13 births in Group 2 (POR = 2.7; 95% CI: 0.3-22.8) and four children with CAs among 78 births in Group 3 (POR = 1.6; 95% CI: 0.6-4.5).

Table III shows the birth outcomes in Group 1, stratified according to maternal radiotherapy (yes/no) and the three calendar periods of Hodgkin's disease diagnosis. Stratification according to radiotherapy suggested a slightly lower risk (except for stillbirths) of adverse birth outcomes in women who had received radiotherapy. In addition, the POR for CAs increased with calendar time of Hodgkin's disease diagnosis. Stratification according to sex of the newborns did not substantially change the effect estimates (data not shown).

Multiple linear regression analyses indicated that newborns in all three groups had nearly the same adjusted mean birth weight as newborns in the comparison cohort (data not shown).

Discussion

This nationwide cohort study on the relation between maternal Hodgkin's disease and adverse birth outcome did not show any increased risk of preterm birth or low birth weight at term, and no substantial increased risk of stillbirth for newborns of women with previous Hodgkin's disease. However, we can not rule out the possibility of an increased risk of CAs for newborns of these women.

The accuracy of our risk estimates depends on several factors. The main strength of the study is the underlying uniform health care system, with essentially complete registration of cancers and births and complete follow-up on CAs diagnosed during the first year of life, allowing for a population-based design. Information on CAs in the Hospital Discharge Registry is generally of high quality, with an 85% correct coding rate [21]. The quality of most outcome variables in the MBR is high, but its data on gestational age are subject to some misclassification [23]. This misclassification, however, is probably non-differential between mothers with Hodgkin's disease and cancer-free mothers.

Although our study population was large compared with other studies, a limitation is the imprecise effect estimates caused by the small number of outcomes. Furthermore, the data lacked clinical detail on radiation fields, doses, and duration of treatment, and we had no information on chemotherapy or disease stage. Information on radiotherapy (yes/no) obtained from the CR may be inaccurate, because the data are not routinely validated. However, a study of childhood cancer survivors reported that 97 of 110 patients treated with radiotherapy (88%) and 78 of 79 patients not treated with radiotherapy (99%) were correctly coded in the CR [24].

Women with early-stage Hodgkin's disease, which is often located above the diaphragm, were probably more likely than women with more advanced stages to receive radiotherapy, since the typical treatment of early-stage disease in our study period has been either radiation alone (with minimal effect on the gonads in case of supradiaphragmatic location), or a few series of combination chemotherapy followed by radiation. In contrast, later stages of Hodgkin's disease have typically been treated with six series of combination chemotherapy and only rarely radiotherapy. Thus, the distribution of Hodgkin's disease stage could bias the estimates of the radiotherapy-stratified analyses. This may help explain our finding of a lower risk of adverse birth outcomes for women who were treated with radiotherapy, compared with women who were not.

Fetal abnormalities may lead both to miscarriage [25] and to induced abortion, but we had no data on these outcomes. Thus, selection bias could have occurred if women with Hodgkin's disease had more miscarriages and induced abortions related to fetal abnormalities than did comparison mothers. Such bias would lead us to underestimate the risk of CAs in newborns of women with Hodgkin's disease.

It has been suggested that mutagenic exposure of germ cells (*i.e.* chemotherapy or radiation) may decrease the proportion of male newborns in female survivors of cancer due to sex-linked lethal mutations [4]. Our data, however, showed no substantial decrease in the male proportion of newborns in Group 1, indicating that earlier treatment for Hodgkin's disease is not a risk factor for early male abortion. For newborns in Group 2, there was an increase in the male

proportion compared with newborns of comparison mothers. This finding is surprising and may be due to chance.

We believe that our study is the first one to estimate relative risks for CAs among newborns of women with Hodgkin's disease. The increased risk estimates for CAs among newborns of women diagnosed with Hodgkin's disease during or shortly after pregnancy were imprecise. However, it is important to emphasize that teratogens increase the rate of specific CAs but not all CAs [26], and we were unable to evaluate the risk of specific CAs. Small cohort studies can detect only large increases in the risk of specific CAs, and are limited in their ability to provide an assurance of safety. Our finding of a higher risk of CAs for newborns of women who were diagnosed with Hodgkin's disease from 1991 to 2000 (before their pregnancy) may be a diagnostic bias caused by a recently increased interest in the risk of CAs after maternal cancer treatment.

On the whole, our findings are in line with the existing studies. Janov *et al.* did not find any substantial increased risk of low birth weight and no CAs among newborns of 15 women with pre-pregnancy Hodgkin's disease compared with the general population [27]. Likewise, Swerdlow *et al.* reported no increased risk of preterm birth, low birth weight, stillbirth, CAs or chromosomal abnormalities among 49 children of 16 women and 11 men who had previously been treated for Hodgkin's disease compared with the general population [3]. Another cohort study, which compared 52 births by 29 women previously treated for Hodgkin's disease with births by the women's siblings [28], found no overall increased risk of CAs and stillbirths combined among children of Hodgkin's disease patients. The study also found no association of birth outcome with radiotherapy alone (supra- or

infradiaphragmatic), whereas women treated with both chemotherapy and radiation were more likely to give birth to an abnormal child (P=0.047). The three studies, however, were all based on small study populations and did not control for potential confounders.

Recently, a large cohort study of female survivors of childhood cancer found that 19.2% of 337 women with childhood Hodgkin's disease had a preterm birth compared with 12.5% among sibling controls [29]. Another study reported 11 stillbirths among 729 births of female survivors of childhood Hodgkin's disease, corresponding to a RR of 1.6 (95% CI: 0.64-4.03) (30). We found no increased risk of preterm birth and only one stillbirth among 192 women, of whom more than 75 % had been diagnosed with Hodgkin's disease in adulthood (≥20 years of age at diagnosis).

Our finding of an increased risk of a preterm delivery for women diagnosed with Hodgkin's disease during pregnancy mainly reflected a high rate of elective early delivery, probably to allow an early start of cancer therapy. This finding is consistent with other studies on pregnant cancer patients [31;32]. Smith *et al.* identified 172 cases of Hodgkin's disease diagnosed from 9 months preceding delivery until 12 months after delivery and found relative risks of 2.4 (95% CI: 1.6-3.5) for preterm birth, and 3.6 (95% CI: 1.5-8.9) for very low birth weight [31]. The authors suggested that these findings reflected a higher rate of elective early deliveries to allow initiation of therapy. In contrast, a historical cohort study by Lishner *et al.* which included 40 births of women who were pregnant between 9 months before and three months after their first treatment for Hodgkin's disease, reported no increased risk of preterm birth or induced deliveries [33]. Furthermore,

the study indicated no difference in mean birth weight compared with controls, and no increased risk of stillbirths. Overall, the findings of Lishner *et al.* corroborate our data, with the exception of their result for preterm births.

In conclusion, the overall data of this nationwide cohort study are reassuring regarding the risks of adverse birth outcome for women with Hodgkin's disease. However, we cannot rule out the possibility of an increased risk of CAs in offspring of women diagnosed with Hodgkin's disease before pregnancy.

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Table I. Characteristics of births by women with Hodgkin's disease and by women in the comparison cohort.

	Group 1		Group 2		Group 3	
	Women with HD (N=192)	Comparison cohort (N=9,247)	Women with HD (N=15)	Comparison cohort (N=706)	Women with HD (N=85)	Comparison cohort (N=4,089)
Maternal age at delivery, number (%)						
<25 years	27 (14.1)	1,916 (20.7)	5 (33.3)	176 (24.9)	19 (22.4)	937 (22.9)
25-29 years	74 (38.5)	3,528 (38.2)	7 (46.7)	284 (40.2)	36 (42.4)	1,627 (39.8)
30-34 years	69 (35.9)	2,628 (28.4)	2 (13.3)	175 (24.8)	22 (25.9)	1,101 (26.9)
≥ 35 years	22 (11.5)	1,175 (12,7)	1 (6.7)	71 (10.1)	8 (9.4)	424 (10.4)
Age at delivery (years)						
Mean (+/- SD)	29.0 (+/- 4.4)	28.6 (+/- 4.9)	26.5 (+/- 4.4)	28.0 (+/- 5.0)	28.0 (+/- 4.9)	28.2 (+/- 4.8)
Range	16-38	15-47	20-36	16-45	18-41	16-46
Parity, number (%)						
1	135 (70.3)	4,204 (45.5)	10 (66.7)	346 (49.1)	42 (49.4)	1,848 (45.2)
≥ 2	57 (29.7)	5,031 (54.5)	5 (33.3)	358 (50.9)	43 (50.6)	2,238 (54.8)
Data missing	0 (0.0)	12 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	3 (<0.1)
Calendar period of birth, number (%)						

1973-1986	59 (30.7)	2,771 (30.0)	7 (46.7)	319 (45.2)	31 (36.5)	1,472 (36.0)
1987-1994	52 (27.1)	2,540 (27.4)	3 (20.0)	144 (20.4)	30 (35.3)	1,458 (35.7)
1995-2002	81 (42.2)	3,936 (42.6)	5 (33.3)	243 (34.4)	24 (28.2)	1,159 (28.3)
Offspring (sex), number (%)						
Male	96 (50.0)	4,735 (51.3)	11 (73.3)	353 (50.1)	52 (61.2)	2,101 (51.4)
Female	96 (50.0)	4,500 (48.7)	4 (26.7)	351 (49.9)	33 (38.8)	1,985 (48.6)
Data missing*	0 (0.0)	12 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	3 (<0.1)
Gestational age (weeks)†						
Mean (+/- SD)	39.5 (+/- 2.1)	39.5 (+/- 1.9)	37.0 (+/- 3.4)	39.6 (+/-1.7)	39.5 (+/- 1.8)	39.6 (+/- 1.8)
Range	26-42	23-44	33-42	23-44	31-43	25-44
Birth weight (g)†						
Mean (+/- SD)	3,462 (+/- 581)	3,464 (+/- 571)	2,938 (+/- 649)	3,450 (+/- 539)	3,412 (+/- 576)	3460 (+/- 556)
Range	803-5,000	655-5,600	1,690-4,400	570-5,200	1,870-4,720	820-5,530

Group 1: Births by women diagnosed with Hodgkin's disease before pregnancy.

Group 2: Births by women diagnosed with Hodgkin's disease during pregnancy.

Group 3: Births by women diagnosed with Hodgkin's disease within two years after giving birth.

* Births with missing data on sex were all stillbirths who had no CPR-number.

† Stillborn babies were excluded from the analyses of mean gestational age and mean birth weight.

Table II. **Crude and adjusted prevalence odds ratios of birth outcome in women with Hodgkin's disease**

	Hodgkin's disease Cohort Outcome/Total (%)	Comparison Cohort Outcome/Total (%)	Crude Prevalence odds ratio* (95 % CI)	Adjusted Prevalence odds ratio† (95 % CI)
Births in Group 1	(N=192)	(N=9,247)		
Preterm Birth‡	12/191 (6.3)	479/9,162 (5.2)	1.2 (0.7 - 2.2)	1.1 (0.6 – 2.0)
Low birth weight at term‡	2/177 (1.1)	145/8,649 (1.7)	0.7 (0.2 - 2.7)	0.6 (0.2 - 2.6)
Stillbirth	1/192 (0.5)	35/9,247 (0.4)	1.4 (0.2 - 10.1)	2.0 (0.3 - 15.4)
CAs‡§	11/181 (6.1)	323/8,673 (3.7)	1.7 (0.9 - 3.1)	1.7 (0.9 - 3.1)
Births in Group 2	(N=15)	(N=706)		
Preterm Birth‡	8/15 (53.3)	30/704 (4.3)	25.7 (8.7 - 75.4)	26.6 (8.5 – 83.0)
Low birth weight at term‡	0/7 (0.0)	9/674 (1.3)	-	-
Stillbirth	0/15 (0.0)	2/706 (0.3)	-	-
CAs‡§	1/13 (7.7)	18/606 (3.0)	2.7 (0.3 - 22.1)	2.7 (0.3 – 22.8)
Births in Group 3	(N=85)	(N=4,089)		
Preterm Birth‡	5/85 (5.9)	205/4,080 (5.0)	1.2 (0.5 - 2.9)	1.2 (0.5 – 2.9)
Low birth weight at term‡	0/80 (0.0)	48/3,866 (1.2)	-	-
Stillbirth	0/85 (0.0)	9/4,089 (0.2)	-	-
CAs‡§	4/78 (5.1)	124/3,742 (3.3)	1.6 (0.6 - 4.4)	1.6 (0.6 - 4.5)

Group 1: Birth outcome in women diagnosed with Hodgkin's disease before pregnancy.

Group 2: Birth outcome in women diagnosed with Hodgkin's disease during pregnancy.

Group 3: Birth outcome in women diagnosed with Hodgkin's disease within two years postpartum.

* Controlled for month and year of the birth and county of mother's residence by matching.

† Further adjusted for maternal age (<25 yr, 25-29 yr, 30-34 yr and ≥35 yr) and parity (1, 2+). Calendar period of the

birth (1973-1986, 1987-1994, 1995-2002) was also included as an independent variable in the model.

† Stillborn babies were excluded from the analyses of preterm birth, low birth weight at term and congenital abnormalities (CAs).

‡ Data on congenital abnormalities (CAs) included births from 1977 to 2002.

Table III. Birth outcome stratified by treatment with radiotherapy and calendar period of Hodgkin's disease diagnosis for women diagnosed with Hodgkin's disease before pregnancy (Group 1).

	Group 1 (N=192)							
	Preterm birth		Low birth weight at term		Stillbirth		CAs*	
	Outcome/Total (%)	Adjusted OR† (95% CI)	Outcome/Total (%)	Adjusted OR† (95% CI)	Outcome/Total (%)	Adjusted OR† (95% CI)	Outcome/Total (%)	Adjusted OR† (95% CI)
Radiotherapy ‡								
Yes (N=100)	4/99 (4.0)	0.7 (0.2-1.8)	1/93 (1.1)	0.5 (0.1-3.6)	1/100 (1.0)	4.6 (0.5-38.5)	4/90 (4.4)	1.2 (0.4-3.3)
No (N=88)	8/88 (9.1)	1.8 (0.8-3.7)	1/80 (1.3)	0.9 (0.1-6.5)	0/88 (0.0)	-	6/87 (6.9)	1.9 (0.8-4.4)
Time of HD diagnosis								
1970-1980 (N=66)	4/65 (6.1)	1.0 (reference)	0/60 (0.0)	1.0 (reference)	1/66 (1.5)	1.0 (reference)	1/55 (1.8)	1.0 (reference)
1981-1990 (N=64)	2/64 (3.1)	0.6 (0.1-2.4)	2/62(3.2)	1.9 (0.5-8.1)	0/64 (0.0)	-	3/64 (4.7)	1.4 (0.4-4.4) §
1991-2000 (N=62)	6/62 (9.7)	1.8 (0.8-4.1)	0/55 (0.0)	-	0/62 (0.0)	-	7/62 (11.3)	3.1 (1.4-6.9) §

* Data on congenital abnormalities (CAs) included births from 1977 to 2002.

† Controlled for month and year of birth and county of mother's residence by matching and further adjusted for maternal age and parity. Stillborn children were excluded from the analyses of preterm birth, low birth weight at term and congenital abnormalities.

‡ Data on radiotherapy were missing for 4 women.

§ Wald chi-square test, $p = 0.25$