Reproductive outcomes in females following treatment for childhood cancer

by

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Abstract

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This province-wide study was conducted to determine the risk of adverse reproductive outcomes in female childhood cancer survivors who received abdominal-pelvic radiation and/or chemotherapy with alkylating agents in comparison with those who were treated by non-sterilizing surgery only. Females diagnosed with any histologically confirmed malignancy before age 20 and between the years 1964 to 1988, who survived for at least 5 years after diagnosis and attained 18 years of age, and are currently alive were ascertained through the Ontario Cancer Registry. Reproductive outcomes, collected through a telephone-administered questionnaire, and treatment data, abstracted from medical records, were obtained for 830 participating subjects.

Results indicate that survivors who received alkylating agents and abdominal-pelvic radiation were more likely to be post-menopausal than those receiving surgery (RR=2.58; 95%CI=1.14-5.80), especially for those diagnosed after puberty or diagnosed with lymphoma. Women treated with abdominal-pelvic radiation were found to have a fertility deficit of about 23% as compared to the surgery group. Fertility deficits were greater in women diagnosed after puberty and for those diagnosed with lymphoma and treated with alkylating agents plus abdominal-pelvic radiation and those diagnosed with renal tumours and treated with abdominal-pelvic radiation. There was evidence that the risks of menopause and infertility increased with increasing dose of abdominal-pelvic radiation and by amount of alkylating agents received.

There was no evidence of an increased risk of having a spontaneous abortion or an infant

with a birth defect for women treated with abdominal-pelvic radiation and/or alkylating agents. However, survivors receiving abdominal-pelvic radiation were more likely to have a low birth weight infant (OR=3.64; 95%CI=1.33-9.96), a premature low birth weight infant (OR=3.29; 95%CI=0.97-11.1) or an infant with a perinatal death (OR=2.41; 95%CI=0.50-11.5), compared to those receiving surgery. The risk of perinatal deaths and low birth weight infants (all and premature) significantly increased with dose of radiotherapy directed to the abdomen.

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TABLE OF CONTENTS

Page No.

Chapter 4: DISCUSSION

LIST OF TABLES

LIST OF APPENDICES

Chapter 1: INTRODUCTION AND REVIEW OF LITERATURE

1. Introduction

Over the last three decades, many children with cancer have been offered a realistic opportunity of long term cure. The improvements in therapy have resulted in a five-year survival of about 68 percent (Boring et al., 1994). However, with this success has come new concerns about the potential long term toxic effects of modern aggressive cancer therapies on normal host tissues. Little attention has been paid to the risk of gonadal dysfunction resulting from anti-cancer therapy, partially because of the absence of any immediate or life threatening symptoms and in part because of the absence, in the past, of a group of long term survivors who were concerned about their reproductive potential (Sherins and Mulvihill, 1989). However, with the number of long term cancer survivors who may be at risk of gonadal injury increasing, it is important to answer questions concerning their ability to reproduce and to have "normal" live born infants.

This dissertation describes a retrospective cohort study which was conducted to determine the risk of adverse reproductive outcomes (i.e. early menopause, infertility and spontaneous abortion in the cancer survivor, and perinatal mortality, low birth weight and birth defect in the offspring) in female survivors of childhood cancer. Of primary interest is the effect of anti-cancer treatment on reproductive function in these women.

Childhood survivors of cancer represent a cohort of people exposed to high doses of possible mutagens, that is chemicals and ionizing radiation designed to interfere with the normal function of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein synthesis in the cells (Mulvihill and Byrne, 1985). The ability of childhood cancer survivors to become pregnant and to have normal live born children is a question of considerable interest to oncologists,

medical geneticists and epidemiologists who are concerned about the somatic and genetic effects of anti-cancer therapy. Epidemiologic studies can contribute information on which to base counselling of long term survivors of pediatric malignancies and their families about possible reproduction-related risks. Information on this topic is needed for advising the increasing number of long term survivors and their spouses about the possible risks. Determination of lack of excess risk is equally important so that survivors can be reassured. By having this knowledge, survivors can make informed decisions about an important life goal.

This chapter will begin with a brief review of the patterns of incidence and mortality of childhood cancers, the changes in the treatment for childhood cancers and reproductive biology of females. Then the literature on the initial effects of cancer therapy on the ovary and the late effects of cancer therapy on infertility, early menopause and pregnancy outcomes will be discussed. In addition, the literature relating to the trends and etiologic factors of adverse reproductive outcomes will be reviewed. Chapter 2 describes the methods used in this study. The univariate and multivariate analysis of reproductive outcomes and cancer therapy are presented in Chapter 3. A discussion of the results, advantages and limitations of the study, methodological issues and potential biases, recommendations for further research and conclusions are presented in Chapter 4.

2. **Patterns of incidence and mortality of childhood cancers**

Although cancer in childhood and adolescence is a rare event, it is an important cause of morbidity and mortality in this age-group. About 1,300 children (persons less than 20 years old) in Canada develop cancer each year and about 20% die of the disease (McCourt et al., 1993). International time trends show a remarkably stable pattern in the incidence of childhood

cancers between 1959 and 1977 (Breslow and Langhloz, 1983). The incidence of cancer in childhood in Canada has also remained relatively stable over this time period, with a gradual increase since this time. The risk of developing childhood cancer in Canada has increased by about 30% since 1969, with the increase largely due to acute lymphocytic leukemia (ALL) and tumours of the brain and central nervous system and in the younger age groups (children less than 5) (McCourt et al., 1993). Overall, similar increases in childhood cancer incidence in approximately similar time periods have been reported in the Surveillance Epidemiology and End Results (SEER) registries in the United States, in the Manchester Children's Tumour Registry in northwestern England, and in Queensland, Australia (Blair and Birch, 1994; Bunin et al., 1996; McWhirter and Petroeschevsky, 1990).

In addition to this increase in incidence rates there appears to be a dramatic trend of decreasing childhood cancer mortality in most countries (from 1955 to 1974), with a highly significant decrease in Canada, the USA, France, Germany, the Netherlands, Norway, Switzerland and England and Wales (West, 1984). A recent review of cancer statistics in the United States shows a 38% reduction in the overall cancer mortality for children under 15 from 1973 to 1988 (Bleyer, 1993). The mortality rate has declined by more than 50% among patients with ALL, Hodgkin's and non-Hodgkin's lymphoma and soft tissue sarcoma. This fall in mortality is due almost entirely to the improvements that have occurred in the treatment of children with cancer.

A comparison of survival rates reported by SEER for the periods 1960 to 1963 and 1983 to 1989, reveals an overall 40 percent increase in the 5-year survival rates for children with cancer (Boring et al., 1994). The most dramatic improvements in survival have been among patients with ALL, non-Hodgkin's lymphoma, and Wilms' tumours. A recent investigation in

Britain of long term survivors, treated between 1960 and 1981, showed that the survival prospects are very good among children surviving at least 3 years after treatment for cancer. For most of the tumours considered, over 80% of those children were alive 10 years later (Hawkins, 1989).

The types of cancer seen in children are different to those seen in adulthood by predominantly being found in the deeper tissues of the body, i.e. brain, bone and bone marrow, and lymph glands (NCIC, 1990). This distinction reflects differences in growth rates of various organs and differences in environmental exposures which may cause childhood cancer (i.e. prenatal exposure to diethylstilbestrol, prenatal and postnatal irradiation, prenatal viral infections, exposure to magnetic fields and chemicals and parental occupations) and to the etiologic contribution of various types of single gene disorders (Greenberg and Shuster, 1985).

The most common malignancy in childhood (0-14) is leukemia accounting for a third of all cases (32%) and of deaths (35%) due to cancer (NCIC, 1996). Much of the fall in mortality from all forms of cancer in childhood is also attributed to improved treatment of leukemia. Malignant neoplasms of the brain and other parts of the nervous system are the next most common cancer, accounting for about 21% of malignancies in children and lymphomas are the third, accounting for 12% of the cases. These three types of cancer together account for over half the incidence of cancer in childhood in Canada (NCIC, 1996).

Cancer is rarely found at birth, but the incidence increases sharply during the first year to about 20 per 100,000 and then gradually declines to about 10 per 100,000 at ages 5 to 19. ALL (2 to 4 years of age), neuroblastoma (first year of life), Wilms' tumour (2 to 4 years of age), retinoblastoma (0 to 2 years of age) and primary liver cancers occur most often in children

under five years of age. The lymphomas and bone tumours occur more frequently in children over 10 years of age (Pratt, 1985).

3. **Description and changes in cancer therapy for childhood cancers**

Radiotherapy and chemotherapy are often designed specifically to interact with cellular DNA and to block its function. The toxic effects of anti-cancer therapy are often seen in those tissues or organs with high cell turnover rates, such as bone marrow, orointestinal mucosa, gonads, and epidermis. Although children appear to tolerate the acute toxicities of therapy better than do adults, the growing child may be more vulnerable to the delayed adverse sequelae of cancer therapy, such as effects on growth and fertility (Blatt and Bleyer, 1989).

The goal of radiation therapy is the local-regional control of tumour cells. The local deposition of ionizing radiations cause ionization (and excitation) of atoms of the absorbing material (i.e. tissue) which can result in damage to any part of a cell (Parker, 1990). Radiation-induced changes to DNA such as single or double strand breaks, damage to bases and cross-linking of DNA strands or between DNA and chromosomal proteins, is the most crucial in relation to cell survival (Hill, 1987). Cell survival is dependent on the type of radiation, radiation dose, cell-cycle position (i.e. most sensitive in mitotic phase or interphase) and number of fractionated treatments. The radiation dose is measured by the amount of energy imparted per unit mass and is quoted in rads or grays (one rad equals one centigray (cGy)).

Radiation therapy is divided into two groups: external-beam irradiation and brachytherapy. For external beam therapy, which is most often administered in pediatric oncology, a well defined x-ray or gamma ray beam is directed to a specified anatomic volume (Ekun and Moulder, 1989). With photon-beam therapy the maximal energy of the beam defines

the quality of irradiation. The orthovoltage beams (100-400 keV, 1 KeV=1,000 electron volts) deliver 100% of the energy on the surface, losing energy quickly below the superficial tissues. Megavoltage machines (with peak energies usually above 1 to 2 MeV, 1 MeV= 1 million electron volts) deposit less than 60% of the maximal dose on the surface. The widespread availability of radiation therapy was initially facilitated by the distribution of cobalt-60 teletherapy units (1.2 MeV) which directly emitted gamma rays from the continuous decay of a radioactive cobalt-60 source. These units were either augmented or replaced by medium energy (4 to 6 MeV) linear accelerators. Currently, linear accelerators which produce x-rays with precise beam definition are more popular because of their higher peak energies (4 to 48 MeV), higher dose rates, reduced absorption in bones, and less scattering in tissue (Parker, 1990).

In brachytherapy, radioactive sources are applied directly within or around a given tumour site through intracavity applications, interstitial implants and mold applications. Brachytherapy is normally not used in the treatment of children with cancer. However, with the development of radioactive isotopes (i.e., iodine-125) there has been a renewed interest in the application of radiation sources into tissues or body cavities of children for tumours such as retinoblastoma and soft tissue sarcoma (Parker, 1990).

Cancer chemotherapeutic drugs function similarly to radiation in that they work during active cell division through modification of DNA synthesis, transcription, or mitotic spindle function (Boyd, 1993). The four major classes of antineoplastic agents used in pediatric oncology are alkylating agents, anti-metabolites, plant alkaloids, and anti-tumour antibiotics. Alkylating agents are cell cycle phase non-specific and are highly carcinogenic, mutagenic and teratogenic (Balis et al., 1989). These compounds affect nuclear DNA through the addition of akyl groups (alkylation) to nucleic acids, producing breaks in the DNA molecule as well as cross-linking of

its twin strands (Haskell, 1990). The nitrogen mustards (i.e. cyclophosphamide, melphalan) and the nitrosoureas (i.e., carmustine, lomustine) are the most frequently used alkylating agents in the treatment of childhood cancers. The anti-metabolites (cell cycle phase-dependent) are structural analogues of normal metabolites that are required for cell function and replication and therefore interfere with the synthesis of DNA or RNA. Methotrexate is the most widely used anti-metabolite in pediatric oncology (Haskell, 1990). The two groups of agents from plant derivatives (plant alkaloids) are the vinca alkaloids and the epipodophyllotoxins. The vinca alkaloids, vincristine and vinblastine, are extracted from the periwinkle plant and arrest mitoses by binding to tubulin and thus interfering with normal spindle formation necessary for cell division. The epipodophyllotoxins, etoposide and teniposide, do not bind to tubulin but instead inhibit the synthesis of DNA and cause strand breaks (Close and D'Angio, 1992). The clinically useful anti-tumour antibiotics are natural products of various strains of the soil fungus Streptomyces and are cell cycle phase non-specific. They are intercalators becoming inserted between DNA base pairs, and block DNA and RNA synthesis. Other useful drugs that do not fit in the categories above include hormones and hormone antagonists and miscellaneous agents such as asparginase and the corticosteroids (Close and D'Angio, 1992).

The successes in survival of childhood cancer were brought about by the rational combination of the three important therapeutic modalities, that is surgery, radiation therapy and chemotherapy and not as a result of any new major scientific or therapeutic discoveries (Hammond, 1986). Radiation therapy was the first modality to be added to surgery or to replace it. As a result, decreased death rates began to be seen for Wilms' tumour and Hodgkin's disease by 1955. The increase in survival was seen for most of the other common pediatric solid tumours, such as rhabdomyosarcoma, lymphoma, Ewing's sarcoma, and osteosarcoma by 1965

following the use of anticancer drugs (i.e., use of adjuvant chemotherapy) along with surgery and radiotherapy as initial treatments (Balis et al., 1989). By the late 1960s the use of chemotherapy had also made a significant impact on the treatment of ALL (Hammond, 1986)

Today, almost all chemotherapy regimens use combinations of antitumour drugs. Combining active agents into multi-drug protocols was first demonstrated in the early 1970s with ALL. Such combination chemotherapy has improved both the remission rate and duration of remission compared to single-agent therapy. Over time, clinical experience has shown that if these drugs are administered alone, they are minimally effective against even the most responsive tumours as the tumours may often become resistant to the treatment (Boyd, 1993).

With the long term survival of children with cancer has come the recognition of the potential late effects of treatment. This had led to the reduction of therapy to modify the long term side effects for types of cancer where the cure rates are high (Craft and Pearson, 1989). For example, age-adjusted doses of radiation therapy are given to children since it was recognized that they were more susceptible to damage, dose-for-dose. Also, as multi-modality therapy toxicity was realized, compromises were reached with local treatments (i.e. radiation) rather than with systemic chemotherapy (D'Angio, 1992).

4. **Reproductive biology**

Reproductive toxicants are agents that interfere with the normal production of gametes or with the normal function of the genital tract. The mechanism by which female gametes mature and eventually become fertilized is relevant to understanding how these agents may prevent fertilization or permit fertilization but interfere with the survival of the resulting conceptus (Scialli, 1992).

The human ovary produces oocytes and secretes steroid hormones. Germ cells formed during the third week of embryonic development, migrate from the wall of yolk sac to the primitive gonad and differentiate into oogonia which multiply by mitosis. Oocytes are derived from oogonia which have reached their last mitotic division and entered the prophase of their first meiotic division. At birth, the ovaries contain up to 2 million primary oocytes which are in the diplotene stage of the first meiotic division. These oocytes remain inactive until puberty (age 9 to 15 years) although they continue to disappear with about 400,000 remaining by the time ovulation commences (Scialli, 1992). At each menstrual cycle each month during ovulation, a few primary oocytes complete the first meiotic division and begin the second meiotic division and form a secondary oocyte. Only upon fertilization will the secondary oocyte complete the second meiotic division.

The feedback mechanisms that control the normal menstrual cycle operate on the hypothalamus and pituitary. The pituitary gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which drive the menstrual cycle, are released in response to the gonadotropin releasing hormone (GnRH) which is synthesised in the hypothalamus. Appropriate pituitary gonadotropin secretion is required to establish a regular menstrual cycle. The ovary responds to gonadotropin stimulation by follicle maturation, ovulation, and cyclic, sequential production of estradiol and progesterone. There has been a secular trend towards an earlier age of menarche in girls in North America and Europe. Improved socioeconomic standards, general health and nutrition are believe to be the reason for this decline in the age at puberty (Shalet and Wallace, 1992).

As all of the oocytes in females are present before birth, ova and follicles destroyed by reproductive toxicants cannot be replenished by the production of new germ cells. With the

depletion of oocytes, menstruation will cease and, eventually, estrogen production will cease as well. This will result in primary ovarian failure, with abnormally low estradiol and progesterone levels giving rise to increased levels of FSH and LH (Chapman, 1982). In addition, any sublethal damage to germ cells from reproductive toxicants will be present for the individual's lifetime. This could result in genetic effects in the offspring as well as influencing a women's ability to carry a pregnancy to term (Sherins and Mulvihill, 1989).

5. **Initial effects of cancer therapy on the ovary**

5.1 Radiation:

The initial adverse responses of the ovary to ionizing radiation are ovarian failure (elevated levels of FSH and/or LH) (Shalet et al., 1976; Scott, 1981; Stillman et al., 1981), germ cell destruction (Himelstein-Braw et al., 1977) and amenorrhea (Shalet et al., 1976; Hunter et al., 1980; Horning et al, 1981). These effects vary by age, dose, and site of treatment.

The ovaries of a newborn female child contain a finite number of oocytes (about 2 million) reducing in number with increasing age, until menopause when about 2,000 oocytes survive. This process of reduction of number of oocytes (atresia) is accelerated by radiation or hormonal treatments (Baker, 1971). Therefore, the size of the radiation dose required to produce gonadal impairment and sterility in females is related to age at time of radiotherapy or more precisely, to the number of oocytes present. For women over 40, who have few remaining oocytes, permanent menopause and sterility can result from radiation exposures of 600 cGy to lower abdominal sites, while for girls and young women (in their twenties and thirties), a total dose of 2,000 cGy is required (Lushbaugh and Casarett, 1976).

The site of radiotherapy is also important, with a higher percentage of women experiencing ovarian failure if they received whole-abdominal radiation, spinal radiation or total body radiation. Radiation therapy-induced gonadal damage is inversely related to the distance from the treatment site to the gonads. Shalet et al. (1976) examined ovarian function 1 to 26 years after completion of therapy in 18 female patients who were treated for abdominal tumours during childhood. All of the 16 women who had received whole-abdominal radiation at doses ranging from 2,000 to 3,000 cGy over 25 to 44 days had evidence of ovarian failure. In another study, the overall incidence of gonadal suppression was lower but still significant, with 30% of the girls suffering complete suppression of ovarian function as a result of whole-abdominal radiation at doses ranging from 3,000 to 3,300 cGy for treatment of nephroblastoma (Scott, 1981). In a larger study of 182 long term survivors of childhood cancer the odds of ovarian failure was 19.7 when both ovaries were within the field of radiation compared to other radiated patients (Stillman et al., 1981). Wallace et al. (1989) followed 19 females treated for abdominal tumours in childhood with megavoltage whole abdominal radiation and found that at 400 cGy the surviving fraction of oocytes is 50%, assuming exponential inactivation of the oocytes with increasing dose. This analysis indicated that the surviving fraction of oocytes and the predicted age at ovarian failure can be estimated if the dose of radiation received by the ovary is determined. The histological evidence in 12 children with abdominal tumours whose ovaries were examined at autopsy indicated that abdominal radiation between 2,000 and 3,000 cGy destroys small follicles and impairs follicular development in those that remain (Himelstein-Braw et al., 1977).

Patients with Hodgkin's disease are often treated with external-beam radiation to the inverted-Y, modified inverted-Y, mantle and inguinal fields. The dose of radiation received by

the ovaries in these fields can be reduced by an operative procedure (oophoropexy) which moves the ovaries into a different anatomical position and by using individually shaped lead pelvic blocks. The effectiveness of this technique has largely been examined from studies of older women treated for Hodgkin's disease and has proved of limited value in preserving ovarian function (Hunter et al., 1980; Thomas et al., 1975; Ray et al., 1970). A more recent investigation has shown that a sufficient period of observation is necessary to determine whether ovarian function has been preserved in young women after oophoropexy and pelvic radiation. In 13 of 19 patients, who received only total lymphoid irradiation, amenorrhea was temporary lasting for several months to 4 years after therapy. This study also found that the probability of regular menses was significantly related to age at treatment, with patients below 30 having the highest probability of recovery (Horning et al., 1981). In another study of 43 young women treated for Hodgkin's disease at the Stanford University Medical Center from 1961 to 1981, of those treated only with radiation, ovarian function was retained in all 11 girls less than 13 years treated with upper abdominal radiation and in all 7 treated to the pelvis following oophoropexy (Donaldson and Kaplan, 1982). A more recent study of this cohort, treated from 1965 to 1986, found that 75 of the 86 (87%) girls treated for Hodgkin's disease have normal menstrual function. Of the 11 girls who developed ovarian failure, 3 did not have an oophoropexy prior to pelvic radiation and of those who had an oophoropexy 4 received high dose radiation (4,000-4,500 cGy) (Ortin et al., 1990).

Cranial-spinal radiation may impair gonadal function in young girls treated for ALL or central nervous system tumours. However, minimal ovarian dysfunction is seen when treatment for these cancers included only cranial radiation. Cranial irradiation may result in premature menarche (precocious puberty) and short menarche secondary to activation of the hypothalamic-

pituitary-gonadal axis, where as spinal radiation may produce end-organ damage and delayed menarche. Ahmed et al. (1983), examined 4 prepubertal girls who had received cranial-spinal radiation for medulloblastoma. Each of these girls had regular periods with gonadotropin values in the normal range. However, another study reported primary ovarian damage in 7 out of 11 prepubertal girls (64%) treated with cranial-spinal radiation alone for brain tumours. There was an increased prevalence in younger girls (2 to 10 years of age) probably due to greater mobility of the ovarian position in relation to the spinal field (Livesey and Brook, 1988). In a larger study, of 97 long-term female survivors of childhood ALL (Hamre et al., 1987), elevated levels of FSH and/or LH were found in 93% of patients who received craniospinal plus abdominal radiotherapy, 49% for craniospinal radiotherapy and in only 9% for cranial radiotherapy. A radiation therapy dose relationship was seen only in females receiving cranial-spinal radiation, with females receiving 2,400 cGy having a higher risk of increased FSH and LH than females receiving 1,800 cGy. A study of 24 girls treated for ALL, 14 prepubertal and 10 pubertal, showed that ovarian function was well preserved after prolonged treatment, when all but one of the girls had cranial cobalt therapy. This study suggested the patients treated with cranial radiotherapy have a tendency to show several signs of early maturation: advanced bone age, early initiation of sexual development and early start of menses (Pasqualini et al., 1987). Another study (Quigley et al., 1989) of 20 girls treated for ALL with combination chemotherapy and cranial radiation (2,400 cGy), also reported early puberty, with 82% of the girls reaching menarche at an earlier age despite primary gonadal damage (i.e., indicated by increasing levels of FSH and LH).

A few studies have examined gonadal function following bone marrow transplant which included total body irradiation (TBI) (Saunders 1991). These studies have shown that the

majority of girls prepubertal at time of TBI administration have a significant delay in the onset of menses or fail to achieve menses. Gonadal failure occurred in all who were postpubertal at transplant for up to a few years. In one study, only 4 of 17 post-pubertal girls demonstrated recovery of ovarian function 3 to 5 years after bone marrow transplant (Sanders et al., 1986). Another study showed that TBI was the only significant factor after marrow transplantation influencing ovarian failure. That is, seven years following transplant the probability of having normal ovarian function was 0.92 after cyclophosphamide alone and was 0.24 after cyclophosphamide plus TBI (Sanders et al., 1988).

5.2 Chemotherapy:

Ovarian failure has also been associated with chemotherapy, with toxicity being related to both dose (Chapman et al., 1979; Rivkees and Crawford, 1988) and age (Chapman et al, 1979; Waxman et al., 1982; Schilsky et al., 1981; Shamberger, Sherins et al., 1981; Kreuser et al., 1987). The nature of the chemotherapy is also significant, with alkylating agents most commonly associated with persistent infertility (Rivkees and Crawford, 1988; Damewood and Grochow, 1986). These agents appear to cause major damage to normal as well as malignant cells by forming covalent linkages with bases in DNA resulting in single-strand breaks and cross-links (Erlichman, 1987).

Girls treated with single alkylating agents such as cyclophosphamide for nephrotic syndrome (Pennisi et al., 1975; Etteldorf et al., 1976; Lentz et al., 1977; Parra et al., 1978; Watson et al., 1986; Degroot et al., 1974) or alkylating agents in combination with plant alkaloids for Hodgkin's disease (i.e., MOPP, MVPP, COPP) (Horning et al., 1981, Chapman et al., 1979; Waxman et al., 1982; Schilsky et al., 1981; Cunningham et al., 1982; Andrieu and

Ochoa-Molina, 1983, Kreuser et al., 1987) may be capable of a normal puberty and regular menses. However, they may have pathological or clinical evidence of ovarian failure. Histologic examination of the ovaries of these young girls has shown destruction of resting oocytes, absent primordial follicles and depression in follicular maturation (Himelstein-Braw et al., 1978; Nicosia et al., 1985). In one study, over 20% of ovaries at autopsy of 31 prepubertal females treated with one or more cytotoxic drugs for leukemia showed no follicular growth and the remaining children had ovaries with incomplete follicular development (Himelstein-Braw et al., 1978). In another investigation, it was found that 50% of the 21 pre, intra and postpubertal girls who died 1 day to 2 months after cessation of multi-agent chemotherapy for extragonadal tumours had a lower complement of ovarian follicles than control subjects who died from accidental or non-neoplastic causes (Nicosia et al., 1985). This impaired follicular maturation may prove reversible but if a serious depletion of primordial follicles has occurred following exposure to chemotherapy in childhood, then premature menopause may result. The severity of the follicular depletion depends on the number and activity of follicles present at the initiation of chemotherapy. Prepubertal ovaries, not yet under cyclic hormonal control, are most protected from chemotherapy. Consequently, reproductive potential is related to age: the younger the patient, the larger the reserve of oocytes remaining after chemotherapy to reestablish the normal ovulatory state (DiSaia, 1989).

Prepubertal gonads may be more resistant than postpubertal gonads to damage by alkylating agents. Various investigations have shown that the ovarian function of prepubertal females is unaffected by treatment with cyclophosphamide (Pennisi et al., 1975; Etteldorf et al., 1976; Lentz et al., 1977; Parra et al., 1978; Watson et al., 1986; Degroot et al., 1974). These studies found no evidence of menstrual dysfunction in women who had received

cyclophosphamide for nephrotic syndrome during childhood. In fact many of these patients have gone on to have successful pregnancies. Patients were followed from 1 to 17 years after treatment, with duration of treatment ranging from 2 months to 2 years at dosages of 2 to 5 mg/kg/day or total doses of 8.6 to 65.5 grams. Studies of ovarian function in postpubertal women following treatment with cyclophosphamide have found an increased frequency of amenorrhea (Kumar et al., 1972; Chapman et al., 1979; Warne et al., 1973). These investigations have shown that amenorrhea may be reversible after short periods of treatment and in younger women (Chapman et al., 1979).

Studies of the effect of combination chemotherapy such as MOPP therapy (methylchloret-hamine, vincristine, procarbazine and prednisone), MVPP therapy (methylchlorethamine, vinblastine, procarbazine and prednisone) and COPP (cyclophospamide, vincristine, procarbazine, predinsone) for Hodgkin's disease has shown gonadal toxicity, with the incidence of ovarian failure being highly correlated with age at time of chemotherapy. Women under age 30 at time of treatment had the lowest risk of amenorrhea (Horning et al., 1981; Chapman et al., 1979; Rivkees and Crawford, 1988, Kreuser et al., 1987). As well, ovarian failure occurs after fewer cycles of MVPP in older women than in those in their teens and early twenties (Chapman et al., 1979).

Siris et al., (1976) evaluated ovarian function in 35 girls treated with a combination of steroids, vincristine, methotrexate, and 6-mercaptopurine (POMP therapy) for ALL. Twenty-eight of the patients, after a median time of 74 months after diagnosis and 49 months of treatment, had normal pubertal progress and/or initiation of menses. Abnormalities appeared only in 6 whose onset of leukemia was during puberty or after menarche and one who was prepubertal at diagnosis. In another investigation of 9 girls treated for ALL, 3 of them who

received cyclophosphamide had ovarian failure (Shalet et al., 1977). However, a longer follow-up is necessary to assess the impaired ovarian function in this series as they were evaluated only 6 months after treatment. Women aged 15 to 30 treated with high dose methotrexate and vincristine for osteosarcoma had regular menses (Shamberger, Rosenberg et al., 1981) in contrast to women over 35 who developed amenorrhea or irregular vaginal bleeding with hormonal changes (Shamberger, Sherins et al., 1981).

Ovarian dysfunction has also been reported for female survivors of brain tumours when chemotherapy treatment with alkylating agents such as carmustine or lomustine is used along with cranial irradiation (Livesey and Brook, 1988; Ahmed et al. 1983). Ovarian damage was seen in 18 of 21 girls treated with these nitrosoureaus alone (i.e., carmustine or lomustine) or in combination with procarbazine for childhood brain tumours (Clayton et al., 1989). However, the ovarian dysfunction caused by these chemotherapeutic agents may be reversible with all of the girls entering or progressing through puberty spontaneously.

6. **Late effects of cancer therapy on infertility, early menopause and pregnancy outcomes**

As shown from endocrine status and histopathological studies, cancer treatment could be a cause of infertility in survivors, owing perhaps to elevated levels of gonadotropin hormones and genetic damage or depletion of ovarian germ cells. The ability to conceive a child following cancer in childhood has been examined in a 5-centre National Cancer Institute (NCI) retrospective cohort study. This study estimated the overall fertility of female survivors to be 7% less than that of their sibling controls (relative fertility, 0.93), among those at risk of pregnancy (Byrne et al., 1987). The women were more affected by radiation below the diaphragm (relative fertility, 0.78) than by chemotherapy with alkylating agents (relative fertility,

1.02). Women treated with surgery only had almost no fertility deficit (relative fertility, 0.98). Data on a sub-sample of the above cohort also found no significant differences between survivors and control group according to three criteria of infertility (never menstruating, unsuccessful attempts to become pregnant, and a definite diagnosis of infertility problems) (Teeter et al., 1988). Another study, also found that the live birth rate of first births in young females treated for leukemia during childhood, was not significantly lower than in the general population (Nygaard et al., 1991). However, females who had received cranial radiation of the central nervous system for leukemia had a lower birth rate than those without radiation. Possible explanations for this finding were that cranial radiation harm to the neuroendocrine system could possibly become evident later as reduced fertility in addition to neuropsychological effects of central nervous system tumours which could affect behavioural pattern and therefore influence reproduction.

Further analyses of the NCI cohort indicated a considerable risk of early menopause among those survivors treated between the ages of 12 through 19, and in those treated with radiation below the diaphragm in combination with alkylating agents (Byrne et al., 1992). For these women, the risk of menopause was significantly increased (Relative Risk estimate (RR)=4.1) overall and was greatest during the first 5-year period of follow-up (ages 21-25). The decrease in risk after age 25 may indicate loss of a population of damaged ova, leaving women whose ova are relatively unaffected (Byrne, 1990). The menopausal rate for women treated with surgery alone was not significantly different from the rate for the sibling controls (RR=1.0). Although this cohort was large (831 females, 1374 sibling controls), all females studied were diagnosed prior to 1975, so results can not contribute to knowledge concerning the effects of more recent therapies.

For patients who are fertile after anti-cancer therapy there are concerns about the ability to have full-term pregnancies and normal children. The largest source of data on the genetic effects of preconception radiation exposures in humans has come from studies of offspring of Japanese survivors of Hiroshima and Nagasaki (Schull et al., 1981). A positive, but non-significant effect of parental radiation has been associated with major congenital anomalies, stillbirths, and neonatal deaths in their offspring. However, survivors of childhood cancer have been exposed differently than the Japanese survivors in terms of dose and types of agents.

Most adverse pregnancy outcomes result from a complex interaction between biological, behavioral, and environmental factors (Braken, 1984). Among the known etiologic factors, medical risks predating pregnancy, such as maternal genetic factors associated with the cancer or its treatment, could contribute to the risk of an adverse reproductive outcome. Conceptions after treatment reflect survival of germ cells exposed to mutagens. Adverse reproductive outcomes might represent mutagenicity, direct germ cell toxicity, or an altered ability to maintain normal gestation (Mulvihill et al., 1987). Germ cell mutations in survivors could, in theory, result in a high rate of spontaneous abortions with chromosomal anomalies especially in the first trimester, or stillbirths or birth defects in offspring. Damage to the vasculature and elastic properties of the uterus may lead to positional deformities, early delivery, and low birth weight offspring (Byrne, 1990).

In contrast to fertility, pregnancy outcomes in childhood cancer survivors have been studied more extensively. Several reports have found no excess of adverse pregnancy outcomes among patients who completed moderate to high dose single agent or combination chemotherapy before conception. In an early investigation, Li and Jaffe (1974) evaluated 64 pregnancies in 29 female childhood-cancer survivors of diverse tumour types. They found no evidence of

chemotherapy-associated genetic injury, which was measured as fetal loss, sex-ratio disturbance, number of birth defects and occurrence of cancer or other disorders in the offspring. In a larger investigation by the same authors, there was no excess of fetal or neonatal deaths, stillbirths, spontaneous abortions or major or minor anomalies in 159 pregnancies of 84 childhood survivors compared to the general population (Li et al., 1979). Two recent studies, which examined 30 to 47 pregnancies in two groups of 23 women following moderate to high-dose combination chemotherapy, also did not report an increased risk of abnormal births (Blatt et al., 1980; Hall and Green, 1983).

Other investigations have examined the effects of radiation on pregnancy outcomes, most notably that given for the treatment of Wilms' tumour. The first was a pilot study of 27 women who reported 43 pregnancies following completion of treatment for Wilms' tumour (Green et al., 1982). There was no excess in spontaneous abortions, congenital anomalies or cancer in the offspring of this group. However, of the 33 offspring of women who received orthovoltage abdominal radiation, 10 (30%) weighed less than 2,500 grams at birth. Of these, 7 were delivered before 38 weeks of gestation and 3 died during the perinatal period.

This study population was subsequently enlarged to include seven pediatric oncology centres in the United States and France to examine the pregnancy outcomes among patients with Wilms' tumour (Li et al., 1987). This study found that 30% of the pregnancies in 60 women who had received abdominal radiation had adverse outcomes (i.e., 11 fetal deaths, 22 low birth-weight infants and 1 neonatal death) as compared to an absence of adverse outcomes for the non-radiated females. Compared to the general population, the abdominally radiated women had an increased perinatal mortality rate (RR=7.9) and an excess of low birth weight infants (RR=4.0). Of the low birth-weight infants, 19 were delivered prematurely and 5 suffered neonatal deaths.

No effect on male-female ratio, rate of major congenital anomalies or cancers in offspring was detected in this investigation. Another retrospective cohort study examined 33 pregnancies of 26 female survivors of Wilms' tumours and 38 sibling controls (Byrne et al., 1988). More females survivors than sibling controls reported a low birth weight baby (17% versus 3%), a preterm delivery (28% versus 3%) or a baby with a birth defect (33% versus 10%). The female survivors had a four-fold significant increased risk for an adverse pregnancy outcome.

In a larger investigation in Britain, pregnancy outcomes in all childhood tumours diagnosed under the age of 15 that sometimes require direct abdominal radiation, were examined (Hawkins and Smith, 1989). The proportion of first singleton children with a low birth weight, born to abdominally radiated female survivors of Wilms' tumour was 45%, in contrast to an absence of low birth weight infants in females not previously radiated. Among survivors of other tumour types, there was no statistically significant difference between those abdominally radiated and those not radiated, although numbers were small. Abdominally radiated female survivors of Wilms' tumour also had an increased risk of being nulliparous and having a spontaneous abortion. These reports were extended and found that radiation therapy directed to the abdomen or pelvis for tumours other than Wilms' tumour also resulted in excess rates of perinatal (RR=5.4) and neonatal (RR=10.1) mortality and low birth weight infants (RR=4.3) compared to the general population (Garber et al., 1990). Possible explanations for the findings of low birth weight in these studies include radiation-induced somatic damage to the women's abdominopelvic structures (uterine vascular insufficiency or fibrosis) as well as genito-urinary malformations associated with Wilms' tumour complex (Smith and Hawkins, 1989).

A recent analysis of the British study examined whether therapy potentially mutagenic to germ cells (i.e., direct radiation of the abdomen or gonads or chemotherapy with alkylating

agents) is associated with an increased risk of miscarriage, serious congenital abnormalities, or altered sex-ratio. This study did not show an association of exposure to therapy potentially mutagenic to germ cells with altered sex-ratio or the occurrence of serious congenital abnormalities in the offspring of female survivors. The excess of miscarriages (17% versus 9%) among the pregnancies seen in the exposed females was entirely explained by abdominal or gonadal radiation received and therefore this association also was not as a result of a germ cell mutation (Hawkins, 1991).

A few investigations have also reported pregnancy outcomes following treatment for Hodgkin's disease, non-Hodgkin's lymphoma (NHL) and ALL. Studies which reported between 9 to 28 pregnancies in females following radiation and chemotherapy treatment during childhood or adolescence for Hodgkin's disease and NHL suggested that these pregnancies do not have an increased risk of abnormal outcomes (i.e., congenital malformations, spontaneous abortions, or stillbirths) (Green, 1986; Green, Sigelstein et al., 1989). Several case reports have reported normal children born to female patients successfully treated as children prior to 1978 for ALL (Moe et al., 1979; Nesbit et al., 1979). A case series which examined 17 pregnancies also suggests that there is no increased risk of adverse pregnancy outcomes after treatment for ALL during childhood or adolescence (Green, Hall et al., 1989).

Several studies have examined the risk of birth defects in the offspring of cancer survivors. The overall rate of major malformations (about 4%) from a combined analysis of fourteen large series of childhood cancer survivors is similar to the expected rates in the general population (Mulvihill and Byrne, 1992). Recent investigations which examined children and adolescents treated with mutagenic chemotherapeutic agents other than alkylating agents or

survivors of ALL also did not find an increased risk of congenital anomalies in the children of these cancer survivors (Green et al., 1991; Kenney et al., 1996).

The small numbers of long term cancer survivors and offspring reported in the literature have allowed only minimal power, which is further reduced when subgroups of treatments or malignancies are considered. Evidence to date suggests an increased risk of low birth weight infants and preterm deliveries among female cancer survivors, especially those treated with abdominal radiation for Wilms' tumour. There is still uncertainty concerning similar effects on other adverse pregnancy outcomes among survivors of other childhood tumours and the effects of more recent therapies on reproduction and outcomes of pregnancy.

7. **Etiologic factors of adverse reproductive outcomes**

7.1 Menopause and Infertility:

The menopause is defined by the World Health Organization (WHO) as the permanent cessation of menstruation (following 12 months of amenorrhea) resulting from loss of ovarian follicular activity (Sowers and La Pietra, 1995). The reported average age at menopause ranges from 48 to 52 years in North American and European populations. It is not always clear whether reported age at menopause represents age at cessation of menses or age at cessation of menses plus one year or whether it includes information contributed from women with surgical menopause. Smoking is considered a major risk factor for an earlier age at natural menopause, with women who smoke having an age at onset 1 to 2 years earlier than women who do not smoke (Brambilla and McKinlay, 1989; McKinlay et al., 1992). Other potential risk factors which may influence age at menopause include nutritional status and other reproductive attributes. Some studies have suggested that greater height and weight may contribute to a later

age at menopause (Sowers and La Pietra, 1995). Women who had shorter menstrual cycles (less than 26 days) and who are nulliparous have an earlier onset of menopause (Whelan et al., 1990; Stanford et al., 1987). Early age at menarche and oral contraceptive use may be associated with a later onset of menopause, although a few studies have suggested no relationship with age at menopause (Whelan et al., 1990; Stanford et al., 1987; Brambilla and McKinlay, 1989).

Infertility can be measured in a few ways. Childlessness can be used as an indicator of infertility by examining percentage of women never pregnant, or with no children ever born (Belsey, 1984). Sterility, conception delay, and unrecognized embryo loss are each components of what is called infertility (Westhoff, 1991). A more standard definition of "infertility" used is failure to conceive during a 12 month period of sexual relations without contraception. There are two general types of infertility: primary infertility means conception has never occurred and secondary infertility refers to the couple's inability to achieve another pregnancy when the women has already had one or more children (Boyer, 1993). Data from three independent surveys in late 1991 and early 1992, estimated that the prevalence of one-year infertility among Canadian women 18 to 44 years of age, married or cohabitating for at least one year, was 8.5% (Dulberg and Stephens, 1993). If males or females surgically sterilized were excluded from the denominator, one year infertility was 15.4%. Data from a U.S. population-based study, the National Survey of Family Growth, showed that the percentage of infertile women decreased from 1965 (11.2%) to 1982 (8.4%). However, when surgically sterile couples are excluded from the denominator, overall percent of infertile couples has remain constant at about 14% (Westhoff, 1991).

The WHO task force suggested that 36% of infertility in women was a result of a tubal factor, 33% as a result of ovulatory disorders (i.e., polycystic ovarian disease, premature

ovarian failure), 6% as a result of endometriosis, and no demonstrable cause for 40% (Healy et al., 1994). Infertility increases with age showing a modest increase between ages 30 to 34 (13.6%), followed by a more substantial increase at older ages 35 to 39 (24.4%) and 40 to 44 (27.2%) (Westoff, 1991). Use of illegal (heroin, cocaine) and legal substances (alcohol, cigarette smoking) are also potential causes of infertility. Cigarette smoking, as an independent risk factor, increases infertility by one and a half to two times (Millson, 1993). In addition, fertility can be affected by strenuous exercise, eating disorders and by occupational exposures to ionizing radiation, nitrous oxide, textile dyes, lead, mercury and cadmium (Healy et al., 1994). Obstruction of or infections in the tubes of the reproductive system may be associated with sexually transmitted diseases (i.e., gonorrhoea and chlamydia) or with other infections (Belsey, 1984; Westhoff, 1991). Tubal infertility can also follow a therapeutic abortion, puerperal infection, suppurative appendicitis, peritonitis of other causes or abdominal surgery (Healy, 1994))

7.2 Adverse pregnancy outcomes:

Adverse pregnancy outcomes are caused by a variety of biological, behavioural, and environmental factors and the interaction between these factors. Table 1.1 lists important risk factors for each of the adverse pregnancy outcomes of interest in this study. A discussion of the definitions, prevalence, incidence, and trends over time of these pregnancy outcomes follows below.

The definition of spontaneous abortion is based on the stage of embryonic development when viability is not possible outside the uterus. The usual current criterion for a spontaneous abortion is the death or expulsion of an embryo or fetus before 20 weeks of gestation and a fetal

weight of less than 500 grams, although these criteria are not universally accepted (Brent and Beckman, 1994). The definition of spontaneous abortion can include pregnancy loss before 20 or 28 weeks gestation. However, from a statistical standpoint it's not crucial which gestational criterion is used since the majority (91%) of spontaneous abortions have occurred by 20 weeks of gestation (Wilcox, 1983). The risk of miscarriage increases to about week ll and then decreases again with the majority of early miscarriages (before 12th week) having gross chromosomal anomalies (Kallen, 1988). Estimates of pregnancy loss are more reliably reported after the first missed menstrual period. The reported early loss rate among clinically recognized pregnancies is between 12% and 15% in cohort studies (Hertz-Picciotto and Samuels, 1988; Stirrat GM; Brent and Beckman, 1994). The risk of spontaneous abortion is between 8% and 17% from studies of reproductive histories (Modvig et al., 1990). Various factors have been considered as possible determinants of spontaneous abortions with 50 to 60% due to chromosomal abnormalities. The important causes of spontaneous abortions include maternal age, maternal cigarette smoking and alcohol drinking, maternal and paternal occupational exposures (eg., organic solvents, pesticides, nitrous oxide, lead), maternal physical occupational exertion, and maternal conditions (eg., diabetes, syphilis, cervical incompetence) (Klein and Stein, 1984; Kline et al., 1989; Brent and Beckman, 1994; Savitz et al., 1994; Gold and Tomich, 1994).

Perinatal deaths include stillbirths (fetal deaths of greater than or equal to 20 weeks gestation or greater than or equal to 500 grams weight) plus early neonatal deaths (deaths of a live born infant of less than 7 days) (Campbell, 1993). For fetal deaths the gestational cut point can vary between countries from 16 weeks to 28 weeks. For international comparisons, standard perinatal statistics are restricted to infants and fetuses weighing 1000 grams or more, or when

birth weight is unavailable, the corresponding gestational age of 28 weeks. The reason for combining these two types of mortality is that the causes of both are related and do not vary independently of one another, and therefore prevention focuses attention on the period surrounding birth (Peron and Strohmenger, 1985). There is also no biological difference between a stillbirth and an early neonatal death (Kallen, 1988). Perinatal mortality rates reflect standards of obstetric and pediatric care as well as the social condition of the population, but should be supplemented with birth weight distributions of the population when making comparisons between countries (Bakketeig et al., 1984; Golding, 1991). Perinatal mortality rates have been steadily declining throughout the Western world, including Canada (Golding, 1991; Bakketeig et al, 1984). The perinatal death rate (including fetal deaths of 28 or more weeks) in Ontario has decreased from 35.7 per 1,000 births in 1950 to 7.4 per 1,000 births in 1992. Improvements in perinatal mortality rates are as a result of lower birth weight mortality rates rather than a change in birth weight distributions (Silins et al., 1985). Perinatal mortality risks are positively correlated with low birth weight, with risk factors similar to those which increase the incidence of low birth weight (Peron and Strohmenger, 1985). Perinatal mortality is determined by a complex interaction between many biological (maternal age, low maternal body mass index, maternal diabetes) and social factors (lower maternal education and social class, maternal cigarette smoking, maternal occupational exposures and physical exertion) (Golding, 1991).

The WHO definition of low birth weight is less than 2500 grams (5.5 lbs.). Definitions of low birth weight should include gestational age as well as birth weight so that the distinction between low birth weight due to intrauterine growth retardation (infants of 37 weeks or more gestation) and low birth weight due to preterm labour (less than 37 weeks gestation) can be made (Alberman, 1984). Intrauterine growth retardation is more marked for its association with

morbidity than mortality, and infants small for gestational age have lower neonatal and postneonatal mortality rates than do infants appropriate for gestational age of comparable birth weights (Behrman, 1985). Low birth weight accounts for 75% of early neonatal deaths in Canada, and is a significant contributor to both infant and childhood morbidity (Silins et al., 1985; Kramer, 1987). Although there has been a steady decline in rate of perinatal mortality over the past 25 years due to improved survival of very low birth weight infants, there has been minimal reduction in rate of low birth weight infants. In Canada the rate of low birth weight is 5.5% and 5.6% in Ontario. Over the past 30 years, this rate has not changed dramatically. A meta-analysis of 895 studies related to low birth weight concluded that in developed countries the factors with well established causal impacts on intrauterine growth and gestational duration are cigarette smoking, poor gestational nutrition, low prepregnancy weight, female sex of infant, short stature, prior prematurity or spontaneous abortion or in utero exposure to diethylstilbestrol (Kramer, 1987).

Most birth defects have a multifactorial etiology involving interaction of genetic and environmental factors. The causes of 65-75% of malformations is unknown, 15-25% are caused by genetics and 10% by environmental factors (Brent and Beckman, 1994). Environmental factors include maternal conditions (diabetes, alcoholism, smoking), infectious agents (rubella, toxoplasmosis, syphilis), and chemical exposures (occupational, licit and illicit drug use) (Brent and Beckman, 1994). Birth defects (also known as congenital anomalies or congenital malformations) include a large and highly diverse group of physical and metabolic diseases, which have their origin at some time prior to birth. As most birth defects are laid down early in pregnancy and may result in a miscarriage, no more than the tip of the iceberg for some malformations survive long enough to be born. The proportion of live and stillborn infants

affected by these malformations (birth prevalence) is less than the incidence (Leck, 1994). In developed countries, about 1 in 40 or 2.5% of total (live plus still) births are affected by severe structural defects and 2.3 per 1000 infants (including stillbirths) die from malformations by the age of 5 years which represents 15% of those affected (Leck, 1994). It has been estimated that 3 to 6% of offspring are malformed (Brent and Beckman, 1994).

Table 1.1: Risk factors for pregnancy outcomes

Risk Factor	Spontaneous Abortion	Perinatal Death	Low Birth Weight	Birth Defect
Demographics: Maternal				
Age	increase with age	U-shaped relationship	U-shaped relationship	-for most age effect is not large -increase with age for (Neural tube defect (NTD),cleft lip, Down syndrome)
Socioeconomic status (SES)	inconclusive	lower SES	lower SES	lower SES for NTD
Ethnicity	inconclusive	highest for Blacks	highest for Blacks	highest for South Asians, lower in Blacks
Education	inconclusive	lower education	lower education	lower education for some birth defects
Behavioural & Environmental				
Smoking	-increased by 30% -dose response -increased by a factor of 1.2 for every 10 cigarettes per day	-increased by 30% -increased risk of late fetal deaths	-increased 2-fold -dose response -third trimester smoking -increased by a factor of 1.5 for every 10 cigarettes per day	no major general effect of smoking, (association with NTD, facial clefts, congenital heart defects)
Alcohol	increased by a factor of 1.26 for each drink per day	-inconclusive, few studies	yes, especially with heavy smokers -first trimester drinking	elevated rate of heart, genital, CNS, and musculoskeletal defects.

Risk Factor	Spontaneous Abortion	Perinatal Death	Low Birth Weight	Birth Defect
Licit and illicit drug use	-anticonvulsants (risk is small) -cocaine use, inconclusive	-antihypertensive agents -cocaine use, unknown for other illicit drugs, few studies	-marijuana -cocaine	-anticonvulsants, antihypertensives, retinoids, thalidomide, DES, aminoperitin -inconclusive for heroin, methadone, marijuana, LSD
Occupation: Physical Exertion	prolonged standing, long work week, heavy lifting, bending, shift work, fixed evening and nights	-prolonged standing, long work week, tiring work, few breaks	shift work, heavy lifting,long work weeks	none
Occupation: Maternal Exposure	-organic solvents(dry cleaners, shoe workers, painters, electronic, graphic and semiconductor workers) -agriculture worker -nitrous oxide, ethylene oxide, ionizing radiation, anaesthetic gases, and antineoplastic drugs (medical workers) -lead (metal worker, soldering)	-pesticides (agriculture worker) -organic solvents (laboratory and leather workers) -manufacturing industry	-agriculture, electrical and leather workers -conflicting results for exposure to solvents -electronic assembly -service and manufacturing	-antineoplastic drugs, nitrous oxide (medical workers) -agricultural workers -organic solvents (laboratory workers, printing, painting pharmaceutical, toluene) -lead (metal workers, smelter, soldering) -service occupations

Risk Factor	Spontaneous Abortion	Perinatal Death	Low Birth Weight	Birth Defect
Occupation: Paternal Exposure	-organic solvents (toluene, painters, wood workers, motor vehicle mechanics, petroleum refineries, rubber manufacturing) -lead, vinyl chloride -pesticides -anesthetic gases (anesthesiologists, dentists)	-hospital workers and textile industries	-ceramics, rubber, benzene, body shop workers and painters	-suggestive relationships with organic solvents, wood products, metals and pesticides. -printing and textile industry -food processors
Medical Risks Predating Pregnancy				
Body Mass Index	none	-low body mass index	-low weight for height -poor weight gain	none
Illnesses	-poorly controlled diabetes -epilepsy -hematological and cardiac diseases -PKU (untreated) -hyperthyroidism and hypothyroidism	-diabetes	-diabetes -hypertension -renal disease	-diabetes -thyroid disease -PKU -epilepsy
Recurrent outcomes	-miscarriage -premature births	-perinatal deaths	-low birth weight -miscarriage	-stillbirths -miscarriages -congenital anomalies

Risk Factor	Spontaneous Abortion	Perinatal Death	Low Birth Weight	Birth Defect
Medical Risks in Current Pregnancy				
Complications during pregnancy	-incompetent cervix -conception with IUD in place	-placenta previa -abruptio placenta -uterine rupture -complications of umbilical cord -respiratory distress -bleeding -multiple births	-incompetent cervix -placenta previa -abruptio placenta -PROM -preeclampsia toxemia -parity -short interpregnancy interval -first or second-trimester bleeding -multiple births	-bleeding
Infections	-syphilis -herpes simplex 2 -cytomegalovirus -toxoplasmosis -HIV -malaria -rubella	-chlamydia -syphilis -HIV	-rubella -cytomegalovirus -urinary tract infections	-herpes simplex II -rubella -syphilis -toxoplasmosis -cytomegalovirus

Chapter 2: METHODS

1. Overview of study

This study employed a retrospective cohort design using the Ontario Cancer Registry (OCR) to identify a large cohort of female childhood cancer survivors. Reproductive-related experiences of those survivors who had received chemotherapy with alkylating agents and/or abdominal-pelvic radiation were compared to those who received non-sterilizing surgery only. By using an internal comparison group this study was able to determine whether treatment, rather than having cancer, influences the risk of menopause, infertility or an adverse reproductive outcome. Data on a number of adverse reproductive endpoints of interest and potential confounding variables were ascertained from the survivors themselves through an interviewer-administered questionnaire, while cancer treatment details were abstracted from medical records.

2. Objectives

The primary objectives of this study were :

1. To determine whether there is an increased risk of menopause and infertility in those female survivors of childhood cancer who received chemotherapy with alkylating agents and/or abdominal-pelvic radiation compared to those who received non-sterilizing surgery.

2. For those female survivors who had pregnancies, to determine whether there is an increased risk of having an adverse pregnancy outcome (defined as a spontaneous abortion; a perinatal death; a low birth weight infant or a common birth defect in offspring) associated with these major forms of treatment (i.e., chemotherapy which included alkylating agents or abdominal-pelvic radiation) compared to non-sterilizing surgery.

3. Design and Methods

3.1 Identification of study subjects:

3.1.1 Description of the Ontario Cancer Registry:

The OCR is a population-based cancer registry operated by the Ontario Cancer Treatment and Research Foundation (OCTRF). The OCR contains information on all newly diagnosed cancer in Ontario residents since 1964. To produce incidence data, the OCR relies on four major sources of routinely collected data, namely, hospital discharges, pathology reports, death certificates, and reports of patients referred to the OCTRF's eight Regional Cancer Centres (RCCs) and the Princess Margaret Hospital (PMH). Once these source files have been processed, they are computer-linked using the Generalized Iterative Record Linkage System. Then, a set of computerized rules known as 'Case Resolution' is applied to the linked records, to allocate the appropriate site of disease, histology, date and method of diagnosis, residence and other person-specific information. The data elements included in each patient's tumour record are shown in Appendix A. A recent study estimates that the OCR is at least 95 percent complete (Robles et al., 1988).

The OCR uses a site-based classification system. All of the data have either been originally classified or converted from earlier revisions (Sixth, Seventh, Eighth) to the International Classification of Diseases (ICD-9). Identification of the organ or anatomical site involved is of more importance in classification of adult tumours than childhood tumours where a classification scheme based on morphology would be more appropriate. Childhood neoplasms are mostly found in the deep tissues of the body such as the brain, bone and bone marrow, lymph glands, and fewer in the skin and the cells lining the internal organs (NCIC, 1990). Therefore, the site and histology of cancer for survivors in this study will be reclassified

according to the diagnostic categories provided by the International Agency for Research in Cancer (IARC). This new international classification has been developed from that used by the Manchester Children's Tumour Registry (Birch and Marsden, 1987). Tumours have been divided into 12 diagnostic groups based on the incidence of childhood malignancy and is related to histological features.

3.1.2 Criteria for selection:

Females who are in the OCR and satisfy the following criteria were included:

1. Diagnosed with any malignancy (excluding non-melanotic carcinoma of skin) which is histologically confirmed by a pathology report, or has mention of histological confirmation on a hospital chart or from the patient's physician.
2. Diagnosed before age 20.
3. Diagnosed with first primary cancer between 1964 and 1988, inclusive.
4. Survived for at least 5 years after diagnosis and alive at time of study.
5. Survived to at least 18 years of age.
6. Resident of Ontario at time of diagnosis.

Age less than 20 years at diagnosis was chosen as in Ontario the majority of patients of this age would be treated in oncology divisions in pediatric departments and hospitals. The time period of eligibility was chosen to maximize the number of survivors eligible for the study, at time of cohort selection (April 1, 1993). The start year (1964) represents when the OCR began to collect data on incident cases of cancer and the end year (1988) represents the last year in which subjects could have been included in the study as they had to have survived 5 years after their diagnosis. Survival of 5 years from date of diagnosis was chosen as this would define a

group of women who for the most part have completed their therapy and who have been successfully treated for their malignancy. Some patients will develop a second primary cancer or have a relapse but these patients are readily identifiable. Any treatment received or reproductive outcomes occurring after a second primary cancer or a relapse (after the first five years of diagnosis), will be excluded from the analysis. Subjects were to be 18 years of age and alive at time of study as it was decided it would be advisable not to include proxy respondents for a study collecting information on reproductive health. A recent study concluded that errors in reporting of reproductive events by husbands as proxy informants of their wives may be substantial and may compromise study validity (Fikree et al., 1993). Subjects were to be residents of Ontario at time of diagnosis as this is one of the criteria used in the process of cancer registration of the OCR.

3.1.3 Ascertainment of study subjects:

Female childhood cancer survivors who appeared to meet the above criteria (those without histological confirmation were included initially and were later excluded if no evidence of histological confirmation was found) were identified from the OCR. Based on the OCR incidence data file, there were 2,165 females who satisfied the study inclusion criteria as of April 1, 1993 (when the study cohort was identified). Of these, 268 of the subjects have since been deemed ineligible (16 deceased; 28 diagnosed after age 19; 199 non-malignant tumours; 8 male; and 17 non-residents of Ontario at time of diagnosis) and 52 were untraceable in that a current physician could not be identified from medical records. In addition, there were 264 subjects whose cancer diagnoses could not be confirmed because their medical records had been destroyed. Identifying and diagnostic information such as subject's full name, alternate names,

date of birth, vital status, cancer site and histology, and age and date of diagnosis were retrieved from the OCR database for all subjects and was copied directly into the computerized study management system. Standard patient reports were printed from the OCR database for all survivors. In addition to containing summary tumour records, these reports listed all of the source records received by the OCR for each patient, that is, hospital separation, pathology, RCC and PMH records. This information was used as an aid to locating cancer survivors and their physicians as well as for verification of diagnosis.

3.2 Study Instruments:

3.2.1 Questionnaire:

A questionnaire was developed by the study team in consultation with such subject matter experts as Dr. H. Bryan (Neonatologist, Mount Sinai Hospital) and Dr. M. Greenberg (Chief of Oncology, The Hospital for Sick Children) (both collaborators on the study), Ms. A. Vatter-Fitzgerald (Pediatric Database Manager, Toronto-Bayview Regional Cancer Centre) and staff of the Cancer Information Service (CIS). The questionnaire focused primarily on the subject's pregnancy history with additional questions on: demographic details; menstrual and fertility history; and oral contraceptive and hormone use (Appendix B). The information collected on the pregnancy history, included the outcome of each pregnancy (i.e., live birth, stillbirth, spontaneous or therapeutic abortion), age at pregnancy, duration of gestation, date of outcome and delivery complications, in addition to sex, birth weight, and congenital conditions and survival status of live born children. The questionnaire also requested information on common risk factors for adverse pregnancy outcomes. This information included selected maternal demographic (e.g. education, race), behavioral and environmental (e.g. smoking and alcohol use,

occupational exposures), and medical (e.g. illnesses, medication use) factors prior to and during the pregnancies.

The questionnaire was pretested on two groups of people. The first pretest relied on study staff members, friends and colleagues and was used to assess the general layout of the questionnaire, the appropriateness of the wording of the questions, and the clarity of instructions. There were 28 questionnaires returned with comments. This pretest resulted in clarification of instructions in the questionnaire and improvements in the wording of the questions.

The second pretest was conducted on a population sample and was intended to assess the study contact procedures and help to develop the introductory scripts and the interviewer manual, in addition to the questionnaire. The subjects were identified by random selection of 100 female names from the municipal assessment rolls at Scarborough City Hall. Since our study cohort concerns only women aged 18 to 50, we conducted telephone interviews only with subjects who were between these ages.

Letters and questionnaires were mailed to 56 subjects with telephone listings (obtained from Bell Directory Assistance), which was followed in two weeks by a telephone interview. The letter outlined the purpose of the pretest study, who in the household was eligible to participate and confidentiality of responses. Of these, 2 were returned undeliverable or could not be followed up because of an incorrect phone number, 12 were ineligible (i.e., no female between 18 and 50 years of age), 2 did not receive the questionnaire, and 8 were lost to follow-up. For the remaining 32 subjects who were eligible and received the questionnaires, 24 (75%) responded to the telephone interview and 8 (25%) refused to participate. Telephone interviews required from 5 to 30 minutes, with 15 minutes being the average.

Subjects were asked additional questions (not contained in the questionnaire) after completion of the interview. These questions were developed to assess the subject's perception of the questionnaire and included initial reaction to receiving the cover letter and questionnaire, any difficulties in answering and understanding questions, and acceptability of the length of the interview. Upon completion of an interview the interviewer recorded her perception of the subject's comprehension before assistance, difficulty after interviewer assistance and the reliability of responses.

Approximately three-quarters (72.7%) of the subjects had a positive initial reaction to receiving the covering letter and the questionnaire. A typical positive response was "I feel this type of research is extremely valuable". The remaining 27.3% had a negative initial reaction. A typical negative response was "I thought it (the questionnaire) was too long initially until I read it over". None of the pretest subjects found any of the questions difficult to understand but a few (8.7%) found one or more questions difficult to answer. Respondents indicated difficulty in recalling events during their pregnancies if they occurred far in the past. Most respondents (82.6%) felt that the questionnaire was a reasonable length.

Interviewers indicated that almost all respondents (91.3%) understood all items with no assistance. For the few subjects (8.7%) who had some difficulty understanding items, all had no difficulties after interviewer assistance. Interviewers recorded that they felt all responses were reliable on 100% of the questionnaires. Subjects responded to all items on the questionnaire.

3.2.2 Definitions of reproductive outcomes:

Specific information collected from the questionnaire responses were used to define the reproductive outcomes of interest in this study. Menopausal status was determined from the

responses to the questions, "Have you stopped having periods?" and "Have you ever used hormonal supplement pills?". Infertility was measured in three different ways: from the response to the question, "Have you ever tried for one year or more to become pregnant, and been unable to?"; from the response to the question "Have you ever been told you had a fertility problem?"; and as never had a pregnancy.

Women were classified as having a particular adverse pregnancy outcome according to their responses to questions regarding the outcome of the pregnancy, the number of weeks of the pregnancy, the birth weight of live-born infants and whether the infant had a birth defect or died prior to their first birthday. A women was recorded as having a spontaneous abortion if she specified having a fetal loss after at least 4 weeks gestation and prior to 20 weeks gestation. Women who reported having had a stillbirth (a fetal death of greater than or equal to 20 weeks gestation) or an early neonatal death (a death occurring prior to the first week of life) were classified as having an infant with a perinatal death. A women had a low birth weight infant if she reported having a live birth whose birth weight was less than 2,500 grams and had a premature low birth weight infant if, in addition to being low birth weight, the infant was born prior to 37 weeks gestation. Women who stated they had a child diagnosed at birth or during the first year of life with a birth defect, were classified as having a child with a congenital anomaly. Ten major congenital anomalies that are relatively common and easily diagnosed, were selected for this analysis.

3.2.3 Cancer treatment abstraction form:

The treatment abstraction form (Appendix C) was based primarily on forms used for other treatment-related studies and was revised by the study team in consultation with such study

matter experts as Dr. M. Greenberg (Chief of Oncology, The Hospital for Sick Children), Dr. R. D. T. Jenkin (C.E.O., Toronto-Bayview Regional Cancer Centre) and Dr. W. R. Tsang (Radiation Oncologist, Ontario Cancer Institute/Princess Margaret Hospital). The form was initially pretested on a sample of 45 subjects seen at PMH. The information collected included: type of therapy (e.g., chemotherapy, radiotherapy, or surgery), dates of therapy and site where appropriate. For radiation therapy, dose, number of fractions and fields, field size and type of machine used were additionally noted. For chemotherapy, type, dose, and routes of administration of each chemo-therapeutic agent and weight and height for each subject at time of chemotherapy were also recorded.

A treatment abstraction manual giving full instructions on how to abstract treatment data in a standardized fashion and providing codes for type or site of surgery, site of radiation treatment, type of machine used during radiotherapy, type of chemotherapy used and route of administration etc. was prepared to guide the abstractors.

3.2.4 Definitions of treatment groups:

Specific information collected from the treatment abstraction form was used to define the treatment groups of interest in this study. Subjects were classified into one of five mutually exclusive treatment groups (i.e., non-sterilizing surgery, chemotherapy with alkylating agents, abdominal-pelvic radiation, alkylating agents plus abdominal-pelvic radiation and all other treatments). The non-sterilizing surgery group, which was the comparison group, included subjects who received only surgery for the treatment of their cancer, excluding a total or subtotal hysterectomy, bilateral oophorectomy or bilateral salpingectomy. Subjects who received chemotherapy were divided into two groups according to the class of chemotherapeutic agents

received. Those who received chemotherapy with any of the following drugs: busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, lomustine, melphalan, nitrogen mustard, or procarbazine were grouped as having chemotherapy with alkylating agent. Subject receiving chemotherapy without alkylating agents (i.e. anti-tumour antibiotics, anti-metabolites, plant alkaloids or other drugs such as dexmethasone or L-asparginase) were classified as having chemotherapy with non-alkylating agents. Subjects who received radiation were also divided into two groups according to the site of radiation treatment. Subjects who received any radiation treatment to the pelvis, abdomen, lumbar and/or sacral spine, whole body radiation, hip joint or femur were defined as having abdominal-pelvic radiation. Those subjects receiving radiation above or below the abdominal-pelvic area (i.e., cranial, thorax, thoracic spine, upper mantle or extremities) were classified as having non-abdominal pelvic radiation. The "other treatment" group comprised of subjects who received chemotherapy without alkylating agents and/or radiation above or below the abdomen.

3.3 Study Procedures:

3.3.1 Computerized management/entry systems:

A computerized study management system was developed, using the database program FoxPro. Screens developed contained subject identifying information, data on cancer diagnosis, names of institutions where subjects were seen along with corresponding dates and chart numbers, physician information and subject status with respect to interview and return of treatment consent form. The study management system was designed to generate regular reports of study progress as well as physician and subject letters, mailing labels, consent forms and lists

of physicians or subjects requiring follow-up. Data entry screens for input of questionnaire and treatment data were developed with built-in consistency checks and skip patterns.

3.3.2 Confirmation of cancer diagnoses and identification of physicians:

Cancer records received by the OCR, that is, RCC and PMH records, hospital separations, and pathology reports, were examined from patient reports for each study subject. The computerized system "Oncology Patient Information System (OPIS)" was accessed for those subjects ever seen at a RCC. Names and telephone numbers of treating physicians, as well as last dates of contact with addresses of patients were obtained for 758 study subjects from OPIS. For subjects seen at PMH (N=461), names of treating physicians and patient addresses were extracted from the OCR database. For survivors who had a pathology report but were not seen at a RCC or PMH (N=296), physician names were obtained from the pathology records stored at the OCR (on microfiche or as paper records). Relevant information on the family physician was recorded in preference to other physicians specified. If no family physician was named, then information was recorded for a physician selected in the following order of preference: physician whose speciality corresponded to diagnosis of subject; physician whose address was in same geographic area as subject; and any other physician listed. Current physician address information was sought from the 1994 Canadian Medical Directory, the College of Physicians and Surgeons Information Services and directory assistance from Bell Canada.

Survivors without RCC, PMH or pathology reports in the OCR (i.e. with only hospital separation data) lacked both physician information and evidence of histological confirmation (N=650). Attempts were made to confirm these diagnoses and identify physicians through review of hospital charts. Since a recent OCR study had reported that when further information

was sought for childhood cancers (ages 0-14) without supporting pathology, only 36.5% were confirmed as having a malignant disease (Weir and Holowaty, 1993), it was expected that many of these cases would not actually have cancer.

For patients seen at the Hospital for Sick Children (HSC), hospital records were reviewed by study staff; permission to access these records was granted by the HSC Research Ethics Board. For subjects seen at other hospitals, a letter and list of patients seen at that hospital were sent to 120 hospitals across the province. These lists included: the OCR identification number; surname; given name; date of birth; admission date; discharge date; and hospital chart number (when available). The letter requested that a copy of specific information relevant to the diagnosis of cancer, such as pathology reports, results of diagnostic tests, consultation reports and final/summary notes, be forwarded to the OCR. Physician names were obtained from the manual review of hospital charts at the HSC or the confirmatory records provided by the other hospitals.

For subjects who were seen at a RCC or had a pathology report stored in the OCR but for whom we were unable to identify an appropriate physician, physician information was requested from the hospitals in which they were seen according to OCR. A letter and list of patients were sent to 53 hospitals in Ontario and four out-of-province cancer registries. The physician names were obtained from the records sent by the hospitals.

3.3.3 Physician contact:

Physicians of eligible subjects were sent an introductory letter, study description and consent form (Appendices D and E). In addition to introducing the study, the letter stressed that written physician consent to contact subjects was required by the University of Toronto Human

Subjects Committee and the OCTRF. It also notified physicians of the service being provided by the Cancer Information Service (CIS) in support of this study (the CIS is a toll-free, province wide, telephone inquiry service which provides up-to-date information about cancer and cancer-related resources). CIS staff worked with the study staff to develop a package of information which would be relevant for this study. CIS staff were prepared to discuss with the subjects of this study (or their physicians or families) any questions they had regarding the late effects of cancer treatment on fertility and pregnancy outcomes and to provide appropriate referrals where needed.

In addition to asking physicians to provide consent and the current address or name change information for each patient, the consent form requested indication of the patient's state of knowledge regarding her cancer diagnosis (only those with knowledge of their cancer diagnosis were to be contacted) and whether she had had a second primary cancer diagnosis; the latter assisted with the collection of treatment information. If the subject had had a central nervous system tumour, the physician was also asked if she was "mentally challenged". Subjects who were reported as being "mentally challenged" were not contacted for this study as inclusion would necessitate proxy responses from a parent or other family member.

Physicians were telephoned two weeks after mailing if they did not return the consent form. Reminder letters were sent two weeks later to those who stated over the telephone that they would give consent but had not done so. An alternate physician was identified where possible when a physician did not wish to give consent because he/she had not seen the patient in many years.

3.3.4 Subject tracing:

Subjects' current addresses were obtained from either the OCR, OPIS, or the physician consent form. For those with no current address in either, information from the Ministry of Transportation driver's licence file was used. Permission to access this file was received from the Ontario Ministry of Transportation. The driver's licence file is a computerized file which contains addresses, as of last renewal or contact, of all individuals who have ever had a driver's licence in Ontario; this file is periodically purged of records for drivers with whom there has been no contact for seven years. This file also contains information on surname changes. For those survivors who did not have a driver's licence, other sources such as information sent from hospital charts and telephone directories were searched. We were unable to secure permission from the Office of the Registrar General (ORG) of Ontario to use information from marriage records (for married name and address at time of marriage), or birth certificates (for parents' names and addresses). The ORG's current policy is that their records are not to be used (directly or indirectly) for the purpose of locating and/or contacting individuals.

3.4 Data collection:

3.4.1 Questionnaire administration:

After physician consent was secured, subjects were sent an introductory letter, the questionnaire, and a consent form for access to cancer treatment data (Appendices F, B, and G). Subjects seen at the HSC were also sent an Information Form (required by the HSC Ethics Review Board) containing pertinent information summarized from the introductory letter (Appendix H). The letter outlined the study, informed subjects they were being asked to participate and provided a telephone number to call (collect) if they had concerns. The letter

also indicated that an interviewer would call to record answers or set up a future time to do so. Information was recorded by a telephone-administered questionnaire. This was deemed to be a less expensive method of collecting high quality data for subjects covering such a large geographic area, than in-person interviews. Having the questionnaire in advance allowed respondents time to recall dates and events and to check records, prior to being interviewed; this was expected to reduce inaccuracies in recall and incomplete data that commonly occur in retrospective studies. In addition, the interviewer was able to provide clarification where required. These methods were expected to result in high response rates and provide more complete data than a self-administered questionnaire (which often requires a telephone follow-up for clarification/amplification).

Study subjects were called by an interviewer two weeks after study material was mailed out to record questionnaire responses. Subjects whose telephone numbers were unavailable were asked to call the study office (collect). If a subject was unavailable to be interviewed at initial contact, call-back arrangements were made. Calls were made at different times during the day and evening, including weekends. Periodically, a list of subjects whose study status remained "incomplete" 4 or more weeks after mailing was generated for review by the study coordinator. Reminder letters and a second questionnaire and consent form were sent to these subjects.

Interviewers were specially trained by the study coordinator and a consultant. The interviewers practised administering the questionnaire over the telephone to each other, and to the study coordinator. A manual was prepared to provide specific instructions to the interviewers on how to conduct the interview in a standardized fashion and to handle problems that arose, and suggested neutral probes. The manual also provided codes for some partially closed-ended questions and standard definitions to be employed when explaining medical terms to subjects.

Scripts were developed for introductions, questions, etc.. The interviewers also referred subjects to CIS if they had any questions about late effects of cancer treatment or became distressed during the interview (CIS received at least 20 calls from study subjects requesting information or wanting a referral). Interviewers were unaware of the 'exposure status' of respondents, as treatment information was abstracted by different study staff, was not available to interviewers and was not collected until after the interview was complete.

3.4.2 Collection of treatment information:

Detailed treatment information is not routinely collected by the OCR. However, the names of all hospitals and RCCs to which a patient was admitted for cancer, and dates of admission, are stored in the OCR database. This information was used to identify the location of medical records pertaining to anti-cancer therapy for each survivor. Treatment data were abstracted from the records of institutions where a subject was seen in relation to their diagnosis of cancer. Since subjects were asked to sign a permission to access treatment form, treatment information were not obtained from medical records for subjects who refused to sign this form.

Cancer therapy data were obtained primarily from existing treatment information collected and stored at major children's hospitals or RCCs in the province. Treatment records dating back 20 or more years were available from the RCCs and hospitals such as PMH and HSC, where at least 90% of the children were seen. In addition, Ontario hospitals are required by law to keep records for at least 10 years after the 18th birthday for minors.

All radiotherapy in Ontario is conducted at the RCCs or PMH. Approval to abstract treatment data was obtained from all of the RCCs and PMH, and study staff did all abstraction

at these centres. Radiotherapy information was found to be of high quality and documented in a standardized fashion, and had been retained at least for the period covered by the OCR.

Chemotherapy is administered at the RCCs and PMH as well as other hospitals. For those survivors not seen at RCCs or PMH, the necessary information on chemotherapy was collected from these other hospitals. Smaller hospitals in Ontario and out-of-province registries were requested to send either treatment information which they had abstracted from the charts or copies of the relevant medical records. One of the study abstractors reviewed the charts at larger hospitals. All hospitals contacted for chart review complied. Names of drugs, dates of therapy and routes of administration were generally recorded in the charts, although exact dose information and height and weight of the subject were not always available.

3.5 Data reliability/validity:

3.5.1 Validity of questionnaire data:

The accuracy of selected pregnancy data collected by interview was independently assessed for a random sample of respondents currently residing in Ontario through the use of vital statistics records. For the validation process, the relevant vital statistics records, i.e. live and still birth certificates and death certificates routinely collected by the Office of the Registrar General (ORG) of Ontario, have been accepted as the "gold standard". Data from the ORG are routinely collected in a standardized fashion, are believed to be of good quality and are accessible for all subjects (for events occurring in Ontario) from one source. Although pregnancy information could have been obtained from the subject's medical chart, there are potential error sources in hospital records and difficulties in obtaining complete data (Hewson and Bennett, 1987). For example, there could be considerable variability in the recording of past reproductive

events in medical records from different hospitals across the province and they could be unavailable for some subjects as hospital records can be destroyed after 10 years from last visit.

Vital statistic records were searched for a 5% random sample of "normal birth weight" live births and for all stillbirths, infant deaths, neonatal deaths and low birth weight infants reported by the respondents currently residing in Ontario. To determine the accuracy of data collected by the interview, certain variables (i.e. date of event, age of mother at event, birth weight, and gestational age) were abstracted from the relevant ORG certificates onto a specially prepared form and compared to the questionnaire.

Study data were corrected for any of the birth or death outcomes of interest that were ascertained as not having occurred. Assessment of the validity of reproductive data is an important component of the study and its results will affect the weight placed on the study results.

3.5.2 Reliability of treatment data:

The treatment data on a sample of 30 subjects (about 4 % of study cohort whose treatment data were abstracted) were re-abstracted by another abstractor as a check on the reliability of the data. Abstraction was conducted independently, with both abstractors not having access to treatment data obtained from the other abstractor. Subjects who were treated at the Toronto-Bayview, Hamilton and Ottawa Regional Cancer Centres, the Princess Margaret Hospital, and other hospitals in Ontario and out-of-province were chosen. The comparison of abstracted treatment data was conducted blind to the identity of the abstractors.

Data collected were compared within the following three treatment groups: surgical procedures, radiotherapy and chemotherapy. Dates and type/site of surgery were compared for

the surgical procedures. Dates, type of machine, site of radiotherapy, total dose, number of fractions, number of fields, and field size were compared for radiotherapy treatment. The name of each drug, dates given, whether or not it was given in combination with other drugs, total dose for each drug, and the route of administration were compared for chemotherapy treatment.

4. **Sample size**

In order to evaluate study power at the time of study design the following information was required: size of the eligible cohort, age- and time-specific years of follow-up (post-diagnosis); population fertility and reproductive outcome rates; and treatment categories (radiotherapy and/or chemotherapy and surgery only). Based on the 1990 OCR incidence data, there were 1,991 females who satisfied the study inclusion criteria. There were approximately equal numbers of survivors in each of the diagnostic time periods: 1964-69, 1970-74, 1975-79, and 1980-88. This reflects the interaction of the criteria used for selection. For example, survivors diagnosed recently have a higher survival rate, but will have been followed for the shortest time allowing fewer to have attained reproductive age. On the other hand, those diagnosed earlier will have had poorer survival but more opportunity to reach reproductive age.

Years of survival post diagnosis were calculated by subtracting date of diagnosis from selection date, if the patient's status was 'alive' in the OCR. The last death clearance conducted at OCR linked death certificates until the end of 1989 to the incident patient master file. Therefore, to ensure that all apparently eligible survivors were alive at time of study, current status had to be determined for those whose status in 1990 or 1991 was not explicitly identified during the routine registry process of follow-up (of course, actual status of these subjects was ascertained during the process of subject identification, diagnostic confirmation and physician

consent). By applying the 1990 all causes mortality rates (6 per 1000 per annum for females aged 15-44), it was expected that about twenty-two further survivors would have died in 1990 or 1991, for an estimated eligible study population of 1,969.

The numbers of person-years of follow-up were generated for each survivor for the 5-year age groups within an age range where reproduction was most likely, i.e., between 15 and 49 years of age, and for single years between 1964-1991. To estimate the expected number of offspring in this cohort, (assuming the same fertility as the general population) the Ontario year-age specific fertility rates were applied to the person-years in the corresponding year-age group. The expected number of live births under these assumptions was 2,247.

It was necessary to decrease the number of survivors further for those subjects expected to have non-malignant conditions and for those subjects and their physicians who were expected to refuse to participate or to be untraceable. From a small pilot study (N=200) to determine the feasibility and utility of using OCTRF records, the drivers licence file, and HSC medical records as aids to confirming cancer diagnosis and locating cancer patients and their physicians it was estimated that about 30% of the female cancer survivors with no supporting pathology (19%) would be confirmed as having a malignant disease. Although a recent study (Weir and Holowaty, 1993) reported that 36.5% of childhood cancers (diagnosed between 1975 and 1985) without supporting pathology could be confirmed as having a malignant disease, it was assumed that the percentage would be somewhat lower in our study as we were including female cancer survivors who were diagnosed earlier (i.e. between 1964 and 1988). The pilot study also estimated that 97% of physicians would be identified using the above mentioned methods and that address information would be found for 89% of subjects. Recent case-control studies at the OCTRF have experienced low rates of physician refusal to permit patient contact, at

approximately 2.5%. It was estimated that 8% of the subjects would refuse to participate, based on average response rates obtained in similar studies (Byrne et al., 1987; Green et al., 1982; Li et al., 1987).

The number of survivors and the expected number of live births were therefore reduced to allow for cases not histologically verified (13.3%), physicians who could not be located (3%), physician refusal (2.5%), cancer survivors who could not be traced (11%) and non-responders (8%). Therefore, the number of survivors expected to participate was 1,318 and the expected number of live births 1,505. These calculations assumed that physician and subject tracing and response rates were the same across age, period of diagnosis and treatment subgroups. An estimate of the number of pregnancies for these survivors was 2,042, based on the ratio of live births to pregnancies as conservatively estimated from a study conducted in Ontario (Narod and Khazen, 1989).

Subjects in this study will be classified by type of treatment and their reproductive outcomes will be compared to an internal comparison group (survivors who do not receive radiotherapy or chemotherapy). Reproductive outcomes of survivors will also be compared to the general population. The advantages of using an internal comparison group are that the exposed and unexposed cohort members will be subject to the same follow-up procedures, and will presumably have similar factors influencing their participation and response.

Treatment information from a recent OCTRF study that examined the association between chemotherapy or radiotherapy for cancer and anomalous offspring, was utilized to estimate the expected sizes of the exposed and unexposed groups in this cohort (Dodds et al., 1993). Using treatment information for the subset of subjects who overlapped with the proposed study (i.e., females, diagnosed before age 20, during a similar time period and having a similar distribution

of diagnoses), it was estimated that approximately 21% of female survivors in this study would have received chemotherapy, 34% would have received radiotherapy and 50% would have been treated without radiotherapy or chemotherapy.

4.1 Power calculations:

In order to estimate the power of this study for outcomes such as perinatal deaths and low birth weight, Ontario adverse pregnancy outcome rates for 1978 were applied to the estimated number of live births, to determine the expected number of outcomes in the comparison group (i.e., survivors who do not receive radiotherapy or chemotherapy). This year, which is the mid year in this series of live births, was selected to control in a limited way for temporal changes in the rates. In Ontario the perinatal death rate (stillbirths of greater than or equal to 20 weeks gestation plus early neonatal death) was 14.5 per 1000 total births (stillbirths plus live births) and the percentage of live-born infants whose birth weight was less than 2500 grams was 6.23% in 1978 (Vital Statistics, 1978).

The rate of infertility was estimated from results of the National Survey of Family Growth population-based studies, conducted in the U.S.. Based on interviews of women about their pregnancies, use of family planning and infertility services and physical ability to bear children, these studies estimated that about 14.3% (excluding surgically sterile) of married women aged 15-44 were infertile in 1976 (Westhoff, 1991). The number of infertile women will be estimated from the number of female survivors expected to be married. A study which examined marriage rates in childhood cancer survivors estimated that 86.1% of female survivors diagnosed prior to 1975, and treated without chemotherapy or radiotherapy would have been married (Byrne et al., 1989)

Frequency of spontaneous abortion in studies with retrospective data collection is usually measured by the fetal death rate, which relates the number of pregnancy losses before 20 weeks of gestation to the total number of pregnancies identified. An estimated fetal death rate of 12.5%, which was obtained from retrospective studies conducted in the mid 1970's (Kline et al., 1989), was employed in this power calculation.

For birth defects, it is estimated that 3 to 6% of offspring are malformed (Brent and Beckman, 1994). For this power calculation, the minimum number of birth defects (3%) was applied to the total number of births.

The radiotherapy group was expected to consist of approximately 448 survivors (512 live births, 694 pregnancies), and the chemotherapy group of 277 survivors (316 live births, 429 pregnancies). To simplify power calculations, the size of the comparison group was assumed to be equal to that of the radiotherapy group and twice as large as the chemotherapy group. The numbers of live births and pregnancies estimated need to be reduced for the radiotherapy group, who were shown in a recent study to have a relative fertility of 0.78 as compared to their siblings; both the chemotherapy and surgically treated group had almost no fertility deficit (Byrne et al., 1987). Appendices I and J show the expected numbers of each outcome in the comparison group and the minimal detectable relative risks for both treatment groups, assuming 80 percent power and a one-tailed alpha of 0.05 (Breslow and Day, 1987). For the more common reproductive outcomes (i.e., infertility, spontaneous abortions, low birth weight infants), study power for each treatment group was expected to be good. For the more rare pregnancy outcomes (i.e., perinatal deaths, birth defects), however, power would be very limited.

5. Use of Human Subjects

The survivors of childhood cancer were identified through the OCR. The OCR, maintained by the OCTRF, is legally supported by the Cancer Act (Appendix K) which provides for use of patient identification information for epidemiologic research (Section 7 (1)), provided appropriate safeguards of confidentiality are maintained. The OCTRF also has the important duty (Cancer Act Section, 5(f)) of ensuring the adequate recording and compilation of information on cancer patients. This act provides legal protection for health care institutions or personnel who provide information on cancer patients to the OCTRF (Section 7(2)). Approval to identify and contact survivors was received from OCTRF (Appendix L).

Written consent to contact the survivors was sought from physicians (Appendix E). In addition to asking physicians to provide consent for their patient to be contacted, the consent form requested indication of the patient's state of knowledge regarding her cancer diagnosis (only those with knowledge of their cancer diagnosis were contacted). The reason for ensuring that the subject was aware of her cancer diagnosis was so that we could obtain written consent from them for access to their cancer treatment information. After physician consent was secured, subjects were sent an introductory letter, questionnaire, and consent form for access to treatment data (Appendices F and G). The cover letter to all subjects referred to prior contact with the physician, described the study, and provided the names and telephone numbers of the principal investigator and study co-ordinator to call (collect) with questions or concerns.

The survivors were informed that all responses were confidential, that they were under no obligation to participate and could refuse to do so without adverse consequences. All subjects consented to participate verbally, before being interviewed, at their leisure and in complete freedom of any pressure. Subjects were free to stop the telephone interview at any time.

Each questionnaire (and corresponding treatment abstraction form) was given a unique identification number, and names and addresses of subjects were kept on a separate form. All identifying information was kept in a locked file cabinet in a locked study office. Questionnaire and treatment data were stored separately from identifying information in the computer. Access to identifying information in the data management system was password-protected with access to authorized staff only (study coordinator, epidemiologist and research clerk). All analyses and reports used groups of subjects so that no individual could be identified. Approval of study procedures and the subject introductory letter and consent form, physician letter and consent form, and questionnaire was received from the University of Toronto Human Ethics Review Committee on October 18, 1993 (Appendix M).

The only foreseeable risk to the subject, aside from inconvenience of being interviewed, was the possible psychological trauma that could result from being asked to participate in a study referring to a major life event that may have been unpleasant. We attempted to minimize this by having the interviewers emphasize the importance of the results of this study to future young cancer patients and by referring subjects to the CIS when they had questions about late effects of cancer treatment or became distressed during the interview. Although there might have been a slight inconvenience for a few subjects in being interviewed, this should be outweighed by the fact that this study may provide new information for reproductive counselling of long-term survivors of pediatric malignancies and their families.

The individual subjects in this study are unlikely to benefit immediately from results of this research, except for the younger subjects who have not yet started their families. All subjects and consenting physicians were sent a summary of the results upon completion of the study.

6. Statistical Methods

6.1 Analysis of data reliability and validity:

The questionnaire and treatment data were checked for consistency, credibility and completeness of responses by examining frequencies for categorical variables and ranges and means for continuous variables. To assess the validity of questionnaire data, means and standard deviations of differences were used to compare selected pregnancy data from the questionnaire to the relevant live birth, stillbirth or death certificates, for the same subject (Bland and Altman, 1995). To check the reliability of treatment data, percentage agreement between the two abstractors was calculated for selected variables collected on the treatment abstraction form. The kappa statistic could not be used for the assessment of reliability of the treatment data because of the sparseness of the data (i.e., small number of subjects included in the reliability study and large number of categories for some of the variables).

Univariate distributions by treatment groups of interest were examined (i.e., non-sterilizing surgery, alkylating agents, abdominal-pelvic radiation, alkylating agents plus abdominal-pelvic radiation and all other treatments). For categorical variables, unmatched 2xK tables were constructed and Chi-square statistics were calculated. Medians were examined for continuous variables such as age and year at diagnosis, years of follow-up, age at interview, age at menstruation and age at menopause. Descriptive analyses were done by using the computer program SAS (1990).

6.2 Analysis of reproductive outcomes:

The associations between the reproductive outcomes of interest and type of cancer treatment were assessed by estimating the risk ratios and odds ratios along with their 95%

confidence intervals. These estimates refer to the ratio of risk (or odds) of disease in a specific treatment group to the risk (or odds) in the comparison group (i.e. non-sterilizing surgery). Risk ratios (RR) and odds ratios (OR), along with their confidence intervals, were calculated with EGRET statistical software package (1988) or SAS (1990).

6.2.1 Analysis of menopause and infertility:

The risk ratio estimates of menopause were calculated using a stratified Cox-proportional hazards regression model. As the Cox-proportional hazards assumption was not realistic for all of the data, a stratified analysis according to 2 age groups (i.e., $<= 30$, >30) was used. This model fits different underlying hazard functions for individuals in the different strata (i.e., age at end of follow-up groups), but with common beta coefficients for the variables in the model. This analysis was chosen as subjects had variable entry points and lengths of time to end of follow-up. Time to event was calculated from age at which a woman started menstruating or age following treatment, whichever came later, to age at end of follow-up.

To assess one of the measures of infertility (relative fertility), and account for variable entry points and lengths of time to end of follow-up, a Cox-proportional hazards regression model was used to estimate the time to first pregnancy of women in the specific treatment groups of interest compared to women receiving non-sterilizing surgery. A time-dependent analysis showed that the hazard ratios did not change with age; therefore, the proportional hazards model of Cox could be used for this analysis. As age at marriage was unknown and as marriage rates did not differ between the treatment groups, time of follow-up was counted from age at menstruation or age at end of treatment, whichever came later, to age at first pregnancy, censoring on age at end of follow-up.

For both of the above mentioned analyses, age at end of follow-up was one of age at menopause, age at second primary cancer, age at relapse (after 5 years of diagnosis) or age at interview (which ever occurred first). Any menopausal events or pregnancies occurring after age at end of follow-up were excluded from any further analyses.

Odds ratio estimates for the other two measures of infertility (i.e., reported difficulty becoming pregnant and reported having been told they had a fertility problem) were estimated using unconditional logistic regression. A person-years analysis was not used for these two measures as even though subjects entered the cohort at different times, they were followed for an adequate length of time for these two outcomes to occur. The outcome "difficulty becoming pregnant for one year or more" only included subjects who were married or lived as married and therefore only included subjects who would have had the opportunity to try to become pregnant. As the women in this study were at least 18 years of age at interview, they could have had the opportunity to have been told by a physician they had a fertility problem.

The particular age used in the age-adjustment process differed according to whether the regression model used accounted for varying lengths of follow-up. Age at end of follow-up was utilized for analyses using Cox-proportional hazards model, which accounts for different lengths of follow-up. Age at interview was used for two of the measures of infertility (i.e., difficulty becoming pregnant and fertility problem) which did not consider length of follow-up.

To assess the effect of dose of radiotherapy to the pelvis or abdomen on risk of menopause or infertility, subjects who had received abdominal-pelvic radiation were divided into three subgroups according to dose. For the analysis of risk of menopause and time to first pregnancy, the low dose group comprised subjects who received less than 2,000 cGy (as other studies have shown that about 2,000 cGy are required to cause menopause and infertility in

young girls). Subjects receiving more than 2,000 cGy were divided into two groups according to whether their total dose of abdominal-pelvic radiation was above or below the median dose of 3,500 cGy.

To summarize subjects' exposure to chemotherapy with alkylating agents, an alkylating-agent score was developed based on the number of alkylating agents received by each patient and the number of months each drug was taken. The following drugs were included in this class: busulfan, carboplatin, carmustine, chlorambucil, cisplatine, cyclophospamide, dacarbazine, ifosfamide, lomustine, melphalan, nitrogen mustard and procarbazine. Each drug-month of use was given a score of 1. Thus, use of a single alkylating agent for six months was assigned a score of 6 and use of two alkylating agents for 6 months was assigned a score of 12, and so on. All the scores corresponding to the patient's treatment course were added together and rounded to the nearest integer. This method of calculating a score for the doses of alkylating agents received was obtained from a recent study which examined breast cancer and other second neoplasms after childhood Hodgkin's disease (Bhatia et al., 1996). The score is a measure of the amount of alkylating agent received and was calculated to assess the effect of subjects' exposure to alkylating agent on risk of menopause or infertility. For the analysis of risk of menopause and time to first pregnancy, subjects with scores up to the 50th percentile were considered to be in the low dose group (1-13), those with scores between the 50th and 75th percentile were considered to be in the medium dose group (14-21) and those with scores above the 75th percentile (>21) were considered to be in the high dose group.

Further subgroup analyses of interest were conducted. A stratified analysis by diagnosis before and after puberty (age at onset of menstruation) was examined to determine if risk of menopause and time to first pregnancy was influenced by time at diagnosis in relation to

menarche. In addition, the association between diagnostic group and risk of menopause and time to first pregnancy was examined by two different methods. In the first approach, the main analysis was repeated with the exclusion of subjects diagnosed with specific tumours that could result in an early menopause or reduced fertility (i.e., central nervous system tumours or gonadal and germ cell tumours). For the second approach, those subjects with a specified diagnosis were compared to all other survivors within treatment groups who received abdominal-pelvic radiation and/or chemotherapy with alkylating agents. This analysis was conducted within treatment groups so that the effect of treatment could be controlled for while examining the effect of diagnostic group. These subgroup analyses had reduced power to detect associations but may be helpful in generating hypotheses which could be tested in future studies.

6.2.2 Analysis of pregnancy outcomes:

Odds ratios for all of the adverse pregnancy outcomes were estimated using unconditional logistic regression and adjusted by age at pregnancy. A person-year analysis was not used as this analysis included only women who had had pregnancies. Any pregnancy outcomes after age at end of follow-up were excluded from this analysis. For the analysis of adverse pregnancy outcomes, information collected on common risk factors from the questionnaire were considered as potential confounders (Appendix N). The risk factors were identified before data collection to be related to the pregnancy outcomes of interest on the basis of substantive knowledge. As data were collected on a large number of risk factors, only those with a prevalence of greater than 5% in the study cohort were examined further. Risk factors of low prevalence were not considered because they would not be responsible for a significant proportion of the variation within or between treatment groups. Those risk factors whose distribution among the exposed

(i.e., survivors receiving alkylating agents, abdominal-pelvic radiation, alkylating agents plus abdominal-pelvic radiation and all other treatments) was not the same as the distribution among the unexposed (i.e., non-sterilizing surgery) (based on a chi-square test and a p-value of 0.15) were assessed separately for each pregnancy outcome.

A subset of confounders was chosen for each pregnancy outcome from the total list of risk factors eligible for control by using a backward elimination process and the data-based criterion (inclusion of the potential confounder changes the estimate of effect by more than 10%). A model that contained the treatment groups and all potential confounders (i.e. related to pregnancy outcome in literature and distribution of factor in exposed differed from the unexposed) was fitted for each pregnancy outcome. The potential confounder whose regression coefficient had the largest p-value was removed from the model, unless the p-value was less than 0.10 in which case the step-wise procedure stopped. The model with the remaining (K-1) variables was then fitted, and the odds ratio estimates for the treatment groups were compared between it and the model with all (K) variables. If the discrepancy between the odds ratio estimates for the treatment groups was less than 10%, the risk factor was permanently removed from the model and if the discrepancy was greater than 10% the risk factor was placed back into the model. For the next fitted model, again the potential confounder whose regression coefficient had the highest p-value was removed and the odds ratio estimates for the treatment groups were compared for a discrepancy of more than 10% between the models with and without the risk factor. The procedure continued until the model contained only those confounders that had p-values less than 0.10 and/or changed the risk estimates of the treatment groups by more than 10%.

To assess the effect of dose of radiotherapy to the pelvis or abdomen on risk of adverse pregnancy outcomes, subjects who had received abdominal-pelvic radiation were divided into two groups for the pregnancy analysis, with the low dose group comprising subjects whose total dose of abdominal-pelvic radiation was below or equal to the median ($<= 2,500$ cGy) and the high dose group comprising subjects whose total dose was above the median ($>2,500$ cGy).

To determine the effect of subjects' exposure to chemotherapy with alkylating agents to adverse pregnancy outcomes, subjects were divided into two groups based on their alkylating-agent score (based on the number of alkylating agents received by each patient and the number of months the drug was taken). Subjects with scores up to the 75th percentile were considered to be in the low dose group (1-20), and those above the 75th percentile (>20) were considered to be in the high dose group.

Since pregnancy outcomes for an individual are not independent, it was important to determine if the results obtained from the unconditional logistic regression would be altered significantly if the correlation between repeated observations was considered. Therefore, regression models for each of the pregnancy outcomes were adjusted to account for this lack of independence, using a generalized estimating equation approach (Zeger and Liang, 1986). The "working" correlation matrix chosen for this model assumed that the repeated observations for a subject were independent.

Chapter 3: RESULTS

1. Participation of cohort

Of the female childhood cancer survivors identified from the Ontario Cancer Registry (OCR) who met the study criteria, 1,581 had both a histologically confirmed malignancy and a physician who could be identified and sent a letter and consent form (Table 3.1). Consent forms were returned from physicians for 1,329 (84%) patients, consent to contact being granted for 1,108 eligible patients. Many of the physicians in this study contacted their patients and asked if they were interested in participating before giving consent. Physicians refused to give consent for 109 patients who were determined to be ineligible (26 deceased; 7 diagnosed after age 19; 58 non-malignant tumours; and 18 non-residents of Ontario at time of diagnosis), or were apparently eligible but were unaware of cancer diagnosis (N=20), living outside North America (N=17), too ill to participate (N=47) or not interested in participating (N=28). Some physicians were also unwilling to give consent for patients whom they had not seen for many years (N=252). For each of these subjects we attempted to identify a more current physician, but were unsuccessful. The rate of physician consent for patient contact was 75.3%, (calculated by dividing the number of consents to contact (N=1,108) by consents received for eligible patients (N=1,220) plus physician refusals (N=252)).

We contacted 1,108 of the study subjects by mail: 864 of these were interviewed. Only 46 subjects refused to participate: the majority being for health (N=17) or personal reasons (N=19). Some of the subjects (N=44) were found to be ineligible when contacted and 154 subjects were lost to follow-up. The subject interview response rate was 81.2% (calculated by dividing the number of subjects interviewed (N=864) by eligible subjects contacted (N=910) plus subjects lost to follow-up (N=154)).

We received 823 consent forms for treatment abstraction from the participating subjects. Only 27 subjects refused to give us consent to abstract detailed treatment information from their charts and 14 subjects were lost to follow-up after being interviewed. Treatment data were collected for 816 subjects. We were unable to collect treatment information for 7 subjects as their medical charts were unavailable (5 were destroyed in a fire and 2 could not be located). Of the 48 subjects whose treatment data were not abstracted, we were able to infer treatment further (i.e., non-sterilizing surgery (N=7), sterilizing surgery (N=1), radiation to abdomen (N=2), radiation above or below abdomen (N=2), chemotherapy including alkylating agents (N=2)) for 14 of them based on their site, histology, year and age at diagnosis. Therefore, there were 830 subjects with interview data and sufficient treatment data for analysis.

There were 564 subjects who were potentially eligible for this study but who did not participate for the reasons listed above (Table 3.1). These were compared to subjects who did participate with respect to age at diagnosis, age at start of study, year of diagnosis, years of follow-up (post-diagnosis), diagnostic group and primary source of OCR records (Tables 3.2 and 3.3).

Subjects who participated did not differ significantly by age at diagnosis from non-participating subjects (Chi-square=2.8, p=0.42, degrees of freedom (df) =3) (Table 3.2). However, participating and non-participating subjects did differ significantly by age at start of study (Chi-square=6.2, p=0.045, df=2), by year of diagnosis (Chi-square=14.4, p=0.001, df=2), and by years of follow-up (Chi-square=15.5, p=0.001, df=3). Non-participating subjects would have been older at start of study (37.9% being over 30 years of age) and more likely to have been diagnosed prior to 1975 (39.7% diagnosed between 1964 and 1974). As a result, the non-participating subjects had greater years of follow-up with 55.9% having survived

16 years or more post-diagnosis. These results reflect the difficulties encountered in identifying physicians and medical records of subjects diagnosed prior to 1975.

Participants and non-participants also differed by diagnostic groups, with participants being diagnosed most often with lymphomas (30%) and non-participants being diagnosed most often with epithelial neoplasms (26.1%) and central nervous system tumours (21.3%) (Table 3.3). Physicians of subjects with epithelial neoplasms would have been more difficult for us to locate as many of these subjects may have had only surgical treatment and therefore, been admitted to only one hospital. The resulting pathology reports for such patients may not have had the names of the family physicians. The elevated number of non-participants with central nervous system tumours reflects our decision to not contact subjects with central nervous system tumours who were reported as being "mentally challenged" by their physicians. Most (84.1%) of the OCR records used for confirmation of cancer diagnoses and identification of physicians for the participating group were obtained from the Regional Cancer Centres (RCCs) or Princess Margaret Hospital (PMH) as compared to 57.3% for the non-participating subjects. The identifying and medical information kept on the RCCs or PMH records permitted improved follow-up of subjects seen at these medical facilities.

2. **Quality of data**

2.1 Interviewer assessment of participant's responses:

Of the 864 subjects who participated in the study, 801 were telephone interviewed (8 requiring assistance by a parent) and 63 returned their questionnaire by mail. Telephone interviews required from 1 to 52 minutes, with 9 minutes being the average and 5 minutes being the most frequently occurring length of interview.

As in the pretest, the interviewer recorded her perception of the subject's comprehension before assistance, difficulty after interviewer assistance and the reliability of responses after the interview. Interviewers indicated that almost all respondents (94.4%) understood all items with no assistance. For the few subjects who had some difficulty understanding items (i.e., 4.7% having difficulty with <20% of the items and 0.9% with >20% of the items), most (95%) had none or few difficulties after interviewer assistance. Interviewers recorded that they felt responses were reliable for 97.1% of the questionnaires.

2.2 Validity of questionnaire data:

Data were collected from the vital statistics records in the Office of the Registrar General (ORG) of Ontario for a 5% (N=25) random sample of reported "normal birth weight" live births and for all reported low birth weight infants (47), stillbirths (13), infant deaths (2), and neonatal deaths (5) for respondents residing in Ontario at time of interview. Since the evaluation of the questionnaire data occurred as treatment data were being collected, some of the birth outcomes assessed may not have been included in the final analyses as a pregnancy may have occurred before treatment or there may have been no treatment data available for a subject.

Birth certificates were located for 20 (80%) of the 25 "normal birth weight" live births. There was exact agreement on the sex, date of birth, and birth order of these live births between the interview data collected and birth certificates for all of the subjects. There was exact agreement on duration of pregnancy (in weeks) for approximately 45% of the women. The mean difference was 0.35 weeks, with women reporting a shorter gestational period on the questionnaire. There was agreement on having a full term pregnancy (i.e., between 38-42 weeks) for all women. For 70% of the subjects, there was exact agreement between birth weight

reported during the interview and at time of delivery. The mean difference was about 16 grams for birth weight for those whose birth weight disagreed, with women reporting slightly higher birth weights during the interview (Table 3.4).

To determine the accuracy of reporting age at pregnancy from the interview, the agreement between age at pregnancy (within one year) from the interview and age at birth on the birth certificate was examined. There was exact agreement, so defined, for 95% of births. The mean difference was 0.75 years between age at pregnancy and age at birth, which reflects the difference in the age of women from the beginning to the end of pregnancy.

Of the 47 low birth weight infants (according to the interview), 41 (87%) birth certificates were located in the ORG. There was exact agreement for all of the subjects on the sex of the live birth and there were a few small discrepancies for date of birth and birth order between the interview data collected and birth certificates. There was disagreement on the birth date for 3 subjects with the difference being minimal for 2 subjects (within 1 year) and greater for one subject (2 years). This latter subject had reported both her second and third pregnancy as being in the same year although her ages at pregnancy differed; therefore, the year of birth for her second pregnancy was corrected in the study database to agree with her reported age for that pregnancy. One subject reported her low birth weight infant as being her first live birth when the birth certificate stated that it was her third live birth. All other information reported by this mother on the questionnaire matched the birth certificate exactly.

Exact agreement between the interview and birth certificate was 49% for duration of pregnancy, and 56% for birth weight. The mean difference was 0.83 weeks for duration of pregnancy with women reporting a slightly shorter gestational period on the questionnaire, the range of differences being 2 to 8 weeks. The mean difference was 57 grams for birth weight,

with women reporting slightly lower birth weights during the interview. Only three of the low birth weight infants were recorded as being of "normal" birth weight on their birth certificates, with the differences in birth weight being less than 500 grams. The birth weights of these three infants were corrected in the study database to reflect their status as not being low birth weight. However, these mothers will still be coded as having had a low birth weight infant and will be included in the pregnancy analysis as all three did have another child that was correctly recorded as being low birth weight. Exact agreement between age at pregnancy (within one year) from the interview and age at birth on the birth certificate was 95%. The mean difference was 0.44 years between age at pregnancy and age at birth, which reflects in part the difference in the age of women from the beginning to the end of pregnancy.

Of the 41 low birth weight infants whose certificates were examined, 11 were not independent in that they had one or more siblings who were also reported to be of low birth weight. Therefore, a re-analysis of the data was performed including either the first low birth weight infant or including a random sample of one of the low birth weight infants of women who reported more than one. Both of these re-analyses of the 30 subjects gave the same results as described above.

Of the 13 reported stillbirths, 11 (85%) stillbirth certificates were located in the ORG and reviewed. There was good agreement for 10 of the subjects (within one year) and a slight discrepancy for one subject (within 2 years) on the age of mother at time of stillbirth between the questionnaire data and the stillbirth certificate (results not shown).

Of the 5 neonatal deaths and 2 infant deaths identified from the questionnaires, 4 (57%) were located in the ORG and reviewed. There was exact agreement for all of the subjects on age

of infant at death, cause of death, and age of mother at death of child between the questionnaire and death certificate (results not shown).

Thus, it appears that selected pregnancy data from the questionnaire are generally accurate. The actual reasons for some of the birth or death certificates not being located in the ORG are unknown. Since a high percentage of the certificates were identified, likely explanations for those not located include: the birth or death outcome did not occur in Ontario; the child's last name at time of birth or death was not the same as the mother's; or the child was given up for adoption.

2.3 Reliability of treatment data:

The treatment data on a sample of 30 subjects (about 4%) were re-abstracted by a second abstractor. Data were compared within the following three treatment groups: surgical procedures, radiotherapy and chemotherapy (Table 3.5).

For the surgical procedures, there was exact agreement between the two abstractors for dates and type/site of surgery with the exception of a few discrepancies on type/site of surgery (Appendix O). There was disagreement on the code chosen for the site of surgery for two subjects, although both abstractors recorded the site of surgery in the identical words. Also, for three subjects minor surgeries such as small excisions or biopsies were recorded by one abstractor and not by the other; these discrepancies reflect different interpretations of instructions on whether minor surgeries should be included.

For radiotherapy treatment, there was exact agreement between the two abstractors for number of fractions and fields and end dates of radiotherapy. There were small discrepancies on the start dates of radiotherapy (all within 20 days) for two subjects, type of machine (coded

incorrectly) for three subjects and field size (all within 10 centimetres) for 2 subjects. There was disagreement on the code chosen for site of radiotherapy (Appendix P) for four subjects, although both abstractors recorded sites within the same anatomical area. For example, for the same subject one abstractor recorded site 5b (abdomen whole/partial) and the other recorded site 6b (paraaortic nodes and spleen). There was disagreement on total dose of radiotherapy (greater than 30 cGy) given for two subjects, with the difference being minimal for one subject (140 cGy) and greater for the other subject (2,265 cGy). This large discrepancy reflects the difficulty in interpreting medical records kept prior to 1975.

For chemotherapy treatment, there was exact agreement between the two abstractors on whether or not the drug was given in combination with other drugs and on the names of the drugs while there were small discrepancies on the start date (all within 21 days) for two subjects, the stop dates (all within one month) for four subjects and the route of administration (coded incorrectly) for one subject. There was disagreement on total drug dose (greater than 20 milligrams) for four subjects, with the difference being slight for three of these (between 75 and 177 milligrams) and larger for one subject (595 milligrams). The discrepancies on total dosage reflect differences in start/stop dates of chemotherapy recorded by the two abstractors and also reflect the difficulty in interpreting medical records kept prior to 1975.

Treatment data were re-abstracted for all of the discrepancies indicated between the two abstractors and the necessary corrections were made to the study database. The discrepancies between the two abstractors appeared to be random, with each abstractor responsible for a similar number of abstraction errors. From the re-abstraction study is appears that the treatment data are reliable with the exception of total dosage of radiotherapy or chemotherapy given prior to 1975. As a result, any treatment information that was collected from earlier medical records

was re-abstracted by a second abstractor. In addition, the treatment abstraction manual was revised with clarification of instructions regarding which codes to use and how to calculate actual radiation and chemotherapy dosage given versus proposed dosage.

3. **Results pertaining to participants**

3.1 Treatment groups:

Subjects with anti-cancer therapy data were classified into a treatment group according to what type of surgery (ie. sterilizing or non-sterilizing), radiation (i.e. abdominal-pelvic or non-abdominal-pelvic) or chemotherapy (i.e., alkylating agents or non-alkylating agents) they received. Subjects who were found to have had no anti-cancer therapy (N=3) were categorised into the non-sterilizing surgery group. Only treatment that occurred prior to menopause, before a second primary cancer or within the 5 years after diagnosis was included. Four subjects were excluded from any further analyses as they had had a second primary cancer before age at menstruation and therefore any reproductive outcomes of interest would have occurred after their second primary cancer. Of the remaining 826 subjects, 33 (4.0%) had never had a menstrual period (Table 3.6). A further 74 subjects either became menopausal before (N=4) or during (N=39) treatment, or were of unknown menopausal status at the end of treatment (N=31) (as they had been on birth control pills from time of diagnosis to time of interview). The remaining 719 subjects who were still menstruating after treatment were included in further analyses.

Subjects still menstruating following treatment differed by treatment received, age at diagnosis and diagnostic group from those who never menstruated (N=33) and from those who became menopausal during treatment (N=39) (Tables 3.7 and 3.8). Of the 33 subjects who had never had a menstrual period, most received abdominal-pelvic radiation alone (39.4%) or in

conjunction with alkylating agents (33.3%), were diagnosed prior to 9 years of age (75.8%) and had renal tumours (36.4%). Subjects who became menopausal during treatment because of sterilizing surgery were diagnosed most often between 15 and 19 years of age (81.8%) and diagnosed with gonadal and germ cell tumours (68.2%). Subjects who became menopausal during other forms of treatment were most likely to have had abdominal-pelvic radiation plus chemotherapy with alkylating agents (47.1%), were diagnosed between 15 and 19 years of age (70.6%) and were diagnosed with lymphoma (76.5%).

Table 3.9 shows the distribution of the survivors according to treatment group. Of the subjects classified (N=719), 162 (22.5%) received non-sterilizing surgery or no treatment, 150 (20.9%) received chemotherapy with alkylating agents, 154 (21.4%) received abdominal-pelvic radiation, 71 (9.9%) received chemotherapy with alkylating agents and abdominal-pelvic radiation and 182 (25.3%) received chemotherapy other than alkylating agents and/or radiation above or below the abdomen. For the subjects who were classified as having abdominal-pelvic radiation (N=225), the total dose of radiotherapy to the pelvis or abdomen ranged from 29 to 6,500 cGy, with a median dose of 3,000 cGy. Of the subjects who were categorized as having received chemotherapy with alkylating agents (N=221), all but one had the necessary information (i.e. duration of use of alkylating agents) to assign them an alkylating agent score (based on the number of alkylating agents received and the number of months each drug was taken). The scores ranged from 1 to 110, with 13 as the median.

About half of the survivors in this cohort were 15-19 years of age at diagnosis and a third were diagnosed between 1981 and 1988 (Table 3.10). The treatment groups differed significantly by age at diagnosis, (Chi-square=73.3, p=0.001, df=12) and by year of diagnosis (Chi-square=81.6, p=0.001, df=8). Survivors who received chemotherapy with alkylating agents

were older at diagnosis (56% being 15 to 19 years of age) and more likely to have been diagnosed after 1980 (58% being diagnosed between 1981 to 1988). In contrast, survivors who received abdominal-pelvic radiation were younger at diagnosis (26% being less than 5 years of age), and more likely to have been diagnosed between 1964 to 1974 (48%). Subjects who received both chemotherapy with alkylating agents and abdominal-pelvic radiation were intermediate to those receiving either of these treatments alone. These results reflect the predominant diagnostic groups in these treatment groups and criteria for entry into the cohort.

The most common diagnostic groups for the survivors were lymphomas (28.8%), epithelial neoplasms (17.9%), central nervous system tumours (12.8%) and leukemia (11.1%). Of the subjects diagnosed with lymphoma, the majority (81.2%) had Hodgkin's disease and of those diagnosed with epithelial neoplasms most had carcinoma of the thyroid (55.0%) or melanoma (28.7%). The treatment groups also differed by type of cancer diagnosis (Table 3.11). Subjects receiving chemotherapy with alkylating agents either alone or in combination with abdominal-pelvic radiation were more often diagnosed with tumours that occur in children over 10 years of age, namely lymphomas and bone tumours. Subjects who received abdominal-pelvic radiation were more likely to be diagnosed with tumours that occur in children under 4 years of age, namely renal tumours (24.0%) and central nervous system tumours (17.5%). Those in the comparison group (non-sterilizing surgery) were most often diagnosed with epithelial neoplasms (53.7%) and those receiving other treatments were most likely to be diagnosed with lymphoma (26.4%) or leukemia (23.1%).

3.2 Physical and socio-demographic characteristics:

The survivors were between 18 and 49 years of age at time of interview, with a median age of 28. The age at interview distribution was positively skewed reflecting a young group of survivors (approximately 60% were less than 30 years of age). The distribution of age at interview differs significantly (Chi-square=20.7, p=0.001, df=4) by treatment received, with those who received alkylating agents being younger (72% between 18 to 29 years of age) than those survivors who received any other treatments (Table 3.12). Approximately 75% of the survivors had more then 10 years of follow-up (from age at diagnosis to interview). The treatment groups also differed significantly by years of follow-up (Chi-square=84.0, p=0.001, df=12). Survivors who received chemotherapy with alkylating agents have the fewest years of follow-up with only 26.6% having survived 16 years or more post-diagnosis. In contrast, survivors who received abdominal-pelvic radiation have the greatest years of follow-up, with 63.6% having survived 16 years or more post-diagnosis.

Most of the survivors reported their racial background as being white (94.7%), had a post-secondary education (67.7%), and had been married or living with someone (61.2%) (Table 3.13). Education level was derived from information reported in two questions, namely current enrolment status and highest level of education. The median body mass index (calculated by dividing the subject's weight (kg) by her height (meters) squared) was 21.8, with a positively skewed distribution reflecting survivors with a low body mass index (62.6% had a body mass of less than or equal to the average in this cohort). Distributions for race, education, marital status and body mass index were examined for the treatment groups. The distributions of subjects by racial group (Chi-square=4.69, p=0.32, df=4), education (Chi-square=0.80,

p=0.94, df=4), marital status (Chi-square=6.8, p=0.15, df=4), and body mass index (Chi-square=7.87, p=0.10, df=4) did not differ significantly by cancer treatment received.

3.3 Menopause:

Of the subjects who had had a menstrual period following treatment, there were 63 (8.8%) who were classified as being menopausal (Table 3.14). Of these, 54 stated they had stopped having periods, and 9 had been on hormone supplements (Premarin or Provera) for more than 5 years and were still taking them at time of interview. Among those post menopausal, 29 (46%) stated that their periods stopped due to surgery and 34 (54%) stated that their periods stopped for other reasons (i.e., treatment, naturally, an eating disorder or chemically induced).

The median age at starting menstruation for subjects still menstruating following treatment was 13 years and was similar across the treatment groups. The proportion of subjects who were post-menopausal differed significantly (Chi-square=11.8, p=0.019, df=4) by treatment received. This preliminary analysis does not take into account different periods of follow-up. Those survivors who received abdominal-pelvic radiation or abdominal-pelvic radiation and alkylating agents were more likely to be post-menopausal (13% and 15.5% respectively) than those who received alkylating agents alone (4.7%), other treatments (6.6%) or non-sterilizing surgery (8.0%). Those subjects who received non-sterilizing surgery were more likely to have had a surgical versus non-surgical menopause (69.2% of those who were menopausal), while those who received alkylating agents and abdominal-pelvic radiation were more likely to have had a non-surgical menopause (90.9% of those who were menopausal).

Age at menopause was determined as the age the subject reported they stopped having periods. For subjects who were classified as being menopausal but did not state they had stopped having periods (i.e. were still taking Premarin and Provera), age at menopause was taken to be age started taking hormonal supplements. Amongst those who had experienced menopause, the median age at menopause was 24 and differed between the treatment groups, with those who received both alkylating agents and abdominal-pelvic radiation (median age at menopause was 22) and those who received other treatments (median age at menopause was 19) having the lowest ages at menopause.

Risk ratio estimates (RR), adjusted by age at end of follow-up, were calculated to determine whether risk of menopause differs between treatment groups (Table 3.15). A significantly elevated risk was seen in women who received both abdominal-pelvic radiation plus chemotherapy with alkylating agents (RR=2.58; 95% CI 1.14-5.80) compared to the non-sterilizing surgery group. For women who received abdominal-pelvic radiation only the risk was elevated but was not significantly different from the comparison group. There was no increase in risk for women treated with chemotherapy with alkylating agents alone or other treatments.

Risk ratios were also calculated to determine if the risk of surgical or non-surgical menopause differs by treatment group. The risk of surgical menopause did not differ between the treatment groups, except for those who received other treatments, although the confidence intervals were wide. However, women treated with alkylating agents plus abdominal-pelvic radiation had a significantly elevated risk of non-surgical menopause (RR=5.96; 95%CI 1.86-19.1) and women treated with abdominal-pelvic radiation had a non-significant elevated risk.

To assess whether risk of menopause differs by age at diagnosis in relation to age at puberty, risk ratios were estimated separately for subjects diagnosed before and after puberty

(Table 3.16). Women diagnosed before puberty had a non-significant increased risk of menopause when treated with abdominal-pelvic radiation alone or in conjunction with alkylating agents. No subjects were treated before puberty with chemotherapy with alkylating agents and post-menopausal to evaluate the risk in this subgroup.

Women diagnosed after puberty had a significantly elevated risk of menopause when treated with abdominal-pelvic radiation plus alkylating agents compared to the surgery group (RR=3.23; 95%CI 1.33-7.82). Although, this risk ratio estimate was not significantly different from the risk ratio estimate for those diagnosed before puberty. About 63% of the women treated after puberty with abdominal-pelvic radiation and alkylating agents were menopausal as a result of their treatment, 87% of them receiving a total abdominal-pelvic radiation dose of greater than 2,000 cGy and 63% of them receiving a total amount of alkylating agents that was above the median for the survivors in this study (i.e., an alkylating agent score above 13).

To determine whether risk of menopause is affected by total dose of abdominal-pelvic radiation or by alkylating-agent score (cumulative number of months alkylating agents taken), age-adjusted risk ratios were calculated and compared to the non-sterilizing surgery group (Table 3.17). There was evidence that the risk of menopause increased significantly with increasing dose of abdominal-pelvic radiation (Test for trend, Chi-square=11.2, p=0.0008). Women in the highest dose group (>=3,500 cGy) had a significantly elevated risk of menopause (RR=3.27; 95%CI 1.57-6.81). The risk of menopause also increased significantly by alkylating-agent score (Test for trend, Chi-square=4.31, p=0.038). Women with an alkylating-agent score of 1-13 had no increase in risk, those with a score of 14-21 had a non-significant 2-fold increased risk, and those with a score of greater than 21 had a significantly elevated risk of menopause (RR=3.08; 95%CI 1.15-8.21).

Subjects diagnosed with central nervous system tumours or gonadal and germ cell tumours may experience menopause as a result of their diagnosis rather than their treatment. Therefore, a re-analysis of the data (which included 41 menopausal events) was performed with the exclusion of these two diagnostic groups (Table 3.18). The significantly elevated risk of menopause seen in women who received both abdominal-pelvic radiation plus chemotherapy with alkylating agents (RR=2.49; 95%CI 1.02-6.06) was repeated in this re-analysis.

The effect of diagnostic group on the risk of menopause was also evaluated by determining the risk for those subjects with a specified diagnosis compared to all other subjects, within a particular treatment group (Table 3.19). The risk of menopause for survivors diagnosed with lymphoma did not differ significantly to that for other survivors within the same treatment groups, for those treated with chemotherapy with alkylating agents or for those treated with abdominal-pelvic radiation alone. However, subjects diagnosed with lymphoma and treated with chemotherapy with alkylating agents plus abdominal-pelvic radiation had a non-significant 3-fold increased risk of menopause compared to those diagnosed with other tumours within this treatment group. There were not enough subjects to similarly evaluate the risk for any other diagnostic group.

3.4 Infertility:

Of the women who were exposed to pregnancy (that is married or lived as married and menstruating after the age of 18), 57 (15.5%) stated that they had difficulty becoming pregnant for one year or more (Table 3.20). Of these women, 36 (63.2%) had primary infertility and 21 (36.8%) had secondary infertility (the women had previously conceived, but were subsequently unable to conceive). Of the 36 subjects who had primary infertility, 18 went on to have one

pregnancy or more. Of the 34 pregnancies reported from subjects with primary infertility, there were 8 spontaneous abortions, 1 perinatal death, 4 low birth weight infants and 4 infants had congenital anomalies. Of the 21 subjects who had secondary infertility, 12 went on to have one or more pregnancy. Of the 15 pregnancies reported, there were 4 spontaneous abortions, 1 perinatal death, 3 low birth weight infants and 1 infant with a congenital anomaly. The proportion of subjects who were infertile for at least one year did not differ significantly by treatment group (Chi-square=2.68, p=0.61, df=4).

As the group of survivors in this study comprised predominantly young women, the true fertility status of many may be unknown because they have not yet tried to become pregnant. Therefore, infertility was also examined by whether a subject had ever been told by a physician she had a fertility problem (note that this need not imply a diagnosed problem, but could be speculation only). Of subjects who were still menstruating, 131 (18.2%) had been told they had or might have had a fertility problem and/or were on medication to increase fertility. The proportion of subjects who had been told they had a fertility problem did differ significantly by treatment group (Chi-square=40.3, p=0.001, df=4). Those survivors receiving chemotherapy with alkylating agents and abdominal-pelvic radiation were most likely to have been told they had a fertility problem (39.4%).

Percentage ever pregnant is also an indication of fertility. In this cohort 340 (47.3%) of the subjects had had one or more pregnancy. The proportion of subjects ever pregnant differed significantly between treatment groups (Chi-square=9.7, p=0.046, df=4). Those survivors receiving non-sterilizing surgery were the most likely to have had one or more pregnancies (57.4%) while those receiving abdominal-pelvic radiation alone (42.2%) or in conjunction with alkylating agents (40.8%) were the least likely.

Odds ratio estimates (OR) were calculated separately for two measures of infertility: difficulty becoming pregnant for at least one year and having reported a fertility problem, adjusted by age at interview (Table 3.21). Women treated with abdominal-pelvic radiation had greater than 2-fold increased risk of having difficulty becoming pregnant for at least one year relative to the non-sterilizing surgery group. Women treated with alkylating agents and/or abdominal-pelvic radiation had a significant increased risk of having been told they had a fertility problem compared to the surgery group, with the risk being about 9-fold in those receiving both types of treatment. Women receiving other treatments did not have an increased risk of being infertile for at least one year or of having a fertility problem in comparison to the surgery group.

An analysis of time to first pregnancy (relative fertility) was conducted, with and without censoring on age at menopause, while controlling for marital status and age at end of follow-up (Table 3.22). The data were censored on age at menopause to account for differences in risk and age at menopause between treatment groups. However, the data were also analyzed without censoring on age at menopause thereby allowing premature menopause to be included as a cause of infertility. When follow-up is censored on age at menopause, treatment with abdominal-pelvic radiation was associated with a non-significant fertility deficit of 23%. There was no apparent effect of alkylating agents administered alone or in combination with abdominal-pelvic radiation or other treatments. However, when the data were not censored by age at menopause, women treated with abdominal-pelvic radiation alone or in conjunction with alkylating agents had a non-significant fertility deficit of about 24% and 21% respectively.

To assess whether relative fertility differs by age at diagnosis in relation to age at puberty, relative fertility was examined separately for subjects whose diagnosis was before and after puberty. For women diagnosed prior to puberty, results were similar regardless of

censoring on age at menopause or not. Women diagnosed before puberty did not have a fertility deficit when treated with abdominal-pelvic radiation and/or alkylating agents as compared to the surgery group (Table 3.23). In fact, women treated with both abdominal-pelvic radiation and alkylating agents had about a 2-fold increased chance of becoming pregnant.

Women diagnosed after puberty had a 16% fertility deficit when treated with abdominal-pelvic radiation alone and had no fertility deficit when treated with alkylating agents alone or in conjunction with abdominal-pelvic radiation as compared to the surgery group (censoring on age at menopause) (Table 3.24). However, women treated with abdominal-pelvic radiation alone or in conjunction with alkylating agents (not censoring on age at menopause) had non-significant fertility deficits of 22% and 29% respectively.

To determine whether relative fertility changes with total dose of radiation directed at the abdomen and/or pelvis or with alkylating-agent score (cumulative number of months alkylating agents taken), age-adjusted risks were calculated and compared to the non-sterilizing surgery group (Table 3.25). There was evidence that the fertility deficit rises significantly with increasing dose of abdominal-pelvic radiation (Test for trend, Chi-square=5.75, p=0.017). Women treated with 2,000-3,499 cGy had a fertility deficit of about 25% (censoring or not censoring on age at menopause) and those in the highest dose group (> =3,500 cGy) had a 32% fertility deficit when censoring on age at menopause and a significant fertility deficit of 43% when not censoring on age at menopause. The fertility deficit also rose with increasing alkylating-agent score (Test for trend, Chi-square=6.73, p=0.41). Women with alkylating-agent scores of 1-13 or 14-21 had no fertility deficit, while those with scores greater than 21 had a fertility deficit of 22% when censoring on age at menopause and 33% when not censoring on age at menopause.

Subjects diagnosed with central nervous tumours or gonadal and germ cell tumours may experience infertility as a result of their diagnosis rather than their treatment. Therefore, a re-analysis of the data was performed with the exclusion of these two diagnostic groups (Table 3.26). The fertility deficits observed in women who received abdominal-pelvic radiation (censoring by age at menopause) and for women treated with abdominal-pelvic radiation alone or in conjunction with alkylating agents (not censoring on age at menopause) were repeated in this re-analysis.

The effect of diagnostic group on the risk of infertility was also evaluated by determining the risk for those subjects with a specified diagnosis compared to all other subjects, within a particular treatment group (Table 3.27). There was no fertility deficit for survivors diagnosed with lymphoma when compared to other survivors among those treated with chemotherapy with alkylating agents or among those who received abdominal-pelvic radiation alone. However, women diagnosed with lymphoma and treated with alkylating agents plus abdominal-pelvic radiation had a non-significant 41% fertility deficit compared to other survivors in that treatment group. Too few subjects were diagnosed in any of the other tumour groups and treated with chemotherapy with alkylating agents plus abdominal-pelvic radiation, to evaluate the risk for any other subgroup. Other than lymphoma, the next two most common diagnostic groups for each of the other two treatment groups were examined. For those diagnosed with bone tumours or leukemia and treated with alkylating agents there was no fertility deficit in comparison to other survivors in the treatment group. The same result was seen for women diagnosed with central nervous tumours and treated with abdominal-pelvic radiation. However, women diagnosed with renal tumours and treated with abdominal-pelvic radiation had a significant fertility deficit of 54% when compared to other survivors in this treatment group.

3.5 Pregnancy Outcomes:

Of the 696 singleton pregnancies that occurred following cancer treatment, there were 469 live births, 112 spontaneous abortions, 69 therapeutic abortions, 5 ectopic pregnancies, 17 perinatal deaths, and 28 currently pregnant women (i.e., who were pregnant at time of interview). Of the live births, there were 32 low birth weight infants and 22 children with congenital defects. The proportion of pregnancies resulting in spontaneous abortion or perinatal death did not differ significantly by treatment group (Table 3.28). However, the proportion of live births resulting in a low birth weight infant (Chi-square=13.3, p=0.01, df=4) or an infant with a congenital anomaly (Chi-square=10.3, p=0.04, df=4) did differ significantly by treatment group. Live births of women treated with abdominal-pelvic radiation were more likely to result in a low birth weight infant (16.0%) and those in women receiving non-sterilizing surgery were most likely to result in an infant with a congenital anomaly (9.5%).

The association between type of cancer treatment and having an adverse reproductive outcome was evaluated, while adjusting for age at pregnancy and other potential confounders (Appendix N) (Table 3.29). This analysis was conducted using pregnancy as the unit of analysis. Any treatment that occurred prior to a pregnancy determined which treatment group was associated with that particular pregnancy. The odds ratio of having a spontaneous abortion was similar across the treatment groups. The index of spontaneous abortions used in this analysis includes all pregnancies in the denominator except for ectopic pregnancies and therapeutic abortions. If therapeutic abortions are included in the denominator, the odds ratio estimates for spontaneous abortions do not change by more than 10% and are also similar across treatment groups (results not shown). The risk of having a perinatal death was elevated by about 2.5 times for women treated with abdominal-pelvic radiation alone or in combination with alkylating

agents, but was not significantly different from the comparison group. Survivors receiving abdominal-pelvic radiation were significantly more likely to have a low birth weight infant (OR=3.64; 95%CI 1.33-9.96) compared to those receiving surgery. The risk of having a premature low-birth weight infant was also increased in women receiving abdominal-pelvic radiation (OR=3.29; 95%CI 0.97-11.1). Women in all of the treatment groups had a decreased risk of having an infant with a congenital anomaly compared to the non-sterilizing surgery group, although only significantly for those with "other treatments".

To assess whether risk of having an adverse reproductive outcome changed with total dose of radiation directed at the abdomen and/or pelvis, risks were calculated and compared to the non-sterilizing surgery group (Table 3.30). As there were fewer subjects (N=152) in the analysis of pregnancies, subjects who received abdominal-pelvic radiation were divided into only two dose groups. The odds ratio estimates of spontaneous abortion and congenital anomaly did not rise with increasing dose of abdominal-pelvic radiation. The odds ratio estimates of perinatal deaths and low birth weight infants increased with dose of radiotherapy directed to the pelvis or abdomen. For perinatal deaths the odds ratio was 1.96 (95%CI 0.27-14.3) for the low dose group (< =2,500 cGy) and 4.33 (95%CI 0.74-25.4) for the high dose group (>2,500 cGy). The odds ratio for low birth weight infants was 2.10 (95%CI 0.58-7.66) for the low dose group and 3.49 (95%CI 1.26-9.72) for the high dose group. A similar result was obtained for premature low birth weight infants.

The effect of increasing alkylating-agent score on the risk of adverse pregnancy outcomes could only be examined for spontaneous abortions, because of the small number of other pregnancy outcomes within the subgroup of women receiving chemotherapy with alkylating agents (N=164). The risk of having a spontaneous abortion rose with increasing alkylating-agent

score. Women with alkylating-agent scores of 1-20 did not have an increased risk of having a spontaneous abortion (OR=0.80; 95%CI 0.44-1.47), while those with scores greater than 20 had an increased risk of having a spontaneous abortion (OR=1.58; 95%CI 0.78-3.48) (results not shown).

We could not examine the association between diagnostic group and risk of adverse pregnancy outcomes as a result of the small number of pregnancies in particular diagnostic groups within treatment groups.

As pregnancies from the same individual are not independent, a re-analysis of the pregnancy data was conducted using a generalized estimating equation approach (GEE) which adjusts for the correlation between repeated pregnancy outcomes for the same subject. For all of the pregnancy outcomes the beta coefficients using unconditional logistic regression were similar to those obtained using GEE. The standard errors were slightly different using GEE, however the differences were such that they would not have changed the significance level of any of the pregnancy outcomes of interest.

TABLE 3.1: Participation of female childhood cancer survivors (1964-1988)

Characteristic	No. of Survivors
Survivors with a histological confirmed malignancy and an identified physician for contact	**1,581**
Ineligible	-109
Unaware of cancer diagnosis	-20*
Subject ill, unwilling to participate, outside country	-92*
Physician refusal	-252*
Survivors with physician consent who were sent a questionnaire	**1,108**
Ineligible	-44
Subject unwilling to participate	-46*
Lost to follow-up	-154*
Survivors interviewed	**864**
Survivors with interview and treatment data	**830**

*** N=564, not known to be ineligible (assumed eligible)**

TABLE 3.2: Difference in age at diagnosis, age at start of study, year of diagnosis and year of follow-up between participants and non-participants

Characteristics	Participants (N=864)	Non-Participants (N=564)
Age at diagnosis (%)		
0-4	14.1	14.7
5-9	13.4	16.1
10-14	21.5	22.0
15-19	51.0	47.2
Age at start of study (%)		
18-24	34.3	30.0
25-30	34.0	32.1
31-48	31.7	37.9
Year of diagnosis (%)		
1964-74	33.3	39.7
1975-80	30.8	33.9
1981-88	35.9	26.4
Years of follow-up (%)		
5-10	27.3	18.6
11-15	25.0	25.5
16-20	25.4	28.9
21-30	22.3	27.0

TABLE 3.3: Difference in diagnostic groups and location of medical charts between participants and non-participants

Characteristic	Participants (N=864)		Non-participants (N=564)	
	No.	%	No.	%
Diagnostic group				
Lymphoma	259	30.0	70	12.4
Epithelial neoplasm	142	16.4	147	26.1
CNS tumour	104	12.1	120	21.3
Leukemia	90	10.4	62	11.0
Soft-tissue sarcoma	64	7.4	32	5.7
Renal tumour	59	6.8	27	4.8
Gonadal and germ cell	52	6.0	46	8.2
Bone tumour	51	5.9	30	5.3
Other*	43	5.0	30	5.3
Primary source of OCR record				
RCC	478	55.3	200	35.5
PMH	249	28.8	123	21.8
All other hospitals	137	15.9	241	42.7

***Other includes sympathetic nervous system tumours, retinoblastoma, hepatic tumours, and other and unspecified malignant neoplasms.**

TABLE 3.4: Differences in selected pregnancy data between the questionnaire and the birth certificate

Characteristic	Normal birth weight(> =2500 grams) (N=20 infants)		Low birth weight (<2500 grams) (N=41 infants)	
	Mean Difference	95%CI*	Mean Difference	95%CI*
Duration of pregnancy (weeks)	-0.35	-2.7 to 2.0	-0.83	-4.3 to 2.6
Birth weight (grams)	15.9	-106.3 to 130.1	-57.3	-474.4 to 359.8
Age at pregnancy/ birth** (years)	-0.75	-1.8 to 0.33	-0.44	-1.8 to 0.87

*** CI, confidence interval.**

**** Age at pregnancy was recorded on the questionnaire and age at birth was recorded on the birth certificate.**

TABLE 3.5: Reliability of treatment data

Treatment	Agreement (%)
Surgery (N=15)	
Site*	87
Date**	100
Radiotherapy (N=22)	
Site*	82
Date began**	91
Date ended**	100
Number of fractions/fields	100
Type of machine	86
Dose (within 30 cGy)	91
Chemotherapy (N=10)	
Drug	100
Route of administration	90
Date began**	80
Date ended**	60
Dose (within 20 milligrams)	60

*** See appendices O and P for categories.**
****Agreement for date includes day, month, and year.**

TABLE 3.6: Distribution of menstrual history among survivors

Characteristic	Survivors	
	Number	(%)
Ever had a menstrual period (N=826)*		
Yes	793	96.0
No	33	4.0
Menopausal status (N=793)		
Menopausal before treatment	4	0.5
Menopausal during treatment	39	4.9
Menstruating following treatment	719	90.7
Unknown	31	3.9

*** Excludes subjects who had a second primary cancer before menstruation (N=4).**

TABLE 3.7: Difference in treatment received and age at diagnosis by menopausal status*

Characteristic	Never menstruated (N=33)	Menopausal during treatment: Sterilizing surgery (N=22)	Menopausal during treatment: Other (N=17)	Menopausal status unknown (N=31)	Still menstruating (N=719)
Treatment (%) **					
Sterilizing surgery	15.2	100.0	0.0	0.0	0.0
Surgery	0.0	0.0	0.0	29.0	22.5
CT with AA	6.1	0.0	23.5	22.6	20.9
Abd-pelvic rad	39.4	0.0	29.4	22.6	21.4
CT with AA and abd-pelvic rad	33.3	0.0	47.1	12.9	9.9
Other treatments	6.1	0.0	0.0	12.9	25.3
Age at diagnosis (%)					
0-4	36.4	0.0	0.0	0.0	14.2
5-9	39.4	9.1	0.0	0.0	13.5
10-14	15.2	9.1	29.4	6.5	23.2
15-19	9.1	81.8	70.6	93.6	49.1

*** Excludes subjects menopausal before treatment and subjects who had a second primary cancer before menstruation (N=8).**
**** Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal pelvic radiation.**

TABLE 3.8: Difference in diagnostic group by menopausal status*

Diagnostic group (%)	Never menstruated (N=33)	Menopausal during treatment: Sterilizing surgery (N=22)	Other (N=17)	Menopausal status unknown (N=31)	Still menstruating (N=719)
Lymphoma	15.2	0.0	76.5	54.8	28.8
Epithelial neoplasm	0.0	4.6	5.9	19.4	17.9
CNS tumour	6.1	0.0	0.0	16.1	12.8
Leukemia	9.1	0.0	0.0	0.0	11.1
Soft-tissue sarcoma	6.1	18.2	5.9	3.2	7.4
Bone tumour	0.0	0.0	5.9	0.0	6.5
Renal tumour	36.4	0.0	0.0	0.0	6.4
Gonadal and germ cell	18.2	68.2	5.9	3.2	4.0
Other**	9.1	9.1	0.0	3.2	5.0

*** Exclude subjects menopausal before treatment and subjects who had a second primary cancer before menstruation (N=8).**
****Other includes sympathetic nervous system tumours, retinoblastoma, hepatic tumours, and other and unspecified malignant neoplasms.**

TABLE 3.9: Distribution of cancer therapy received (N=719*)

Treatment	NUMBER (%)
Non-sterilizing surgery or no treatment**	162 (22.5)
Chemotherapy with alkylating agents	150 (20.9)
Abdominal-pelvic radiation	154 (21.4)
Chemotherapy with alkylating agents and abdominal-pelvic radiation	71 (9.9)
Radiation (above or below abdomen) and/or chemotherapy other than alkylating agents***	182 (25.3)

*** Includes subjects who were menstruating following treatment.**
**** Referred to as "Non-sterilizing surgery" in subsequent tables.**
***** Referred to as "Other Treatments" in subsequent tables.**

TABLE 3.10: Age at diagnosis and year of diagnosis according to treatment groups

Characteristic	Treatment received*					
	All survivors (N=719)	Surgery (N=162)	CT with AA (N=150)	Abd-pelvic rad (N=154)	CT with AA and abd-pelvic rad (N=71)	Other treatments (N=182)
Age at diagnosis (%)						
0-4	14.2	4.9	6.0	26.0	16.9	18.1
5-9	13.5	7.4	8.7	16.2	11.3	21.4
10-14	23.2	22.2	29.3	18.2	23.9	23.1
15-19	49.1	65.4	56.0	39.6	47.9	37.4
Year of diagnosis (%)						
1964-74	34.1	27.8	12.7	48.1	33.8	45.6
1975-80	30.9	33.3	29.3	22.1	39.4	34.1
1981-88	35.0	38.9	58.0	29.9	26.8	20.3

*** Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal pelvic radiation.**

TABLE 3.11: Diagnostic groups according to treatment received

Diagnostic groups (%)	Treatment received*					
	All survivors (N=719)	Surgery (N=162)	CT with AA (N=150)	Abd-pelvic rad (N=154)	CT with AA and abd-pelvic rad (N=71)	Other treatments (N=182)
Lymphoma	28.8	1.2	49.3	25.3	62.0	26.4
Epithelial neoplasm	17.9	53.7	2.0	15.6	0.0	8.2
CNS tumour	12.8	17.9	2.0	17.5	2.8	17.0
Leukemia	11.1	0.0	15.3	4.6	11.3	23.1
Soft-tissue sarcoma	7.4	11.1	10.7	2.6	5.6	6.0
Bone tumour	6.5	1.9	13.3	2.0	8.5	8.2
Renal tumour	6.4	1.9	0.0	24.0	1.4	2.8
Gonadal and germ cell	4.0	7.4	6.0	2.6	1.4	1.7
Other**	5.0	4.9	1.3	5.8	7.0	6.6

*** Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal pelvic radiation.**

****Other includes sympathetic nervous system tumours, retinoblastoma, hepatic tumours, and other and unspecified malignant neoplasms.**

TABLE 3.12: Distribution of age at interview and years of follow-up by treatment received

Characteristic	Treatment received*					
	All survivors (N=719)	Surgery (N=162)	CT with AA (N=150)	Abd-pelvic rad (N=154)	CT with AA and abd-pelvic rad (N=71)	Other treatments (N=182)
Age at interview (%)						
18-29	57.3	48.8	72.0	59.1	56.3	51.7
30-49	42.7	51.2	28.0	40.9	43.7	48.3
Years of follow-up (%)						
5-10	25.2	27.8	44.7	20.1	18.3	13.7
11-15	24.9	29.0	28.7	16.2	23.9	25.8
16-20	26.3	23.5	20.0	29.2	38.0	26.9
21-30	23.6	19.8	6.6	34.4	19.7	33.5

*** Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal pelvic radiation.**

TABLE 3.13: Distribution of selected physical and socio-demographic characteristics among participants by treatment received

Characteristics	Treatment received*					
	All Survivors (N=719)	Surgery (N=162)	CT with AA (N=150)	Abd-pelvic rad (N=154)	CT with AA and abd-pelvic rad (N=71)	Other treatments (N=182)
Race (%)						
White	94.7	96.3	90.6	95.5	95.8	95.1
Other	5.3	3.7	8.7	4.5	4.2	4.9
Missing			0.7			
Education (%)						
< = High school	32.3	33.3	32.0	30.5	29.6	34.1
> High school	67.7	66.7	67.3	69.5	70.4	65.9
Missing			0.7			
Marital status (%)						
Never married	38.8	30.2	41.3	39.6	40.9	42.9
Married/lived as married	61.2	69.8	58.7	60.4	59.1	57.1
Body mass index (%)						
14-22	64.0	62.4	65.3	69.5	70.4	56.0
23-45	36.0	37.6	34.0	30.5	29.6	42.9
Missing			0.7			1.1

*** Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal pelvic radiation.**

TABLE 3.14: Distribution of menstrual history among participants by treatment received

Characteristic	Treatment received*					
	All Survivors (N=719)	Surgery (N=162)	CT with AA (N=150)	Abd-pelvic rad (N=154)	CT with AA and abd-pelvic rad (N=71)	Other treatment (N=182)
Median age at menstruation	13.0	12.5	13.0	13.0	13.0	12.0
Menopause** (no.(%))						
Yes	63 (8.8)	13 (8.0)	7 (4.7)	20 (13.0)	11 (15.5)	12 (6.6)
No	656 (91.2)	149 (92.0)	143 (95.3)	134 (87.0)	60 (84.5)	170 (93.4)
Type of menopause** (no.(%))						
Surgical	29 (46.0)	9 (69.2)	5 (71.4)	10 (50.0)	1 (9.1)	4 (33.3)
Non-surgical	34 (54.0)	4 (30.8)	2 (28.6)	10 (50.0)	10 (90.9)	8 (66.7)
Median age at menopause**	24.0	31.0	33.0	29.5	22.0	19.0

*** Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal-pelvic radiation.**

**** Type of menopause and median age at menopause among post-menopausal survivors.**

TABLE 3.15: Age-adjusted risk ratios (RR) and 95% confidence intervals (95%CI) by type of menopause according to treatment received

Treatment*	Type of menopause		
	All (N=719)	Surgical (N=685)	Non-surgical (N=690)
Surgery			
RR	1.00	1.00	1.00
n	13	9	4
CT with AA			
RR (95%CI)	0.77 (0.30-1.97)	1.80 (0.56-5.82)	0.46 (0.08-2.54)
n	7	5	2
Abd-pelvic rad			
RR (95%CI)	1.62 (0.80-3.28)	1.21 (0.49-3.03)	2.55 (0.79-8.19)
n	20	10	10
CT with AA and abd-pelvic rad			
RR (95%CI)	2.58 (1.14-5.80)**	0.46 (0.06-3.67)	5.96 (1.86-19.1)**
n	11	1	10
Other treatments			
RR (95%CI)	0.75 (0.34-1.65)	0.30 (0.09-0.98)***	1.90 (0.57-6.30)
n	12	4	8

*** Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; Abd-pelvic rad, abdominal-pelvic radiation; n denotes the number of menopausal events.**
****p=0.022 (for all), p=0.003 (for non-surgical).**
*****p=0.047.**

TABLE 3.16: Age-adjusted risk ratios (RR) and 95% confidence intervals (95%CI) for menopause according to age at diagnosis in relation to age at puberty

Treatment*	Age at diagnosis	
	Before puberty (N=269)	After puberty (N=450)
Surgery		
RR	1.00	1.00
n	2	11
CT with AA		
RR (95%CI)	---	0.86 (0.33-2.27)
n	0	7
Abd-pelvic rad		
RR (95%CI)	1.90 (0.39-9.29)	1.87 (0.83-4.25)
n	7	13
CT with AA and abd-pelvic rad		
RR (95%CI)	2.16 (0.29-16.1)	3.23 (1.33-7.82)**
n	2	9
Other treatments		
RR (95% CI)	0.81 (0.15-4.44)	1.00 (0.40-2.52)
n	4	8

*** Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; Abd-pelvic rad, abdominal-pelvic radiation; n denotes number of menopausal events.**

**** p=0.01.**

TABLE 3.17: Age-adjusted risk ratios (RR) and 95% confidence intervals (95%CI) for menopause by total dose of radiation to pelvis and/or abdomen and by alkylating agent score

Treatment*	n	RR (95%CI)
Non-sterilizing surgery (N=162)	13	1.00
Abdominal-pelvic radiation (cGy) (N=225)		
< 2,000	4	1.02 (0.29-3.59)
2,000-3,499	9	1.36 (0.57-3.25)
>=3,500	18	3.27 (1.57-6.81)**
Alkylating agent score*** (N=220)		
1-13	6	1.13 (0.41-3.09)
14-21	4	1.90 (0.52-6.92)
>21	8	3.08 (1.15-8.21)**

*** 71 subjects had both abdominal-pelvic radiation and chemotherapy with alkylating agents.**
****p=0.002 (for abdominal-pelvic radiation), p=0.025 (for alkylating agent score).**
***** Alkylating agent score denotes the cumulative number of months all alkylating agents were taken.**

TABLE 3.18: Age-adjusted risk ratios (RR) and 95% confidence intervals (95%CI) for menopause for survivors whose diagnosis does not include CNS tumours or gonadal and germ cell tumours and all survivors

Treatment*	Selected survivors** (N=598)	All survivors (N=719)
Surgery		
RR	1.00	1.00
n	10	13
CT with AA		
RR (95%CI)	0.79 (0.28-2.26)	0.77 (0.30-1.97)
n	6	7
Abd-pelvic rad		
RR (95%CI)	0.97 (0.40-2.36)	1.62 (0.80-3.28)
n	10	20
CT with AA and abd-pelvic rad		
RR (95%CI)	2.49 (1.02-6.06)***	2.58 (1.14-5.80)***
n	10	11
Other treatments		
RR (95%CI)	0.36 (0.12-1.06)	0.75 (0.34-1.65)
n	5	12

*** Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; Abd-pelvic rad, abdominal-pelvic radiation; n denotes the number of menopausal events.**

**** Excludes survivors diagnosed with CNS tumours or gonadal and germ cell tumours.**

*****p=0.045 (for selected survivors), p=0.022 (for all survivors).**

TABLE 3.19: Age-adjusted risk ratios* (RR) and 95% confidence intervals (95%CI) for menopause for survivors within selected treatment group according to diagnostic group

Diagnostic group	Treatment**		
	CT with AA (N=150)	Abd-pelvic rad (N=154)	CT with AA and abd-pelvic rad (N=71)
All other tumours			
RR	1.00	1.00	1.00
n	3	14	4
Lymphoma			
RR (95%CI)	0.87 (0.15-5.22)	1.08 (0.40-2.91)	2.85 (0.54-14.9)
n	4	6	7

*** Adjusted for alkylating agent score for CT with AA group; adjusted for abdominal-pelvic radiation dose for abd-pelvic rad group; adjusted for abdominal-pelvic radiation dose and alkylating agent score for CT with AA and abd-pelvic rad group.**

**** Abd-pelvic rad indicates abdominal-pelvic radiation; and CT with AA, chemotherapy with alkylating agents, n denotes number of menopausal events.**

Table 3.20: Distribution of fertility outcomes among participants by treatment received

Characteristic	Treatment received*					
	All Survivors	Surgery	CT with AA	Abd-pelvic rad	CT with AA and abd-pelvic rad	Other Treatments
Difficulty becoming pregnant** (no.(%))						
Yes	57 (15.5)	15 (13.8)	8 (11.9)	16 (20.8)	4 (18.2)	14 (15.1)
No	311 (84.5)	94 (86.2)	59 (88.1)	61 (79.2)	18 (81.8)	79 (84.9)
Fertility problem (no.(%))						
Yes	131 (18.2)	15 (9.3)	35 (23.3)	33 (21.4)	28 (39.4)	20 (11.0)
No	588 (81.8)	147 (90.7)	115 (76.7)	121 (78.6)	43 (60.6)	162 (89.0)
Pregnant (no.(%))						
Ever	340 (47.3)	93 (57.4)	68 (45.3)	65 (42.2)	29 (40.8)	85 (46.7)
Never	379 (52.7)	69 (42.6)	82 (54.7)	89 (57.8)	42 (59.2)	97 (53.3)

***Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal-pelvic radiation.**

****Includes married or lived as married subjects only, yes indicates tried to become pregnant for one year or more but was unable to.**

TABLE 3.21: Age-adjusted odds ratios and 95% confidence intervals of fertility outcomes by treatment received.

Treatment*	Difficulty becoming pregnant** (N=368)	Fertility problem (N=719)
Surgery	1.00	1.00
CT with AA	1.35 (0.51-3.54)	4.95 (2.47-9.93)***
Abd-pelvic rad	2.17 (0.96-4.91)	3.39 (1.71-6.71)***
CT with AA and abd-pelvic rad	1.68 (0.48-5.86)	9.10 (4.27-19.38)***
Other treatments	1.15 (0.51-2.60)	1.32 (0.64-2.73)

***Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and abd-pelvic rad, abdominal-pelvic radiation.**
****Includes married or lived as married subjects only, time period for trying to become pregnant was one year or more.**
*****$p < 0.001$.**

TABLE 3.22: Adjusted relative fertility and 95% confidence intervals by treatment received

Treatment*	Relative fertility**	
	Censoring on age at menopause	Not censoring on age at menopause
Surgery	1.00	1.00
CT with AA	1.06 (0.77-1.46)	1.09 (0.80-1.51)
Abd-pelvic rad	0.77 (0.56-1.06)	0.76 (0.55-1.04)
CT with AA and abd-pelvic rad	1.01 (0.66-1.53)	0.79 (0.52-1.21)
Other treatments	1.02 (0.76-1.37)	1.00 (0.75-1.34)

***Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal-pelvic radiation.**
****Relative fertility indicates the rate of first pregnancy in the survivors as compared with the non-sterilizing surgery group, adjustment for marital status and age at end of follow-up.**

TABLE 3.23: Adjusted relative fertility and 95% confidence intervals by treatment received for survivors whose diagnosis was before puberty (N=269)

Treatment*	Relative fertility**	
	Censoring on age at menopause	Not censoring on age at menopause
Surgery	1.00	1.00
CT with AA	1.16 (0.46-2.93)	1.25 (0.49-3.20)
Abd-pelvic rad	1.48 (0.70-3.16)	1.51 (0.71-3.23)
CT with AA and abd-pelvic rad	1.81 (0.72-4.58)	1.88 (0.74-4.76)
Other treatments	1.37 (0.63-2.98)	1.40 (0.64-3.04)

***Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal-pelvic radiation.**
****Relative fertility indicates the rate of first pregnancy in the survivors as compared with the non-sterilizing surgery group, adjustment for marital status and age at end of follow-up.**

TABLE 3.24: Adjusted relative fertility and 95% confidence intervals by treatment received for survivors whose diagnosis was after puberty (N=450)

Treatment*	Relative fertility**	
	Censoring on age at menopause	Not censoring on age at menopause
Surgery	1.00	1.00
CT with AA	1.03 (0.74-1.45)	1.04 (0.74-1.46)
Abd-pelvic rad	0.84 (0.57-1.24)	0.78 (0.53-1.16)
CT with AA and abd-pelvic rad	1.02 (0.62-1.65)	0.71 (0.44-1.16)
Other treatments	1.28 (0.92-1.78)	1.17 (0.85-1.63)

***Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal-pelvic radiation.**
****Relative fertility indicates the rate of first pregnancy in the survivors as compared with the non-sterilizing surgery group, adjustment for marital status and age at end of follow-up.**

TABLE 3.25: Adjusted relative fertility and 95% confidence intervals by total dose of radiation to pelvis and/or abdomen and by alkylating agent score

Treatment	Relative fertility*	
	Censoring on age at menopause	Not censoring on age at menopause
Non-sterilizing surgery (N=162)	1.00	1.00
Abdominal-pelvic radiation (cGy)(N=225)		
< 2,000	1.42 (0.86-2.36)	1.50 (0.91-2.49)
2,000-3,499	0.78 (0.54-1.13)	0.76 (0.52-1.11)
> =3,500	0.68 (0.45-1.03)	0.57 (0.38-0.86)**
Alkylating agent score*** (N=220)		
1-13	1.04 (0.74-1.47)	0.98 (0.69-1.38)
14-21	1.34 (0.83-2.15)	1.42 (0.88-2.29)
>21	0.78 (0.47-1.28)	0.67 (0.41-1.10)

***Relative fertility indicates the rate of first pregnancy in the survivors as compared with the non-sterilizing surgery group, after adjustment for marital status and age at follow-up. 71 subjects had both abdominal-pelvic radiation and chemotherapy with alkylating agents.**
**** p=0.008 for > = 3,500 cGy.**
***** Alkylating agent score denotes the cumulative number of months all alkylating agents were taken.**

TABLE 3.26: Adjusted relative fertility and 95% confidence intervals by treatment received for survivors with the exception of those diagnosed with CNS tumours and gonadal and germ cell tumours (N=598)

Treatment*	Relative fertility**	
	Censoring on age at menopause	Not censoring on age at menopause
Surgery	1.00	1.00
CT with AA	1.04 (0.74-1.47)	1.08 (0.76-1.52)
Abd-pelvic rad	0.78 (0.55-1.11)	0.79 (0.55-1.12)
CT with AA and abd-pelvic rad	0.94 (0.61-1.47)	0.75 (0.48-1.16)
Other treatments	1.09 (0.79-1.51)	1.09 (0.79-1.51)

***Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal-pelvic radiation.**
****Relative fertility indicates the rate of first pregnancy in the survivors as compared with the non-sterilizing surgery group, adjustment for marital status and age at end of follow-up.**

TABLE 3.27: Adjusted relative fertility* and 95% confidence intervals by diagnostic group within treatment groups

	Treatment**		
Diagnostic group	Abd-pelvic rad (N=152)	CT with AA (N=150)	CT with AA and abd-pelvic rad (N=71)
Lymphoma	1.52 (0.81-2.83)	1.24 (0.76-2.02)	0.59 (0.15-2.29)
Renal tumour	0.46*** (0.24-0.88)		
CNS tumour	1.05 (0.42-2.60)		
Leukemia		0.91 (0.39-2.10)	
Bone tumour		1.05 (0.54-2.05)	

***Relative fertility indicates the rate of first pregnancy in the survivors in a particular diagnostic group as compared with survivors with all other tumours, within a specified treatment group, censoring on age at menopause.**

**** Abd-pelvic rad indicates abdominal-pelvic radiation; and CT with AA, chemotherapy with alkylating agents. Adjustment, adjusted for marital status and age at end of follow-up for all treatment groups; adjusted for abdominal-pelvic radiation dose for abd-pelvic rad group, adjusted for alkylating agent score for CT with AA group and adjusted for abdominal-pelvic radiation dose and alkylating agent score for CT with AA and abd-pelvic rad group.**

*****p=0.019.**

Table 3.28: Distribution of adverse pregnancy outcomes by treatment received

Pregnancy outcomes**	Treatment received*					
	All survivors	Surgery	CT with AA	Abd-pelvic rad	CT with AA and abd-pelvic rad	Other treatments
Spontaneous abortions (no.(%))						
Yes	112 (18.9)	35 (21.2)	25 (22.1)	19 (19.6)	9 (17.0)	24 (14.5)
No	482 (81.1)	130 (78.8)	88 (77.9)	78 (80.4)	44 (83.0)	142 (85.5)
Perinatal deaths (no.(%))						
Yes	17 (3.5)	4 (3.1)	1 (1.1)	4 (5.1)	2 (4.6)	6 (4.2)
No	465 (96.5)	126 (96.9)	87 (98.9)	74 (94.9)	42 (95.4)	136 (95.8)
Low birth weight infants (no.(%))						
Yes	32 (6.8)	7 (5.6)	2 (2.3)	12 (16.0)	3 (7.1)	8 (5.8)
No	437 (93.2)	119 (94.4)	85 (97.7)	63 (84.0)	39 (92.9)	131 (94.2)
Congenital anomalies (no.(%))						
Yes	22 (4.7)	12 (9.5)	2 (2.3)	4 (5.3)	1 (2.4)	3 (2.2)
No	447 (95.3)	114 (90.5)	85 (97.7)	71 (94.7)	41 (97.6)	136 (97.8)

***Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal-pelvic radiation.**

**** Percentages indicate all pregnancies excluding therapeutic abortions or ectopic pregnancies for spontaneous abortion, total births (live plus stillbirths) for perinatal deaths; live births for low birth weight infants and infants with congenital anomalies.**

Table 3.29: Adjusted odds ratios and 95% confidence intervals for adverse pregnancy outcomes by treatment received

Pregnancy outcomes*	Treatment received**				
	Surgery	CT with AA	Abd-pelvic rad	CT with AA and abd-pelvic rad	Other treatments
Spontaneous abortions	1.00	1.06 (0.59-1.90)	0.91 (0.48-1.70)	0.76 (0.34-1.72)	0.63 (0.35-1.11)
Perinatal deaths	1.00	0.38 (0.04-3.80)	2.41 (0.50-11.5)	2.62 (0.40-17.2)	1.83 (0.44-7.62)
Low birth weight infants					
All	1.00	0.49 (0.10-2.47)	3.64*** (1.33-9.96)	1.13 (0.27-4.70)	1.16 (0.40-3.30)
Premature	1.00	--	3.29 (0.97-11.1)	1.78 (0.39-8.08)	1.50 (0.47-4.77)
Congenital anomalies	1.00	0.23 (0.05-1.12)	0.45 (0.12-1.70)	0.27 (0.03-2.16)	0.22*** (0.06-0.82)

***Adjusted, adjusted by age at pregnancy for all pregnancy outcomes; adjusted by maternal smoking during pregnancy and paternal occupational exposure to agricultural chemicals for perinatal deaths; adjusted by number of cigarettes smoked during pregnancy for low birth weight infants; adjusted by maternal endocrine condition and paternal occupational exposure to organic solvents for congenital anomalies.**

**** Surgery indicates non-sterilizing surgery; CT with AA, chemotherapy with alkylating agents; and Abd-pelvic rad, abdominal-pelvic radiation.**

*****p=0.012 for low birth weight (all), p=0.023 for congenital anomalies.**

TABLE 3.30: Adjusted odds ratios (OR) and 95% confidence intervals (95%CI) for pregnancy outcomes by total dose of radiation to pelvis and/or abdomen (N=316 pregnancies)

Pregnancy outcome*		Abdominal-pelvic radiation dose	
	Surgery	Low Dose (< =2,500 cGy)	High Dose (> 2,500 cGy)
Spontaneous abortion			
OR (95%CI)	1.0	1.31 (0.68-2.53)	0.48 (0.21-1.11)
n	35	20	8
Perinatal death			
OR (95%CI)	1.0	1.96 (0.27-14.3)	4.33 (0.74-25.4)
n	4	2	4
Low birth weight			
All			
OR (95%CI)	1.0	2.10 (0.58-7.66)	3.49 (1.26-9.72)**
n	7	5	10
Premature			
OR (95%CI)	1.0	2.69 (0.52-13.9)	3.65 (1.10-12.1)***
n	5	3	7
Congenital anomaly			
OR (95%CI)	1.0	0.47 (0.09-2.20)	0.35 (0.07-1.70)
n	12	3	2

***Adjusted, adjusted by age at pregnancy for all pregnancy outcomes; adjusted by maternal smoking during pregnancy and paternal occupational exposure to agricultural chemicals for perinatal deaths; adjusted by maternal endocrine condition and paternal occupational exposure to organic solvents for congenital anomalies; n denotes the number of pregnancy outcomes.**

****p=0.017.**

*****p=0.035.**

Chapter 4: DISCUSSION

1. Summary

The primary objectives of this study were to determine whether female childhood cancer survivors treated with chemotherapy with alkylating agents and/or abdominal-pelvic radiation were at an increased risk of menopause, infertility, or an adverse pregnancy outcome as compared to those treated with non-sterilizing surgery. Results indicated that survivors who received both chemotherapy with alkylating agents and abdominal-pelvic radiation were more likely to be post-menopausal than those receiving surgery alone, especially if they were diagnosed after puberty. In addition, the risk of menopause was increased for women diagnosed with lymphoma and treated with alkylating agents and abdominal-pelvic radiation compared to women diagnosed with other tumours in this treatment group. Women who received abdominal-pelvic radiation were at a slightly increased risk of being infertile, measured as "having tried unsuccessfully to become pregnant for more than one year" or as time to first pregnancy. Fertility deficits were greater in women diagnosed after puberty than in women diagnosed before puberty. Of the diagnostic groups examined, survivors diagnosed with lymphomas and treated with alkylating agents plus abdominal-pelvic radiation and those diagnosed with renal tumours and treated with abdominal-pelvic radiation had elevated fertility deficits when compared to survivors diagnosed with other tumours in those treatment groups. There was evidence that the risks of menopause and infertility increased with increasing dose of abdominal-pelvic radiation and by amount of alkylating agents received.

There was no evidence of an increased risk of having a spontaneous abortion or an infant with a birth defect for women treated with abdominal-pelvic radiation and/or alkylating agents compared to the surgery group. However, survivors receiving abdominal-pelvic radiation were

significantly more likely to have a low birth weight infant and were at increased risk of having a premature low birth weight infant or having an infant who died perinatally. The risk of having an infant with a perinatal death or low birth weight (all and premature) increased with dose of radiotherapy directed to the pelvis or abdomen.

In the remainder of this chapter, the results of this study are compared with previous findings reported in the literature by treatment received, by age at diagnosis relative to age at puberty, by abdominal-pelvic radiation dose or amount of chemotherapy with alkylating agents received and by diagnostic group. The risk of adverse reproductive outcomes in female childhood cancer survivors are also compared to the risk in the general population. Then the advantages and limitations of this study and methodological issues and potential biases are discussed. The chapter ends with recommendations for further research and final conclusions.

2. Comparison of study results to literature

2.1 Effects of cancer treatment:

Radiation to the gonads and chemotherapy, especially with alkylating agents, can result in ovarian failure, germ cell destruction, and amenorrhea (Shalet et al., 1976; Stillman et al., 1981; Himelstein-Braw et al., 1977; Rivkees and Crawford, 1988). Although recovery may occur, the possible depletion of germ cells may lead to early menopause. In this study there is evidence of a significantly elevated risk of menopause for women who received both chemotherapy with alkylating agents plus abdominal-pelvic radiation (RR=2.58; 95% CI 1.14-5.80) and a non-significant elevation in risk for women who received abdominal-pelvic radiation (RR=1.62; 95%CI 0.80-3.28) compared to the non-sterilizing surgery group (Table 3.15). The only other study that examined the risk of early menopause following treatment for childhood

cancer was the multi-centre NCI study (Byrne et al., 1992). In the NCI study, 5-year survivors of childhood cancer who were still menstruating and diagnosed with cancer before age 20 were compared to sibling controls. The NCI study also found a significantly increased risk of early menopause (RR=4.1) among those survivors diagnosed with cancer between the ages of 13 and 19 and treated with radiation below the diaphragm in combination with alkylating agents (Byrne et al., 1990). Women treated with surgery only (i.e., non-sterilizing) had the same risk of menopause as sibling controls. Therefore, our use of the surgery group as the comparison group seems justified. In general, the results of the NCI study are similar to those from our study although the two studies do comprise females treated during different time periods. Females in the NCI cohort were diagnosed prior to 1975 and were treated primarily with radiotherapy or surgery and were most likely not exposed to multi-agent chemotherapy. In contrast, the majority (65.0%) of females in our study were diagnosed after 1975 and were treated with more aggressive and multi-agent chemotherapy. Although it was assumed that women treated with alkylating agents alone in our study may have had an increased risk of menopause, this was not observed (RR=0.77; 95%CI 0.30-1.97).

Endocrine status and histopathological studies have shown that cancer treatment could be a cause of infertility in female survivors, owing to elevated levels of gonadotropin hormones and genetic damage or depletion of ovarian germ cells (Stillman et al., 1981; Nicosia et al., 1985). In this study, women treated with abdominal-pelvic radiation had greater than twice the risk of having tried unsuccessfully to become pregnant for at least one year relative to the non-sterilizing surgery group (Table 3.21). In addition, women treated with chemotherapy with alkylating agents and/or abdominal-pelvic radiation had a significantly increased risk of having been told by a physician that they had a fertility problem compared to the surgery group, with

the risk being about 9-fold in those receiving both types of treatment. In our study, about 55% of the 131 subjects were told they might have or had a fertility problem as a result of their cancer or cancer treatment.

Data on a sub-sample of the NCI cohort found no significant differences between survivors and sibling controls according to two criteria of infertility: unsuccessful attempts to become pregnant for a year or more; and a definite diagnosis of a fertility problem (Teeter et al., 1988). However, these results are for male and female survivors combined and does not examine the risk for the different treatment groups as was effected in our study. As in our study, the survivors in the NCI study were more likely to have been advised by a physician to avoid a pregnancy, especially if they had been treated with combined radiation and chemotherapy.

In our study, fertility was also analyzed by comparing time to first pregnancy in the treatment groups of interest to that in the referent group (i.e., relative fertility). Treatment with abdominal-pelvic radiation was associated with a relative fertility of 0.77 (censoring on age at menopause) which was not significantly different from one (Table 3.22). There was no apparent effect of alkylating agents administered alone or in combination with abdominal-pelvic radiation or of other treatments. However, when the data are not censored by age at menopause (thereby allowing premature menopause to be included as a cause of infertility), women treated with abdominal-pelvic radiation alone or in conjunction with alkylating agents had a non-significant fertility deficit of 24% and 21% respectively. The ability to conceive a child following cancer in childhood was examined in the NCI cohort study (Byrne et al., 1987). This study also found that the women were more affected by radiation below the diaphragm (relative fertility, 0.78) than by alkylating agents (relative fertility, 1.02). Women treated with surgery only had almost

no fertility deficit. This finding also justifies our use of the non-sterilizing surgery group for comparison.

For survivors who are fertile after cancer therapy, there are concerns about their ability to have full-term pregnancies and normal children. Conceptions following treatment reflect survival of germ cells exposed to mutagens (i.e. ionizing radiation and chemotherapeutic agents). Adverse reproductive outcomes might reflect mutagenicity, direct germ cell toxicity, or an altered ability to maintain normal gestation (Mulvihill et al., 1987).

There is no evidence of an increased risk of having a spontaneous abortion for women treated with abdominal-pelvic radiation and/or alkylating agents compared to the surgery group (Table 3.29). Other studies have also found no evidence of an increased risk of spontaneous abortion among survivors of all childhood cancers (Li and Jaffe 1974; Li et al., 1979; Blatt et al., 1980). However, a British study found that abdominally-radiated female survivors of Wilms' tumour had an increased risk of spontaneous abortion compared to cancer patients who did not receive abdominal radiation, although the excess did not reach statistical significance at the 5% level (Hawkins and Smith, 1989). The excess of miscarriages (17% versus 9%) observed among all pregnancies seen in the females in this study was entirely explained by abdominal or gonadal radiation received and was not as a result of a germ cell mutation (Hawkins, 1991).

In our study, survivors receiving abdominal-pelvic radiation were significantly more likely to have a low birth weight infant (OR=3.64) and were at an increased risk of having a premature low-birth weight infant (OR=3.29) or an infant with a perinatal death (OR=2.41) compared to those receiving surgery (Table 3.29). Various other investigations have examined the effects of radiation on pregnancy outcomes, most notably that given as treatment for Wilms' tumour. All of these studies found an excess of 17% to 45% of low birth weight infants (less

than 2500 grams at birth) among live births of women who had received abdominal radiation (Green et al., 1982; Li et al., 1987; Byrne et al., 1988; Hawkins and Smith, 1989) compared to 3% or less among live births of non-radiated females. Of the low birth weight infants in these studies, 70 to 100% were delivered prematurely and 23 to 30% died neonatally. Radiation therapy directed to the abdomen or pelvis for any tumour other than Wilms' tumour also resulted in excess rates of perinatal and neonatal mortality and low birth weight infants when compared to population rates (Garber et al., 1990).

Possible explanations for the findings of low birth weight in these studies has been discussed in a recent commentary (Smith and Hawkins, 1989). This paper concluded that the impaired birth weight is most likely not indicative of a germ cell mutation but instead a result of radiation-induced somatic damage to the women's abdominopelvic structures (uterine vascular insufficiency or fibrosis) as well as genito-urinary malformations associated with the Wilms' tumour complex. The adverse pregnancy outcomes seen in women receiving abdominal-pelvic radiation seem to be associated with premature delivery. These infants seem to develop at a normal rate but are delivered prematurely and consequently have an increased risk of being of low-birth weight or of dying perinatally.

Women in all of the treatment groups had a decreased risk of having an infant with a congenital anomaly compared to the non-sterilizing surgery group (Table 3.29). Previous studies have not found an increased risk of birth defects in the offspring of cancer survivors (Hawkins, 1991; Dodds et al., 1993; Mulvihill and Byrne, 1992). Recent investigations which examined children and adolescents treated with mutagenic chemotherapeutic agents other than alkylating agents and survivors of acute lymphoblastic leukemia also did not find an increase risk of

congenital anomalies in the children of these cancer survivors (Green et al., 1991; Kenney et al., 1996).

There are some possible explanations for not observing an increased risk of congenital anomalies in female childhood cancer survivors (Dodds et al., 1993). Firstly, cancer patients who have received potentially mutagenic therapy may be more likely to undergo prenatal screening and consequently may have a higher rate of therapeutic abortions than the general population or in our study those survivors who only had surgery. However this was not the case in our study, as the rate of reported therapeutic abortions did not differ by treatment received. Secondly, survivors of childhood cancers who received potentially mutagenic therapy may have reduced fertility, and increased rates of stillbirths and spontaneous abortions which would therefore decrease their likelihood of having live born offspring. In our study, women who were treated with abdominal-pelvic radiation did have increased risks of infertility and of having an infant with a perinatal death (which includes stillbirths). However, there was no difference in the risk of spontaneous abortion in the treatment groups. Also, the women who had pregnancies (N=340) in this study received chemotherapy with alkylating agents and/or abdominal-pelvic radiation at lower doses than our study cohort as a whole (i.e., all survivors who were menstruating following treatment (N=719). Germ cell mutation might also be revealed by a difference in the male-female ratio between treatment groups. Data from the present study did not show a significant difference between the sex-ratio for live births among the treatment groups of interest and the non-sterilizing surgery group (results not shown).

2.2 Effects of age at diagnosis:

Reproductive potential is related to age at treatment: the younger the patient, the larger the reserve of oocytes remaining after treatment to re-establish a normal ovulatory state. For those receiving radiotherapy, the size of the dose required to produce gonadal impairment is related to age at treatment which relates to the number of oocytes present (Lushbaugh and Casarett, 1976). For those receiving chemotherapy, prepubertal ovaries, not yet under cyclic hormonal control (Lentz et al., 1977; Parra et al., 1978; Watson et al., 1986), may be more resistant than postpubertal gonads to damage by alkylating agents (Kumar et al., 1972; Chapman et al., 1979).

In this study, the risks of menopause and infertility were examined separately for subjects diagnosed before and after puberty. It was expected that the risks of menopause and infertility would be increased in women diagnosed after puberty more than in women diagnosed before puberty. As anticipated, women diagnosed before puberty did not have a significantly increased risk of menopause or a fertility deficit when treated with abdominal-pelvic radiation alone or in conjunction with alkylating agents as compared to the surgery group. However, women diagnosed after puberty and treated with abdominal-pelvic radiation plus alkylating agents had a significantly elevated risk of menopause compared to the surgery group (RR=3.23; 95%CI 1.33-7.82) (Table 3.16). Women diagnosed after puberty had a 16% fertility deficit when treated with abdominal-pelvic radiation and no fertility deficit when treated with alkylating agents alone or in conjunction with abdominal-pelvic radiation as compared to the surgery group in the analysis censoring on age at menopause (Table 3.24). However, women treated post-puberty with abdominal-pelvic radiation alone or in conjunction with alkylating agents had non-significant fertility deficits of 22% to 29% respectively, when censoring on age at menopause was not done.

Aside from the biological explanation that prepubertal ovaries not under cyclical control may be more resistant to anti-tumour therapy, another possible explanation for the reduced risk of menopause or infertility in women diagnosed prior to puberty could be explained by selection bias into the study and then into the analysis (Byrne et al., 1992). Women diagnosed before puberty had to have reached 18 years of age and still be menstruating to be included in the analysis. This study did show that treatment before puberty affects ovarian function. Subjects who had never had a menstrual period were diagnosed primarily prior to 9 years of age (75.8%), most of them (72.7%) receiving abdominal-pelvic radiation alone or in conjunction with alkylating agents.

2.3 Effects according to dose of abdominal-pelvic radiation:

For girls and young women (in their twenties and thirties) a total dose of about 2,000 cGy is required to produce gonadal impairment and sterility (Lushbaugh and Casarett, 1976). The site of radiotherapy is also important, with a higher percentage of women experiencing ovarian failure if they received whole-abdominal radiation (Shalet et al., 1976; Stillman et al., 1981), or scatter dose to their abdomen from spinal radiation (Livesey and Brook, 1988; Hamre et al., 1987) or total body radiation (Sanders et al., 1988). In our study, there was evidence that the risks of menopause and infertility increased significantly with increasing dose of abdominal-pelvic radiation. Women in the highest dose group ($>=$3,500 cGy) had a significantly elevated risk of menopause (RR=3.27; 95%CI 1.57-6.81), a 32% fertility deficit when censoring was done on age at menopause and a significant fertility deficit of 43% when there was no censoring on age at menopause (Tables 3.17 and 3.25).

There was no evidence of an increased risk of spontaneous abortion or congenital anomaly with rising dose of abdominal-pelvic radiation. However, the risk of perinatal deaths and low birth weight infants (all and premature) increased with increasing dose of radiotherapy directed to the pelvis or abdomen (Table 3.30). For perinatal deaths and low birth weight infants the increase was about 2-fold from the low to high dose group. To our knowledge, our study has been the only one that has examined the risks of adverse pregnancy outcomes among female cancer survivors by total dose of radiation directed at the abdomen or pelvis.

2.4 Effects according to dose of chemotherapy with alkylating agents:

The effects of chemotherapy on female ovarian failure are also dose dependent (Chapman et al., 1979; Rivkees and Crawford, 1988; Barton and Waxman, 1990). The nature of the chemotherapy is also significant, with alkylating agents most commonly associated with persistent infertility. Alkylating agents such as cyclophosphamide have been found to be more gonadotoxic than non-alkylating agents such as doxorubicin (Ahmed et al., 1983; Barton and Waxman, 1990). Girls treated with alkylating agents may have pathological or clinical evidence of ovarian failure (Himelstein-Braw et al., 1978; Nicosia et al., 1985). In this study we examined the effects of amount of alkylating agent received on risks of menopause and infertility by developing an alkylating agent score. This score was based on the number of alkylating agents received by each patient and the number of months each drug was taken.

The risk of menopause significantly increased and the fertility deficit increased by alkylating-agent score. Women in the highest dose group (ie., a score of greater than 21) had a significantly elevated risk of menopause (RR=3.08; 95%CI 1.15-8.21) and had a fertility

deficit of 22% with censoring on age at menopause and 33% with no censoring on age at menopause, when compared to the surgery group (Tables 3.17 and 3.25).

We could not examine the effect of increasing alkylating-agent score on the risk of adverse pregnancy outcomes, except for spontaneous abortions, because of the small numbers of pregnancy outcomes within the subgroup of women receiving chemotherapy with alkylating agents. The risk of spontaneous abortions did increase with increasing alkylating-agent score, although the increased odds ratio (OR=1.58) in the high dose group did not reach statistical significance at the 5% level. Several reports have found no excess of adverse pregnancy outcomes among patients who completed moderate to high dose single agent or combination chemotherapy before conception. These studies found no excess of fetal or neonatal deaths, stillbirths, spontaneous abortions and number of birth defects in offspring (Li and Jaffe 1974; Li et al., 1979; Blatt et al., 1980; Hall and Green, 1983).

2.5 Effects of diagnostic group:

For survivors of childhood cancer the risk of adverse reproductive outcomes may result from their diagnosis (i.e., the effects of the tumour on behavioural patterns or structural damage to reproductive organs or germ cells) as opposed to the treatment received for that diagnosis. Two different methods were used to separate out the effect of diagnosis from treatment on the risk of menopause or infertility. In the first approach, the main analysis was repeated with the exclusion of subjects diagnosed with specific tumours (i.e., central nervous system tumours or gonadal and germ cell tumours) who may experience menopause or infertility as a result of their diagnosis rather than their treatment. For survivors diagnosed with central nervous system tumours, neuro-psychological effects of central nervous damage caused by the tumour could

affect behavioural patterns and influence sexual life (Nygaard et al., 1991). For survivors diagnosed with gonadal and germ cell tumours, structural damage caused by the tumour to the gonads or germ cells may increase the risk of menopause or infertility. In the re-analysis of the data with the exclusion of these two diagnostic groups, the significantly elevated risk of menopause seen in women who received both abdominal-pelvic radiation and chemotherapy with alkylating agents was still evident as were the fertility deficits observed in women who received abdominal-pelvic radiation (censoring and not censoring by age at menopause) and in women treated with abdominal-pelvic radiation in conjunction with alkylating agents (not censoring on age at menopause) (Tables 3.18 and 3.26).

For the second approach, those subjects with a specified diagnosis were compared to all other subjects within a particular treatment group. The risk of menopause for survivors diagnosed with lymphoma and treated with chemotherapy with alkylating agents only or abdominal-pelvic radiation alone did not differ significantly to that for other survivors within the same treatment group. However, for survivors diagnosed with lymphoma and treated with abdominal-pelvic radiation and chemotherapy with alkylating agents the risk of menopause was increased about 3-fold compared to that of other survivors within this treatment group (Table 3.19). The elevated risk of menopause for these women may result from the type of alkylating agents received and/ or the radiation dose to the ovaries compared to the other diagnostic groups within this treatment group. It could also be reflecting a difference in the distribution of severity of diagnostic groups among women treated with alkylating agents and abdominal-pelvic radiation than among those treated with other treatments. Although, any treatment or reproductive outcomes from metastatic disease would not have been included in this analysis. There were not enough subjects to similarly evaluate the risk for any other diagnostic group. The NCI study

found that it was the type of treatment used, rather than the particular cancer diagnosis, that increased the risk of menopause. Its finding of an elevated risk for women treated for Hodgkin's disease was explained by the exposure of these women to radiation below the diaphragm plus alkylating agents (Byrne et al., 1992).

To assess fertility after treatment, those diagnostic groups with sufficient numbers within each treatment group (chemotherapy with alkylating agents and/or abdominal-pelvic radiation) were examined (Table 3.27). There was no fertility deficit for survivors diagnosed with lymphoma when compared to other survivors, among those treated with chemotherapy with alkylating agents or abdominal-pelvic radiation alone. However, women diagnosed with lymphoma and treated with alkylating agents plus abdominal-pelvic radiation had a non-significant 41% fertility deficit compared to other survivors in that treatment group. Therefore, the elevated risk for these women with lymphoma may also result from the types of alkylating agents received or a higher abdominal-pelvic radiation dose to the ovaries than the other diagnostic groups. In the NCI study, a significant deficit in fertility (23%) was also observed among survivors of Hodgkin's disease for female and male survivors combined (Byrne et al., 1987). For the other diagnostic groups examined in our study, only women diagnosed with renal tumours and treated with abdominal-pelvic radiation had a significant fertility deficit of 54% when compared to other survivors in this treatment group. In the NCI study, survivors of Wilms' tumour had a non-significant increased relative fertility of 1.47. However, their analysis included both male and female survivors and was examined for all treatment groups combined compared to sibling controls. As Wilms' tumours are primarily treated with abdominal radiation, combining treatment groups in the NCI study would result in a similar analogy to our study. However, the effects of treatment on male and female fertility may be different, with male

fertility more susceptible to alkylating agents (relative fertility, 0.34) and female fertility more susceptible to abdominal radiation (relative fertility, 0.70) (Byrne et al., 1987).

The association between diagnostic group and risk of adverse pregnancy outcomes was not examined because the small numbers of outcomes in particular diagnostic groups within treatment groups. Several previous studies have reported an excess of low birth weight infants and perinatal deaths among female survivors of Wilms' tumour treated with abdominal-pelvic radiation (Smith and Hawkins, 1989). However, female survivors of tumours other than Wilms' tumours and treated with abdominal-pelvic radiation have also been shown to have excess rates of low birth weight infants and perinatal deaths (Garber et al., 1990). These findings suggest that it may be the treatment, such as radiation-induced damage to the uterus, that results in early delivery and, consequently, premature low birth weight infants or infants with perinatal deaths. Studies have not found an increase risk of adverse reproductive outcomes in female survivors treated for Hodgkin's disease, non-Hodgkin's lymphoma or acute lymphoblastic leukemia (Donaldson and Kaplan, 1982; Green, 1986; Green, Sigelstein, et al., 1989; Green, Hall, et al., 1989).

3. **Comparison of study results to general population**

Reproductive outcomes of interest in female survivors of childhood cancer were compared to the general population. The average age of starting menstruation for female survivors still menstruating following treatment was 12.6 and similar to that in the general population (Forrest, 1993). Amongst those who had experienced menopause, the average age at menopause was 26.5. The median age at natural menopause is referred to as being about 50 years in the general population and has not changed over the last century (Stanford et. al.,

1987). The very early average age of menopause in our cohort represents only a small fraction (8.8%) of the survivors who have become menopausal, as the majority of the women (60%) were under 30 years of age at interview and none were over age 50. As age-specific rates of menopause were not available one can not control for the different age distributions between the study cohort and the general population, and therefore compare the average age at menopause or number of menopausal events between these two groups.

To determine if the number of surgical menopauses observed in the female survivors in this cohort differs from the number expected in the general population, age- and time-specific hysterectomy rates (unadjusted for prior hysterectomies) for Ontario were applied to the person-years in the corresponding year- (1964-1993) and age- groups (20-34, 35-49). From this calculation it was estimated that 28 hysterectomies would be expected to occur in our cohort. As the number of hysterectomies observed was 29, there appears to be no difference in the number of surgical menopauses between the female survivors and the general population. Our analysis found that the risk of surgical menopause did not differ between the treatment groups, although the risk of non-surgical menopause did (Table 3.15).

Of the survivors who were married or lived as married, 15.5% stated that they had difficulty becoming pregnant for a year or more. Those receiving abdominal-pelvic radiation alone or in conjunction with alkylating agents were more likely to have difficulty becoming pregnant (20.8% and 18.2% respectively). One-year infertility (absence of a pregnancy during the specified time period) among Canadian women aged 18-44 who had been married or cohabitating for at least one year, was estimated from pooled data from three independent national surveys conducted between 1991 and 1992. When surgically sterilized males or females are excluded from the denominator, one-year infertility, determined in a similar way as in our

study, was estimated to be 15.4% (Dulberg and Stephens, 1994), and is not very different from that estimated for the survivors overall. However, as the age distribution in our cohort is almost certainly younger than in the survey population, the infertility for the survivors overall may be greater than in the general population. In addition, difficulty becoming pregnant for more than one year was more likely to occur for those treated with abdominal-pelvic radiation alone (20.8%) or in conjunction with alkylating agents (18.2%) as compared to the general population.

Of the pregnancies surviving to at least 4 weeks gestation for the female survivors, 18.9% resulted in spontaneous abortion. The index of spontaneous abortions used in this analysis includes all reported pregnancies in the denominator with the exclusion of therapeutic abortions. The proportions ranged between 14.5% and 22.1% among the different treatment groups, and were not significantly different. When therapeutic abortions are omitted from the denominator, the percentages are slightly inflated. By including therapeutic abortions in the denominator, the rate for spontaneous abortions tends to be underestimated as a proportion of the pregnancies undergoing induced abortion that may have gone on to miscarry (Narod and Khazen, 1989). When therapeutic abortions are included in the denominator, the proportions of spontaneous abortions ranged between 13.4% and 18.3% among the different treatment groups, and was 16.9% overall. The risk of spontaneous abortions ranges from between 12% and 15% in cohort studies among clinically recognized pregnancies (Stirrat, 1990). Therefore, female cancer survivors have slightly higher risks of spontaneous abortions as compared to cohorts selected from the general population.

As age-specific perinatal death rates were unavailable from published vital statistics, a comparison was made between the number of stillbirths observed in the female survivors and the number expected based on the general population. Age- and time-specific stillbirth rates for

Ontario were applied to the number of live births occurring in the corresponding year- (1965-1994) and age-groups (15-19, 20-24, 25-34, 35-39). From this calculation it was estimated that 3 stillbirths would be expected to occur in our cohort, which is significantly lower than the number observed (N=14). The difference between observed and expected number of stillbirths was greatest for those receiving abdominal-pelvic radiation alone (3 versus 0.46) or in conjunction with alkylating agents (3 versus 0.26).

Of the live births reported among the female survivors, there were 32 (6.8%) low birth weight infants. Age- and time-specific low birth weight rates for Ontario were applied to the number of live births which occurred in the corresponding year- (1965-1994) and age-groups (15-19, 20-24, 25-34, 35-39). From this calculation it was estimated that 23.9 low birth weight infants would be expected to occur in our cohort, which is lower than the number observed. The difference between observed and expected number of low birth weight infants varies by treatment group. There were minimal differences between the observed and expected number of low birth weight infants for those who received non-sterilizing surgery, chemotherapy with non-alkylating agents and/or radiation above or below the abdomen or chemotherapy with alkylating agents and abdominal-pelvic radiation. For those receiving alkylating agent alone, the number of low birth weight infants observed (N=2) was about half the number expected (N=4.5). For those receiving abdominal-pelvic radiation alone, the observed number of low birth weight infants (N=12) was about 3 times the number expected (N=3.8). The results from the comparison of the observed to expected number of low birth weight infants are similar to the odds ratios obtained for survivors in the treatment groups of interest to those receiving surgery alone (Table 3.29).

Of the live births among the female survivors, 4.7% of the offspring had a congenital anomaly which is comparable to the general population. It has been estimated that 3 to 6% of offspring are malformed, which represents the background risk for maldevelopment (Brent and Beckman, 1994). However, the proportion of offspring with congenital anomalies differed by treatment group. For those who received chemotherapy with alkylating agents alone and/or abdominal-pelvic radiation or received other treatments the risk was either less than or equal to that of the general population. A possible explanation for observing the decreased risk of congenital anomalies in our study could be related to accuracy of recall of birth defects obtained from maternal questionnaires. A recent study found that the sensitivity (61%) of maternal responses about having a child with a birth defect indicated that a large proportion of serious birth defects may be missed or not accurately recalled (Rasmussen et al., 1990). A similar result (sensitivity 74%) was found using a smaller sample size (Axelsson and Rylander, 1984). The type of defect was the most important factor in determining the sensitivity of the maternal response. Malformations not recalled by mothers tended to be those that were less serious (i.e. hypospadias) or lethal (i.e. anencephaly). These studies suggest that questionnaire data on malformations need to be interpreted cautiously, if not properly validated by medical records or registry data.

However, for survivors receiving non-sterilizing surgery the risk of having an offspring with a congenital anomaly was double that in the general population. Of the 12 (9.5%) birth defects reported, 5 were congenital heart defects (of which 3 reported to have a blood relative with the same condition at birth), 2 were club foot, 2 were hip displacements, 1 was a hip displacement and clubfoot, and 1 was a cleft palate.

4. **Advantages and limitations of study**

4.1 Power of study to detect significant differences:

The expected numbers of subjects and pregnancies estimated by our pre-study sample size calculations were greater than the numbers actually obtained. There are several reasons why fewer females might have participated than anticipated. Firstly, a number of assumptions were generated from a small pilot study and from previous studies regarding the numbers of survivors and their physicians expected to be ineligible, to refuse to participate, or to be untraceable. Assumptions generated about survivors were quite similar to what actually happened. For example, 12.2% of survivors had diagnoses not histologically verified when 13.3% was assumed; 7.1% were untraceable when 11% was assumed; and 7.9% refused to be interviewed or have their treatment data abstracted when 8% was assumed. However, assumptions made about participation of physicians were inaccurate. For example, it was assumed that only 3% of physicians would be untraceable based on the pilot study, which reflected the proportion of subjects whom no physician was identified in the OCR and HSC medical records. However, physicians were not actually contacted during the pilot study and consequently a greater number of physicians were actually found to be untraceable (14.6%) when addresses were sought and contact was attempted. This was primarily due to physician migration, retirement, or death and was a more serious problem for survivors diagnosed prior to 1975. In addition, the rate of physician refusal was estimated based on recent OCTRF case-control studies which primarily obtain physician consent for subjects diagnosed within the year prior to study. As our study was a retrospective cohort study, subjects were diagnosed at anytime between 1964 and 1988. Therefore, a substantial number of physicians refused to give consent (11.6%) in our study because they had not seen their patient for many years.

Secondly, for all the assumptions made in the sample size calculations it was presumed that physician and subject tracing and response rates would be the same across age, period of diagnosis and diagnostic subgroups. However, a comparison of participating and non-participating subjects suggests that response rates varied by these factors. For example, compared to participating women non-participating women were older at start of study (37.9% being over 30 years of age), more likely to have been diagnosed prior to 1975 (39.7%), and diagnosed most often with epithelial neoplasms (26.1%) and central nervous system tumours (21.3%). These results reflect the difficulties encountered in identifying physicians and medical records of subjects diagnosed prior to 1975 and in locating physicians of subjects receiving only surgical treatment (i.e. for epithelial neoplasms) and our decision to not contact subjects with central nervous system tumours who were reported as being "mentally challenged" by their physicians. The result of this was fewer pregnancies and less opportunity for other events of interest (e.g. menopause; infertility).

Thirdly, the number of female survivors assumed to have received surgery only (i.e. the comparison group) was also imprecise. The number was based on treatment information from a recent OCTRF study that examined the associations between cancer treatment and anomalous offspring (Dodds et al., 1993). It was assumed as a result of this study that 50% of the survivors would have surgery only when in fact about half this number (22.5%) received surgery alone. This difference may be partially explained by the large number of subjects with epithelial neoplasms (26.1%) who were potentially eligible but who did not participate due to difficulties encountered in identifying a physician for them. The result of fewer surgery only subjects is lower precision (wider confidence intervals) than anticipated for risks associated with the reproductive outcomes.

Since there were fewer female cancer survivors who participated and thus fewer reproductive outcomes of interest than expected the estimated smallest detectable significant risk and odds ratios were lower than could be achieved by the study; certain non-significant findings from the subgroup analyses and for pregnancy outcomes such as congenital anomalies and perinatal deaths may have been significant if the sample size had been larger. However, the numbers of women (N=719) and/or pregnancies (N=696) included in this analysis are comparable to those in the NCI cohort (831 women) and only slightly smaller then the British cohort (1037 women, 944 pregnancies) of female survivors. However, our study has the largest number of more recently treated women (i.e., 65.9% treated after 1975).

4.2 Selection of comparison group:

Our study uses internal controls: women who had chemotherapy or radiotherapy are compared to women who were treated only by surgery. Other possible control groups for this cohort could have been population or sibling controls. Female survivors of this study were compared to the general population by utilizing Ontario age- and calendar- specific rates as well as estimates from special surveys. However, such a comparison on its own is usually not ideal, for the general population may differ considerably from the cohort under study with respect to desire to become pregnant, genetic disposition and important risk factors for adverse reproductive outcomes. The choice of sibling controls would adjust for any differences among families, that is genetic, lifestyle, and environmental factors that may render the production of abnormal offspring more similar among families (Simon, 1980). In addition, this group has been shown to be relatively easy to identify and locate and highly co-operative in other studies (Byrne et al., 1987; Byrne et al., 1992). However, the number of same sex siblings will vary among

patients. In a recent investigation, about 64% of cancer survivors interviewed had at least one sibling of the same sex (Byrne et al., 1987). Therefore, the pooling of siblings across families may not result in adequate control of inter-family influences.

One of the advantages of using an internal control group is that it decreases the size and cost of the study and uses the same follow-up procedures for the exposed and unexposed cohort members. In addition, the selection of a referent group of women who received only non-sterilizing surgery seems appropriate because in the NCI study the surgery only group did not have an increased risk of menopause or infertility when compared to their sibling controls (Byrne et al, 1987; Byrne et al., 1992). Using an internal control group can help to separate the effects on reproductive outcomes of treatment from those of having cancer. Population controls may have more pregnancies than cancer patients, as having cancer (and not the treatment) may affect the women's desire to become pregnant. It has been shown from this and one other study that women who have cancer may be more likely to be told they might have a fertility problem by their physician and therefore not try to become pregnant (Teeter et al., 1987). Also, the choice of an internal control group may separate out the effects of treatment from any association that may exist between infertility or adverse pregnancy outcomes and a possible genetic disposition to childhood cancer. However, surgically-treated cancers have less ability to metastasize and may represent a different type of genetic background from those cancers requiring chemotherapy and/or radiotherapy.

4.3 Abdominal-pelvic radiation dose:

From the treatment data collected for this study, subjects could be classified as to whether they received radiation to the abdomen or pelvis (yes/no) and to the total amount of radiation

received to this area. Our study found an increased risk of some reproductive outcomes (i.e. menopause, infertility, low birth weight infants, perinatal deaths) in women receiving abdominal-pelvic radiation and found an increased risk with dose of abdominal-pelvic radiation for these outcomes. That is, abdominal-pelvic radiation doses above 3,500 cGy significantly increased the risk of menopause and infertility and abdominal-pelvic radiation doses above 2,500 cGy significantly increased the risk of low birth weight infants (all and premature) and increased the risk of perinatal deaths.

However, determination of actual radiation dose to critical structures (e.g. ovaries, uterus) was not possible in our study since information on gonadal dose was not obtained. Therefore, we were unable to comment on how much radiation is harmful to one or both ovaries. This would be the type of information which would be necessary to influence future management.

5. **Methodological Issues**

5.1 Design of Study:

This study employed a retrospective cohort design, in that women comprising the cohort were identified by characteristics in their past, and information about their exposure (cancer treatment) and outcomes (reproductive outcomes) was obtained from some defined time in the past to the present (Kelsey et al., 1986). The advantage of using this design over a prospective cohort study is that a study can be completed in less time and at considerably less cost. A disadvantage in using this design is that information available on the cohort may not be complete, since it would have been collected in the past for other purposes (cancer diagnosis and treatment). However, for this study there existed a relevant cohort that could be identified from

a population-based cancer incidence registry generally with adequate records of exposure available dating back to the start of the study. A recent study estimates that the OCR is at least 95% complete (Robles et al., 1988). Another possible problem with this design is that information on other variables which may play an important confounding role are likely to be unavailable on past records. However, since reproductive outcomes in this study were obtained from a questionnaire, information on the potentially confounding variables were also obtained through direct interview.

In addition, selection bias can occur in retrospective cohort studies if subjects remaining in the study differ from subjects lost to follow-up with respect to exposure status and/or disease occurrence (Choi and Noseworthy, 1992). As previously stated, participating and non-participating subjects did differ in our study by year of diagnosis, age at start of study and by diagnostic group. Additional follow-up of non-participants diagnosed prior to 1975 would not have significantly altered our results as similar results to our study have been shown in previous studies of survivors primarily diagnosed prior to 1975. However, inclusion of these subjects as well as non-participants older at start of study and diagnosed with epithelial neoplasms would have contributed additional reproductive events and enhanced precision of estimates. Under-ascertainment of disease occurrence (i.e., reproductive events) results in diminished precision of the estimates and can affect the magnitude and direction of the association. It is unlikely the misclassification of reproductive outcomes occurred in our study as the same procedures to identify reproductive events were used for the entire cohort. In addition, interviewers were unaware of the exposure status of the respondents.

Female survivors who appeared to meet all of the study criteria but were not alive at the start of the study were excluded from participating as proxy respondents were not incorporated

in our study. Selection bias could also occur if these women differed from women remaining in the study with respect to exposure status and/or disease occurrence. It was estimated that there could have been potentially 112 females (about 5% of the cohort identified from the OCR (N=2165)) who would have fallen into this category. Including these women into our study would have increased the sample size only slightly and therefore it is doubtful that the magnitude or direction of the associations would have been markedly changed. Also, since the accuracy of reporting reproductive events by proxy informants is questionable it was prudent not to include these women.

5.2 Use of existing treatment data:

Cancer therapy data were abstracted primarily from existing treatment records collected and stored at major children's hospitals or regional cancer centres in the province where a subject was seen in relation to her diagnosis of cancer. These data are collected and kept primarily for purposes other than epidemiologic research. The desired treatment data were abstracted and tabulated onto a special form for the purpose of this study. Advantages of using existing data are that exposure data can be collected from a large number of subjects at relatively lower cost within a relatively shorter time. However, there is the possibility of recording errors and missing data.

For cancer treatment data, the best records are at the source where the patient was treated. A re-abstraction study found the treatment data collected for this study to be generally reliable. As all radiotherapy in Ontario is conducted at one of the nine RCCs or PMH, radiotherapy information was found to be of high quality and documented in a standardized fashion. Chemotherapy is also administered at the RCCs and PMH as well as the HSC and at

other hospitals. Since most of the subjects in this study were treated at the RCCs, PMH or the HSC, chemotherapy information for these survivors was also found to be complete and in a standardized format.

5.3 Questionnaire data:

Reproductive outcomes were ascertained from respondent's recall of events through a telephone-administered questionnaire. Other sources could have been utilized to ascertain reproductive outcomes of interest. Live births, infant deaths, and stillbirths could have been collected from the Office of the Registrar General (ORG) in Ontario through record linkage. Data from the ORG are routinely collected in a standardized fashion, and are accessible for all subjects from one source. Pregnancy information could have also been obtained from the subject's medical chart or linkage with computerized hospital separation data (HMRI). However, there are potential error sources and difficulties in obtaining complete data from these sources as well as problems with access and consistency between records. In ascertaining reproductive outcomes by record linkage of relevant ORG certificates or HMRI data, not all events of interest would have been available (eg. menopause and infertility). In addition, with the linkage of ORG certificates or HMRI data there could be problems due to name changes (especially for females) as well as the limitation of ascertaining only events occurring inside the province. The assumption that medical records are always more "objective" and accurate, has not always been supported. For example, a recent study showed that different criteria appear to have been used within different hospitals for recording past reproductive events and possible omissions and errors were found in recording certain procedures and medications prescribed (Hewson and Bennett, 1987). Medical records could also be unavailable for some subjects in Ontario as

hospital records can be destroyed after 10 years from last visit. Another potential error source in medical records data could arise from the abstraction process itself. In addition, common risk factors for adverse pregnancy outcomes are not recorded on medical records data or in vital statistics records. Information on potentially confounding variables such as smoking history, medication use during pregnancy, complications during pregnancy, etc., are available only through the use of a questionnaire.

There are potential error sources from women's questionnaire responses that must be considered. One possible source of error could be memory deficit. Previous studies have shown that women recall with acceptable accuracy age at menarche, age at menopause, oral contraceptive use, number of prior pregnancies and gestational age and birth weight of infant (Hakim et al., 1992; Harlow and Linet, 1987; Seidman et al.,1987; Gayle et al., 1988). When the accuracy of selected pregnancy data for this study was independently assessed through the use of vital statistics records, information such as dates and age of mother at birth events, birth weight, and gestational age were also found to be generally accurate. However, a few studies have found that maternal recall was not as good for certain pregnancy outcomes (i.e., miscarriages and birth defects), drug exposure during pregnancy, diagnostic x-rays, hospitalization during pregnancy or infectious or flu-like illnesses (Axelsson and Rylander 1984; Rasmussen et al., 1990; Tilley et al., 1985; Bryant et al., 1989). A study by Wilcox and Horney (1984) found that 75% of recorded abortions from prospective menstrual diaries were recalled by personal interviews. The major factor of recall for spontaneous abortion was the length of pregnancy, with 93% of those occurring after 13 weeks being recalled. However, this bias toward the detection of later abortions is shared by medical records and therefore would be unavoidable, regardless of data collection method used. Two studies found that a large

proportion (close to 25%) of birth defects may be missed from histories obtained through maternal interviews (Axelsson and Rylander, 1984; Rasmussen et al., 1990). However, one of the studies suggested that the low sensitivity in their study may be as a result of the manner in which the question about birth defects was asked, being asked as an open-ended question (Rasmussen et al., 1990). Therefore, another possible source of error could be ambiguous questioning. A few studies have shown low accuracy on recall of various exposures during pregnancy if an open-ended questionnaire is used (Feldman et al., 1989). For example, a recent study has shown that completeness of ascertainment of drug exposure in pregnancy is dependent on how the mother is questioned and is related to the specificity of the questions asked (Mitchell et al., 1986). Report of drug use in pregnancy improved when list of drugs' names were used as opposed to an open-ended question.

In this study, various methods were implemented to improve recall and accuracy of data collected by the questionnaire and therefore minimize information bias. Information bias occurs when the estimated effect is distorted either by an error in measurement or by misclassifying a subject for exposure and/or outcome variable (Choi and Noseworthy, 1992). Interviewers were specially trained by the study coordinator and a consultant and were periodically monitored by the study coordinator. As telephone interviews are generally not conducive to allowing respondents time to obtain information from other sources, the accuracy and completeness of answers may be compromised (Dillman, 1978). To allow respondents time to recall dates and events and to check records, subjects in our study received the questionnaire by mail in advance of being telephone-interviewed. Recall of responses was also enhanced by preparing a questionnaire with no open-ended questions and a few partially close-ended questions. Potential interviewer and questionnaire biases were lessened by specially training interviewers and

providing them with a detailed manual and scripts with specific instructions on how to conduct the interview in a standardized fashion and how to handle problems using neutral probes. Knowledge of the subject's prior exposure can result in diagnostic suspicion bias. This was not a problem in our study since interviewers were unaware of the "exposure status" of respondents. Treatment data were abstracted after the interview and was completed by different staff. From the comparison of study results to the general population the accuracy of recall of reproductive events seems reasonable, especially for surgical menopause, infertility, and low birth weight infants.

6. **Further research**

As most children diagnosed with cancer can realistically hope for long-term survival and cure, researchers and clinicians are becoming increasingly concerned about possible late effects of treatment. Previous studies of late effects in long-term survivors have primarily been conducted at single institutions with good patient follow-up. These investigations have generally enrolled a small number of survivors and have had limited statistical power. A few larger-scale retrospective cohort studies have been conducted in the past; however these studies employed subject diagnosed primarily prior to 1975. These retrospective studies, as well as our study, have shown that multi-centre collaborative efforts will be necessary to attain large enough sample sizes to detect risks with adequate power. Currently, a US NCI-sponsored multi-institutional collaboration has been initiated which proposes to include 25,000 survivors of cancer diagnosed under 21 years of age. This study will investigate the long-term effects of cancer and its associated treatment. In Canada, a nationwide data collection system for identifying the causal factors associated with childhood cancer incidence and/or recurrence is being developed. The

Canadian Childhood Surveillance and Control Program will also assess spatial and temporal trends in the incidence, mortality and survival of childhood cancers, the long term effects associated with childhood cancer and its treatment and evaluate the effectiveness of various treatment modalities.

In addition to retrospective studies, a well designed longitudinal study could be used to accurately study reproduction after childhood cancer. The enrolment of a large number of survivors, followed up for a long time, with periodic evaluation would allow for complete evaluation of all events of interest (not just reproductive-related events). As many pediatric centres are currently setting up follow-up clinics for childhood cancer survivors, late effects of survivors could be ascertained prospectively, but this still would not be possible unless standardized prospective data are collected.

Although previous studies as well as the current study have found an increased risk of some reproductive outcomes (i.e. infertility, low birth weight infants, perinatal deaths) in women receiving abdominal-pelvic radiation, few studies have calculated radiation dose to critical structures i.e., ovaries, uterus. For management of these patients it would be of interest to determine how much radiation is harmful to one, or both ovaries. A recent study describes how to estimate the surviving fraction of oocytes if the dose received by the ovary is calculated (Wallace et al., 1989). This information could predict the age at ovarian failure and specify when reproductive outcomes such as menopause and infertility may occur.

7. **Conclusions**

The results from this study are broadly similar to those reported in the literature for reproductive outcomes in female survivors of childhood cancers. The first objective of this study

was to determine whether female childhood cancer survivors were at an increase risk of menopause and/or infertility. In this study there was evidence that women treated with abdominal-pelvic radiation and alkylating agents had an increased risk of having an early menopause, especially for those diagnosed after puberty. Also, women treated with abdominal-pelvic radiation were found to have an increased risk of being infertile measured as difficulty becoming pregnant for more than one year and also measured as time to first pregnancy. The above mentioned results were also reported in a 5-centre NCI study conducted in the United States. Both our cohort and the NCI cohort were similar in that they identified large cohorts of female childhood cancer survivors using comparable entry criteria. However, females studied in the NCI cohort were primarily treated prior to 1975 and were compared to their siblings. In addition, our study observed that the risks of menopause and infertility increased with increasing dose of abdominal-pelvic radiation and by amount of alkylating agents received.

The second objective of this study was to determine whether female childhood cancer survivors were at an increased risk of adverse pregnancy outcomes. A significant increased risk was seen for low-birth weight infant for females treated with abdominal-pelvic radiation and an increased risk for premature low-birth weight infants. These results agree with those of a large British study that examined pregnancy outcomes associated with all types of childhood tumours sometimes requiring direct abdominal radiation. The British study was analogous to ours in that it utilized an internal control group, comparing survivors who received and did not receive alkylating agents and/or abdominal radiation. However, female survivors in the British study included women treated primarily prior to the 1970s and diagnosed under the age of 15. As well, our study observed that the risk of low birth weight infants (all and premature) increased with dose of radiotherapy directed to the abdomen and pelvis.

Previous studies have been limited, being based mainly on small numbers of patient and/or patients treated primarily prior to the early 1970s. As the female survivors in our cohort were primarily diagnosed after 1975, our study investigated a different patient population with a higher proportion of survivors, treated with more current therapeutic programs. The results suggest that the increased risks observed in previous studies of female survivors treated prior to 1975 have not changed for those females treated after 1975. Of course, the numbers of study subjects who have been treated more recently was limited as many may have not yet attained reproductive age.

The success of current therapies for children with cancer is well recognized, therefore, the results from this study are not intended to suggest changes to treatment modalities. The intent of this study was to provide some preliminary answers regarding effects of recent therapies and will pave the way for subsequent investigations, when larger numbers of survivors become available. As the prevalence of childhood cancer survivors in the adult population is increasing, documentation of adverse outcomes of pregnancy will be particularly important for the allocation of resources from a public health perspective. It has been estimated that by the year 2000, one out of every 900 young adults (16 to 44 years of age) will be a survivor of childhood cancer (Robison, 1992). Although the results of this study may not have any significant economic impact on health care, there will be the opportunity to affect "quality of care" in that more precise answers will be available to those having undergone such treatment.

After therapy ends, patients should be informed about their future fertility and the possibility of healthy children. A female survivor of childhood cancer who receives both abdominal-pelvic radiation and chemotherapy with alkylating agents may have a smaller window of fertility as a result of their risk of early menopause. In addition, women who receive

abdominal-pelvic radiation are at a slightly increased risk of being infertile. The results from this study should offer some reassurance to female cancer survivors who received abdominal-pelvic radiation and/or chemotherapy with alkylating agents about the risk of congenital anomalies and spontaneous abortions. However, women who have had previous abdominal or pelvic radiation (especially those who receive greater than 2,500 cGy) may require special monitoring during pregnancy, as they are at an increased risk of having low birth weight infant (all and premature) or an infant with a perinatal death.

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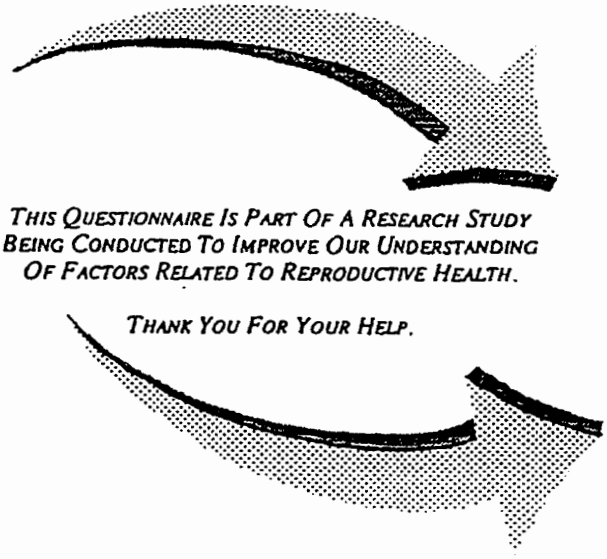
Appendix A: Data Elements in Patient's Record

1. Admission Status
2. Age at Diagnosis
3. Age Group
4. Autopsy Flag
5. Best Source
6. Birth Date
7. Cancer Centre Registration Date
8. Cause of Death Code
9. Combined Source for Patient
10. Combined Source for Primary
11. Days Spent in Hospitals
12. Death Certificate Number
13. Diagnosis Date
14. Earliest Cancer Centre Chart and Case Number
15. Earliest Source
16. Elapsed Days
17. Elapsed Days Flag
18. Given Name 1
19. Given Name 2
20. Group number
21. Hospital Chart Number
22. ICD9 Code Reported
23. ICD9 Code Resolved
24. ICDO-M Histology Code Reported
25. ICDO-M Histology Code Resolved
26. Incident Case Flag
27. Last Date
28. Latest MOH Residence Code
29. Method of Confirmation
30. MOH Hospital Code
31. Number of Hospital Records
32. Number of Pathology Records
33. Number of Primaries (ALL)
34. Number of Primaries (Incident)
35. NYSIIS Code
36. OHIP Code
37. OHIP Number
38. Original Diagnosis Year
39. Place of Birth
40. Postal Code
41. Province of Death
42. Record Type
43. Residence at Diagnosis (MOH)
44. Residence at Diagnosis (SGC)
45. Sequence Number
46. Sex Code
47. Status Code
48. Surname
49. Treatment Date

APPENDIX B: Questionnaire

RESEARCH QUESTIONNAIRE



THIS QUESTIONNAIRE IS PART OF A RESEARCH STUDY BEING CONDUCTED TO IMPROVE OUR UNDERSTANDING OF FACTORS RELATED TO REPRODUCTIVE HEALTH.

THANK YOU FOR YOUR HELP.

DEPARTMENT OF PREVENTIVE MEDICINE AND BIOSTATISTICS
FACULTY OF MEDICINE, UNIVERSITY OF TORONTO
TORONTO, ONTARIO, M5S 1A8

Although an interviewer will be calling to record your answers, you may find it helpful to fill out the questionnaire ahead of time.

Circle numbers where choices are given and write in your answers where space is provided.

1. What is your date of birth? _____ / _____ / 19 _____
   day month year

2. How tall are you? _____ **feet** _____ **inches** *or* _____ **centimetres**

3. What has been your average weight as an adult? _____ **pounds** *or* _____ **kilograms**

4. Which of the following groups best describes your racial background?

   1 **White**
   2 **Black**
   3 **Asian**
   4 **Native American Indian, Inuit**
   5 **Other** *Please specify* _____
   8 **Don't know**

5. Are you currently enrolled as a student in a degree or diploma programme?

   1 **No**
   2 **Yes**

6. What is the highest level of education that you have completed?

   1 **Some or all elementary or grade school**
   2 **Some secondary or high school**
   3 **Completed secondary or high school**
   4 **Some or all community college, technical college or hospital school of nursing**
   5 **Some university**
   6 **Completed university**

The next few questions are about your menstrual history.

7. Have you started menstruating (having your period)?

   1 No *Go to question 9*

   2 Yes ⟶ At what age did you start? _____

8. Did your first period start by itself?

   1 No

   2 Yes *Go to question 10*

   8 Don't know

9. What is the reason that you never had a menstrual period or that your first period did not start by itself? In what year was this first diagnosed?

1	No ovaries	19__
2	Underdeveloped ovaries	19__
3	No uterus (womb)	19__
4	Underdeveloped uterus	19__
5	Other problems with ovaries	19__
6	Other problems with uterus	19__
7	Problems with pituitary gland	19__
8	Other *Please specify* _____	19__
9	Never went to see a doctor	
88	Don't know	

If you have had a period please continue. If not, go to question 87, page 17.

10. Have you stopped having periods?

    1 No

    2 Yes ⟶ a) At what age? _____

    b) How did your periods stop?

    1 Naturally

    2 Due to surgery

    3 Other *Please specify* _____

    8 Don't know

11. Have you ever used birth control pills regularly for any reason?
(e.g., contraception, regulation of periods)

1 No

2 Yes ⟶ *Please fill in the chart below for each period of time that you used birth control pills.*

Age started	_____	_____	_____	_____
Age stopped	_____	_____	_____	_____

The following questions concern all of the pregnancies you have had including live births, stillbirths, ectopic (tubal) pregnancies, miscarriages and therapeutic abortions.

Space is provided for information on your first four pregnancies. For the fifth and subsequent pregnancies, information will be collected at time of interview.

12. How many times have you been pregnant? _____

If you have never been pregnant, go to page 17.

13. Prior to your first pregnancy, have you ever been hospitalized, had surgery or been prescribed medication for any of the following conditions?

1 **High blood pressure**
2 **Heart disease**
3 **Chronic kidney disease**
4 **Diabetes**
5 **Anemia**
6 **Epilepsy**
7 **Conditions of the pituitary, adrenal or thyroid glands**
9 **None of the above**

First Pregnancy

14. How old were you at the start of this pregnancy?

_____ years old

15. What was the outcome of the pregnancy?

1 **Live birth (single or multiple)**

2 **Stillbirth**

3 **Miscarriage or spontaneous abortion**

4 **Ectopic (tubal) pregnancy**

Go to next pregnancy, page 7; if no other pregnancy, go to page 16

5 **Therapeutic abortion**

Go to next pregnancy, page 7; if no other pregnancy, go to page 16

6 **Now pregnant** *Go to page 17*

16. How many weeks did this pregnancy last?

_____ weeks

17. During this pregnancy, were you hospitalized as a result of an accident or injury?

1 No

2 Yes → During which month(s)? _____

18. During this pregnancy, did you have any of the following conditions? During which months?

		month(s) of pregnancy
1	**Bleeding/spotting**	_____
2	**Toxemia/eclampsia**	_____
3	**Vomiting requiring hospitalization**	_____
4	**Placenta previa**	_____
5	**Incompetent cervix treated with sutures**	_____
6	**Anemia requiring a blood transfusion**	_____
9	**None of the above**	

19. During this pregnancy, did you have any of the following illnesses? During which months?

		month(s) of pregnancy
1	**German measles (rubella)**	_____
2	**Hepatitis**	_____
3	**Red measles**	_____
4	**Influenza**	_____
5	**Urinary tract infection**	_____
6	**Cytomegalovirus**	_____
7	**Syphilis**	_____
8	**Genital herpes**	_____
9	**AIDS**	_____
10	**Toxoplasmosis**	_____
99	**None of the above**	

20. During this pregnancy, did you have any radiation to the lower back or to the abdomen below the waist [including radiation therapy, x-ray, IVP (intravenous pyelogram), or barium enema]?

1 No

2 Yes → During which month(s)? _____

First Pregnancy

21. Were you employed during this pregnancy?

1 No

2 Yes

a) During which month(s)?

_____

b) What was/were your job title(s)?

_____

c) What was/were the type of industry or business?

_____

d) Did this job involve any of the following?

1 Standing more than 3 hrs a day

2 Working more than 40 hrs a week

3 Carrying loads of 10 kg/22 lbs or more

4 Work on industrial machine or assembly line

5 Routine work or work requiring little attention

6 Shift work

9 None of the above

e) During this time were you directly exposed at work to any of the following?

1 Ionizing radiation

2 Lead

3 Organic solvents

4 Agricultural chemicals

5 Nitrous oxide

6 Ethylene oxide

7 Anti-cancer drugs

9 None of the above

22. In the 3 months preceding this pregnancy, was the father of the child employed?

1 No

2 Yes

a) What was/were his job title(s)?

_____

b) What was/were the type of industry or business?

_____

c) During this time was he directly exposed at work to any of the following?

1 Ionizing radiation

2 Lead

3 Organic solvents

4 Agricultural chemicals

9 None of the above

23. During this pregnancy, did you smoke cigarettes?

1 No

2 Yes → a) During which month(s)?

_____

b) How many cigarettes per day? _____

24. During this pregnancy, did you drink any alcoholic beverage?

1 No

2 Yes → a) During which month(s)?

_____

b) How many drinks per week? _____

First Pregnancy

25. During this pregnancy, did you use any of the following medications? During which months?

		month(s) of pregnancy
1	**Hormones to prevent miscarriage** *(e.g., DES/ estrogen/premarin)*	_____
2	**Other medications to prevent miscarriage**	_____
3	**Prescription anti-nausea pills**	_____
4	**Thyroid medication**	_____
5	**Anti-seizure medication**	_____
6	**Antibiotics**	_____
7	**Prescription sedatives, tranquilizers, or sleeping pills**	_____
8	**High blood pressure pills**	_____
9	**Insulin**	_____
10	**"Recreational" drugs** *(e.g., LSD/cocaine)*	_____
99	**None of the above**	

26. At any time during the year before you became pregnant, did you take birth control pills?

1 **No**

2 **Yes**

→ Were you still taking the pill when you became pregnant?

1 No → How many months before you became pregnant did you stop taking the pill? _____ **months**

2 Yes → For how many months after you became pregnant did you continue taking the pill? _____ **months**

27. At the time you became pregnant, did you have an IUD (intrauterine device) in place?

1 No

2 Yes

If the outcome of this pregnancy was not a live birth, go to the next pregnancy, page 7. If no other pregnancy, go to page 17.

28. Did you have any of the following conditions at delivery?

1 **Breech presentation**

2 **Premature (less than 38 weeks) rupture of membrane**

3 **Prolonged (more than 24 hours) rupture of membrane**

4 **Abruptio placenta**

9 **None of the above**

29. What was the date of the delivery?

_____ / _____ / _____
day **month** **year**

30. What is the sex and weight at birth for each live baby delivered from this pregnancy (e.g., if single, twins, triplets etc.)?

____ sex ____ lbs ____ oz *or* ____ gms

____ sex ____ lbs ____ oz *or* ____ gms

____ sex ____ lbs ____ oz *or* ____ gms

____ sex ____ lbs ____ oz *or* ____ gms

If no other pregnancy, go to page 16.

Second Pregnancy

31. How old were you at the start of this pregnancy?

_____ years old

32. What was the outcome of the pregnancy?

1 **Live birth (single or multiple)**

2 **Stillbirth**

3 **Miscarriage or spontaneous abortion**

4 **Ectopic (tubal) pregnancy**

Go to next pregnancy, page 10; if no other pregnancy, go to page 16

5 **Therapeutic abortion**

Go to next pregnancy, page 10; if no other pregnancy, go to page 16

6 **Now pregnant** *Go to page 16*

33. How many weeks did this pregnancy last?

_____ weeks

34. During this pregnancy, were you hospitalized as a result of an accident or injury?

1 No

2 Yes → During which month(s)? _____

35. During this pregnancy, did you have any of the following conditions? During which months?

		month(s) of pregnancy
1	**Bleeding/spotting**	_____
2	**Toxemia/eclampsia**	_____
3	**Vomiting requiring hospitalization**	_____
4	**Placenta previa**	_____
5	**Incompetent cervix treated with sutures**	_____
6	**Anemia requiring a blood transfusion**	_____
9	**None of the above**	

36. During this pregnancy, did you have any of the following illnesses? During which months?

		month(s) of pregnancy
1	**German measles (rubella)**	_____
2	**Hepatitis**	_____
3	**Red measles**	_____
4	**Influenza**	_____
5	**Urinary tract infection**	_____
6	**Cytomegalovirus**	_____
7	**Syphilis**	_____
8	**Genital herpes**	_____
9	**AIDS**	_____
10	**Toxoplasmosis**	_____
99	**None of the above**	

37. During this pregnancy, did you have any radiation to the lower back or to the abdomen below the waist [including radiation therapy, x-ray, IVP (intravenous pyelogram), or barium enema]?

1 No

2 Yes → During which month(s)? _____

Second Pregnancy

38. Were you employed during this pregnancy?

1 No

2 Yes

a) During which month(s)?

_____

b) What was/were your job title(s)?

_____

c) What was/were the type of industry or business?

_____

d) Did this job involve any of the following?

1 **Standing more than 3 hrs a day**

2 **Working more than 40 hrs a week**

3 **Carrying loads of 10 kg/22 lbs or more**

4 **Work on industrial machine or assembly line**

5 **Routine work or work requiring little attention**

6 **Shift work**

9 **None of the above**

e) During this time were you directly exposed at work to any of the following?

1 **Ionizing radiation**

2 **Lead**

3 **Organic solvents**

4 **Agricultural chemicals**

5 **Nitrous oxide**

6 **Ethylene oxide**

7 **Anti-cancer drugs**

9 **None of the above**

39. In the 3 months preceding this pregnancy, was the father of the child employed?

1 No

2 Yes

a) What was/were his job title(s)?

_____

b) What was/were the type of industry or business?

_____

c) During this time was he directly exposed at work to any of the following?

1 **Ionizing radiation**

2 **Lead**

3 **Organic solvents**

4 **Agricultural chemicals**

9 **None of the above**

40. During this pregnancy, did you smoke cigarettes?

1 No

2 Yes → a) During which month(s)?

_____

b) How many cigarettes per day? _____

41. During this pregnancy, did you drink any alcoholic beverage?

1 No

2 Yes → a) During which month(s)?

_____

b) How many drinks per week? _____

Second Pregnancy

42. During this pregnancy, did you use any of the following medications? During which months?

		month(s) of pregnancy
1	**Hormones to prevent miscarriage** *(e.g., DES/ estrogen/premarin)*	_____
2	**Other medications to prevent miscarriage**	_____
3	**Prescription anti-nausea pills**	_____
4	**Thyroid medication**	_____
5	**Anti-seizure medication**	_____
6	**Antibiotics**	_____
7	**Prescription sedatives, tranquilizers, or sleeping pills**	_____
8	**High blood pressure pills**	_____
9	**Insulin**	_____
10	**"Recreational" drugs** *(e.g., LSD/cocaine)*	_____
99	**None of the above**	

43. At any time during the year before you became pregnant, did you take birth control pills?

1 **No**

2 **Yes**

→ Were you still taking the pill when you became pregnant?

1 **No** → How many months before you became pregnant did you stop taking the pill? _____ **months**

2 **Yes** → For how many months after you became pregnant did you continue taking the pill? _____ **months**

44. At the time you became pregnant, did you have an IUD (intrauterine device) in place?

1 **No**

2 **Yes**

If the outcome of this pregnancy was not a live birth, go to the next pregnancy, page 10. If no other pregnancy, go to page 17.

45. Did you have any of the following conditions at delivery?

1 **Breech presentation**

2 **Premature (less than 38 weeks) rupture of membrane**

3 **Prolonged (more than 24 hours) rupture of membrane**

4 **Abruptio placenta**

9 **None of the above**

46. What was the date of the delivery?

_____ / _____ / _____
day **month** **year**

47. What is the sex and weight at birth for each live baby delivered from this pregnancy (e.g., if single, twins, triplets etc.)?

____ sex ____ lbs ____ oz *or* ____ gms

____ sex ____ lbs ____ oz *or* ____ gms

____ sex ____ lbs ____ oz *or* ____ gms

____ sex ____ lbs ____ oz *or* ____ gms

If no other pregnancy, go to page 16.

Third Pregnancy

48. How old were you at the start of this pregnancy?

_____ years old

49. What was the outcome of the pregnancy?

1 **Live birth (single or multiple)**

2 **Stillbirth**

3 **Miscarriage or spontaneous abortion**

4 **Ectopic (tubal) pregnancy**

Go to next pregnancy, page 13; if no other pregnancy, go to page 16

5 **Therapeutic abortion**

Go to next pregnancy, page 13; if no other pregnancy, go to page 16

6 **Now pregnant** *Go to page 16*

50. How many weeks did this pregnancy last?

_____ weeks

51. During this pregnancy, were you hospitalized as a result of an accident or injury?

1 No

2 Yes → During which month(s)? _____

52. During this pregnancy, did you have any of the following conditions? During which months?

		month(s) of pregnancy
1	**Bleeding/spotting**	_____
2	**Toxemia/eclampsia**	_____
3	**Vomiting requiring hospitalization**	_____
4	**Placenta previa**	_____
5	**Incompetent cervix treated with sutures**	_____
6	**Anemia requiring a blood transfusion**	_____
9	**None of the above**	

53. During this pregnancy, did you have any of the following illnesses? During which months?

		month(s) of pregnancy
1	**German measles (rubella)**	_____
2	**Hepatitis**	_____
3	**Red measles**	_____
4	**Influenza**	_____
5	**Urinary tract infection**	_____
6	**Cytomegalovirus**	_____
7	**Syphilis**	_____
8	**Genital herpes**	_____
9	**AIDS**	_____
10	**Toxoplasmosis**	_____
99	**None of the above**	

54. During this pregnancy, did you have any radiation to the lower back or to the abdomen below the waist [including radiation therapy, x-ray, IVP (intravenous pyelogram), or barium enema]?

1 No

2 Yes → During which month(s)? _____

Third Pregnancy

55. Were you employed during this pregnancy?

1 No

2 Yes

a) During which month(s)?

_____

b) What was/were your job title(s)?

_____

c) What was/were the type of industry or business?

_____

d) Did this job involve any of the following?

1 **Standing more than 3 hrs a day**

2 **Working more than 40 hrs a week**

3 **Carrying loads of 10 kg/22 lbs or more**

4 **Work on industrial machine or assembly line**

5 **Routine work or work requiring little attention**

6 **Shift work**

9 **None of the above**

e) During this time were you directly exposed at work to any of the following?

1 **Ionizing radiation**

2 **Lead**

3 **Organic solvents**

4 **Agricultural chemicals**

5 **Nitrous oxide**

6 **Ethylene oxide**

7 **Anti-cancer drugs**

9 **None of the above**

56. In the 3 months preceding this pregnancy, was the father of the child employed?

1 No

2 Yes

a) What was/were his job title(s)?

_____

b) What was/were the type of industry or business?

_____

c) During this time was he directly exposed at work to any of the following?

1 **Ionizing radiation**

2 **Lead**

3 **Organic solvents**

4 **Agricultural chemicals**

9 **None of the above**

57. During this pregnancy, did you smoke cigarettes?

1 No

2 Yes → a) During which month(s)?

_____

b) How many cigarettes per day? _____

58. During this pregnancy, did you drink any alcoholic beverage?

1 No

2 Yes → a) During which month(s)?

_____

b) How many drinks per week? _____

Third Pregnancy

59. During this pregnancy, did you use any of the following medications? During which months?

		month(s) of pregnancy
1	**Hormones to prevent miscarriage** *(e.g., DES/ estrogen/premarin)*	_____
2	**Other medications to prevent miscarriage**	_____
3	**Prescription anti-nausea pills**	_____
4	**Thyroid medication**	_____
5	**Anti-seizure medication**	_____
6	**Antibiotics**	_____
7	**Prescription sedatives, tranquilizers, or sleeping pills**	_____
8	**High blood pressure pills**	_____
9	**Insulin**	_____
10	**"Recreational" drugs** *(e.g., LSD/cocaine)*	_____
99	**None of the above**	

60. At any time during the year before you became pregnant, did you take birth control pills?

1 **No**

2 **Yes**

→ Were you still taking the pill when you became pregnant?

1 **No** → How many months before you became pregnant did you stop taking the pill? _____ **months**

2 **Yes** → For how many months after you became pregnant did you continue taking the pill? _____ **months**

61. At the time you became pregnant, did you have an IUD (intrauterine device) in place?

1 **No**

2 **Yes**

If the outcome of this pregnancy was not a live birth, go to the next pregnancy, page 13. If no other pregnancy, go to page 17.

62. Did you have any of the following conditions at delivery?

1 **Breech presentation**

2 **Premature (less than 38 weeks) rupture of membrane**

3 **Prolonged (more than 24 hours) rupture of membrane**

4 **Abruptio placenta**

9 **None of the above**

63. What was the date of the delivery?

_____ / _____ / _____
day **month** **year**

64. What is the sex and weight at birth for each live baby delivered from this pregnancy (e.g., if single, twins, triplets etc.)?

____ **sex** ____ **lbs** ____ **oz** *or* ____ **gms**

____ **sex** ____ **lbs** ____ **oz** *or* ____ **gms**

____ **sex** ____ **lbs** ____ **oz** *or* ____ **gms**

____ **sex** ____ **lbs** ____ **oz** *or* ____ **gms**

If no other pregnancy, go to page 16.

Fourth Pregnancy

65. How old were you at the start of this pregnancy?

_____ **years old**

66. What was the outcome of the pregnancy?

1 **Live birth (single or multiple)**

2 **Stillbirth**

3 **Miscarriage or spontaneous abortion**

4 **Ectopic (tubal) pregnancy**

Go to next pregnancy; if no other pregnancy, go to page 16

5 **Therapeutic abortion**

Go to next pregnancy; if no other pregnancy, go to page 16

6 **Now pregnant** *Go to page 16*

67. How many weeks did this pregnancy last?

_____ **weeks**

68. During this pregnancy, were you hospitalized as a result of an accident or injury?

1 **No**

2 **Yes** → During which month(s)?

_____

69. During this pregnancy, did you have any of the following conditions? During which months?

		month(s) of pregnancy
1	**Bleeding/spotting**	_____
2	**Toxemia/eclampsia**	_____
3	**Vomiting requiring hospitalization**	_____
4	**Placenta previa**	_____
5	**Incompetent cervix treated with sutures**	_____
6	**Anemia requiring a blood transfusion**	_____
9	**None of the above**	

70. During this pregnancy, did you have any of the following illnesses? During which months?

		month(s) of pregnancy
1	**German measles (rubella)**	_____
2	**Hepatitis**	_____
3	**Red measles**	_____
4	**Influenza**	_____
5	**Urinary tract infection**	_____
6	**Cytomegalovirus**	_____
7	**Syphilis**	_____
8	**Genital herpes**	_____
9	**AIDS**	_____
10	**Toxoplasmosis**	_____
99	**None of the above**	

71. During this pregnancy, did you have any radiation to the lower back or to the abdomen below the waist [including radiation therapy, x-ray, IVP (intravenous pyelogram), or barium enema]?

1 **No**

2 **Yes** → During which month(s)?

_____

Fourth Pregnancy

72. Were you employed during this pregnancy?

1 No

2 Yes

a) During which month(s)?

_____

b) What was/were your job title(s)?

_____

c) What was/were the type of industry or business?

_____

d) Did this job involve any of the following?

1 **Standing more than 3 hrs a day**

2 **Working more than 40 hrs a week**

3 **Carrying loads of 10 kg/22 lbs or more**

4 **Work on industrial machine or assembly line**

5 **Routine work or work requiring little attention**

6 **Shift work**

9 **None of the above**

e) During this time were you directly exposed at work to any of the following?

1 **Ionizing radiation**

2 **Lead**

3 **Organic solvents**

4 **Agricultural chemicals**

5 **Nitrous oxide**

6 **Ethylene oxide**

7 **Anti-cancer drugs**

9 **None of the above**

73. In the 3 months preceding this pregnancy, was the father of the child employed?

1 No

2 Yes

a) What was/were his job title(s)?

_____

b) What was/were the type of industry or business?

_____

c) During this time was he directly exposed at work to any of the following?

1 **Ionizing radiation**

2 **Lead**

3 **Organic solvents**

4 **Agricultural chemicals**

9 **None of the above**

74. During this pregnancy, did you smoke cigarettes?

1 No

2 Yes → a) During which month(s)?

_____

b) How many cigarettes per day? _____

75. During this pregnancy, did you drink any alcoholic beverage?

1 No

2 Yes → a) During which month(s)?

_____

b) How many drinks per week? _____

Fourth Pregnancy

76. During this pregnancy, did you use any of the following medications? During which months?

		month(s) of pregnancy
1	**Hormones to prevent miscarriage** *(e.g., DES/ estrogen/premarin)*	_____
2	**Other medications to prevent miscarriage**	_____
3	**Prescription anti-nausea pills**	_____
4	**Thyroid medication**	_____
5	**Anti-seizure medication**	_____
6	**Antibiotics**	_____
7	**Prescription sedatives, tranquilizers, or sleeping pills**	_____
8	**High blood pressure pills**	_____
9	**Insulin**	_____
10	**"Recreational" drugs** *(e.g., LSD/cocaine)*	_____
99	**None of the above**	

77. At any time during the year before you became pregnant, did you take birth control pills?

1 No

2 Yes

→ Were you still taking the pill when you became pregnant?

1 No → How many months before you became pregnant did you stop taking the pill? _____ **months**

2 Yes → For how many months after you became pregnant did you continue taking the pill? _____ **months**

78. At the time you became pregnant, did you have an IUD (intrauterine device) in place?

1 No

2 Yes

If the outcome of this pregnancy was not a live birth, go to the next pregnancy. If no other pregnancy, go to page 16.

79. Did you have any of the following conditions at delivery?

1 **Breech presentation**

2 **Premature (less than 38 weeks) rupture of membrane**

3 **Prolonged (more than 24 hours) rupture of membrane**

4 **Abruptio placenta**

9 **None of the above**

80. What was the date of the delivery?

_____ / _____ / _____
day **month** **year**

81. What is the sex and weight at birth for each live baby delivered from this pregnancy (e.g., if single, twins, triplets etc.)?

____ sex ____ lbs ____ oz *or* ____ gms

____ sex ____ lbs ____ oz *or* ____ gms

____ sex ____ lbs ____ oz *or* ____ gms

____ sex ____ lbs ____ oz *or* ____ gms

If no other pregnancy, go to page 16. Information on subsequent pregnancies will be collected at time of interview.

If you have never had a live birth, go to page 17.

82. If any of your children were diagnosed **at birth or during the first year of life** with any of the following conditions, please indicate the pregnancy number.

Please specify if any of the child's blood relatives (i.e., grandparents, parents, aunts, uncles, cousins) had the same condition **at birth or during the first year of life.**

		Pregnancy Number	Relative with condition
1	Down's syndrome	_____	_____
2	Anencephaly (exposed brain)	_____	_____
3	Spina bifida (open spine)	_____	_____
4	Hydrocephalus (water around or within the brain)	_____	_____
5	Cleft lip (hare lip)	_____	_____
6	Cleft palate (hole in roof of mouth)	_____	_____
7	Hole in the heart or other congenital heart defect	_____	_____
8	Pyloric stenosis (stomach blockage)	_____	_____
9	Hip displacement	_____	_____
10	Club foot	_____	_____
99	None of the above		

83. Did any of your children die prior to their first birthday?

1 No

2 Yes ⟶ *Please fill in the chart below for each child who died prior to his/her first birthday.*

Pregnancy number	Cause of death	Months of age at death
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

The next few questions are about any problems you or your partner(s) may have had becoming pregnant.

84. Have you ever tried for one year or more to become pregnant, and been unable to?

1 No

2 Yes ⟶ *Please fill in the chart below for each period of time you tried to become pregnant. Include age started, number of months tried and if a problem was diagnosed for you, your partner, or both.*

Age started	Number of months tried	Was a problem diagnosed?	If yes, who was diagnosed?
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

85. Has a doctor ever told you that you had a fertility problem?

1 No

2 Yes ⟶ What was the problem?

1 **Anatomical** *(e.g., tubal blockage, fibroid tumors of womb, ovarian cysts)*

2 **Hormonal/glandular** *(e.g., failure to ovulate)*

3 **Other** *Please specify* _____

4 **No specific problem diagnosed**

86. Did you ever take medication to increase fertility?

1 No

2 Yes ⟶ a) What was the medication? _____

b) How many months did you take it? _____

87. Have you ever been married or lived as married?

1 No

2 Yes

Thank you for your help.

Childhood Cancer Survivors Study - Treatment abstraction Summary Sheet

(1) Subject ID # __ __ __ __

Data Abstraction Log

(2) Name	Hospital / Clinic (3) Chart #	(4) Last Date Seen (from chart)	Date Planned (5.a)	Date Completed (5.b)	Initial (5.c)	(5.d) Name of hospital/clinic referred to for ca treatment (specify Rx)	(6) - Supervisor Edited

(7) Treatment data abstracted from regional cancer clinic and/or hospital

0 = No, (if no) → Rx information from : (a) R = Registry records (OCR)
(b) S = Subject telephone interview
(c) U = Unkown

1 = Yes

(7a) Recurrence/Relapse

0 = No

1 = Yes (if yes) Date: __ __ __ __ __ __
Date: __ __ __ __ __ __
Date: __ __ __ __ __ __
(dd/ mm/ yr)

Type of treatment abstracted:

(8) Surgery (Circle answer)
0 = No surgery
1 = Surgery to reproductive organs (Code 10,11,12,20,21,22,60,61,62)
2 = Surgery to endocrine glands (Code 30,40,50)
3 = Surgery to other than #1 or #2 (code 98)
4 = Surgery (other medical) (#13,14,15,23,24,25, 31,41,51,63,64,65)
9 = Unknown

(9) Radiotherapy (Circle answer)
0 = No
1 = Yes
9 = Unknown

(10) Chemotherapy (Circle answer)
0 = No
1 = Yes
9 = Unknown

		Inital
(11)	Abstractor: Completed & checked all data collection	__
(12)	Supervisor: Checked & clarified all data collection	__ __
(13)	Data Entry Clerk: Entered & checked all data	__

October 31st, 1994

Date of Interview: (1) _ _ _ _ _ _ (2) Subject's I.D. # _ _ _ _ _

(3)

Surgery

Complete this section at end of abstracting all surgery information

(Circle answer) 1 = No
2 = Yes [Chart noted Surgery at another hospital or clinic

(4) Chart noted surgery at another hospital :

Hosp/Clinic_____ Surgery date:_____

Hosp/Clinic_____ Surgery date:_____

(5) Day Mo Yr	(6) Surgery Type or Site	(7) Code	(8) Hospital / Clinic	(9) Comments:
_ _ _ _ _ _		_ _ _ _		
_ _ _ _ _ _		_ _ _ _		
_ _ _ _ _ _		_ _ _ _		
_ _ _ _ _ _		_ _ _ _		

(10) Surgery Comments:_____

11-unilateral Oophorectomy (14)
12-Bilateral Oophorectomy (15)
22-Total Abd. Hysterectomy (25)
30-Thyroidectomy(part/whole) (31)
40-Hypophysectomy(pit.gland) (41)
50-Adrenalectomy(one/both) (63)
61-Unilateral salpingectomy (64)
62-Bilateral Salpingectomy (65)

10-Ovary(unspecified) 13
20-Uterus(unspecified) 23
21-Subtotal hysterectomy(w/o cervix) 24
60-Salpingectomy(unsp) 63
80-unknown site ; reproductive organ
98-Other surgery than mentioned above for cancer treatment ;

(November 28, 1994)

CSS - RADIOTHERAPY

Date of Interview ____________ Subject I.D. # _ _ _ _

(3) *Complete this section at end of abstracting all radiotherapy information*

(Circle answer) 1 = No 2 = Yes [Chart noted radiotherapy at another hospital or clinic

(4) Chart noted XRT at another hosp/clinic : (1) (2)

Hosp/clinic ____________ Date of XRT ________

Hosp/clinic ____________ Date of XRT ________

(5) Date Began day mo yr	(6) Date Ended day mo yr	(7) Type code	(8) Site Code	Description	(9) Total Dose cGy or Rads	(10) # of Fractions	(11) # of fields	(12) Field size	(13) Hospital /comment
______	______	__	__	________	____	__	_	__x__	________
______	______	__	__	________	____	__	_	__x__	________
______	______	__	__	________	____	__	_	__x__	________
______	______	__	__	________	____	__	_	__x__	________
______	______	__	__	________	____	__	_	__x__	________
______	______	__	__	________	____	__	_	__x__	________
______	______	__	__	________	____	__	_	__x__	________
______	______	__	__	________	____	__	_	__x__	________
______	______	__	__	________	____	__	_	__x__	________

Type Code:

1 = Internal
2 = Cobalt 60: 6-25 MEV
3 = Othovoltage: 250 kV
4 = Linear Accelerator Electrons: 6-25 MEV
5 = External, other/unspecified
6 = I-131
8 = Other
9 = Unknown type

Site Code:

1 = Brain/skull (whole or part)
2a = Cranial }
2b = Spine }
3 = Neck (bilateral)
4 = Neck (unilateral) & Head/neck (other)
5a = Thorax (whole/partial)
5b = Abdomen (whole/partial)
6a = Upper mantle
6b = Paraaortic nodes & spleen
7 = Inverted Y
8 = Pelvis (whole/ hemi/ partial)
9 = Hip joint /or femur
10a = Spine (thoracic)
10b = Spine (lumbar)
10c = Spine (Sacral)
11 = whole body irradiation (TBI)
12 = Others/ outside the above regions e.g. distal extremities
13 = Missing

(14)

Radiotherapy Comments: ____________

Enter Additional radiotherapy on extra radiotherapy form and page number as P.2.1, P.2.2, P.2.3, etc.)
(If chemotherapy was given, go to Page 3)

Date of Interview ___ ___ ___ Subject I.D. # _ _ _ _

(1) (2)

(3) *Complete this section at end of abstracting all chemotherapy information*

(Circle answer) 1 = No / 2 = Yes [Was additional chemotherapy given elsewhere

(4) Additional chemo/Other hospitals

Hosp/clinic ____________________ Chmo date __________

Hosp/clinic ____________________ Chmo date __________

(5) Date Began day mo yr	(6) Date Ended day mo yr	(7) Combi-nation	Drug Name	(8) Drug Code	(9) Dose Total -	(10) Mg/gm/µg/Unit	(11) Route	(12) Weight (kg)	(13) Height (cm)	(14) Comments :

(7) **Combination code:**

1 - Drug use in a combination (multiple-agent therapy)

2 - Drug use alone

(10) **Dose total (measurement)**

1 = mg
2 = gm
3 = µg
4 = Unit

(11) **Route Code:**

1 = Oral (Often recorded as P.O.)
2 = subcutaneous (S.C.)
3 = Intramuscular (I.M.)
4 = Intravenous (I.V.)
5 = Intrathecal (I.T.)
8 = Other (specify) ______
9 = Unknown

 (for further chemotherapy and comments, go to Page 4)

CSS - CHEMOTHERAPY

Date of Interview ______________ Subject I.D. # _ _ _ _

Date Began day mo yr	Date Ended day mo yr	Combi -nation	Drug Name	Code	Dose Total - Mg/gm/µg/Unit	Route	Weight (kg)	Height (cm)	Comments :

Chemotherapy Comments:______________________________

Additional chemotherapy enter on extra chemotherapy form and page number as P.4.1, P.4.2, P.4.3, etc.)

APPENDIX D: Physician Letter

Department of Preventive Medicine and Biostatistics
Faculty of Medicine, University of Toronto
Toronto, Ontario, M5S 1A8

1~

Dr. 2~ 3~
4?~
5~
6~, 7~ 8~

Re: A Study of Reproductive Outcomes in Female Childhood Cancer Survivors

Dear Dr. 3~ :

I am writing to request your cooperation in the above study which we are conducting through the Ontario Cancer Treatment and Research Foundation, and the University of Toronto. This study has been funded by the Ministry of Health. A summary of the study is attached.

Your patient (named on the attached form) is eligible for our study. I request your written permission to send her a study questionnaire (**The Human Subjects Committee at University of Toronto requires written consent from an attending physician prior to contact with the patient).** Telephone interviews will be conducted with the patients who agree to participate. Please indicate to us whether your patient has been made aware of her cancer diagnosis in childhood and if she has had any additional primary cancer diagnoses, subsequent to her first diagnosis. If you do not feel that you are the most appropriate physician to give consent for this patient, could you please suggest another physician for us to contact. Strict confidentiality of all information will be maintained. Please complete the form and return it in the enclosed envelope.

If your **patient** has questions about issues related to the subject of this study i.e., the late effects of cancer treatment on fertility or pregnancy outcomes, she may call Ms. Nancy O'Brien at the Cancer Information Service (we will provide the toll free phone number to the patient upon request). Ms. O'Brien would be happy to discuss any of your questions as well. We have worked with the Cancer Information Service to develop a package of relevant information.

If you have any concerns about the study or would like to see a copy of the letter or questionnaire sent to the patients, please call the Study Coordinator, Ms. Isabel Fan or me collect at (416) 978-7251.

Yours sincerely,

Loraine D. Marrett, PhD
Principal Investigator
encl.

APPENDIX E: Physician Consent Form

Department of Preventive Medicine and Biostatistics
Faculty of Medicine, University of Toronto
12 Queens Park Crescent West, 3rd Floor McMurrich Building
Toronto, Ontario M5S 1A8, (416) 978-7251

PHYSICIAN CONSENT FORM

Study of Reproductive Outcomes in Female Childhood Cancer Survivors

Re: **FIRSTNAME SURNAME1/SURNAME2** Birthdate: MAILDOB

I agree that the above-named patient may be invited to participate in the study.

Signature:_____ Date:_____
Dr. PHYSFIRST PHYSURNAM

Our records show that this patient was diagnosed with ICDMNEM in 19DIAGYR1.

Has the above-named patient been informed of this diagnosis? (Please check answer)

Yes ____ No ____ (If no, this patient will not be contacted)

Has this patient had any additional primary cancer diagnoses, subsequent to the above-mentioned diagnosis?

Yes ____ No ____

If yes, please indicate site of cancer diagnosis and date of diagnosis.

Site:_____ Date of diagnosis: _____

PLEASE COMPLETE FOR THIS PATIENT:

Name: _____/ _____/ _____/ _____
(current surname) (first name) (middle name) (maiden/other)

Street Address: _____

Town/City/Postal Code: _____

Telephone No.: (_____) _____ Approximate Date of Most Recent Contact: _____

(PHYSID) (CASEID)

APPENDIX F: Subject Letter

Department of Preventive Medicine and Biostatistics
Faculty of Medicine, University of Toronto
Toronto, Ontario, M5S 1A8

STREET
CITY, PROV POSTAL

Dear FIRTSTNAME SURNAME :

Treatment for many cancers of childhood has improved dramatically over the past 20 years. With the resulting increase in number of survivors of childhood cancer, there is an urgent need to determine whether there are any long term health effects of these therapies. It is likely that a number of studies will be conducted in this area over the next few years.

We are presently conducting a study of reproductive effects among females who had cancer and certain other types of tumors as children. We are writing to ask for your help in this study. Dr. PHYSURNAM has agreed that we may contact you for this study and send you a questionnaire about women's health. An interviewer will be calling you in about a week to answer any questions you might have about the study and to record your answers. If it is more convenient you may call the study coordinator, Ms. Isabel Fan at (416) 978-7251 (collect) to arrange a time to complete the questionnaire. Please take a few minutes to look over the questionnaire so that we will require as little of your time as possible on the telephone.

There are different types of therapy for these conditions, including surgery, radiotherapy and chemotherapy. We wish to see if the type of therapy received affects menstruation and a woman's ability to become pregnant and have children. We are asking for your consent to abstract relevant treatment information from your medical records. **Please sign the permission form and return it in the enclosed envelope to the study office.**

All of your responses and all treatment information abstracted will be handled as confidential, and will be used for research purposes only. Study results will be reported in terms of groups so that the identification of individuals will never be possible. The study analysis will be completed in late 1995. We will send all participants a copy of the results when available.

Participation in this study is voluntary, and you are free to skip any questions that you do not wish to answer, to stop the interview at any time or to refuse access to treatment information from your medical records. However, in order for the results of this study to be informative and truly representative of females with these childhood conditions, it is important that we receive the cooperation of as many women as possible. Only with such information will we be able to understand possible risks and to provide any necessary reproductive counselling.

Please do not hesitate to call (collect) Ms. Fan if you have any questions or concerns. Thank you for your cooperation and assistance.

Sincerely,

Loraine D. Marrett, PhD
Associate Professor, University of Toronto

APPENDIX G: Subject Consent Form

Department of Preventive Medicine
Faculty of Medicine, University of Toronto
12 Queens Park Crescent West, 3rd Floor McMurrich Building
Toronto, Ontario M5S 1A8, (416) 978-7251

Permission to Access Cancer Treatment Information

Research Project: A Study of Reproductive Outcomes in Female Childhood Cancer Survivors

Investigator: Loraine D. Marrett, PhD

I acknowledge that the research procedures described on the attached letter of 1-, have been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been assured that records relating to me and my care will be kept confidential and that no information will be released or printed that would disclose personal identity without my permission.

I hereby consent to the abstraction of cancer/tumor treatment information available from my medical records.

Signature: _____ Date: _____

APPENDIX H: Hospital for Sick Children Clinical Information Form

555 UNIVERSITY AVENUE
TORONTO, ONTARIO
CANADA M5G 1X8
PHONE (416) 813-1500

THE HOSPITAL FOR SICK CHILDREN

CLINICAL INFORMATION FORM

Title of Research Project: A Study of Reproductive Outcomes in Female Childhood Cancer Survivors

Investigators: Loraine D. Marrett, PhD
Telephone: (416) 971-9800

Mark L. Greenberg, MB, ChB
Telephone: (416) 278-7826

Purpose: We are presently conducting a study of reproductive effects among females who had cancer and certain other types of tumors as children. We wish to see if the type of therapy received is important to a woman's ability to menstruate, and to become pregnant and have children.

Description of Research: We have received permission from your doctor to contact you for this study and to send you a questionnaire about women's health. An interviewer will be calling you in about a week to answer any questions you might have about the study and to record your answers. It would be helpful if you could take a few minutes to look over the questionnaire so that we will require as little of your time as possible on the telephone. We will also require your consent to abstract cancer/tumor treatment information from your medical records. Please sign the permission form and return it in the enclosed envelope to the study office.

Confidentiality: Confidentiality will be respected and no information that discloses your identity will be released without your consent. All of your responses and all treatment information abstracted will be handled as confidential, and will be used for research purposes only. Study results will be reported in terms of groups so that the identification of individuals will never be possible.

Participation: Your involvement in this study will include a telephone interview and the return of a signed permission form for access to relevant medical records. Participation in this study is voluntary, and you are free to skip any questions that you do not wish to answer, to stop the interview at any time or to refuse access to treatment information from your medical records.

Potential Harm: There are no known harms associated with participation in this study.

Potential Benefits: You will not benefit directly from participating in this study.
Information collected from this study will we be used to understand possible risks and to provide any necessary reproductive counselling to future survivors of these childhood conditions.

Appendix I:

Expected Number of Outcomes in Comparison group and Minimal Detectable Relative Risk (For Radiation Group) (one-tailed alpha=0.05, beta=0.20)

Outcome	Number Expected	Relative Risk
Infertile	55	1.8
Spontaneous abortions	87	1.4
Perinatal deaths	7	3.5
Low birth weight	32	1.9
Birth defects	15	2.25

* N=448 for radiation group, N=448 for comparison group

Appendix J:

Expected Number of Outcomes in Comparison Group and Minimal Detectable Relative Risk (For Chemotherapy Group) (one-tailed alpha=0.05, beta=0.20)

Outcome	Number Expected	Relative Risk
Infertile	68	1.8
Spontaneous abortions	107	1.4
Perinatal deaths	9	3.75
Low birth weight	39	1.9
Birth defects	19	2.25

* N=277 for chemotherapy group, N=554 for comparison group

APPENDIX K: Cancer Act

CHAPTER 57

Cancer Act

PART I

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

Foundation continued

1. The corporation known as The Ontario Cancer Treatment and Research Foundation, referred to in this Act as the Foundation, is continued. R.S.O. 1970, c. 55, s. 1.

Members

2.—(1) The Foundation shall consist of not fewer than seven members who shall be appointed by the Lieutenant Governor in Council and who shall hold office during pleasure.

Vacancies

(2) The Lieutenant Governor in Council may fill any vacancies that occur from time to time in the membership of the Foundation.

Quorum

(3) Five of the members of the Foundation constitute a quorum for the transaction of business. R.S.O. 1970, c. 55, s. 2.

Chairman, vice-chairman

3.—(1) The Lieutenant Governor in Council may appoint one of the members to be chairman of the Foundation and another of the members to be vice-chairman of the Foundation.

Presiding officer

(2) The chairman shall preside at all meetings of the Foundation at which he is present and in his absence the vice-chairman shall preside and in the absence of both the chairman and the vice-chairman the members present shall elect one of themselves to preside. R.S.O. 1970, c. 55, s. 3.

Advisory medical board

4. Subject to the approval of the Lieutenant Governor in Council, the Foundation may appoint an advisory medical board consisting of such persons representative of the medical faculties of the University of Toronto, Queen's University, The University of Western Ontario and the University of Ottawa, and of radiotherapists, surgeons, pathologists, internists, physicists and the medical profession generally as the Foundation considers appropriate. R.S.O. 1970, c. 55, s. 4, *revised*.

Object

5. The object of the Foundation is to establish and conduct a program of research, diagnosis and treatment in cancer, including,

(*a*) the establishment, maintenance and operation of research, diagnostic and treatment centres in general hospitals or elsewhere;

(*b*) the transportation of patients and escorts to its treatment centres or to the hospital of the Institute for diagnosis, treatment or investigation;

(*c*) the establishment, maintenance and operation of hostels in connection with its treatment centres or the hospital of the Institute;

(*d*) the laboratory and clinical investigation of cancer problems;

(*e*) the co-ordination of facilities for treatment;

(*f*) the adequate reporting of cases and the recording and compilation of data;

(*g*) the education of the public in the importance of early recognition and treatment;

(*h*) the providing of facilities for undergraduate and post-graduate study;

(*i*) the training of technical personnel; and

(*j*) the providing and awarding of research fellowships. R.S.O. 1970, c. 55, s. 5.

Agreements

6. Subject to the approval of the Lieutenant Governor in Council, the Foundation may make agreements with universities, medical associations, hospitals and persons for the purpose of carrying out the object of the Foundation. R.S.O. 1970, c. 55, s. 6.

Information to be confidential

7.—(1) Any information or report respecting a case of cancer furnished to the Foundation by any person shall be kept confidential and shall not be used or disclosed by the Foundation to any person for any purpose other than for compiling statistics or carrying out medical or epidemiological research.

Liability

(2) No action or other proceeding for damages lies or shall be instituted against any legally qualified medical practi-

tioner or any licensed dental surgeon or any hospital in respect of the furnishing to the Foundation of any information or report with respect to a case of cancer examined, diagnosed or treated, by such medical practitioner or dental surgeon or at such hospital. 1972, c. 34, s. 1.

Staff

8. The Foundation may employ a director and officers, clerks and servants and may engage the services of experts and other persons and may pay such director, officers, clerks, servants, experts or other persons such remuneration as it considers proper out of its funds. R.S.O. 1970, c. 55, s. 7.

By-laws

9. Subject to the approval of the Lieutenant Governor in Council, the Foundation may make such by-laws, rules or regulations as are considered expedient for the administration of its affairs. R.S.O. 1970, c. 55, s. 8.

Funds

10. The funds of the Foundation consist of moneys received by it from any source including moneys appropriated for its use by the Parliament of Canada or the Legislature of Ontario, and the Foundation may disburse, expend or otherwise deal with any of its funds in such manner not contrary to law as it considers proper. R.S.O. 1970, c. 55, s. 9.

Expenses

11. The members of the Foundation and its medical advisory board shall be paid such amounts for travelling and other expenses as the Foundation, subject to the approval of the Lieutenant Governor in Council, may determine from time to time. R.S.O. 1970, c. 55, s. 10.

Audit

12. The accounts of the Foundation shall be audited annually by the Provincial Auditor or by such qualified auditor as the Lieutenant Governor in Council designates, in which event the costs of the audit shall be paid out of the funds of the Foundation. R.S.O. 1970, c. 55, s. 11.

Annual report

13.—(1) The Foundation shall after the close of each fiscal year make a report upon its affairs during the preceding year to the Minister of Health and every such report shall contain a financial statement, certified by the auditor, showing all moneys received and disbursed by the Foundation during the preceding year. R.S.O. 1970, c. 55, s. 12 (1).

Idem

(2) The Minister of Health shall submit the report to the Lieutenant Governor in Council and shall then lay the report before the Assembly if it is in session or, if not, at the next ensuing session. R.S.O. 1970, c. 55, s. 12 (2); 1972, c. 1, s. 78 (1).

Power to expropriate land and erect buildings

14.—(1) Subject to the approval of the Lieutenant Governor in Council, the Foundation may acquire by purchase or lease, or may enter upon, take and use without the consent of the owner thereof, any land and buildings that are considered suitable for the purposes of the Foundation and may erect buildings, acquire and install machinery and equipment and purchase all such instruments, materials and appliances and other matters and things that are considered necessary.

Application of R.S.O. 1980, c. 148

(2) Whenever the Foundation exercises the power to enter upon, take or use lands without the consent of the owner thereof, the *Expropriations Act* applies. R.S.O. 1970, c. 55, s. 13.

Right to acquire patents, etc.

15. Subject to the approval of the Lieutenant Governor in Council, the Foundation may apply for, or acquire by purchase, assignment or otherwise, rights in any patent relating to any remedy for the prevention or cure of cancer and may sell and dispose thereof or of any interest therein, and grant or assign any rights that have been acquired by the Foundation thereunder. R.S.O. 1970, c. 55, s. 14.

Property not liable to assessment

16. The real and personal property, business and income of the Foundation is not subject to taxation for municipal or provincial purposes. R.S.O. 1970, c. 55, s. 15.

APPENDIX L: Permission to use Ontario Cancer Registry Records

THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION
7 Overlea Blvd., Toronto, Ontario M4H 1A8 Tel. (416) 423-4240 Fax (416) 423-2017

LA FONDATION ONTARIENNE POUR LA RECHERCHE EN CANCÉROLOGIE ET LE TRAITEMENT DU CANCER
7, boul. Overlea, Toronto Ontario M4H 1A8 Tel. (416) 423-4240 Fax (416) 423-2017

October 28, 1991

Dr. L. Marrett
Director
Epidemiology Research Unit
Division of Epidemiology and
Statistics
The Ontario Cancer Treatment and
Research Foundation
7 Overlea Boulevard
Toronto, Ontario
M4H 1A8

Re: A Retrospective Cohort Study of Reproductive Outcomes in Female Childhood Cancer Survivors

Dear Dr. Marrett:

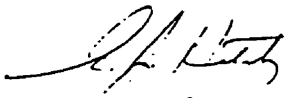
I am pleased to advise you that your application for release of identifying information from the Ontario Cancer Registry for the purpose of the above study has been reviewed and approved. However, this approval is conditional on review and approval of the project by the Ethics Review Committee at the Office on Research Administration at the University of Toronto. You must submit written confirmation of such approval to us prior to the release of this identifying information. Further, could you please complete and return to me the enclosed agreement form.

In the review of this proposal by the Subcommittee on Access to and Use of Cancer Patient Records it was noted that the subjects will not be given a clear explanation of the purpose of this research. We recognize this will not constitute a fully informed consent. However, we understand that some of these subjects may not have a clear understanding of their past history of childhood cancer, and that disclosure of this information may cause appreciable anxiety and distress. We accept that withholding this information will probably not adversely affect the welfare of the subjects. Indeed, it is conceivable that this research could not be practically carried out otherwise (the selection bias would be too great). Again, we are prepared to approve this request if the UofT Ethics

Review Committee waives the requirement for full disclosure of the purpose of the research.

Good luck with your grant applications for this study.

Yours sincerely,



E.J. Holowaty, M.D., F.R.C.P.(C), M.Sc.
Director, Ontario Cancer Registry
Division of Epidemiology and Statistics

EJH:sh
Encl.
cc: Ms. A. Chiarelli
Dr. N. Kreiger
Ms. D. Dale

APPENDIX M: Approval from University of Toronto Ethics Review Committee

University of Toronto

OFFICE OF RESEARCH SERVICES

Approval by Review Committee on the Use of Human Subjects

Principal Investigator	:	Dr. L. Marrett, Preventive Medicine
Title	:	A Province-Wide Retrospective Cohort Study of Reproductive Outcomes in Female Childhood Cancer Survivors (Amendment)
Review Committee	:	Professor A. B. Miller, Preventive Medicine
Documents Submitted to Review Committee	:	Letter dated October 7, 1993 from Dr. Marrett, questionnaire
Subjects	:	As approved March 9, 1992
Procedures	:	As approved July 14, 1993 but with some minor modifications to the questionnaire
Method for Obtaining Consent	:	As approved July 14, 1993
Remarks	:	
Date of Approval	:	October 18, 1993

*During the course of the research, any significant deviations from the approved protocol and/or any unanticipated developments within the research should be brought to the attention of the Office of Research Services.

SP/tf

cc: Review Committee

Susan Pilon
Executive Officer
Human Subjects Review Committee

Simcoe Hall 27 King's College Circle Toronto Ontario M5S 1A1 Telephone 416/ 978-2163 Fax 416/ 971-2010

Appendix N: Potential pregnancy outcome confounders from questionnaire data

Demographics:

Education (< = High School, > High School)*
Race (White, Other)*

Conditions prior to or during pregnancy (Yes/No):

High blood pressure
Heart Disease
Chronic kidney disease
Anemia
Epilepsy
Endocrine conditions (pituitary, adrenal, thyroid)**
Hospitalized for an accident or injury
Radiation to lower back or abdomen

Medications/contraceptives used during pregnancy (Yes/No):

Urinary infection*
Influenza
Herpes/Syphilis/Cytomegalovirus/AIDs
Rubella/Red measles
Hepatitis
Toxoplasmosis
Bleeding/spotting*
Toxemia*
Vomiting requiring hospitalization
Incompetent cervix
Placenta Previa
IUD
Birth control pill
Hormones to prevent miscarriage
Anti-nausea pills*
Thyroid pills**
Anti-seizure pills
Antibiotics**
Sedatives/Tranquillizers/Sleeping pills
High blood pressure pills
Insulin
Recreational drugs (i.e. LSD/Cocaine)

Smoking and alcohol use during pregnancy:

- Smoking (Yes/No)**
- Trimester smoked (Third/First,second or non-smoker)**
- Number of cigarettes (>10/1-10/0)**
- Alcohol (Yes/No)**
- Number of drinks per week (>3,1-2,0)

Employment during pregnancy (Mother):

1. Exposures (Yes/No)
   - Ionizing radiation
   - Lead
   - Organic solvents
   - Agricultural chemicals
   - Nitrous oxide
   - Ethylene oxide
   - Anti-cancer drugs
2. Physical exertion (Yes/No)
   - Standing (>3 hours a day)**
   - Work week (>40 hours)*
   - Heavy loads (>22 lbs)*
   - Assembly line work
   - Routine work**
   - Shift work**

Employment 3 months preceding pregnancy (Father):

1. Exposure (Yes/No)
   - Ionizing radiation
   - Lead
   - Organic solvents**
   - Agricultural chemicals**

Conditions at delivery:

- Breech birth
- Premature rupture of membrane**
- Prolonged rupture of membrane**
- Abruptio placenta

* Prevalence of potential confounder was greater than 5%.
** p-value <0.15.

APPENDIX O: Site of Surgery Codes

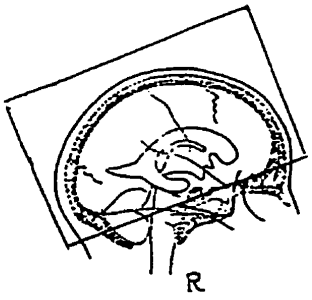
List B - for Surgery Codes (2 digit code) - Page 1, Item #7

For Cancer	other medical	Description
10	13	- Ovary; unspecified; or other than unilateral / bilateral oophorectomy
11	14	- Unilateral oophorectomy - removal of one of the ovary
12	15	- Bilateral Oophorectomy - removal both ovaries
20	23	- Uterus; unspecified, or other than Subtotal / total hysterectomy
21	24	- Subtotal hysterectomy - removal of uterus but cervix is left in place
22	25	- Total hysterectomy - uterus & cervix completely excised
30	31	- Thyroidectomy -- removal of thyroid gland: complete or partial
40	41	Surgery to pituitary gland: - Hypophysectomy - removal/destruction of the hypophysis or pituitary gland
50	51	Surgery to adrenal gland(s): Adrenalectomy -- excision of one or both adrenal glands
60	63	- Salpingectomy -- Removal of uterine tube, unspecified
61	64	- Unilateral salpingectomy for Ca treatment -- Removal of one of the uterine tube
62	65	Bilateral salpingectomy for Ca treatment -- Removal of both uterine tubes
80		Surgery to reproductive organ, but site unknown, for Ca treatment or other medical reason
98		Other surgery than mentioned above for cancer treatment only

APPENDIX P: Radiation Therapy Site Codes

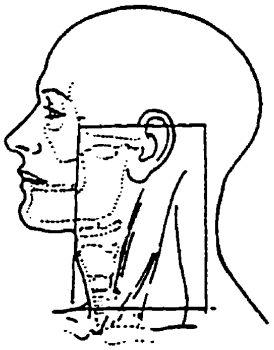
CSS Study: Radiation Therapy Abstraction - SITE CODES -

1. Brain (whole or partial)

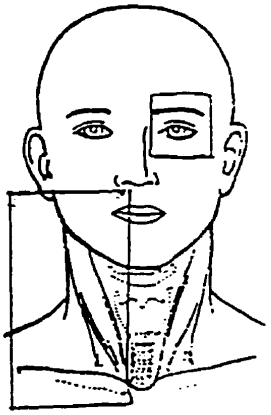


2. Crainial-spinal

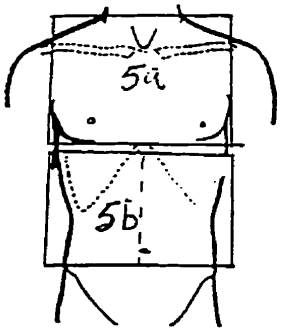
3. Neck (bilateral)



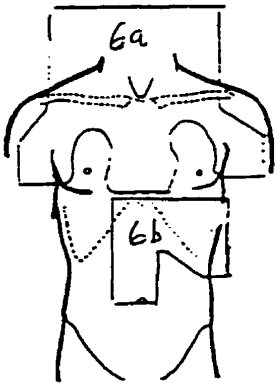
4. Neck (unilateral) & Head / neck (other, e.g. orbit



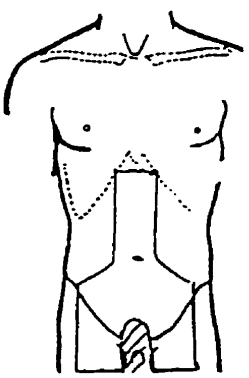
5a [Thorax (whole or partial)
5b [Abdomen (whole or partial)



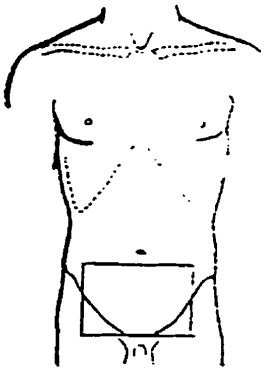
6a [Upper mantle
6b [Paraaortic nodes & spleen



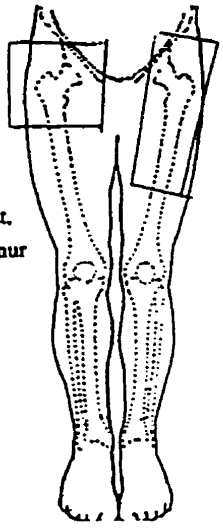
7. Inverted Y



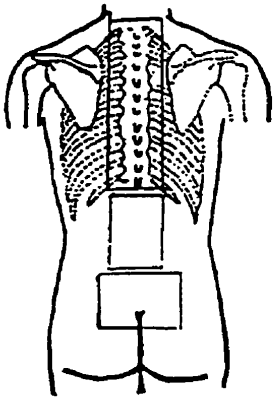
8. Pelvis (whole, hemi pelvis, or partial



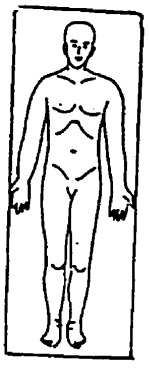
9. Hip joint, and/or femur



10. Spine (thoracic, lumbar, sacral)



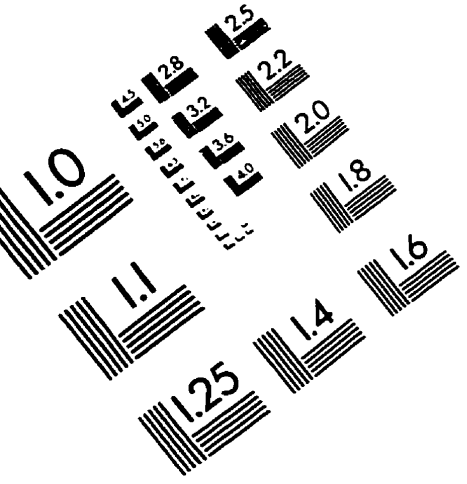
11. Whole body irradiation (TBI)

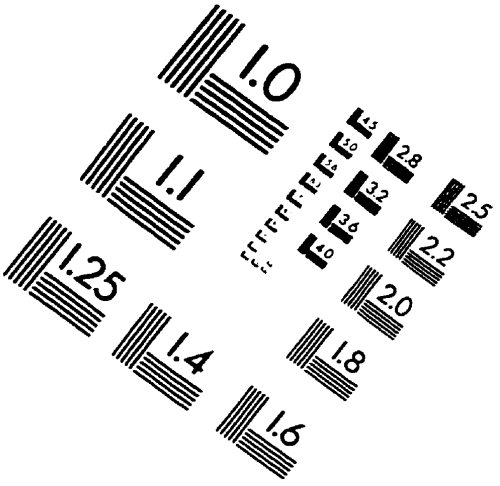


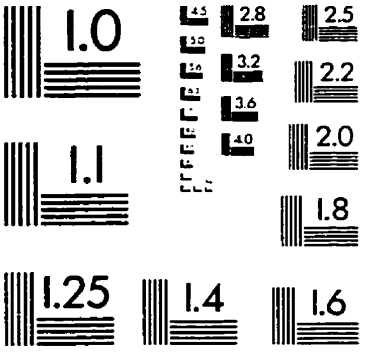
12. Others/ outside the above regions. e.g. distal extremities

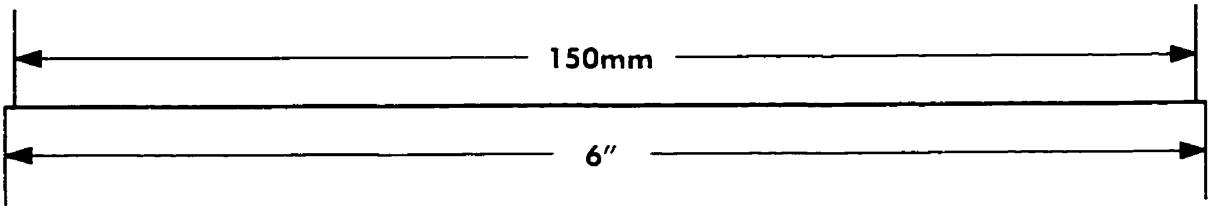
13 [Missing

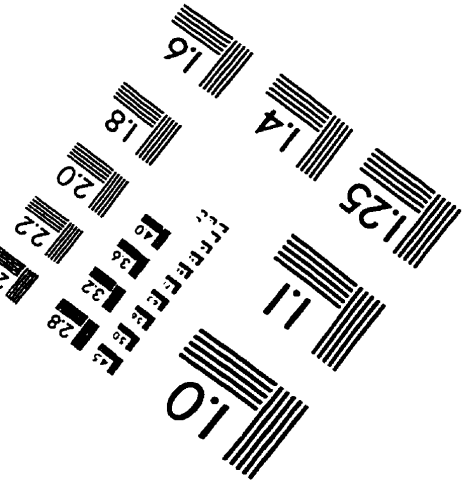
IMAGE EVALUATION TEST TARGET (QA-3)

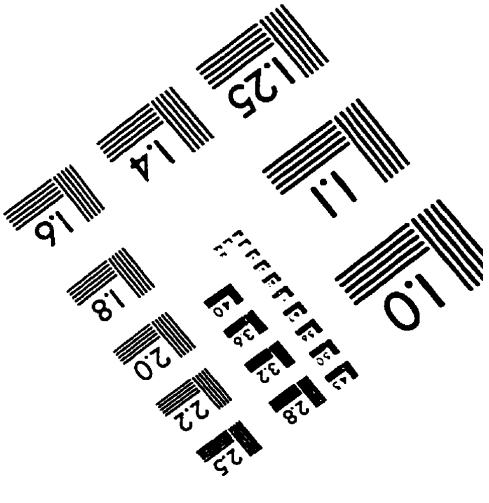












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