Medical and Pediatric Oncology 19:459–466 (1991)

Reproduction Following Treatment for Childhood Leukemia: A Population-Based Prospective Cohort Study of Fertility and Offspring

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Of all children diagnosed with leukemia in Denmark, Finland, Iceland, Norway, and Sweden, 981 had discontinued therapy before 1985 and had been followed up annually after cessation of therapy. Progeny was registered and fertility evaluated among survivors who passed age 18 years without a relapse ($n = 299$).

By April 1989, 48 offspring were registered, one of whom had congenital anomalies. This was no more than expected from the incidence of birth defects in the general population. No childhood malignancies or genetic diseases have so far been diagnosed in the progeny. In the study group, none of the 19 female and 8 male survivors of myeloid leukemias had become parents, and only 4 fathers were reported among the 131 male survivors of acute lymphoblastic leukemia (ALL). However, 23 of the 149 females treated for ALL had delivered 41 children. Fertility was measured as cumulative rates of first birth by maternal age. In a Cox regression analysis, cases who had received prophylactic radiation of the central nervous system (CNS) had a lower first birth rate than those without radiation (rate ratio 0.39, 95% CI 0.15–1.00), indicating that doses of 18–24 Gy to the brain may possibly be a risk factor. By using the Norwegian birth cohort of 1966 as a control group, matching the median year of birth for the study subjects, the group of female ALL survivors as a whole was as likely as the general female population to have given birth up to the age of 23.

The first generation of females successfully treated for childhood ALL seems to have a nearly normal reproductive pattern during young adulthood, without increased risk of congenital anomalies in the offspring. However, cranial radiation as CNS prophylaxis may possibly impair subsequent reproduction.

Key words: leukemia in childhood, long-term survivors, antineoplastic agents adverse effects, radiotherapy adverse effects, fertility, birth defects

INTRODUCTION

The prospect of potential cure for childhood leukemia induced concern about late adverse effects of the disease and its treatment, and it was recognized that impaired fertility in the survivors as well as genetic disease in the offspring could possibly be expected [1–4]. Long-term follow-up studies of large patient cohorts were needed to evaluate the clinical importance of these late effects and relate them to specific diseases and therapy.

The 5 Nordic countries have a total of 23 million inhabitants. Well-organized national health systems enable identification of selected patient populations. This prompted a prospective follow-up investigation of all childhood leukemia patients who had discontinued treatment [5–9]. The objectives of the present study were to compare fertility in the patient group with that of the normal population, and to identify predictive factors. Neuroleukemia prophylaxis had been given as radiotherapy (RT) to 58% of all ALL patients in the cohort, enabling us to study radiation as one factor possibly influencing subsequent fertility. We also wished to

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Received August 7, 1990; accepted February 14, 1991.

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investigate occurrence and nature of anomalies and malignancies in the offspring of survivors of childhood leukemias.

MATERIALS AND METHODS

Patients

Of all children diagnosed before age 15 with childhood leukemias, 981 had electively discontinued therapy by 1985; 963 in primary and 18 in a later remission. By April 1989, 763 patients from the complete cohort had survived without relapse subsequent to cessation of therapy, 299 of whom had passed 18 years of age. These adults formed the present study group, and are characterized according to diagnosis and main treatment category in Table I. The patients had been treated during the period 1958 through 1984 in 79 hospitals in Denmark, Finland, Iceland, Norway, and Sweden. The time interval from cessation of therapy to the end of the study period ranged from 4.3 to 26.5 years.

In the study group, 280 cases were survivors of ALL; 149 females and 131 males with median birth year 1966 and 1967, respectively. At last follow-up, the females ranged in age from 18 to 42 years, but only 30 cases had passed age 25. With a few exceptions of long-term survivors after bone marrow transplantation (BMT), the ALL patients had been treated according to various contemporaneous chemotherapy (CT) protocols [10–14]. Prophylaxis against CNS leukemia was gradually introduced during the years 1971–1973. Methotrexate (MTX) intrathecally, later combined with systemic infusions, was the method of choice in Norway and Iceland [10]. Intrathecal MTX combined with cranial radiation (RT) 18–24 Gy was the standard procedure elsewhere. Of the adult female ALL patients without BMT, 33 cases had not received any CNS prophylaxis, 35 had been given MTX, and 78 had also received RT.

Methods

Patients were included in the study from 1962 until 1985, and annual information was collected directly from physicians in all departments treating and controlling the patients [9]. They provided, on a patient by patient basis and from the year of cessation of therapy, data on relapses, deliveries, life status, and time last seen. Last data collection was completed April 1, 1989. Medical status in the offspring was also reaffirmed at that point.

Fertility in the 149 female adult survivors of ALL was measured as birth rate by maternal age at first delivery, calculated according to the Kaplan–Meier method [15]. Censoring was mainly at the age achieved when the study closed, but in addition, cases were censored at relapse ($n = 5$), death ($n = 3$), and when lost to follow-up ($n = 9$). Fertility estimates for different treatment groups were compared using the logrank rest [16], with a significance level at 5%. The Cox regression model [17] was used to estimate fertility rate ratios comparing patients with and without radiation, while simultaneously controlling for the effects of the following covariates: age at diagnosis (3 categories), age at cessation of therapy (3 categories), and calendar year of treatment start (4 categories). The fertility rate ratios, as measure of relative risk, were reported with 95% confidence intervals (CI).

TABLE I. Adult Survivors of Childhood Leukemia (160 Females, 139 Males) by Diagnosis and Main Treatment Category*

	All categories	CT only	CT + RT	BMT
ALL ($n = 280$)				
Females	149	68	78	3
Males	131	58	71	2
AML ($n = 17$)				
Females	9	5	2	2
Males	8	4	2	2
CML ($n = 2$)				
Females	2	0	0	2
Total no. of cases	299			

*ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMT, bone marrow transplantation; CML, chronic myeloid leukemia; CT, chemotherapy; RT, radiotherapy.

The Norwegian female birth cohort of 1966 with 31,186 individuals was chosen as a reference, permitting comparison until age 23. The population at risk was defined as the midyear population according to data from the Norwegian Central Bureau of Statistics. The Norwegian Medical Birth Registry provided annual parity- and age-specific birth numbers, enabling calculation of cumulative birth rates according to the life table method [15,18,19,21].

The MEDLOG biomedical computer program was used for calculations.

RESULTS

Among the 299 adult survivors of childhood leukemias, 27 patients treated for ALL had become parents (Table II). No children were born to or sired by survivors of myeloid leukemias.

Twenty-three of the 149 adult *female* ALL survivors had delivered 41 children. Most of the mothers had been on antileukemic therapy at least partly during puberty: Seventeen were above 10 years of age and 8 were 15 years or older at cessation. Treatment had been completed prior to conception in all but one patient who conceived while still on maintenance therapy with 6-mercaptopurine (6-MP) (case 1). Medication was withheld in

TABLE II. Survivors With Progeny After Cessation of Therapy for ALL*

Sex & case no.	Year of birth	Age at diagnosis	Treatment length	At first birth: Years after cessation	At first birth: Age	Offspring (*n*)	Comments
Females							
1	1947	12	7	0	19	3	6-MP in first trimester
2	1949	13	2½	11½	27	2	
3	1953	4½	15	2½	22	2	
4	1954	14	7	2½	23½	2	Relapse during initial therapy
5	1956	7½	10	1	18½	3	
6	1958	10	5	10	25½	1	Cyclo; relapse in fourth pregnancy
7	1959	3½	5½	15½	24½	2	Relapse during initial therapy
8	1960	8	7	11½	26	1	
9	1961	3½	5	12½	21	2	
10	1961	11½	3	6	20½	2	RT
11	1961	3½	8½	12	24	2	1 child with congenital anomalies
12	1962	5½	6	7	18½	2	
13	1962	9½	4½	1	15	3	RT
14	1963	8	5	7½	20½	2	RT
15	1963	7½	5	11	23½	2	RT
16	1965	3½	5½	11	20	2	
17	1965	4½	5	9½	19	1	
18	1965	13½	2½	2½	18½	2	MTX
19	1966	10	4	7	21	1	RT, Cyclo; CNS-tumour, mors
20	1967	10½	3	7½	21	1	MTX
21	1967	11½	3	6	20½	1	MTX
22	1968	4½	3	13	20½	1	RT
23	1969	6½	2	11½	20	1	MTX
n = 23		3½-14 (*M* = 8)	2-15 (*M* = 5½)	0-15½ (*M* = 7½)	15-27 (*M* = 20½)	*n* = 41	6 RT, 2 Cyclo, 4 MTX; 1 child with anomalies
Males							
24	1956	4	2	19½	25½	2	
25	1958	10	6½	9	25½	3	Cyclo; first children twins
26	1965	9½	3	10½	23	1	RT
27	1967	13	3½	4½	21	1	RT
n = 4		4-13	2-6½	4½-19½	21-25½	*n* = 7	2 RT, 1 Cyclo; normal children

*Time intervals in years. CNS, central nervous system; Cyclo, cyclophosphamide; *M*, median; MTX, methotrexate (intravenous + intrathecal); RT, radiotherapy (CNS-prophylaxis); 6-MP, 6-mercaptopurine.

the second and third pregnancy month and then continued until birth [6,7]. The antileukemic treatment in 4 of the early patients had only included 6-MP and prednisone. The remaining mothers had been treated with combinations of at least prednisone, vincristine, 6-MP, and MTX. Two cases had been given maintenance therapy with cyclophosphamide. Thirteen of the mothers had been treated before the introduction of CNS prophylaxis. Of the remaining cases, 4 had received intrathecal MTX and MTX infusions (0.5 g/m^2), 5 had received cranial and one craniospinal radiation. All patients had remained in remission after cessation of therapy when their first child was born. One patient suffered a relapse during a later pregnancy (case 7), and another developed a brain tumour and died a year after having delivered her first child (case 19).

Of the 131 adult *male* survivors of ALL, four had fathered 7 children. None of the fathers had had testicular involvement of the disease or had been given testicular RT. Two of the patients had been older than 15 years of age at cessation of therapy, which in one of them included maintenance with cyclophosphamide.

Cumulative First Birth Rates by Maternal Age

The life table estimate of fertility until age 23 for the patient group as a whole was not significantly lower than that of the controls, 21.1% compared to 29.5% (Fig. 1).

Full follow-up times also beyond that age were

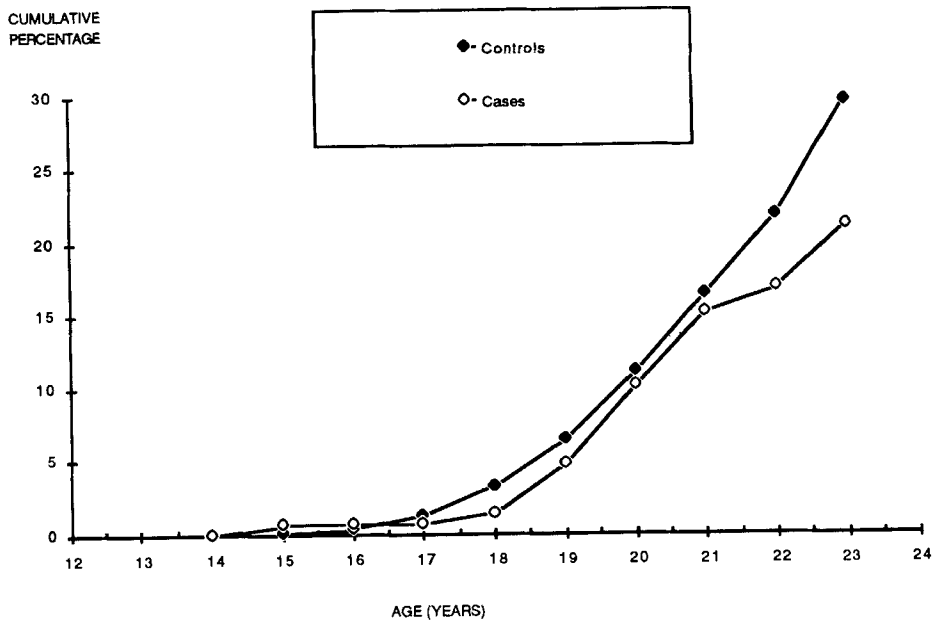


Fig. 1. Cumulative rates of first birth by age in females previously treated for childhood acute lymphoblastic leukemia (cases, $n = 149$) compared to the Norwegian birth year cohort of 1966 (controls, $n = 31,186$).

included in the Kaplan–Meier analysis of the patients (Fig. 2). The group as a whole had a fertility rate of 32.3% at 25 years, and it was lower in patients with radiotherapy than in those without ($P = 0.043$). Excluding cases with bone marrow transplantation, 78 cases of whom 6 were mothers had received CNS-RT, resulting in an estimate of 18.4% at age 25. The corresponding estimate was 41.0% for the 68 cases treated exclusively with CT, 17 of whom had delivered. The unadjusted fertility rate ratio for patients with RT compared to those without was 0.39 (95% CI 0.15–1.00). It was not materially altered after adjustment for calendar year at treatment start, age at diagnosis, and age at ended therapy. Limiting the comparison to patients treated in the era of CNS prophylaxis, patients given combined systemic and intrathecal MTX had a higher fertility rate than those who were irradiated, but the difference was not statistically significant (data not shown).

Offspring

All but one of the 48 live born children were without malformations. The first of two children born to case 11 had multiple congenital defects and died 13 months old.

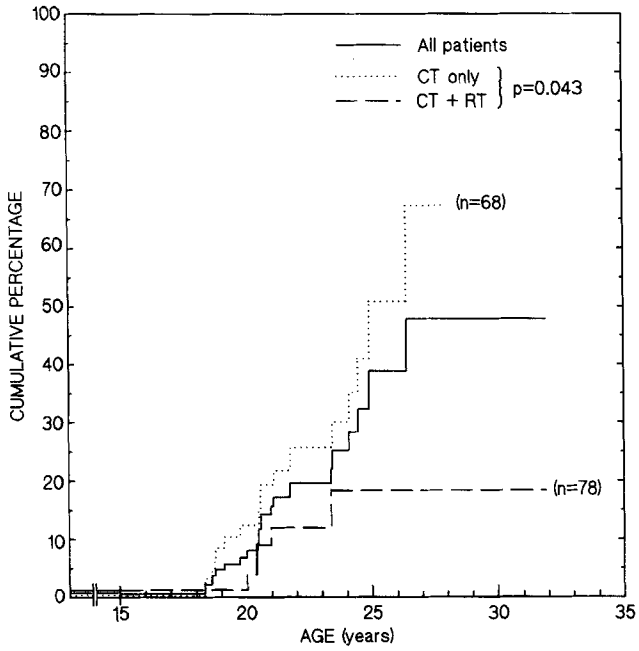
The mother was 24 years old at delivery 12 years after cessation of therapy. The infant was small for gestational age, had exophthalmus, low-sitting ears, marked neck fold, abnormalities of the toes, and profound generalized hypotonic musculature. Internal abnormalities included left-sided pelveoureteric stenosis with hydronephrosis and agenesis of the right kidney. Chromosome analysis was normal.

The remaining children ranged in age from several weeks to 23 years, and had been observed for a total of 284 person years when the study ended. None of them was diagnosed with childhood cancer or genetic disease. First daughter born to patient case 1 had 3 healthy children of her own.

DISCUSSION

Reproduction depends on a complex of biological and psychosocial factors, and cancer survivors may differ from their peers in many ways that can influence subsequent parenthood. Some patients tend to confirm their ability for pregnancy at an early age [22], others delay family life, are less likely to marry, or decide not to have children [2,23,24]. Leukemia per se does not seem to result in limited reproductive capacity, except after gonadal involvement. However, in addition to the psychosocial long-term effects of life-threatening disease during childhood and adolescence, fertility may be impaired by exposure to chemotherapy, radiotherapy, and surgery.

The main *drugs* associated with the achievement of long-term disease-free survival in ALL have been combinations of prednisone, vincristine, L-aspariginase, 6-mercaptopurine, and methotrexate, and later also cy-



Treatment	N	At age 25: n	%	CI
Chemotherapy (CT)	68	10	41.0	21.9-60.1
CT + radiation (RT)	78	7	18.4	3.0-33.8
Bone marrow transplantation	3	0	0	
Total (all categories)	149	17	32.3	18.2-46.4

Fig. 2. Cumulative rates of first birth by age in females previously treated for childhood acute lymphoblastic leukemia, according to treatment category.

clophosphamide, anthracyclines, and cytosine arabinoside.

In females, transient ovarian failure [25,26] and histologic derangements [27–29] may result from several of these combinations given before, during or after puberty. However, most patients undergo normal pubertal development, and an increasing number of pregnancies after treatment are reported [30–32]. Unimpaired fertility has been found in female survivors of childhood cancer treated exclusively with chemotherapy, including alkylating agents [33]. However, with oogenesis completed at birth and the number of oocytes declining by atresia thereafter, a possible additional reduction due to chemotherapy may lead to early menopause and reduced fertility in late age groups [24]. In males, antileukemic drugs have been shown to kill differentiated spermatogonia, induce histologic changes in the testes and cause endocrine disorders [34,35]. The damage is inconsistent [36,37] and often reversible. As spermatogenesis continues throughout life, subsequent reproduction depends on survival of stem spermatogonia, which seem to be more resistant. However, alkylating agents such as cyclophosphamide may cause cessation of germ cell production, and cytosine arabinoside has also been incriminated [3,36–39]. This effect may to some extent be dose related and has been observed in males treated before as well as during and after puberty [3,38,40–43]. The concept that the prepubertal testis may be less susceptible remains to be proven in humans; some studies suggest a higher risk in the sexually more mature patients [33], others show no age relationship [35,39,42]. Although return of spermatogenesis may occur even after a prolonged period of time [3,34,41], a fertility deficit after alkylating agents has been shown in long-term survivors [33].

Radiotherapy may also impair gonadal function [44]. Endocrine abnormalities resulting from cranial radiation including the hypothalamic–pituitary axis may result in deficiencies of anterior pituitary hormones most commonly in the order of growth hormone, gonadotrophins, corticotrophins, and thyrotrophin. Detrimental effects on the CNS tend to be delayed, and it has been shown in a recent study of adult patients that the number and severity of deficiencies increase with time after radiation [45]. Craniospinal radiation, resulting in scatter doses to the gonads, may also cause primary ovarian dysfunction, as shown in a study where ALL patients with this type of CNS prophylaxis were compared to a group with only cranial radiation [48]. Doses of 400 cGy to the ovaries may result in permanent sterility in young females [44,47,48], and doses of 140–300 cGy may cause permanent aspermia in males [33,42,44]. Reduced testicular size and impaired sperm production have been associated both with cranial and testicular radiation [49].

Generational genetic damage from preconceptional exposure of germ cells to radiotherapy or chemotherapy could result in increased incidence of miscarriages and spontaneous abortions, as well as birth defects, malignancies, and genetic disease in the offspring. Clinical studies with this in mind have been conducted since the early 70's [1], but have not proven any increased incidence of disease in the offspring due to anticancer treatment. Although most reports are limited to anecdotal case series, some larger studies suppport this contention [30,50,51]. The apparent lack of affected offspring may possibly be because lethal cell events caused by drugs or radiation prevent the induced abnormalities from being transferred to the next generation. Offspring of atomic bomb victims exposed to single dose radiation did not have a significantly increased incidence of congenital abnormalities or malignancies [52,53]. However, the possibility of generational genetic damage via viable germ cells is supported by a report of increased incidence of childhood leukemia and lymphoma among children fathered by workers exposed to high doses of radioactivity in a nuclear plant before conception [54], as well as the report of induced chromosomal aberrations present in functional human sperm years after therapeutic ionizing radiation [55].

Our study supports the contention that antileukemic chemotherapy alone does not adversely effect reproduction in young *females* who were treated for ALL during childhood. However, although the birth rate in the complete group of such subjects was not significantly lower than in the general population, cases with CNS-RT were less likely to have given birth than those without. If the difference observed between these two treatment groups reflects an adverse effect due to radiotherapy, the pathogenesis remains to be identified. Spinal radiation was not a routine part of CNS prophylaxis in any of the Nordic protocols, so ovarian damage is unlikely. While it is appreciated that cranial radiation doses as low as those given in ALL prophylaxis may cause growth hormone deficiency in children [56], latent additional harm to the neuroendocrine system could possibly become evident later as reduced fertility. In addition, neuropsychological effects of CNS damage [57] could affect behavioral patterns and thus influence sexual life and reproduction.

Although only 3 of the 131 *male* ALL survivors in the study group had received prophylactic testicular radiation, no more than 4 men were known to have fathered children. These data are likely to be incomplete, and in addition men generally become parents 2–3 years later than women. Other studies have shown that male childhood cancer survivors are more prone to damage of the reproductive system, but our results do not permit any conclusions about male fertility after ALL. Poor prognosis and toxic treatment associated with AML and CML are reflected in the small number of adult survivors of myeloid leukemias among our cases, preventing conclusions about fertility also in this group.

Only one of the 48 *children* had anomalies that possibly could be attributed to their parents' previous disease and treatment. As opposed to some of the other survivors with children, the mother of the affected child had received neither alkylating agents nor radiotherapy. This incident was no more than expected from the incidence of birth defects in the general population [18,19,58]. Four additional children born after the study closed are reported to be normal. We have not observed any cases with genetic disease or malignancies in the offspring so far, but most of them have not been followed up long enough to permit evaluation of these other genetic endpoints.

The main *methodical* problem in our analyses was the limited number of cases in higher age groups, resulting in low precision (wide confidence intervals) for the birth rate estimates. However, this was unavoidable, since the study included all possible cases from the countries involved.

An evaluation of fertility more strictly defined as the ability to conceive or sire a pregnancy would require information of all conceptions in individuals known to be at risk for pregnancy. With incomplete registration of spontaneous abortions and miscarriages and changing regulations for elective abortions, it was not possible to obtain reliable information on the total number of conceptions in our patients. The inferences drawn from our investigation are therefore conditional on pregnancies resulting in births. Many individuals start sexual and family life before formal arrangements, and we also found the risk for pregnancy practically difficult to quantify. Some fertility analyses are restricted to married individuals not known to be sterile or voluntarily infertile [33]. However, patients as well as controls were included in the analyses regardless of marital/cohabitation status. In population-based studies, fertility implies de facto reproduction, measured in rates of live births or as proportion with achieved parenthood [20,21], and we evaluated fertility according to this interpretation.

The birth cohort of 1966, matching the median year of birth for the study cases, was used as control group in spite of the disadvantage of short observation time. Although the period total fertility rate in Norway has been virtually constant since 1977, median age at first birth, defined as the age at which half of the individuals in a cohort have at least one child, has increased by more than 2 years since the 1951 birth cohort. It is now expected to have risen beyond age 25 [20], and this trend is similar in all the Nordic countries.

The leukemia survivors are a diverse group in terms of diagnostic subclassification, therapy exposure, age parameters, and hence also with regard to potential late adverse effects. The overall fertility estimate may conceal considerable variability. Our analyses did not reveal any influence of age at diagnosis or age at ended therapy. In this context it may be noted that the majority of mothers had been treated during puberty, an age at which the reproductive system is thought to possibly be more vulnerable to damage than in earlier childhood. The multiplicity of drug combinations, doses, and treatment durations thwarted attempts to separate other factors in a meaningful manner for analysis. Nearly one-third of the adult females had been treated before the era of CNS prophylaxis and according to early systemic treatment principles. Although highly insufficient by modern standards and often of much longer duration, these treatment modalities could possibly have caused less late adverse effects than intensive chemotherapy does. Calendar year of diagnosis, indirectly reflecting intensified treatment protocols, was not significantly associated with reduced fertility. However, our results must be interpreted with care for prediction of fertility and future offspring in patients treated with newer regimens; longer and larger follow-up studies are needed to prove any possible differences.

In addition to obtaining higher precision, a repeat study in 10 years could show if the fertility deficit in

patients with RT compared to those without remains significant when the analysis is restricted to modern treatment groups, where all patients have received intensive chemotherapy and CNS prophylaxis. Also, with a first birth rate estimate closer to a life time probability of parenthood, the effects of some of the social factors mainly influencing reproductive differences in early adulthood would be diminished, and the potential effects of late neuroendocrine damage and early menopause would have time to become evident.

In conclusion, our results indicate that chemotherapy alone, in doses and combinations given to the first generation of ALL survivors, does not result in reduced female fertility in young adulthood. However, radiation as CNS-prophylaxis may possibly be a risk factor, even without the spinal component. This study also suggests that the therapy schedules used do not adversely affect the next generation with regard to congenital anomalies.

ACKNOWLEDGMENTS

Financial support was obtained from the Norwegian Cancer Society.

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