Encouraging patients to reduce or stop smoking is an important aspect of care. Smoking habits were recorded in 76% of patients, which compares well with the 44% found in an audit in 12 Oxfordshire practices in 1986.[24] Weight was recorded in 61% of cases compared with 31% in the Oxfordshire audit.[24] Although heavy alcohol consumption may be as important a risk factor for stroke as smoking, only 40% of cases had a history of alcohol use recorded and only 44% of heavy drinkers had recorded evidence of advice on reducing consumption.

We thank Drs B Hillman and B K Mondal (members of the local steering group); the Department of Health for funding; Professor Richard Alderslade, director of public health, Trent Regional Health Authority; the general practitioners and hospital doctors who took part; and Mrs Greta Pearman.

1 Department of Health. *The health of the nation.* London: HMSO, 1992. (Cm 1523.)
2 Rutstein DD, Brenberg W, Chalmers TC, Child CG III, Fishman AP, Perrin EB. Measuring the quality of medical care: a clinical method. *N Engl J Med* 1976;294:582-8.
3 Department of Health, Welsh Office, Scottish Home and Health Department, Department of Health and Social Security, Northern Ireland. *Report on confidential enquiries into maternal deaths in the United Kingdom 1985-1987.* London: HMSO, 1991.
4 Buck N, Devlin HB, Lunn JN. *The report of the confidential enquiry into perioperative deaths.* London: Nuffield Provincial Hospitals Trust, 1987.
5 Kurji KH, Haines AO. Detection and management of hypertension in general practices in north west London. *BMJ* 1984;288:903-6.
6 Smith WC, Lee AJ, Crombie IK, Tunstall-Pedoe H. Control of blood pressure in Scotland: the rule of halves. *BMJ* 1990;300:981-3.
7 World Health Organisation. *Manual of the international statistical classification of disease: inquiries and causes of death (ninth revision).* Geneva: WHO, 1977.
8 Fleiss JL. *Statistical methods for rates and proportions.* New York: Wiley, 1981.
9 Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ* 1985;291:97-104.
10 Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, *et al.* Blood pressure, stroke, and coronary heart disease. II. Short term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet* 1990;335:827-38.
11 Medical Research Council Working Party. Medical Research Council trial of treatment of hypertension in older adults: preliminary results. *BMJ* 1992;304:405-12.
12 Gordon T, Kannel WB. Predisposition to atherosclerosis in the head, heart, and legs. The Framingham study. *JAMA* 1972;221:661-6.
13 Shaper AG, Phillips AN, Pocock SJ, Walker M, Macfarlane PW. Risk factors for stroke in middle aged British men. *BMJ* 1991;302:1111-5.
14 Gill JS, Zezulka AV, Shipley MJ, Gill SK, Beevers DG. Stroke and alcohol consumption. *N Engl J Med* 1986;315:1041-6.
15 Doll R, Hill AB. Mortality in relation to smoking: ten years' observations of British doctors. *BMJ* 1964;i:1399-410,1460-7.
16 Ritchie LD, Currie AM. Blood pressure recording by general practitioners in north-east Scotland. *BMJ* 1983;286:107-9.
17 Mant D, McKinlay C, Fuller A, Randall T, Fullard EM, Muir J. Three year follow-up of patients with raised blood pressure identified at health checks in general practice. *BMJ* 1989;298:1360-2.
18 Wilson JB. An audit of hypertension in a rural practice. *Practitioner* 1978;220:689-92.
19 Chapman A, Ridout S. Hypertensive care and the small practice. *Practitioner* 1989;233:1018-22.
20 Michael G. Quality of care in managing hypertension by case finding in northwest London. *BMJ* 1984;288:906-8.
21 Hall JA. Audit of screening for hypertension in general practice. *J R Coll Gen Pract* 1985;35:243.
22 Strasser T. Guidelines for the treatment of mild hypertension: memorandum from a WHO/ISH meeting. *J Hypertension* 1986;4:383-6.
23 Taffinder AP, Taffinder GA. An audit of hypertension in general practice. *Practitioner* 1984;228:595-8.
24 Stern D. Management of hypertension in twelve Oxfordshire general practices. *J R Coll Gen Pract* 1986;36:549-51.

(Accepted 24 August 1993)

Second malignant neoplasms after cancer in childhood or adolescence

Jørgen H Olsen, Stanislaw Garwicz, Henrik Hertz, Gudmundur Jonmundsson, Frøydis Langmark, Marjatta Lanning, Sverre O Lie, Peter Johan Moe, Torgil Møller, Risto Sankila, Hrafn Tulinius for the Nordic Society of Paediatric Haematology and Oncology Association of the Nordic Cancer Registries

Abstract

***Objective*—To assess the relative risk of developing a second malignant neoplasm in people with a diagnosis of cancer in childhood and adolescence.**

***Design*—Register based follow up study.**

***Setting*—Populations of Nordic countries.**

***Subjects*—30 880 people under the age of 20 with a first malignant neoplasm diagnosed during the period 1943-87.**

***Main outcome measures*—Relative and attributable risks of second malignant neoplasms by type of first cancer, age at first diagnosis, calendar period, sex, and country. Expected figures were based on the appropriate national incidence rates for cancer.**

***Results*—247 cases of second malignant neoplasms were observed in 238 patients, yielding a relative risk for cancer of 3·6 (95% confidence interval 3·1 to 4·1). The risk changed significantly from 2·6 in people first diagnosed during the 1940s and 1950s to 6·9 among cohort members included in the late 1970s and 1980s. Increases were observed for most types of cancer. Highest levels of the relative risk were seen during the 10 years immediately after first malignant diagnosis. The incidence of second malignant neoplasms attributable to the first cancer and associated treatments, however, showed a consistent rise throughout the 45 years of follow up.**

***Conclusion*—The estimated risks for a second malignant neoplasm were significantly lower than those found in most large hospital based studies but compatible with the results from a similar population based study in the United Kingdom. Extent of risk and cancer pattern were similar among the Nordic countries and are believed to be representative for a large part of the European population.**

Introduction

Cancer occurs in children and adolescents aged under 20 in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) at an annual rate of 136 cases per 1 million. The rates have, in general, been unchanged since the inception of the nationwide cancer registries in all of the countries during the 1940s and 1950s. Survival rates from childhood cancer have improved substantially over the past two to three decades, which implies that a growing number of adults have been exposed to high doses of cytostatic drugs or radiation, or both, during childhood.

The risk for a second malignant neoplasm after cancer in childhood or adolescence seems to be high relative to that in the general population[1-10] and also in comparison to the relative risk for second tumours observed after a first tumour diagnosed late in life.[11] Owing to the rarity of cancer in young people, however, the risk estimates for a second malignant neoplasm among such individuals generally have wide confidence intervals.

In this collaborative study from the Nordic countries, the incidence of second malignant neoplasm was assessed in large, population based cohorts of survivors of a first malignant neoplasm at the age of 0-19 years and compared with the appropriate rates of cancer in

Correspondence to:
Dr J H Olsen, Division for Cancer Epidemiology, Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen, Denmark.

BMJ 1993;307:1030-6

Division for Cancer Epidemiology, Danish Cancer Society, DK-2100 Copenhagen, Denmark
Jørgen H Olsen, *department chief*

Oncology-Haematology Section, Department of Paediatrics, University Hospital, S-221 85 Lund, Sweden
Stanislaw Garwicz, *chief*

Department of Paediatrics, University Hospital, DK-2100 Copenhagen, Denmark
Henrik Hertz, *chief*

Department of Paediatrics, National University Hospital, Postbox 10, IS-121 Reykjavik, Iceland
Gudmundur Jonmundsson, *paediatrician*

Norwegian Cancer Registry, Montebello, N-0310 Oslo 3, Norway
Frøydis Langmark, *director*

Department of Paediatrics, University Hospital of Oulu, Postbox 22, SF-90221 Oulu, Finland
Marjatta Lanning, *chief*

Department of Paediatrics, University Hospital, N-0227 Oslo 1, Norway
Sverre O Lie, *professor*

Department of Paediatrics, University of Trondheim, N-7006 Trondheim, Norway
Peter Johan Moe, *chairman*

Southern Swedish Regional Tumour Registry, University Hospital of Lund, S-221 85 Lund, Sweden
Torgil Møller, *associate professor*

Finnish Cancer Registry, SF-00170 Helsinki, Finland
Risto Sankila, *research fellow*

Icelandic Cancer Registry, Postbox 5420, IS-125 Reykjavik, Iceland
Hrafn Tulinius, *professor*

the general population. The relation between the occurrence of a second tumour and the treatments associated with first malignant neoplasms is not addressed.

Patients and methods

The cohort comprised indiviuals who had been diagnosed before the age of 20 as having a malignant neoplasm. These cases were reported to the cancer registries of Denmark, Finland, Iceland, Norway, and Sweden over a period of 30-45 years (see table I).

Each of the Nordic cancer registries is nationwide and population based; together, they covered a population of 22·5 million in the 1980s. The sources of information on cancer patients were the same throughout the study period.[12] Each registry receives reports of malignant and related diseases from clinicians when a cancer is diagnosed and when changes in the initial diagnosis occur. In addition, notifications are received from departments of pathology and forensic medicine on diagnoses of cancer from necropsies in cancer patients. Except in Sweden, cancer diagnoses based on examination of death certificates alone are included in the files of the registries. Benign tumours of the brain and intracranial meninges and papillomas of the urinary tract are covered by the registries. Basal cell carcinomas of the skin are included only in the Danish data. Tumours have been classified at all registries according to the *International Classification of Diseases, Seventh Revision* (ICD-7), although various modifications and additions to this classification have been used in different periods.

All primary cancers reported are registered regardless of the number of cancers per individual. The registries define multiple independent primary cancers as tumours arising in different organs or as separate tumours with different morphological characteristics arising in the same organ. At the Danish Cancer Registry before 1978, however, a distinction was made only between carcinoma and sarcoma of the same organ.[13] At the Norwegian registry, no distinction was made between morphological subtypes in the same organ in the period 1953-69.[14]

MORPHOLOGICAL GROUPING OF FIRST MALIGNANT NEOPLASM

Patients were selected from the register files and categorised according to the type of first malignant neoplasm that occurred in childhood or adolescence, with a classification scheme for childhood cancers prepared by the International Agency for Research on Cancer (IARC).[15] The diagnostic groups in this scheme are defined mainly in terms of morphology and are based on the *International Classification of Diseases for Oncology* (ICD-O)[16] (see table II).

Both ICD-O and ICD-7 have been used in Denmark and Iceland for coding tumours diagnosed since 1977. So that diagnoses agree with ICD-O we reviewed the original diagnostic information on the first malignant neoplasm included in the present study and diagnosed during the periods 1943-77 (Denmark) and 1955-77 (Iceland). In Norway, the *Manual of Tumour Nomenclature and Coding,*[17] with modifications according to the *Systematized Nomenclature of Medicine,*[18] has been used routinely for coding neoplasms by morphology since 1970. This classification, which is closely related to the ICD-O's morphology coding system, was applied retrospectively to cancers diagnosed in patients under the age of 20 and reported during 1953-69. Thus, the first malignant neoplasms were sorted into the diagnostic groups defined by IARC without difficulty in the Danish, Icelandic, and Norwegian registers.

In Sweden, tumour morphology and tumour behaviour are coded by use of the World Health Organisation C24 code,[19] and in Finland tumour morphology is registered according to a two digit code based on the 1951 version of the *Manual of Tumour Nomenclature and Coding.* For the present study, the Swedish and Finnish cancer registries transcribed the code for tumour site and morphology into the IARC classification scheme for childhood cancer. Problems were encountered only in classifying the subgroups of non-Hodgkin's lymphoma, which were consequently left as a single entity.

SECOND MALIGNANT NEOPLASMS AND ANALYSIS

Record linkages with the files of the national population registers were carried out at the cancer registries to trace patients through 1987, using the personal identification numbers given to everyone residing in any of the Nordic countries. The period of follow up for second tumours was started from the date of diagnosis of the first malignant neoplasm, and person years at risk were accrued up to the date of death, the date of emigration, or the closing date of 31 December 1987, whichever came first.

Cases of second malignant neoplasm were extracted from the files of the cancer registries, irrespective of the interval between first and subsequent tumours and the number of second tumours. For nine patients who had two primary neoplasms registered in the same month and year of diagnosis, the tumours were numbered in the order in which they had been reported to the cancer registry. All second neoplasms were classified according to ICD-7. National sets of incidences by sex and five year age groups and calendar year periods for these tumour categories, were applied to the person years under observation for the national subcohorts to obtain the number of cancers expected had the cohort members experienced the same rate of second malignant neoplasms as that of incident cancers observed in the general population.

The statistical methods were chosen on the basis of the assumption that the observed number of cancer cases in any specific category follows a Poisson distribution. Tests of significance and confidence intervals for the standardised incidence ratio, taken as the ratio of observed to expected cancers, were calculated, using the Miettinen exact confidence limits when the observed number of cases was small; otherwise, an accurate asymptotic approximation was used.[20] Separate analyses were performed for a number of diagnostic subgroups of first malignant neoplasm to evaluate the importance of tumour type as a determinant in the development of a second neoplasm. Finally, multiplicative Poisson models were fitted to the data to describe the relative risk of developing a second malignant neoplasm as a function of time since diagnosis of the first malignant neoplasm, age at diagnosis, period of diagnosis, and sex.[21] Tests for trend were performed as likelihood ratio tests in a model in which the variable in question was replaced by a scored version. Tests for the adequacy of this scoring were also performed (test for linearity).

TABLE I—*Populations and overall cancer incidence in the age group 0-19 years in the Nordic countries and descriptive characteristics of national subcohorts of cancer patients*

Country (period)	Population		Cohort		Follow up (years)	
	Size (millions)*	Incidence†	No of first malignant neoplasms	Person years	Mean	Maximum
Denmark (1943-87)	1·46	131·1	8 602	51 234	5·96	45
Finland (1953-87)	1·53	129·9	6 945	39 698	5·70	35
Iceland (1955-87)	0·08	133·5	363	1 909	5·26	33
Norway (1953-87)	1·20	134·4	5 646	30 609	5·42	35
Sweden (1958-87)	2·21	140·7	9 324	62 243	6·68	30
Nordic cohort	6·48	134·7	30 880	185 603	6·01	45

*Mean population (during the follow up period) in age group 0-19 years.
†Average annual incidence per million children for cancer at all sites combined.

TABLE II—*Crude annual incidence of cancer per million population aged 0-19 years, by main diagnostic group, for national subcohorts and whole cohort*

Diagnostic group*	Denmark (n=8602)	Finland (n=6945)	Iceland (n=363)	Norway (n=5646)	Sweden (n=9324)	Nordic cohort (n=30 880)
I Leukaemias	39·1	37·8	38·2	37·8	35·3	37·2
II Lymphomas and other reticuloendothelial neoplasms	16·3	15·9	14·3	15·0	17·0	16·2
III Central nervous system neoplasms	28·4	27·7	29·0	22·5	33·4	28·8
IV Sympathetic nervous system neoplasms	5·5	5·5	4·8	6·5	6·1	5·9
V Retinoblastomas	2·8	2·7	1·8	2·1	2·8	2·7
VI Renal tumours	6·5	6·1	7·4	6·0	6·3	6·2
VII Hepatic tumours	1·0	0·9	0·7	1·9	1·2	1·2
VIII Malignant bone tumours	7·8	8·4	8·1	9·1	8·0	8·3
IX Soft tissue sarcomas	7·3	8·2	10·3	13·1	8·1	8·9
X Germ cell, trophoblastic, and other gonadal neoplasms	6·3	4·9	7·4	7·8	7·4	6·6
XI Carcinomas and other malignant epithelial neoplasms	8·2	9·5	9·6	10·0	13·4	10·6
XII Other and unspecified malignant neoplasms	2·0	2·3	1·8	2·5	1·6	2·0

*According to classification scheme for childhood cancer.[15]

TABLE III—*Standardised incidence ratios (SIR) and observed numbers (obs) of second malignant neoplasms among 30 880 cohort members with first cancer diagnosed before age 20*

Site of secondary malignant neoplasm (ICD-7 Class No)‡	Subcohorts†							
	Denmark		Finland		Norway		Sweden	
	SIR	Obs	SIR	Obs	SIR	Obs	SIR	Obs
All sites (140-204)	3·0*	84	4·5*	51	4·3*	43	3·4*	64
Buccal cavity and pharynx (140-148)	3·5	2	14·0*	3			3·1	1
Digestive organs (150-159)	4·1*	11	2·7	3	4·8*	3	2·1	3
Respiratory system (160-164)	1·7	3	3·0	1				
Breast (170)	1·5	6	3·8*	6	5·2*	5	1·9	4
Female genital organs (171-176)	0·5	2	1·0	1	0·7	1	0·8	2
Male genital organs (177-179)	4·5*	10			8·0*	7		
Urinary system (180-181)	0·9	1						
Skin (190-191)§	4·1*	17	2·4	2	5·5*	7	1·6	3
Brain and nervous system (192-193)	8·1*	20	7·3*	13	3·1*	4	6·5*	18
Thyroid (194)	3·3	1	9·1*	6	6·7*	3	7·9*	6
Endocrine glands (195)			12·3	1			5·8*	4
Bone (196)	5·3	2	13·3*	5	7·7*	2	3·6	2
Connective tissue (197)	7·0*	2	10·4*	3	16·1*	3	17·7*	8
Lymphatic and haematopoietic tissue (200-204)	1·4	5	3·0	7	3·9*	7	3·4*	12
Secondary and unspecified (198-199)	4·7	2			7·5	1	4·6	1

*$p<0·05$.
†Five cases of second neoplasm were observed in the Icelandic subcohort, to give an overall SIR of 8·0.
‡Including nine patients with two second neoplasms.
§Basal cell carcinomas included in the Danish material.

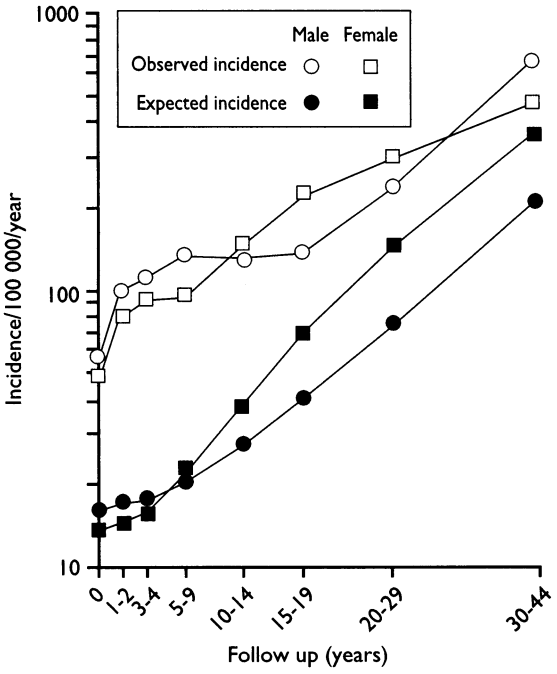
Results

A total of 30 880 first malignant neoplasms were diagnosed among children and adolescents in the Nordic countries during the study period (table I). Overall, the proportion of boys was 55·3%, ranging from 54·3% in Sweden to 59·2% in Iceland. The average annual incidence of cancer in the age group 0-19 years in each country is given in table I for neoplasms at all sites combined and in table II for each of the 12 main diagnostic groups considered. Except for a relatively low incidence of central nervous system neoplasms registered in Norway and a slightly higher incidence of carcinomas and other malignant epithelial neoplasms in Sweden than in the other Nordic countries, the cancer pattern for this age group is remarkably similar in the five Nordic countries. Overall, leukaemia was the most common first malignant neoplasm (27·6%), followed by neoplasms of the central nervous system (21·4%) and lymphomas (12·0%).

Over the entire follow up period, 247 cases of second malignant neoplasm were diagnosed in 238 individuals; 69·0 new primary neoplasms would have been expected in the cohort, yielding a standardised incidence ratio for second tumours of 3·6 (95% confidence interval 3·1 to 4·1) for the five participating countries combined and ranging from 3·0 (2·4 to 3·7) in Denmark to 4·5 (3·3 to 5·9) in Finland (table III). Although they are separately in excess of the expected figures, the five risk estimates for all second tumours combined were not significantly dissimilar across the countries. The country specific relative risks for the main types of second tumour, except for Iceland, are also shown.

The risk estimates based on the entire Nordic cohort for a number of subsites of second malignant neoplasms are given in table IV. High risks were seen for tumour of the central nervous system, thyroid, and bone and connective tissue, with a lower limit of the 95% confidence interval of at least 4·0. Moderate to high risks were observed for tumours of the buccal cavity and pharynx; tumours of the liver, nasal cavity, and testis; non-melanoma skin cancers; and non-Hodgkin's lymphomas, with a lower confidence limit between 2·0 and 4·0. Further, significantly higher risks were seen for cancers of the small and large intestine, pancreas, endocrine glands, and female breast and for malignant melanoma and leukaemia. Risk estimates close to unity were seen for cancers of the larynx and lung, corpus uteri, prostate, kidney, and bladder (table IV). A significant deficit was observed for invasive cervical cancer.

The figure shows the observed and expected sex-specific incidences of second neoplasm for various periods of follow up. Table V gives the sample size at the beginning of each follow up period, as well as the differences and ratios between the incidences. Although the difference between the observed and the expected incidence—that is, the attributable risk—increased steadily throughout the follow up period from 4 to 28 cases per 10 000 cohort members per year, the relative risk was highest during the initial 10 years, with a subsequent decrease. Thus, for women followed up for 30-44 years, the relative risk of 1·3 was no longer



Observed annual incidence of second malignant neoplasm per 100 000 cohort members by sex and period of follow up and expected rates derived from cancer of appropriate national populations specific for age, sex, and calendar time

significantly different from unity (95% confidence interval 0·6 to 2·5). The calculated rates of second tumours in individuals followed up for more than 20-30 years were, however, based on a sample consisting of less than a tenth of the total cohort (table V). It is important to recognise that the composition of this subgroup of long term survivors in terms of diagnosis of the first tumour was appreciably different from that of the total cohort—for example, less than 5% of patients had leukaemia. The cumulative risk for a second malignant neoplasm after 20 years of follow up was 2·6% (SE 0·2%) compared with 0·6% expected; after 45 years, the risk was 12·8% (1·9%) compared with 5·9% (table V).

The relative risk for breast cancer as a second neoplasm seemed to be highest 10-14 years after diagnosis of the first neoplasm (table VI), and relative risks for thyroid cancer and bone and soft tissue cancer seemed to reach a plateau 5-10 years after first diagnosis. The highest risk for leukaemia and malignant lymphoma occurred only 1-4 years after the first neoplasm, and no trend was discernible for brain tumours.

The overall relative risk for a second primary neoplasm was significantly influenced by the calendar period of diagnosis of the first neoplasm. Thus, the relative risk derived from the regression model for a second tumour among the 66 cohort members with a diagnosis of a first malignant neoplasm before 1960 (in the era before chemotherapy) was 2·6 whereas that of the 70 subjects included in the study in 1975 or later was 6·9 ($p<0·05$) (table VII). This effect was due mainly to trends for increasing risk of breast cancer, thyroid cancer, sarcoma, non-Hodgkin's lymphoma, and leukaemia, although the differences in time of diagnosis between early and late cases may also affect the comparisons. No trend was seen for brain tumours (table VII).

Relative risks for second neoplasms at all sites of first malignant neoplasm combined were higher, but not significantly so, in patients whose first neoplasm was diagnosed before the age of 5, than in older children and adolescents (table VII). This result was due particularly to significant downward trends in the risks for thyroid cancer and bone tumours by increasing age at diagnosis of the first tumour. Rising trends were seen in the risks for cancers of the breast and testis, while no significant change was discernible for brain tumours or for leukaemia. In general, the relative risk for a second malignant neoplasm was greater in men than women.

Both the incidence of and cumulative risks for a second malignant neoplasm depended on the type of first tumour (table VIII). Particularly high rates were

TABLE IV—*Observed and expected numbers and standardised incidence ratios of second malignant neoplasms in Nordic cohort by site and subsite*

Subsite of second malignant neoplasm (ICD-7 class No)	Observed	Expected	Standardised incidence ratio (95% confidence interval)
All sites (140-204)	247	69·0	3·6 (3·1 to 4·1)
Buccal cavity and pharynx (140-148)	6	1·2	4·8 (2·0 to 10·1)
Lip (140)	1	0·2	4·5 (0·2 to 22·1)
Tongue (141)	2	0·2	12·7 (2·1 to 42·1)
Salivary gland (142)	2	0·3	6·0 (1·0 to 19·9)
Mouth (143)		0·2	
Pharynx (145)	1	0·3	2·9 (0·1 to 14·4)
Digestive organs (150-159)*	20	5·9	3·4 (2·1 to 5·2)
Oesophagus (150)		0·1	
Stomach (151)	2	1·1	1·8 (0·3 to 6·0)
Small intestine (152)	2	0·2	12·2 (2·0 to 40·2)
Colon/rectum (153-154)	8	3·3	2·4 (1·1 to 4·6)
Liver (155)	4	0·4	10·4 (3·3 to 25·0)
Biliary tract (155·1)		0·2	
Pancreas (157)	3	0·5	6·2 (1·6 to 17·0)
Respiratory system (160-164)	4	2·7	1·5 (0·5 to 3·6)
Nasal cavity (160)	2	0·1	15·8 (2·6 to 52·1)
Larynx (161)		0·3	
Lung (162)	2	2·1	1·0 (0·2 to 3·2)
Breast (170)	21	8·7	2·4 (1·5 to 3·7)
Female genital organs (171-176)*	6	8·6	0·7 (0·3 to 1·4)
Cervix uteri (171)	1	4·8	0·2 (0·0 to 1·0)
Corpus uteri and uterus unspecified (173-174)		0·8	
Ovary	4	2·6	1·5 (0·5 to 3·7)
Male genital organs (177-179)	17	4·6	3·7 (2·2 to 6·0)
Prostate (177)		0·1	
Testis (178)	17	4·4	3·9 (2·3 to 6·3)
Urinary system (180-181)	1	2·4	0·4 (0·0 to 2·0)
Kidney (180)	1	1·3	0·8 (0·0 to 3·7)
Bladder (181)		1·1	
Skin (190-191)	29	8·1	3·6 (2·4 to 5·1)
Melanoma (190)	15	5·2	2·9 (1·6 to 4·8)
Other skin (191)	14	3·0	4·7 (2·7 to 7·8)
Brain and nervous system (193)†	56	8·4	6·7 (5·0 to 8·7)
Thyroid (194)	16	2·2	7·2 (4·1 to 11·7)
Endocrine glands (195)	5	0·9	5·3 (1·9 to 11·8)
Bone (196)	12	1·6	7·5 (4·1 to 12·8)
Connective tissue (197)	17	1·2	13·8 (8·1 to 22·2)
Blood and lymph nodes (200-205)	33	11·4	2·9 (2·0 to 4·1)
Non-Hodgkin's lymphoma (200, 202)	12	2·6	4·6 (2·5 to 7·8)
Hodgkin's disease (201)	6	3·3	1·8 (0·7 to 3·8)
Leukaemia (204)	15	5·3	2·8 (1·6 to 4·7)
Secondary and unspecified sites	4	0·9	4·4 (1·4 to 10·6)

*Includes one case not otherwise specified. †Eye included (one case observed *v* 0·5 expected).

TABLE V—*Observed annual incidence of second malignant neoplasm per 10 000 cohort members by period of follow up and associated estimates of the attributable risk (No of excess cases per 10 000 person years), relative risk, and cumulative risk*

Follow up (years)	Sample size at start of follow up period	Second malignant neoplasm: No	Observed annual incidence (both sexes)*	Attributable risk*: Both sexes	Attributable risk*: Men/women	Relative risk (95% confidence interval): Both sexes	Relative risk (95% confidence interval): Men/women	Cumulative risk (both sexes)
0	30 880	12	5	4	4/4	3·5 (2·0 to 6·2)	3·5/3·6	0·1
1-2	18 520	27	9	8	8/6	5·7 (3·9 to 8·3)	6·0/5·3	0·2
3-4	12 672	21	10	9	9/8	6·1 (6·1 to 9·2)	6·3/5·8	0·4
5-9	10 335	48	12	9	12/7	5·4 (4·1 to 7·2)	6·6/4·3	1·0
10-14	6 867	41	14	11	10/11	4·2 (3·0 to 5·7)	4·6/3·8	1·7
15-19	4 662	33	18	12	10/15	3·2 (2·3 to 4·5)	3·3/3·1	2·6
20-29	3 025	45	26	15	15/15	2·4 (1·8 to 3·2)	3·1/2·0	5·0
30-44	733	20	57	28	45/9	2·0 (1·3 to 3·0)	3·1/1·3	12·8

*Per 10 000 cohort members per year.

TABLE VI—*Relative risk of selected types of second malignant neoplasm by follow up period*

Follow up (years)	Breast (n=21)	Thyroid (n=16)	Bone and soft tissue (n=29)	Leukaemia and lymphoma (n=33)	Brain (n=56)*	Melanoma (n=15)
	Relative risk (95% confidence interval) of second malignant neoplasm					
0			3·3 (0·2 to 16·1)		4·3 (1·4 to 10·5)	32·4 (8·2 to 88·1)
1-2			2·4 (0·1 to 12·0)	5·5 (2·7 to 10·1)	7·8 (3·8 to 14·2)	5·1 (0·3 to 25·2)
3-4			3·1 (0·2 to 15·5)	5·9 (2·6 to 11·6)	7·4 (3·0 to 15·4)	
5-9	4·1 (0·2 to 20·2)	7·6 (1·9 to 20·6)	14·3 (7·0 to 26·2)	3·2 (1·4 to 6·3)	8·7 (4·8 to 14·5)	1·5 (0·1 to 7·2)
10-14	8·2 (3·3 to 17·0)	8·8 (2·8 to 21·2)	14·9 (6·5 to 29·6)	4·3 (1·9 to 8·5)	5·1 (2·1 to 10·7)	2·2 (0·4 to 7·4)
15-19	3·3 (1·2 to 7·4)	4·6 (0·8 to 15·2)	9·3 (2·4 to 25·4)	0·8 (0·0 to 3·9)	9·0 (4·4 to 16·5)	2·0 (0·3 to 6·5)
≥20	1·5 (0·7 to 2·7)	11·3 (4·9 to 22·3)	19·1 (8·3 to 37·8)	1·0 (0·2 to 3·3)	4·9 (2·4 to 9·0)	2·9 (1·2 to 6·0)

*Includes eye.

seen among patients with an initial tumour diagnosis of retinoblastoma or malignant lymphoma. Accordingly, the largest relative risks for second tumours (table IX) were seen in individuals with retinoblastoma (standardised incidence ratio, 7·4) or malignant lymphoma (5·1) and in patients with leukaemia (5·5) or renal tumours (5·5); however, excess risks for a second malignant neoplasm were seen in all of the main diagnostic groups of first malignancies (table IX), and several subtypes of second tumour had particularly strong associations. Cumulative risks over 20 years were in general higher in children diagnosed after the introduction of chemotherapeutic treatments during the 1960s than for children diagnosed before that time (table VIII).

For all diagnostic subgroups except Hodgkin's disease (n=1639) and perhaps bone tumours, men were at higher risk of a second neoplasm than women. The standardised incidence ratio for second tumours among female patients who had survived Hodgkin's disease in childhood or adolescence was 8·6 on the basis of 22 cases, whereas that in male patients was 4·6 on the basis of 12 cases (not shown in tables). The difference in risk between the sexes was due largely to seven cases of female breast cancer, in which the range of ages of patients at first diagnosis was 12-19 years, and two cases of ovarian cancer, with standardised incidence ratios of 14 and 11 respectively.

Discussion

Our follow up of 30 880 children and adolescents with cancer for a maximum of 45 years showed an overall standardised incidence ratio for a second malignant neoplasm of 3·6, on the basis of 247 cases in 238 patients. The risk changed significantly with calendar period of treatment for the first neoplasm. The largest increases in standardised incidence ratio were seen for tumour types that occur relatively infrequently in adulthood—bone, connective tissue, and thyroid cancers and non-Hodgkin's lymphoma; moderate or no increases were seen for tumour types that are more common in the general population—cancers of the respiratory system, genital organs, female breast, and urinary tract.

Most of the second malignant neoplasms in the

TABLE VII—*Relative risk* for second malignant neoplasm by sex and by period and age at diagnosis of first malignant neoplasm*

First malignant neoplasm	Relative risk* (observed No of cases of second malignant neoplasm)								
	All sites	Breast	Testis	Brain†	Thyroid	Bone	Soft tissue	Non-Hodgkin's lymphoma	Leukaemia
Period of diagnosis:									
1943-59	2·6 (66)	1·7 (6)	9·3 (7)	6·1 (13)	3·4 (4)	3·5 (2)	8·4 (4)	1·6 (2)	1·2 (1)
1960-74	3·5 (111)	3·3 (14)	0·8 (2)	6·4 (27)	5·3 (9)	6·2 (7)	11·2 (8)	1·7 (2)	1·8 (5)
1975-87	6·9 (70)	6·1 (1)	3·9 (8)	7·7 (16)	21·7 (3)	13·3 (3)	26·1 (5)	16·4 (8)	6·0 (9)
p Value (test for trend)	<0·001	0·20	0·40	0·39	0·14	0·20	0·22	<0·01	0·03
Age at diagnosis (years):									
0-4	5·6 (64)		1·7 (1)	5·1 (13)	20·8 (5)	21·5 (9)	23·2 (6)	5·9 (4)	2·2 (5)
5-12	3·2 (45)	1·1 (1)	1·4 (1)	7·8 (16)	6·2 (3)	4·7 (2)	6·2 (2)	6·0 (4)	3·7 (5)
13-19	3·2 (138)	2·2 (20)	5·4 (15)	6·9 (27)	5·5 (8)	2·2 (1)	13·5 (9)	3·4 (4)	2·9 (5)
p Value (test for trend)	0·18	0·18	0·12	0·47	0·06	<0·01	0·48	0·42	0·47
Sex:									
Male	4·1 (129)		3·9 (17)	7·2 (33)	8·7 (4)	7·7 (8)	14·1 (9)	5·0 (9)	2·3 (7)
Female	3·2 (118)	2·4 (21)		5·9 (23)	6·9 (12)	7·1 (4)	13·5 (8)	3·7 (3)	3·6 (8)
p Value (test for effect)	0·05			0·42	0·31	0·11	0·07	0·35	0·37

*Each variable was adjusted for the effect of the two others and for time since diagnosis.
†Includes eye.

TABLE VIII—*Observed annual incidence of second malignant neoplasm per 10 000 cohort members by type of first malignant neoplasm and period of follow up, and associated cumulative risk*

First malignant neoplasm		No of second malignant neoplasm	Incidence of second malignant neoplasm/1000 years of follow up			Cumulative risk of second malignant neoplasm (%) years of follow up		
Diagnostic group No*	Year of diagnosis		0-9	10-19	20-29	0-9	0-19	0-29
I Leukaemias (n=8612)	Total period	18	8·0	21·2	0	0·8	2·9	2·9
	1943-59	0					0	
	1960-87	18					3·1	
II Lymphomas (n=3711)	Total period	45	9·5	29·4	51·8	1·0	3·8	8·7
	1943-59	8					1·9	
	1960-87	37					4·2	
III Central nervous system neoplasms (n=6580)	Total period	50	8·1	8·7	17·0	0·8	1·7	3·3
	1943-59	20					1·0	
	1960-87	30					1·9	
IV Sympathetic nervous system neoplasms (n=1346)	Total period	5	6·9	5·1	16·6	0·7	1·2	2·8
	1943-59	1					0	
	1960-87	4					1·4	
V Retinoblastoma (n=612)	Total period	15	12·9	10·6	47·1	1·3	2·3	6·8
	1943-59	4					0	
	1960-87	11					3·2	
VI Renal tumours (n=1439)	Total period	10	3·4	23·7	0	0·3	2·7	2·7
	1943-59	2					0	
	1960-87	8					3·2	
VIII Malignant bone tumours (n=1898)	Total period	16	13·6	15·1	18·0	1·4	2·8	4·6
	1943-59	2					1·4	
	1960-87	14					3·1	
IX Soft tissue sarcomas (n=2036)	Total period	21	9·8	6·5	27·4	1·0	1·6	4·3
	1943-59	9					0·5	
	1960-87	12					2·1	
X Germ cell, trophoblastic, and other gonadal neoplasms (n=1514)	Total period	20	13·4	15·5	26·7	1·3	2·9	5·4
	1943-59	5					1·2	
	1960-87	15					3·3	
XI Carcinomas (n=2380)	Total period	45	11·1	21·5	27·5	1·1	3·2	5·8
	1943-59	15					2·6	
	1960-87	30					3·3	

*According to classification scheme for childhood cancers.[15] The main diagnostic groups of hepatic tumours (group VIII) and other and unspecified tumours (group XII) were excluded from tabulation as only to 0 and 2 second neoplasms respectively, were observed.

TABLE IX—*Observed and expected numbers of second malignant neoplasm, and standardised incidence ratios by type of first malignant neoplasm*

First malignant neoplasm*	Second malignant neoplasm† Site	No observed	No expected	Relative risk (95% confidence interval)
I Leukaemias (n=8612)	All sites	18	3·3	5·5 (3·2 to 8·7)
	Non-Hodgkin's lymphoma	4	0·2	20·4 (6·5 to 49)
	Brain and nervous system	4	0·8	4·8 (1·5 to 11·7)
	Other sites	10	2·3	4·4 (2·3 to 7·9)
II Lymphomas (n=3711)	All sites	45	8·8	5·1 (3·7 to 6·8)
	Thyroid	11	0·3	37·0 (19·4 to 64)
	Breast	10	0·8	12·5 (6·3 to 22)
	Leukaemia	5	0·6	8·1 (3·0 to 18·0)
	Other sites	19	7·1	2·7 (1·6 to 4·2)
III Central nervous system neoplasms (n=6580)	All sites	50	16·8	3·0 (2·2 to 3·9)
	Brain and nervous system	27	2·1	13·2 (8·7 to 19)
	Connective tissue	4	0·3	13·1 (4·2 to 32)
	Skin	5	2·0	2·5 (0·9 to 5·4)
	Other sites	14	12·4	1·1 (0·6 to 1·8)
IV Sympathetic nervous system neoplasms (n=1346)	All sites	5	1·4	3·5 (1·3 to 7·9)
	Leukaemia	2	0·3	7·8 (1·3 to 26)
	Other sites	3	1·1	2·7 (0·7 to 7·2)
V Retinoblastoma (n=612)	All sites	15	2·0	7·4 (4·2 to 12·3)
	Bone	6	0·1	87·9 (36 to 183)
	Connective tissue	2	0·0	43·9 (4·9 to 97)
	Other sites	7	1·9	3·7 (1·6 to 7·3)
VI Renal tumours (n=1439)	All sites	10	1·8	5·5 (2·8 to 9·8)
	Other skin	2	0·0	47·7 (8·0 to 158)
	Other sites	8	1·8	4·5 (2·1 to 8·5)
VII Hepatic tumours (n=279)	All sites	0	0·1	
VIII Bone tumours (n=1898)	All sites	16	4·5	3·6 (2·0 to 5·8)
	Non-Hodgkin's lymphoma	2	0·2	11·9 (2·0 to 39)
	Brain and nervous system	4	0·5	8·3 (2·6 to 20)
	Breast	3	0·6	5·2 (1·3 to 14·2)
	Other sites	7	3·3	2·1 (0·9 to 4·2)
IX Soft tissue sarcomas (n=2036)	All sites	21	7·4	2·8 (1·7 to 4·3)
	Brain and nervous system	7	0·8	8·8 (3·9 to 17)
	Non-Hodgkin's lymphoma	2	0·3	7·6 (1·3 to 25)
	Testis	2	0·5	4·3 (0·7 to 14·1)
	Melanoma	2	0·5	3·7 (0·6 to 12·2)
	Other sites	8	5·4	1·5 (0·7 to 2·8)
X Germ cell, trophoblastic, and other gonadal neoplasm (n=1514)	All sites	20	6·0	3·3 (2·0 to 5·2)
	Testis	8	0·4	21·9 (10·2 to 42)
	Skin	4	0·7	5·7 (1·8 to 13·7)
	Other sites	8	4·9	1·6 (0·8 to 3·1)
XI Carcinomas (n=2380)	All sites	45	15·8	2·9 (2·1 to 3·8)
	Small intestine	2	0·0	51·1 (8·6 to 169)
	Pancreas	1	0·1	7·8 (0·4 to 38)
	Melanoma	6	1·3	4·6 (1·9 to 9·6)
	Testis	3	0·6	4·6 (1·2 to 12·6)
	Leukaemia	2	0·6	3·1 (0·5 to 10·3)
	Ovary	2	0·8	2·6 (0·4 to 8·5)
	Breast	6	2·8	2·1 (0·9 to 4·4)
	Other sites	23	9·4	2·4 (1·5 to 3·7)
XII Other and unspecified (n=473)	All sites	2	1·1	1·9 (0·3 to 6·3)

*Classification scheme for childhood cancers.[15] †International Classification of Diseases, 7th Revision.

breast and testis occurred in patients who had been diagnosed with their first malignancy at the age of 12-19, implying that those organs are particularly vulnerable to carcinogenesis during the physiological changes of puberty. The decreased risk for cancer of the uterine cervix may reflect changed sexual behaviour among the survivors.

This study was conducted in an area of northern Europe with about 22·5 million inhabitants which has been covered since the 1940s and 1950s by the national cancer registries of Denmark, Finland, Iceland, Norway, and Sweden. The validity of the registration is underlined by the striking similarities in the cancer patterns and in overall cancer incidence in this age group in the five Nordic countries, the similarity of incidence overall to that in other countries or areas with high quality cancer registration,[22] and the stability of the rates over the entire registration period.[23] The main determinants of the quality of the data are the availability of personal identification numbers in all the Nordic countries and the multiple sources of information used by each registry.[12]

MAGNITUDE OF THE INCREASE

Although the increased risk for a second malignant neoplasm in this Nordic collaborative study was highly significant, the magnitude of the increase was much smaller than that found in most other large studies of second primary cancers occurring in childhood. Thus in an international, hospital based study reported by the Late Effects Study Group of 14 610 children with a neoplasm diagnosed in one of 10 centres during 1950-70, the relative risk for a second malignant neoplasm was increased sevenfold during 0-4 years of follow up and 10-fold during 5-15 years of follow up, on the basis of a total of 113 second neoplasms.[2] A later follow up of two year survivors in these and three additional institutions found an overall relative risk for a second neoplasm of 15 (95% confidence interval, 13-17).[3] In hospital based, multicentre studies from Japan (1962-84) and Italy (1981-83) of 2609 and 1467 survivors of childhood cancer the overall relative risks were increased 10-fold, but on the basis of only nine and 11 observed cases, respectively, of second tumours.[4,6] In a recently published study of 9720 children in the United States and Canada who had been selected previously for inclusion in any of the clinical trials for acute lymphoblastic leukaemia (1972-88), a total of 43 second malignancies were seen, which gave a relative risk of 6·9 (4·9 to 9·3).[10] In the only population based study reported so far, of relative risk of a second neoplasm in a cohort of 10 106 three year survivors of childhood cancer notified under the national cancer registration scheme of the United Kingdom (1962-81), an overall relative risk of 5·8 (4·6 to 7·2) was seen on the basis of 76 cases.[7] Although still in excess of the overall relative risk of 3·6 seen in our study, the risk estimate found in the British study is compatible with the fivefold increase in risk seen in our study in the subgroup of patients diagnosed with a first malignant neoplasm during the equivalent period (1960-87). The cumulative probability of a second neoplasm within 25 years of three year follow up was estimated as 3·7% (SE 0·6%) in the British study, compared with the 3·5% attained in our study.

To evaluate the potential problem of underreporting of second malignant neoplasm to the national cancer registries, all patients in the Finnish and Danish subcohorts who were still alive at the end of 1979 and 1976 (7211 patients, a quarter of the entire cohort) were linked to the national hospital discharge registers in each country. These register files provide complete coverage of all discharge diagnoses from hospitals and other inpatient clinics in the countries. In Finland the second tumours that were found were already known to the Finnish Cancer Registry, but the review of Danish discharge diagnoses revealed the existence of two additional but unconfirmed cases of second neoplasm. When those cases were included in the analysis the standardised incidence ratio for second neoplasm in the Danish subcohort changed from 3·0 to 3·1. Similar validation was carried out in the British study by writing to the general practitioners of 2000 of the surviving patients and asking specifically about other primary tumours. No additional neoplasms were identified.[7]

CAUSES OF THE INCIDENCE

As was the case in previous studies of second malignant neoplasm, radiation therapy is most likely the principal aetiological factor for the second primaries observed in the Nordic study population. However, the increase in risk already observed in the subgroup of patients whose first tumour was diagnosed in the early, prechemotherapeutic era (1943-59) followed an increasing trend during the intermediate period (1960-74) to reach a highest level in children diagnosed in the most recent period (1975-87), which is characterised by a widespread use of intensive multiple agent chemotherapy for treating cancer. Although the proportion of children with cancer being exposed to

ionising radiation has been relatively unchanged, over the two later periods at least, advances in treatment technology, including the replacement of orthovoltage by megavoltage radiation, may have lowered the risk for second tumours associated with this treatment modality. These trends suggest, in agreement with the the findings of some earlier reports,[24 25] that chemotherapeutic agents have an independent role as risk factors for second malignancies. The true nature of these relationships will be evaluated in a nested case-control design.

The finding in our study of a much higher female to male sex ratio for second tumours in patients treated for Hodgkin's disease is in agreement with that of a recent American study,[26] although the estimated relative risks in that study were four to five times greater than those seen in our study. The difference in risk between the sexes observed in the present study was due largely to the incidence of female breast cancer and ovarian cancer; female breast cancer also seems to account for the findings in the American study.

Variations in the intensity of treatment can probably explain some of the differences in the levels of risk for second neoplasm between the present population based study and several of the earlier hospital based studies, in particular that of the Late Effects Study Group, which were based mainly on treatment centres in the United States.[2 3 24-27] Also, in our study we continued follow up for a maximum of 45 years, with an age limit of 64. The incidence of cancers in adults that are unrelated to radiation and chemotherapy increases with age, resulting in a progressive reduction in the overall measured relative risks associated with treatment given in childhood. Bias due to potentially better ascertainment of patients with a second neoplasm compared with those with only one tumour may also have resulted in an overestimate of relative risks in the hospital based studies, particularly in those that included large numbers of children with a first neoplasm diagnosed in the 1950s or 1960s.

CONCLUSION

In our international, population based study we observed increased risks for almost all types of second malignant neoplasm after cancer in childhood and adolescence, except for cancers of the lung, female genital organs, and urinary system. All of the individual risk estimates in this study are significantly lower than those in most of the hospital based studies. The extent of the risk, the relatively consistent pattern of second tumours across country borders, and the completeness of cancer registration in the Nordic countries convinces us, however, that the described risk pattern for second tumours in individuals who have experienced a cancer in early life is valid for our part of the world and for a large part of Europe.

We thank B Carstesen for assistance with statistical testing and A Bautz for computer assistance.

Clinical implications

- Because of the remarkable improvements in survival from childhood cancer a rising proportion of the adult population has been now exposed at an early age to high doses of cytostatic agents and radiation
- This Nordic cohort study shows that the risk for second tumours among survivors of cancers diagnosed before the age of 20 is 2·5-7 times higher than that of the general population
- Nearly all combinations of first and second tumour seem to be affected
- The relative risk for a second tumour is in general highest during the first 10 years of follow up, but excess risk occurs throughout life
- The risk pattern indicates that the intensive, multiple agent chemotherapy currently used for treatment of childhood cancer is an independent aetiological factor for second tumour

1 Li FP, Cassady JR, Jaffe N. Risk of second tumors in survivors of childhood cancer. *Cancer* 1975;35:1230-5.
2 Miké V, Meadows AT, D'Angio GJ. Incidence of second malignant neoplasms in children: results of an international study. *Lancet* 1982;ii:1326-31.
3 Tucker MA, Meadows AT, Boice JD Jr, Hoover RN, Fraumeni JF Jr. Cancer risk following treatment of childhood cancer. In: Boice JD Jr, Fraumeni JF Jr, eds. *Radiation carcinogenesis; epidemiology and biological significance.* New York: Raven Press, 1984;211-24.
4 Tsunematsu Y, Watanabe S, Inoue R, Minoda K, Tsuchida A, Bessho F, *et al.* Multiple primary malignancies in childhood cancer. *Jpn J Clin Oncol* 1985;15 (Suppl 1):223-33.
5 Olsen JH. Risk of second cancer after cancer in childhood. *Cancer* 1986;57: 2250-4.
6 Terracini B, Pastore G, Zurlo NG, Masera G, Fosati-Bellani F, Castello M, *et al.* Long deaths and second primary malignancies among long-term survivors of childhood cancer: an Italian multicentre study. *Eur J Clin Oncol* 1987;23:499-504.
7 Hawkins MM, Draper GJ, Kingston JE. Incidence of second primary tumours among childhood cancer survivors. *Br J Cancer* 1987;56:399-47.
8 Witherspoon RP, Fischer LD, Schoch G, Martin P, Sullivan KM, Sanders J, *et al.* Secondary cancers after bone marrow transplantation for leukaemia or aplastic anemia. *N Engl J Med* 1989;321:784-9.
9 Nygaard R, Garwicz S, Haldorsen T, Hertz H, Jonmundsson GK, Lanning M, *et al.* Second malignant neoplasms in patients treated for childhood leukemia: a population-based cohort study from the Nordic countries. *Acta Paediatr Scand* 1991;80:1220-8.
10 Neglia JP, Meadows AT, Robison LL, Kim TH, Newton WA, Ruymann FB, *et al.* Second neoplasms after acute lymphoblastic leukemia in childhood. *N Engl J Med* 1991;325:1330-6.
11 Boice JD Jr, Storm HH, Curtis RE, Jensen OM, Kleinerman RA, Jensen HS, *et al.* Multiple primary cancers in Connecticut and Denmark. *Natl Cancer Inst Mongr* 1985;68:3-9.
12 Hakulinen T, Andersen AA, Malker B, Pukkala E, Schou G, Tulinius H. Trends in cancer incidence in the Nordic countries. *Acta Pathol Microbiol Immunol Scand* 1986;94 (Suppl 288):12-21.
13 Jensen OM, Storm HH, Jensen HS. Cancer registration in Denmark and the study of multiple primary cancers, 1943-80. *Natl Cancer Inst Monogr* 1985;68:245-51.
14 Cancer Registry of Norway. *The incidence of cancer in Norway 1982-1986.* Oslo: Cancer Registry of Norway, 1989:7-9.
15 Birch JM, Marsden HB. A classification scheme for childhood cancer. *Int J Cancer* 1987;40:620-4.
16 World Health Organisation. *International Classification of Diseases for Oncology.* Geneva: WHO, 1976.
17 American Cancer Society. *Manual of tumor nomenclature and coding.* New York: American Cancer Society, 1968.
18 College of American Pathologists. *Systematized nomenclature of medicine.* Chicago: College of American Pathologists, 1976.
19 World Health Organisation. *Statistical code for human tumours 1. Classification by anatomical location, malignancy and histology.* Geneva: WHO, 1956. (WHO/HS/CANC/24.1.)
20 Rothman KJ, Boice JD. Epidemiologic analysis with a programmable calculator. Washington DC: US Government Printing Office, 1979. (DHSS Pub/No. (NIH) 79-1649.)
21 Breslow NE, Day NE. *Statistical methods in cancer research.* Vol 2. *The design and analysis of cohort studies.* Lyon: International Agency for Research on Cancer, 1987. (IARC Scientific Publications No 82.)
22 Parkin DM, Stiller CA, Draper GJ, Bieber CA, Terracini B, Young JL, eds. *International incidence of childhood cancer.* No 87. Lyons: International Agency for Research on Cancer, 1988. (IARC Scientific Publication No 87.)
23 Brown PdeN, Hertz H, Olsen JH, Yssing M, Scheibel E, Jensen OM. Incidence of childhood cancer in Denmark. *Int J Epidemiol* 1989;18:546-55.
24 Tucker MA, D'Angio GJ, Boice JD Jr, Strong LC, Li FP, Stovall M, *et al.* Bone sarcoma linked to radiotherapy and chemotherapy in children. *N Engl J Med* 1987;317:588-93.
25 Tucker MA, Meadows AT, Boice JD Jr, Stovall M, Oberlin O, Stone BJ, *et al.* Leukemia after therapy with alkylating agents for childhood cancer. *J Natl Cancer Inst* 1987;78:459-64.
26 Tarbell NJ, Gelber RD, Weinstein HJ, Mauch P. Sex differences in risk of second malignant tumours after Hodgkin's disease in childhood. *Lancet* 1993;341:1428-32.
27 Tucker MA, Jones PHM, Boice JD Jr, Stone BJ, Stovall M, Jenkin RDT, *et al.* Therapeutic radiation at a young age is linked to secondary thyroid cancer. *Cancer Res* 1991;51:2885-8.

(Accepted 23 August 1993)