Evidence of an association between non-Hodgkin's lymphoma and skin cancer

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Abstract

***Objective*—To investigate a possible link between exposure to ultraviolet light and the almost epidemic increase in non-Hodgkin's lymphoma worldwide. Because ultraviolet light is known to cause skin cancers, the association between non-Hodgkin's lymphoma and skin cancer was studied.**

***Design*—Secondary occurrence of either malignant melanoma or squamous cell skin cancer in cohorts of patients with a first diagnosis of either non-Hodgkin's lymphoma or chronic lymphocytic leukaemia, and vice versa, were studied. Expected numbers of subsequent cancers were calculated by sex, age, and period specific national incidence rates multiplied by the person years under observation in the cohorts.**

***Setting*—Denmark (1943-89) and Sweden (1958-89).**

***Subjects*—Four population based cohorts identified in the nationwide cancer registries (34 641 people with non-Hodgkin's lymphoma, 17 400 with chronic lymphocytic leukaemia, 34 989 with malignant melanoma, 25 980 with squamous cell skin cancer). A total of 562 085 person years were accrued for the analysis.**

***Main outcome measures*—The ratios of observed to expected cancers (the standardised incidence ratio) served as a measure of the relative risk.**

***Results*—The relative risk for developing squamous cell skin cancer was 5·5 (95% confidence interval 4·6 to 6·6) among patients with non-Hodgkin's lymphoma and 8·6 (7·2 to 10·3) among patients with chronic lymphocytic leukaemia. The relative risks remained high over more than 15 years of follow up. Relative risks for malignant melanoma were 2·4 (1·8 to 3·2) for patients with non-Hodgkin's lymphoma and 3·1 (2·1 to 4·4) for patients with chronic lymphocytic leukaemia. After squamous cell skin cancer had been diagnosed there was a twofold excess risk for non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. By contrast, in each of the cohorts the general cancer risks excluding skin and lymphoproliferative malignancies were close to the expected.**

***Conclusions*—The occurrence of non-Hodgkin's lymphoma and skin cancer are strongly associated; this supports the hypothesis that the secular increase in exposure to ultraviolet light may have contributed to the increasing incidence of non-Hodgkin's lymphoma in recent decades**

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Introduction

The non-Hodgkin's lymphomas comprise a heterogeneous collection of lymphoproliferative malignancies. Chronic lymphocytic leukaemia, a malignancy originating from lymphocytes, belongs to the non-Hodgkin's lymphoma group although it is classified with the leukaemias in the *International Classification of Diseases* (ICD).[1] Worldwide, lymphomas constitute the seventh most frequently diagnosed malignancy.[2] The estimated number of new cases in 1985 was 316 000—about 4% of all diagnosed cases of cancer worldwide. The incidence of non-Hodgkin's lymphoma has increased dramatically over the past few decades. The annual increase of 2-4% seen in many countries, including Denmark and Sweden, is equal in men and women.[3,4]

Primary and acquired immunosuppression are known to be risk factors for non-Hodgkin's lymphoma. Evidence for this is found in the much higher risk of non-Hodgkin's lymphoma among patients with congenital immunodeficiency syndromes and in patients with iatrogenically induced immunosuppression in conjunction with organ transplantation or cancer treatment.[5-10] Furthermore, patients with AIDS have a substantially increased risk of non-Hodgkin's lymphoma, and 8-27% of the cases of non-Hodgkin's lymphoma diagnosed in the United States in 1992 could be attributable to HIV infection.[11,12] Other conditions related to an excess risk of non-Hodgkin's lymphoma include rheumatoid arthritis[13] and a history of blood transfusion.[14,15]

Except for the contribution made by the recent HIV epidemic, the worldwide rise in incidence remains to be explained.[16,17] Factors causing this trend would need to be ubiquitous and should have increased over time throughout the world. Ultraviolet radiation might be one such factor because of its effect on the immune system.[18] It has been shown that similar temporal trends and geographical patterns exist for non-Hodgkin's lymphoma and non-melanoma skin cancers, supporting the view that increased exposure to sunlight could be involved in the rapid increase in the incidence of non-Hodgkin's lymphoma[19,20] Several animal studies have found a detrimental impact of ultraviolet light on the immune system.[21-23] Exposure to ultraviolet light has increased during the latest decades and is certainly responsible for a steep increase in incidence of both squamous cell skin cancer[24,25] and malignant melanoma.[26,27]

To evaluate the possible association between ultraviolet light and non-Hodgkin's lymphoma further, we established a retrospective cohort study which used malignant melanoma and squamous cell skin cancer as surrogate markers for exposure to ultraviolet light and looked at their association with the development of non-Hodgkin's lymphoma.

Subjects and methods

THE DANISH AND SWEDISH CANCER REGISTRIES

The Danish cancer registry was started in 1943 and the Swedish cancer registry in 1958. Since the initiation of these national registries, cancers have been coded in both countries according to the seventh

edition of the *International Classification of Diseases* (ICD-7), with slight national modifications. In addition, registrations with specific histology and topography have been performed since 1978 according to the *International Classification of Diseases for Oncology* (ICD-O). Notification of newly diagnosed cancers is mandatory in both countries, and most cases are notified by more than one source (clinicians, pathologists, cytologists). The overall reporting is estimated to be close to 99% of all diagnosed cases.[4] A unique 10 digit national registration number ascribed to every citizen ensures accurate identification in the registration of all notified cancers. These registries monitored a combined population of about 13·6 million in 1989.

SELECTION OF STUDY COHORT

We included all patients registered with non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, malignant melanoma, and squamous cell skin cancer according to the following criteria. The non-Hodgkin's lymphoma cohort comprised all cases registered under ICD-7 codes 200 and 202 in Denmark 1943-89 and in Sweden 1958-89. The chronic lymphocytic leukaemia cohort contained all cases under a Danish modification of ICD-7 code 204.0 diagnosed in Denmark 1943-89 and all cases under Swedish modifications of ICD-7 codes 204.0 or 204.1 diagnosed in Sweden 1958-89. The malignant melanoma cohort comprised all cases under ICD-7 code 190 in Denmark 1943-89 and in Sweden 1958-89. The squamous cell skin cancer cohort contained all cases in Sweden 1958-89 and in Denmark 1978-89 (short calendar period because squamous cell skin cancer were coded together with basal cell skin cancers before 1978) under the combined ICD-O topography codes 173.1-173.9 and histology codes 80513-80523, 80703-80763, 80943, and 85603.

Outcome in several non-Hodgkin's lymphoma subgroups can be leukaemic[1] Whether the clinical presentation is predominantly leukaemic or lymphomatous, the process is identical morphologically and phenotypically, and the subgroups represent different clinical presentations of the same population of neoplastic cells. In epidemiological studies, the clinical entity chronic lymphocytic leukaemia should thus be referred to the group of non-Hodgkin's lymphoma, since it is more essential to identify individual disease entities than differences in clinical presentation.

ANALYSIS

We obtained information about date of death and migration status for every individual in the cohorts through linkage to the central population registries in the respective countries by using the unique national registration number. This provided us with accurate data to calculate person years at risk for subsequent malignancies. The patients with systemic malignancies (non-Hodgkin's lymphoma and chronic lymphocytic leukaemia cohorts) were followed for the occurrence of subsequent skin cancers (malignant melanoma and squamous cell skin cancer) and, conversely, the patients with initial skin cancers were followed for the occurrence of subsequent systemic malignancies.

To evaluate the extent to which the cohort members were at a generally increased risk of cancer, even cancers unlikely to be related to ultraviolet light, we also examined, in Denmark, the risk in all four patient cohorts of all types of malignancy except skin neoplasms and lymphomas and leukaemias. The period of follow up for occurrence of cancer started the month following the date of the cohort defining malignancy and continued until death, emigration, or 31 December 1989, whichever came first. Expected numbers of subsequent cancers were calculated by sex and by age and period specific (both in five year intervals) national incidence rates multiplied by the exact person years under observation in the cohorts. The ratios of observed to expected cancers (standardised incidence ratio) served as measures of the relative risk. Confidence limits for the relative risk estimates were calculated, assuming Poisson distribution of the observed cancers.[28]

TABLE I—*Selected characteristics of study cohorts*

Characteristic	Non-Hodgkin's lymphoma (n=34 641)	Chronic lymphocytic leukaemia (n=17 400)	Malignant melanoma (n=34 989)	Squamous cell carcinoma (n=25 980)
No in Denmark	13 752	8 801	13 339	5 117
No in Sweden	20 889	8 599	21 650	20 863
No of men	19 219	11 072	15 645	16 252
No of women	15 422	6 328	19 344	9 730
No of person/years	114 423	54 733	241 526	151 403
Mean age at diagnosis (years)	63	69	56	74
Mean follow up time (years)	3·3	3·1	6·9	5·8

TABLE II—*Relative risk of skin cancers after an initial diagnosis of non-Hodgkin's lymphoma and chronic lymphocytic leukemia in Denmark and Sweden, 1943-89*

Cohort	Subsequent squamous cell carcinoma: Observed	Expected	Relative risk (95% confidence interval)	Subsequent malignant melanoma: Observed	Expected	Relative risk (95% confidence interval)
			Non-Hodgkin's lymphoma			
Overall	116	20·9	5·5 (4·6 to 6·6)	52	21·3	2·4 (1·8 to 3·2)
By sex;						
Men	86	14·1	6·1 (4·9 to 7·6)	32	11·5	2·8 (1·9 to 3·9)
Women	30	6·9	4·4 (2·9 to 6·2)	20	9·8	2·0 (1·2 to 3·2)
By age at diagnosis:						
<60 years	20	3·0	6·7 (4·1 to 10·3)	21	9·0	2·3 (1·4 to 3·6)
≥60 years	96	17·9	5·4 (4·3 to 6·5)	31	12·3	2·5 (1·7 to 3·6)
By years of follow up:						
<1	13	4·2	3·1 (1·7 to 5·3)	13	4·0	3·3 (1·7 to 5·6)
1-4	51	8·3	6·2 (4·6 to 8·1)	21	8·2	2·6 (1·6 to 3·9)
5-9	29	4·6	6·4 (4·3 to 9·2)	10	4·6	2·2 (1·0 to 4·0)
10-14	13	2·2	6·0 (3·2 to 10·3)	5	2·2	2·3 (0·7 to 5·3)
≥15	10	1·8	5·5 (2·6 to 10·2)	3	2·3	1·3 (0·3 to 3·8)
By period:						
1943-57				3	0·7	4·3 (0·9 to 12·5)
1958-77	26	5·7	4·6 (3·0 to 6·7)	15	6·0	2·5 (1·4 to 4·1)
1978-89	90	15·3	5·9 (4·7 to 7·2)	34	14·5	2·3 (1·6 to 3·3)
			Chronic lymphocytic leukaemia			
Overall	120	13·9	8·6 (7·2 to 10·3)	34	10·9	3·1 (2·1 to 4·4)
By sex;						
Men	96	9·8	9·9 (4·9 to 12·0)	22	6·4	3·4 (2·2 to 5·2)
Women	24	4·1	5·9 (3·8 to 8·7)	12	4·5	2·7 (1·4 to 4·7)
By age at diagnosis:						
<60 years	17	1·0	16·5 (9·6 to 26·4)	6	2·4	2·4 (0·9 to 5·4)
≥60 years	103	12·9	8·0 (6·5 to 9·7)	28	8·4	3·3 (2·2 to 4·8)
By years of follow up:						
<1	11	2·9	3·9 (1·9 to 6·9)	6	2·2	2·7 (1·0 to 5·9)
1-4	62	6·6	9·4 (7·2 to 12·1)	18	5·2	3·5 (2·1 to 5·5)
5-9	35	3·0	11·8 (8·2 to 16·4)	9	2·3	3·9 (1·8 to 7·4)
10-14	8	1·0	8·1 (3·5 to 15·9)	1	0·7	1·4 (0·0 to 8·0)
≥15	4	0·6	7·3 (2·0 to 18·6)	0	0·4	0·0 (0·0 to 9·2)
By period:						
1943-57				0	0·2	0·0 (0·0 to 18·4)
1958-77	41	5·0	8·2 (5·8 to 11·1)	13	3·7	3·6 (1·9 to 6·0)
1978-89	79	8·9	8·9 (7·0 to 11·1)	21	7·0	3·0 (1·9 to 4·6)

Results

Table I shows selected characteristics of the cohorts. Initially, separate analyses of the risk of subsequent skin cancers after initial diagnosis of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia and vice versa were made in the two populations. These analyses revealed largely similar results and therefore the data were combined.

Table II shows the risks of subsequent skin cancers in the non-Hodgkin's lymphoma and chronic lymphocytic leukaemia cohorts. The overall relative risk for squamous cell skin cancer was 5·5 (95% confidence interval 4·6 to 6·6) for patients with non-Hodgkin's lymphoma and 8·6 (7·2 to 10·3) for patients with chronic lymphocytic leukaemia. Data show little variation by sex and calendar period. In the chronic lymphocytic leukaemia cohort there seemed to be an age effect for the risk of squamous cell skin cancer.

TABLE III—*Relative risk of non-Hodgkin's lymphoma and chronic lymphocytic leukemia after initial diagnosis of squamous cell carcinoma and malignant melanoma, Denmark and Sweden, 1943-89*

Cohort	Subsequent non-Hodgkin's lymphoma			Subsequent chronic lymphocytic leukaemia		
	Observed	Expected	Relative risk (95% confidence interval)	Observed	Expected	Relative risk (95% confidence interval)
			Squamous cell carcinoma			
Overall	129	64·0	2·0 (1·7 to 2·4)	69	28·7	2·4 (1·9 to 3·0)
By sex;						
Men	87	44·2	2·0 (1·6 to 2·4)	54	21·9	2·5 (1·9 to 3·2)
Women	42	19·8	2·1 (1·5 to 2·9)	15	6·8	2·2 (1·2 to 3·6)
By age at diagnosis:						
<60 years	11	7·2	1·5 (0·8 to 2·7)	3	2·5	1·2 (0·2 to 3·5)
≥60 years	118	56·8	2·1 (1·7 to 2·5)	66	26·2	2·5 (1·9 to 3·2)
By years of follow up:						
<1	35	9·4	3·7 (2·6 to 5·2)	15	4·1	3·6 (2·0 to 6·0)
1-4	51	25·7	2·0 (1·5 to 2·6)	37	11·4	3·2 (2·3 to 4·5)
5-9	27	16·4	1·6 (1·1 to 2·4)	10	7·4	1·4 (0·6 to 2·5)
10-14	13	7·4	1·8 (0·9 to 3·0)	5	3·5	1·4 (0·5 to 3·4)
≥15	3	5·1	0·6 (0·1 to 1·7)	2	2·2	0·9 (0·1 to 3·2)
By period:						
1958-77	44	16·7	2·6 (1·9 to 3·5)	30	11·4	2·6 (1·8 to 3·8)
1978-89	85	47·3	1·8 (1·4 to 2·2)	39	17·3	2·3 (1·6 to 3·1)
			Malignant melanoma			
Overall	67	49·2	1·4 (1·1 to 1·7)	11	12·5	0·9 (0·4 to 1·6)
By sex;						
Men	31	23·0	1·3 (0·9 to 1·9)	9	7·5	1·2 (0·6 to 2·3)
Women	36	26·1	1·4 (1·0 to 1·9)	2	5·0	0·4 (0·0 to 1·4)
By age at diagnosis:						
<60 years	34	20·6	1·6 (1·1 to 2·3)	3	3·9	0·8 (0·2 to 2·3)
≥60 years	33	28·5	1·2 (0·8 to 1·6)	8	8·6	0·9 (0·4 to 1·8)
By years of follow up:						
<1	11	5·9	1·9 (0·9 to 3·3)	3	1·7	1·8 (0·4 to 5·3)
1-4	22	16·4	1·3 (0·8 to 2·0)	5	4·4	1·1 (0·4 to 2·7)
5-9	18	12·1	1·5 (0·9 to 2·4)	1	3·1	0·3 (0·0 to 1·8)
10-14	7	7·2	1·0 (0·4 to 2·0)	2	1·7	1·1 (0·1 to 4·2)
≥15	9	7·6	1·2 (0·5 to 2·2)	0	1·6	0·0 (0·0 to 2·3)
By period:						
1943-57	1	1·5	0·7 (0·2 to 3·7)			
1958-77	18	14·4	1·3 (0·7 to 2·0)	1	3·1	0·3 (0·0 to 1·8)
1978-89	48	33·3	1·4 (1·1 to 1·9)	10	9·4	1·1 (0·5 to 2·0)

In the non-Hodgkin's lymphoma and the chronic lymphocytic leukaemia cohort the risk for squamous cell skin cancer increased with time during the first decade since systemic malignancy. Although remaining high and significantly raised, the relative risk of squamous cell skin cancer decreased slightly thereafter.

The overall relative risk for malignant melanoma was lower than for squamous cell skin cancer, being 2·4 (1·8 to 3·2) for patients with non-Hodgkin's lymphoma and 3·1 (2·1 to 4·4) for patients with chronic lymphocytic leukaemia. There was consistency by age, sex, and calendar period. In contrast to squamous cell skin cancer, the rates for malignant melanoma were fairly stable during the first decade after non-Hodgkin's lymphoma or chronic lymphocytic leukaemia.

Table III shows the risk pattern for the occurrence of subsequent non-Hodgkin's lymphoma and chronic lymphocytic leukaemia in the two skin cancer cohorts. A twofold significant excess risk found in the squamous cell skin cancer cohort (2·0; 1·7 to 2·4) was consistent by sex, age, and calendar period. The relative risk of non-Hodgkin's lymphoma or chronic lymphocytic leukaemia decreased with time since diagnosis of squamous cell skin cancer. The malignant melanoma cohort showed lower risks for non-Hodgkin's lymphoma and chronic lymphocytic leukaemia than the squamous cell skin cancer cohort (1·4 (1·1 to 1·7) *v* 0·9 (0·4 to 1·6)), and the risk of lymphoproliferative malignancy decreased over time since diagnosis of malignant melanoma.

When skin cancers and leukaemias or lymphomas were excluded from the analysis, patients with non-Hodgkin's lymphoma experienced a general risk of subsequent cancer close to the expected (1·2; 1·1 to 1·3). The corresponding relative risk estimate was 1·3 (1·2 to 1·5) for chronic lymphocytic leukaemia, 1·2 (1·1 to 1·4) for squamous cell skin cancer, and 1·0 (0·97 to 1·1) for malignant melanoma.

Discussion

Both malignant melanoma and squamous cell skin cancer are known to be caused by ultraviolet radiation.[24-27] For squamous cell skin cancer, ultraviolet light seems to be the single most important risk factor, whereas the association between ultraviolet light and malignant melanoma seems more complex.[24 25] There are several lines of evidence indicating that immunosuppression may, at least in part, explain the role of exposure to ultraviolet light in oncogenesis. Animal studies have shown that ultraviolet radiation stimulates the outgrowth of melanoma cells and interferes with the development and expression of immunity to skin cancers. They suggest that ultraviolet radiation may cause systemic immunosuppression, induce the production of suppressor T lymphocytes, and modify the expression or elicitation of immune reactions.[8 21-23] Human studies have shown that exposure to solanum (ultraviolet A) or ordinary sunlight decreases hapten skin reactivity and the activity of circulating natural killer cells and increases the numbers of circulating CD8+ suppressor or cytotoxic T cells and non-specific suppressor cell activity.[29 30]

The molecular and pathogenic mechanisms for the development of non-Hodgkin's lymphoma are not understood. Speculation has focused on either immunosuppression or immunostimulation.[31 32] People with certain primary immunodeficiencies, including ataxia telangiectasia, common variable immunodeficiency, and Wiskott-Aldrich syndrome, are at greatly increased risk of developing non-Hodgkin's lymphoma.[5] People with different kinds of acquired immunodeficiencies have also been found to be at increased risk of non-Hodgkin's lymphoma.[6-15] An example is organ transplant recipients, in whom an iatrogenic, immunological disturbance is provoked by the graft and by the immunosuppressive treatment intended to prevent graft rejection. This combination seems to allow lymphoid proliferation to proceed to malignant lymphoma.

In this study we used skin cancer as a surrogate marker for exposure to ultraviolet light to study the possible association between ultraviolet light and development of non-Hodgkin's lymphoma. Ultraviolet light fulfils the requirement of being ubiquitous, and exposure to it has increased in recent decades, as has the incidence of non-Hodgkin's lymphoma.

SYSTEMIC MALIGNANCIES AND SUBSEQUENT SKIN CANCER

In general, we observed stronger associations between initial systemic malignancies (non-Hodgkin's lymphoma or chronic lymphocytic leukaemia) and the development of subsequent skin cancers (squamous cell skin cancer or malignant melanoma) than the reverse. These findings could be explained by differences in dose-response effects to ultraviolet light—more intense exposure to ultraviolet light may be required for the development of non-Hodgkin's lymphoma than for skin cancer. Ultraviolet light has been shown not only to affect the systemic immune system but also to cause local immunosuppression in the skin.[18 23 29 30] Alternatively, the ease with which squamous cell skin cancers or malignant melanomas are diagnosed, compared with the efforts generally needed to establish a diagnosis of a systemic malignancy, raises the possibility that the time gained (lead time) in diagnosing skin cancer after non-Hodgkin's lymphoma or chronic lymphocytic leukaemia is greater than that in the reverse sequence. This may have contributed to the stronger associations observed between initial non-Hodgkin's lymphoma or chronic lymphocytic leukaemia and subsequent squamous cell skin cancer or malignant melanoma than in the opposite sequence. However, neither of the four

analyses of initial non-Hodgkin's lymphoma or chronic lymphocytic leukaemia and subsequent squamous cell skin cancer or malignant melanoma revealed an excess risk of skin cancers in the first years of follow up, which suggests that this reservation is mostly theoretical.

The pattern for subsequent skin cancers showed differences between squamous cell skin cancer and malignant melanoma. There was an appreciable increase in the risk of squamous cell skin cancer in the years immediately following the diagnosis of non-Hodgkin's lymphoma or chronic lymphocytic leukaemia. This risk remained high and was significantly raised for 15 or more years after the diagnosis. Although significantly increased, the risk of malignant melanoma was lower than of squamous cell skin cancer and did not increase with time. Total exposure to ultraviolet light seems more important in squamous cell skin cancer than in malignant melanoma, for which the association with ultraviolet light may depend on more specific exposures, such as sunburns during early childhood.[27] Therefore, the differences in relative risk observed between squamous cell skin cancer and malignant melanoma could be explained by differences in the mechanisms that link ultraviolet light to squamous cell skin cancer rather than malignant melanoma.

Therapeutic immunosuppression has been linked with increased risks of skin cancer and is another likely contributor to increased risk of squamous cell skin cancer after non-Hodgkin's lymphoma or chronic lymphocytic leukaemia.[6 7 10] The non-Hodgkin's lymphoma cohort is made up of patients treated initially with radiotherapy or chemotherapy, or both (those with stage I, high grade non-Hodgkin's lymphoma) and then living without disease for various time periods, together with patients with low grade non-Hodgkin's lymphoma (including chronic lymphocytic leukaemia), for whom periods of treatment are mixed with a "wait and see" policy.[33] Since the low grade is more common than the high grade,[1 34] and since more intensive chemotherapy programmes with curative potential were not introduced until around 1970,[35] most patients within the cohorts had active lymphoma intermingled with treatment periods. Many of the patients were probably intermittently immunocompromised, in particular during the first period after their malignancy was diagnosed.

There is no evidence that malignant melanoma is triggered by immunosuppression or radiation, and indeed the lack of an increasing trend in our data argues against such an association. There is no obvious explanation for the significantly raised risk of malignant melanoma after non-Hodgkin's lymphoma or chronic lymphocytic leukaemia. A common risk factor for skin cancers and non-Hodgkin's lymphoma or chronic lymphocytic leukaemia, such as exposure to ultraviolet light, is yet to be determined

SKIN CANCERS AND SUBSEQUENT SYSTEMIC CANCERS

Squamous cell skin cancer was more closely linked to non-Hodgkin's lymphoma or chronic lymphocytic leukaemia than was malignant melanoma. For both skin cancer cohorts, the risk of developing non-Hodgkin's lymphoma or chronic lymphocytic leukaemia decreased with the time since the diagnosis of squamous cell skin cancer or malignant melanoma. Transient iatrogenic immunosuppression after radiotherapy for skin cancers may be partly responsible for this association, but as squamous cell skin cancer is usually treated with curettage rather than radiotherapy an alternative explanation is needed to link skin cancers to non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. Ultraviolet light acting as a common risk factor for all the malignancies studied would explain the negative trend of non-Hodgkin's lymphoma or chronic lymphocytic leukaemia with time since the diagnosis of squamous cell skin cancer or malignant melanoma. Patients diagnosed as having skin cancers are advised to avoid extensive exposure to sun and are instructed to use lotions that filter ultraviolet light; they are likely to stop accumulating ultraviolet exposure. Non-Hodgkin's lymphoma or chronic lymphocytic leukaemia will occur predominantly in patients with heavy exposure to ultraviolet light before their diagnosis of skin cancer, and these systemic malignancies will occur soon after the skin cancer diagnosis. The increased risk of malignant melanoma observed in the years after non-Hodgkin's lymphoma or chronic lymphocytic leukaemia would comply with this hypothesis, as patients with non-Hodgkin's lymphoma or chronic lymphocytic leukaemia were not advised to avoid exposure to ultraviolet light.

A methodological explanation that should be considered is surveillance or ascertainment bias. Patients with a diagnosis of either non-Hodgkin's lymphoma or chronic lymphocytic leukaemia are usually under medical observation for long periods, during which minor skin lesions may be more easily observed and biopsied. Patients operated for either a malignant melanoma or squamous cell skin cancer may see a doctor for regular check ups, or they may be more aware of lymph node enlargements. Our data do not suggest, however, that such bias would explain the observed findings. For each of the four cohorts under study, the relative risk of developing new cancers at places other than skin and lymphatic or haematopoietic organs was close to what was expected from population data. The relative risk for these other cancers varied from 1·0 in the malignant melanoma cohort up to 1·3 in the chronic lymphocytic leukaemia cohort. Furthermore, data arguing against an excess of skin cancers due to increased surveillance in patients with internal malignancies have recently been provided: in a follow up of 955 patients with anal cancer, nine subsequent cases of skin cancer were observed when 8·9 were expected (relative risk=1·0; 0·5 to 1·9).[36] Therefore, surveillance bias is likely to explain only a small part of the strong associations between skin cancers and systemic cancers found in this study.

Key messages

- The incidence of both non-Hodgkin's lymphoma and exposure to ultraviolet light have increased over the past few decades
- Ultraviolet light is known to be immunosuppressive and to have causal links to skin cancer
- Non-Hodgkin's lymphoma is strongly associated with skin cancer
- Exposure to ultraviolet light may have contributed to the increasing incidence of non-Hodgkin's lymphoma in recent decades

CONCLUSIONS

These data provide evidence of a close association between non-Hodgkin's lymphoma or chronic lymphocytic leukaemia and squamous cell skin cancer or malignant melanoma. This supports the hypothesis of a role for ultraviolet light in the increasing incidence of non-Hodgkin's lymphoma.

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Somatostatin *v* placebo in bleeding oesophageal varices: randomised trial and meta-analysis

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Abstract

***Objective*—To study whether somatostatin or its derivative octreotide is more effective than placebo for treating bleeding oesophageal varices.**

***Methods*—Randomised, double blind trial and meta-analysis with blinded analysis of data and writing of manuscripts.**

***Setting*—Departments of medical and surgical gastroenterology in Copenhagen.**

***Subjects*—Patients suspected of bleeding from oesophageal varices and of having cirrhosis of the liver.**

***Main outcome measures*—Survival, number of blood transfusions, and use of Sengstaken-Blakemore tube.**

***Results*—86 patients were randomised; in each group 16 died within six weeks (95% confidence interval for difference in mortality —19% to 22%). There were no differences between those treated with somatostatin or placebo in median number of blood transfusions (8 *v* 5, P=0·07, 0 to 4 transfusions) or in numbers of patients who needed balloon tamponade (16 *v* 13, P=0·54, −11% to 28%). In a meta-analysis of three trials involving 290 patients somatostatin had no effect on survival compared with placebo (P=0·59, odds ratio 1·16; 0·67 to 2·01). For blood transfusions and use of balloon tamponade there was heterogeneity between the trials with no convincing evidence in favour of somatostatin. No placebo controlled trials have been performed with octreotide.**

***Conclusion*—Within the limited power of this study and meta-analysis we were unable to show a clinical benefit of somatostatin in the emergency treatment of bleeding oesophageal varices.**

Introduction

Somatostatin is a ubiquitous tetradecapeptide hormone. In most experimental studies, both in animals and in humans, it has reduced portal blood flow,[1 2] while the effect on intraoesophageal pressure has been more equivocal.[2 4] Somatostatin and its derivative octreotide are often used for emergency treatment of bleeding oesophageal varices in patients with cirrhosis of the liver.[5-7] Two placebo controlled trials, however, have shown contrasting results.[8 9] We report here a third trial and a meta-analysis of the trials.

PATIENT SELECTION

The patients were enrolled from April 1987 to the end of April 1992. Patients with clinical indication of bleeding oesophageal varices and with verified or suspected cirrhosis of the liver were eligible for the study. Children and pregnant or lactating women were excluded. Informed consent was obtained unless the