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Cancer Morbidity in Blood Recipients—Results of a Cohort Study

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Blood transfusions involve the transfer of relatively large volumes of body fluids and cellular material between individuals. A variety of pathogens like viruses, some of which are associated with development of certain tumours, are known to be transmitted by this route. Blood recipients were identified during 1981–1982 in the register of the hospital blood centre, and in-patients by the in-patient and discharge register of the hospital. Tumour occurrence and vital status were determined by means of the population-based regional tumour register. Age, gender and calendar-year specific rates from the general population were used to calculate expected values. In a cohort study of 3177 blood recipients, increased numbers of malignant lymphomas [13 vs. 4.8 expected, standard morbidity ratio (SMR) 2.70, 95% confidence interval (CI) 1.44–4.62] and skin cancers [12 vs. 5.2 expected, SMR 2.29, 95% CI 1.19–4.01] were seen 3 to 9 years after transfusion. In a second cohort study of 29 910 hospitalised patients, a total of 37 (29.8 expected) malignant lymphomas was found in 28 338 patients with no transfusion and 10 (2.73 expected) in 1572 patients with a transfusion, 3 to 9 years after the hospitalisation. The incidence rate ratio between these groups was 3.11 (95% CI 1.56–6.20) using a Mantel–Haenszel estimator with age stratification. Non-melanomatous skin cancers had an incidence ratio of 2.74 (95% CI 1.25–6.00). We conclude that, in the cohorts discussed here, malignant lymphomas and skin cancer occur more often in blood recipients than in controls. It remains to be established whether this is due to factors covariating with transfusion or by the transfusion itself. Further studies on these putative associations are warranted, as are analytical studies of the epidemiology of malignant lymphomas, especially non-Hodgkin's lymphoma, whose aetiology is still poorly understood.
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INTRODUCTION

DURING A transfusion of human blood products different types of blood cells, proteins and other biologically active compounds, as well as virus particles, might be transferred from the donor to the recipient. Inoculation with virus particles such as hepatitis and HIV are well-known hazards that, with proper precautions, can be avoided [1, 2].

A viral involvement in pathogenesis is probable in a number of human tumour diseases, such as certain papillomas, primary hepatocellular carcinoma, Burkitt's lymphoma and T-cell leukaemia [3]. Hypothetically, transmission of such known or other unknown oncogenic factors might induce a tumour in the blood recipient.

The aim of this work was, therefore, to investigate if blood recipients exhibit a higher incidence of tumours overall or for specific sites, than untransfused control subjects. As such a study can only serve to be hypothesis-generating, any observed increased risk should be confirmed, and a search be initiated for transmissible oncogenic factors.

MATERIALS AND METHODS

Blood recipients were identified from the computer file of the register of blood recipients kept by the Blood Centre, University Hospital, Lund, Sweden. For 1981–1982, the first 2 years of registration, a total of 6323 recipients were retrieved from the file. This cohort constitutes the patient material in the first analysis.

Hospitalised patients during 1981–1982 were identified from the inpatient and discharge register of the University Hospital, Lund. A total number of 38 939 patients from the primary catchment area of the hospital were identified, of which some had received a blood transfusion (see Results), constituting the patient material for the second analysis.

Both cohorts were matched to the population-based regional tumour register, and cases with a diagnosis of a malignant tumour, prior to or within 1 month after the date of first blood transfusion in the first cohort, or the date of first hospital admission in the second cohort, were excluded. In addition, the cohort of hospitalised patients was matched to the blood recipient register, identifying those who had received a blood transfusion during their stay. Thus, all patients with a transfusion in the second cohort constitute a subpopulation of the cohort of blood recipients.

Malignant tumours were identified in both cohorts by means of the regional tumour register, and vital status was ascertained by means of the population register. Follow-up was concluded on 1 January 1991. For the calculation of expected numbers of malignant tumours, age, gender and calendar-year specific rates from the population of Malmöhus county council were used. The number of tumours and person-years at risk per calendar year and 5-year age category were calculated from 36 months after transfusion (latency period) until diagnosis of the first primary tumour, emigration or death. Furthermore, the follow-

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up for an individual was concluded at the age of 80, since diagnosis and reporting of cancer in elderly people may be somewhat less accurate.

The cancer incidences in the cohorts were compared to those of the general population by means of the SMR (standardised morbidity ratio). Confidence intervals (CI) for this parameter for the different sites were calculated assuming Poisson distribution of the number of cases.

For malignant lymphomas (classification numbers ICD 7 = 200–203) and non-melanomatous skin cancers (ICD 7 = 191), the incidence rates were compared directly between the transfusion and no-transfusion groups of the hospitalised patients by means of a stratified Mantel–Haenszel test [4], grouping the person-years into four age strata. Ninety-five per cent confidence intervals for the incidence rate ratios were constructed according to Greenland and Robins [5].

At this time (1981–1982), almost 100% of the blood was given as whole blood and packed red cells, buffy coat included. The total number of blood products given to a specific patient could not be deduced from the register.

The study was approved by the ethics committee at the University of Lund and The National Data Inspection Board, Stockholm.

RESULTS

Blood recipients

Out of the 6323 patients, 2028 had a malignant disease prior to the transfusion, and 374 were aged 80 years or older. Thus, the final cohort consisted of 3921 patients (21 607 person-years). With a latency of 3 years (3177 patients, 16 733 person-years), a total of 134 malignant tumours were observed vs. 113 expected (SMR 1.19, 95% CI 1.00–1.41). An increased incidence was found for tumours of the kidney (9 vs. 3.4, SMR 2.65, 95% CI 1.21–5.03), non-melanomatous skin cancer (12 vs. 5.2, SMR 2.29, 95% CI 1.19–4.01) and malignant lymphomas (13 vs. 4.8, SMR 2.70, 95% CI 1.44–4.62).

Hospitalised patients

Out of the 38 939 patients identified as having been hospitalised during 1981–1982, 2838 had a prior malignant diagnosis and 2974 were aged 80 years or older. The final cohort thus consisted of 33 127 patients, and 2108 of those received a blood transfusion during their hospitalisation. With a latency of 36 months, the no-transfusion group consisted of 28 338 patients (160 592 person-years) and the transfusion group of 1572 patients (8249 person-years).

In the patients who did not receive a blood transfusion, a total of 724 malignant tumours were observed compared to 657 expected (SMR 1.10, 95% CI 1.02–1.19). An increased number of cases were observed for tumours of the liver (primary) (13 vs. 5.1, SMR 2.55, 95% CI 1.36–4.36) and trachea and lungs (73 vs. 50, SMR 1.47, 95% CI 1.16–1.85). For malignant lymphoma, 37 cases were observed compared to 29.8 expected (SMR 1.24, 95% CI 0.88–1.73). The complete results are given in Table 1.

In the patients receiving a blood transfusion, a total number of 69 malignant tumours were observed vs. 66 expected (SMR 1.05, CI 0.82–1.33). An increased incidence was only observed for non-melanomatous skin cancers (8 vs. 3.14, SMR 2.55, 95% CI 1.10–5.03) and for malignant lymphomas, with 10 observed vs. 2.73 expected (SMR 3.66, 95% CI 1.76–6.74). For full details, see Table 2.

Table 1. Malignant tumours observed in 28 338 hospitalised patients without blood transfusion (160 592 person-years)

ICD-7	Site	O	E	SMR	95% CI
140–209	All sites	724	656.93	1.10	1.02–1.19
140	Lip	4	3.74	1.07	0.29–2.74
141,143–144	Oral cavity	9	5.65	1.59	0.73–3.03
142	Salivary glands	4	2.28	1.75	0.48–4.48
145–148	Pharynx	5	3.45	1.45	0.47–3.38
150	Oesophagus	9	5.84	1.54	0.70–2.93
151	Stomach	20	19.56	1.02	0.64–1.60
153	Colon	42	44.87	0.94	0.68–1.27
154	Rectum	29	30.34	0.96	0.65–1.39
1550	Liver, primary	13	5.09	2.55	1.36–4.36
1551–1559	Biliary passages	10	6.13	1.63	0.78–3.00
157	Pancreas	20	17.69	1.13	0.70–1.77
160	Nasal cavity and sinuses	2	1.33	1.51	0.18–5.44
161	Larynx	3	5.70	0.53	0.11–1.54
1620–1621	Trachea and lung	73	49.76	1.47	1.16–1.85
1622	Pleura	4	2.24	1.79	0.49–4.58
170	Breast	94	87.37	1.08	0.87–1.32
171	Cervix uteri	16	16.19	0.99	0.58–1.63
172,174	Corpus uteri	17	15.38	1.11	0.66–1.80
175	Ovary	19	17.46	1.09	0.67–1.72
176	Vulva and vagina	1	2.38	0.42	0.01–2.34
177	Prostate	67	74.19	0.90	0.70–1.15
178	Testis	5	3.86	1.30	0.42–3.02
180	Kidney	21	18.49	1.14	0.72–1.76
181	Urinary tract	32	36.25	0.88	0.61–1.26
190	Malignant melanoma of skin	24	30.03	0.80	0.52–1.20
191	Skin (melanoma excluded)	29	26.77	1.08	0.73–1.57
193	Nervous system	25	24.16	1.03	0.68–1.55
194	Thyroid gland	7	5.17	1.35	0.54–2.79
196–197	Bone and soft tissue	6	5.94	1.01	0.37–2.20
200,202	Non-Hodgkin's lymphoma	22	17.54	1.25	0.80–1.92
201	Hodgkin's disease	4	5.55	0.72	0.20–1.85
203	Multiple myeloma	11	6.70	1.64	0.82–2.94
2040,2050,2060, 2070	Acute leukaemia	9	7.60	1.18	0.54–2.25
2041	Chronic lymphatic leukaemia	9	5.90	1.53	0.70–2.90
2051	Chronic myeloid leukaemia	3	1.63	1.84	0.38–5.38
208	Polycythemia vera	1	1.59	0.63	0.02–3.50

O, observed; E, expected; SMR, standardised morbidity ratio; CI, confidence interval.

Malignant lymphomas

The findings regarding malignant lymphomas (ICD 7 = 200–203) were analysed using a Mantel–Haenszel test. The subgrouping of the hospitalised patients into four age strata is given in Table 3. It should be noted that the transfusion group is older than the no-transfusion group. An estimate of the incidence rate ratio between the two groups was 3.11 (95% CI 1.56–6.20).

Limiting the Mantel–Haenszel analysis to non-Hodgkin's

Table 2. Malignant tumours observed in 1572 hospitalised patients with blood transfusion (8249 person-years)

ICD-7	Site	O	E	SMR	95% CI
140–209	All sites	69	65.87	1.05	0.82– 1.33
140	Lip	0	0.42	0.00	0.00– 8.73
141,143–144	Oral cavity	1	0.53	1.87	0.05–10.42
142	Salivary glands	0	0.22	0.00	0.00–16.72
145–148	Pharynx	0	0.33	0.00	0.00–11.09
150	Oesophagus	2	0.66	3.04	0.37–10.98
151	Stomach	3	2.19	1.37	0.28– 4.01
153	Colon	4	4.87	0.82	0.22– 2.10
154	Rectum	6	3.25	1.85	0.68– 4.02
1550	Liver, primary	0	0.49	0.00	0.00– 7.47
1551–1559	Biliary passages	1	0.65	1.54	0.04– 8.56
157	Pancreas	1	1.89	0.53	0.01– 2.95
160	Nasal cavity and sinuses	0	0.15	0.00	0.00–24.44
161	Larynx	0	0.61	0.00	0.00– 6.00
1620–1621	Trachea and lung	4	5.40	0.74	0.20– 1.90
1622	Pleura	0	0.23	0.00	0.00–16.32
170	Breast	2	7.25	0.28	0.03– 1.00
171	Cervix uteri	0	0.90	0.00	0.00– 4.11
172,174	Corpus uteri	3	1.38	2.18	0.45– 6.37
175	Ovary	1	1.50	0.67	0.02– 3.71
176	Vulva and vagina	0	0.25	0.00	0.00–14.87
177	Prostate	3	9.41	0.32	0.07– 0.93
178	Testis	0	0.14	0.00	0.00–26.30
180	Kidney	5	1.99	2.52	0.82– 5.88
181	Urinary tract	3	4.07	0.74	0.15– 2.15
190	Malignant melanoma of skin	3	2.32	1.29	0.27– 3.78
191	Skin (melanoma excluded)	8	3.14	2.55	1.10– 5.03
193	Nervous system	3	1.97	1.52	0.31– 4.45
194	Thyroid gland	0	0.35	0.00	0.00–10.39
196–197	Bone and soft tissue	1	0.50	2.00	0.05–11.14
200,202	Non-Hodgkin's lymphoma	7	1.71	4.09	1.65– 8.43
201	Hodgkin's disease	1	0.29	3.47	0.09–19.33
203	Multiple myeloma	2	0.73	2.73	0.33– 9.85
2040,2050,2060, 2070	Acute leukaemia	1	0.75	1.33	0.03– 7.41
2041	Chronic lymphatic leukaemia	1	0.70	1.44	0.04– 8.00
2051	Chronic myeloid leukaemia	0	0.13	0.00	0.00–28.38
208	Polycythemia vera	0	0.15	0.00	0.00–24.35

O, observed; E, expected; SMR, standardised morbidity ratio; CI, confidence interval.

lymphoma (ICD 7 = 200 202), the incidence rate ratio between the two groups was 3.45 (95% CI 1.50–7.93).

Data on patients with malignant lymphomas in the transfusion group are given in Table 4. According to the universally applied coding rules of cancer registries, reticuloses and related conditions are included in ICD 7 = 202, thus explaining the case with an eosinophilic granuloma.

The reasons for hospitalisation of the 47 patients who later developed malignant lymphomas were quite different in the two groups. Of the 10 patients who received a blood transfusion, 7 underwent a major surgical procedure, such as arthroplasty of the hip (n = 3), coronary bypass (n = 1), thrombectomy of the subclavian vein (n = 1) and operations on the digestive tract due to bleeding ulcers and perforation (n = 2). The 3 remaining patients in this group were hospitalised due to septicaemia, agammaglobulinaemia and overdosage of anticoagulant, respectively.

Table 3. Distribution of lymphoma cases (ICD 7 = 200–203) and person-years by age group. The incidence rate ratio = 3.11 (95% CI 1.56–6.20)

Age	Transfusion Cases	Transfusion Person-years	No transfusion Cases	No transfusion Person-years
0–19	1	652	2	29 688
20–39	1	1955	4	60 518
40–59	2	2412	7	41 520
60–79	6	3229	24	28 865

In the group of 37 patients without blood transfusions, the range of diagnoses was broad, including infectious diseases (n = 4), metabolic diseases (n = 4), cardiovascular diseases (n = 7), urological diseases (n = 4), gynaecological and obstetric disorders (n = 6), diseases of the eye (n = 2), diseases of the musculoskeletal system and connective tissue (n = 2), injuries and fractures (n = 4), and various rather unspecified conditions (n = 4). A total of 15 out of the 37 patients underwent some surgical procedure, all of them minor, such as endoscopy, ligation of thrombotic vein, transurethral resection, uterine abrasion and cataract operation.

Skin cancer

The incidence rates of non-melanomatous skin cancers (ICD 7= 191) in the transfusion and no-transfusion groups were

Table 4. Age at transfusion, sex, interval to diagnosis and the type of lymphoma in 10 patients with malignant lymphoma after transfusion

Age at transfusion	Sex	Interval between transfusion and diagnosis (months)	Type of lymphoma	Stage
8	F	80	Eosinophilic granuloma of the mandible	
32	F	81	HD, mixed cellularity	IV B
45	M	44	CB/CC NHL	IV_E (intestine)
54	M	66	High-grade B-cell NHL	
61	M	85	Follicular CB/CC NHL	I
65	F	57	Multiple myeloma	
65	M	108	Multiple myeloma	
72	M	72	Follicular CB NHL	II
73	F	38	CB/CC NHL	IV_E (soft tissues)
74	F	63	High grade NHL	IV_E (stomach)

F, female; M, male; HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma; CB, centroblastic; CC, centrocytic.

compared using the same four age strata as in Table 3. An estimate of the incidence rate ratio between the two groups was 2.74 (95% CI 1.25–6.00).

In the transfusion group, all eight tumours were of the squamous cell type. The distribution of subsites was head, face and neck 6, trunk 0 and extremities 2. In the no-transfusion group, 26 of the 29 tumours were squamous cell carcinomas, two were adnexal carcinomas and one undifferentiated carcinoma. The distribution on the same subsites was 19, 2 and 8, respectively.

The number of units transfused, as well as the identity of the donors, have not been investigated further in any of these groups of patients.

DISCUSSION

The most striking finding in this study is the increased incidence of malignant lymphoma and non-melanomatous skin cancer in patients receiving a blood transfusion compared with patients not receiving a transfusion 3 to 9 years after 'exposure'.

This finding was initially observed in the total cohort of blood recipients when compared with the normal background population, but in addition, other tumours, for example, of the kidney, showed an increased SMR, resulting in an almost 20% higher cancer incidence than in the reference population. However, patients receiving a blood transfusion are, by definition, unhealthy in one way or another. Therefore, this comparison is confounding, since premalignant conditions or diseases subject to malignant disease might be over-represented in this group of patients.

In order to reduce this bias, the final comparison and calculations were based on hospitalised patients in one and the same hospital and from the same catchment area, this selection being considered to be the most appropriate achievable. As expected, this cohort showed an overall increased cancer incidence, which was most pronounced for liver cancer and lung cancer, possibly reflecting alcohol- and tobacco-related diseases as a main reason for hospitalisation.

With the exclusion of patients with malignant disease diagnosed prior to or within 1 month of the admission date, the risk of hospitalisation for a known malignancy is minimised. The application of a 36-month latency time further minimises this risk.

Furthermore, none of the reasons for hospitalisation in the 47 lymphoma patients could be identified as being related to any known condition leading to the development of a malignant lymphoma, with the exception of the case with agammaglobulinaemia, a condition which has been associated with an increased incidence of malignancies, including lymphoma [6]. This is the young girl with eosinophilic granuloma.

Although no assessment of the number of units transferred was made, it could be noted that 7 out of the 10 lymphoma patients with transfusion underwent surgical procedures, which often necessitate the transfer of large volumes of blood.

The status of being a blood recipient or not was only assessed in the data files during 1981–1982. Obviously, any person not identified as a blood recipient at that time might have had a transfusion before or after this time window. The effect of this is a dilution of any observed risk, and thus the results are minimum figures.

In the literature, studies on tumour incidence after blood transfusion are scarce, and existing data are based on case–control studies or case reports.

In an Italian case–control study of 242 patients with liver cancer, a significant association with blood transfusion was found with a relative risk of 2.2 for ≥ three transfusions [7]. A few cases of Kaposi's sarcoma in blood-transfused persons [8] have been described. In contrast, in a Jamaican case–control study of non-Hodgkin's lymphoma involving 119 cases and 373 controls, a history of blood transfusion was found to be more common among controls than cases [9].

Theoretically, an increase in incidence of a specific neoplasm after blood transfusion could be due to (i) a covariation of blood transfusion with other factors related to the development of malignancy, (ii) activation of endogenous oncogenic factors, e.g. by temporary immunosuppression or (iii) direct transmission of oncogenic factors with a tumorigenic potential.

The immune status of the recipient can be influenced by the transfusion. Several studies have shown an increased recurrence rate and decreased survival in patients with colorectal cancer receiving blood transfusions compared with no transfusions. In a meta-analysis, a 70% increase in recurrence rate and 30% increase in death rate up to 5 years after operation was found [10]. Most of these studies have been retrospective, and the type of blood product is usually not specified. In a recent prospective study of 58 patients with colorectal cancer, the survival of transfused patients was not significantly shorter [11].

Transmission of viruses with oncogenic capacity [12] might be considered as a possible explanation of the observed increased frequency of malignant lymphoma and skin cancer.

Infection with several human viruses is associated with development of lymphomas. One of those, Epstein–Barr virus (EBV), can give infectious disease after blood transfusion and is thus transmissible [13]. EBV DNA occurs regularly in Burkitt's lymphoma and B-cell non-Hodgkin's lymphomas arising after immunosuppression [14–17]. Whether EBV has an aetiological role in the latter case is still debated.

Human T-cell leukaemia viruses types I and II (HTLV-I and -II) are important risk factors in the development of adult T-cell leukaemia/lymphoma, less frequently hairy cell leukaemia and, probably indirectly, B-cell lymphomas [18]. They are recognised transfusion hazards [19, 20]. There is also suggestive evidence of involvement of HTLV-like viruses in cutaneous T-cell lymphomas, like mycosis fungoides [21]. There are no cases of HTLV infections yet detected among Swedish blood donors [22].

Other human viruses, possibly causing lymphomas, may exist. The potential to promote malignancy of the EBV-related lymphotropic human herpes viruses 6 (HHV6 [23]) and 7 (HHV7 [24]) is not clear. B-cell lymphomas have been observed in HIV-infected persons infected directly in the blood stream [25]. Lymphotropic papova viruses, with a potential to cause malignant transformation *in vitro*, infect African green monkeys, and similar viruses may exist in man [26]. A type D retrovirus, closely related to Mason–Pfizer monkey retrovirus, was recently isolated from an AIDS patient with lymphoma. This virus needs further characterisation [27].

Among other virus-related human cancers, primary hepatocellular carcinoma (HCC) has an established association with hepatitis B and C viruses [28]. The absence of an additional risk of HCC in our study is an indication that transfusion-related hepatitis B and C are infrequent causes of HCC in Sweden. However, since the latency time of HCC may be decades, the observation time is too short in this study.

Numerous reports on increased incidence rates of squamous cell carcinoma of the skin after kidney and heart transplantations exist [29–32]. These increased risks have been associated with

the type and duration of immunosuppressive therapy, but other factors cannot be ruled out. Papilloma viruses are prevalent viruses which are important for the development of papillomas and skin cancers [3, 12]. It is not impossible that they could be transmitted by transfusion. More tentative is the possible transmission by transfusion of activated human endogenous retroviruses [33].

Naturally, this register study provides no evidence as regards the aetiology of the increased incidences of malignant lymphomas and skin cancers observed in blood recipients. It remains to be established whether this is due to factors covariating with transfusion or by the transfusion itself. Our data suggest that such putative transfusion-related malignancies could occur in an appreciable fraction of recipients. This warrants confirmation from other populations.

Furthermore, studies of aetiological factors in malignant lymphomas, especially non-Hodgkin's lymphoma, have a high priority due to the great increase in incidence during the last few decades [34].

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