# Cancer Incidence in Blood Transfusion Recipients

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**Background** Blood transfusions may influence the recipients' cancer risks both through transmission of biologic agents and by modulation of the immune system. However, cancer occurrence in transfusion recipients remains poorly characterized.

**Methods** We used computerized files from Scandinavian blood banks to identify a cohort of 888843 cancer-free recipients transfused after 1968. The recipients were followed from first registered transfusion until the date of death, emigration, cancer diagnosis, or December 31, 2002, whichever came first. Relative risks were expressed as ratios of the observed to the expected numbers of cancers, that is, standardized incidence ratios (SIRs), using incidence rates for the general Danish and Swedish populations as a reference. All statistical tests were two-sided.

**Results** During 5652918 person-years of follow-up, 80990 cancers occurred in the transfusion recipients, corresponding to a SIR of 1.45 (95% confidence interval [CI] = 1.44 to 1.46). The SIR for cancer overall decreased from 5.36 (95% CI = 5.29 to 5.43) during the first 6 months after transfusion to 1.10 or less for follow-up periods more than 2 years after the transfusion. However, the standardized incidence ratios for cancers of the tongue, mouth, pharynx, esophagus, liver, and respiratory and urinary tracts and for squamous cell skin carcinoma remained elevated beyond 10 years after the transfusion.

**Conclusions** The marked increase in cancer risk shortly after a blood transfusion may reflect the presence of undiagnosed occult cancers with symptoms that necessitated the blood transfusion. The continued increased risk of tobacco- and alcohol-related cancers suggests that lifestyle and other risk factors related to conditions prompting transfusion rather than transfusion-related exposures per se are important to the observed cancer occurrence in the recipients.

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Blood transfusions can expose recipients to transmissible biologic agents that are known or suspected to be associated with cancer occurrence (1). Blood transfusions may also cause modulation of the recipient's immune system (2). Various immune system dysfunctions, both congenital and acquired, have been associated with increased risks of several types of cancer (3). The spectrum of transfusion-transmissible biologic agents continuously widens, and neither the underlying mechanisms nor the full clinical implications of transfusion-related immune modulation have been elucidated. Meanwhile, however, some investigators have speculated that blood transfusions could increase the recipient's subsequent risk of cancer (4–10).

A number of studies have specifically examined the association of blood transfusions with cancers that have been strongly linked to transmissible agents (11) and/or to immune modulation (3). For example, the possible association of non-Hodgkin lymphoma with blood transfusion has been studied in eight investigations (12–19). Similarly, due to the risk of transmission of hepatitis viruses that may cause liver cancer, the association of liver cancer with blood transfusion has also been studied repeatedly (20,21). By contrast, few studies have examined the occurrence of cancer in general after a blood transfusion. In a prospective US cohort study of 9539 elderly cancer-free women with self-reported histories of blood transfusion, 440 cancers were observed, corresponding to a relative risk of any cancer of 0.94 (95% confidence interval [CI] = 0.84 to 1.05) (7). In

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a Swedish register-based study of 1572 hospitalized cancer-free transfusion recipients, a total of 69 cancers occurred 3 or more years after the transfusion, corresponding to a relative risk of cancer overall of 1.05 (95% CI = 0.82 to 1.33) (8). Another Swedish cohort study, of 621 women who received blood transfusions during obstetric delivery, observed 41 cases of cancer 21–31 years after the transfusion, corresponding to a risk ratio of 1.04 (95% CI = 0.69 to 1.53) (10). Finally, a British study observed 100 cancers among 12 690 persons who received a blood transfusion in infancy compared with an expected number of 88.9 cancers, corresponding to an estimated relative risk of 1.12 (estimated 95% CI = 0.91 to 1.37) (9).

The combination of small cohorts and limited follow-ups, which resulted in small numbers of cancer cases, limits the conclusions that can be drawn from these studies about the temporal and anatomic patterns of cancer occurrence following blood transfusions. We, therefore, assessed the occurrence of cancer in a large cohort of transfusion recipients that were identified from computerized files of Danish and Swedish blood banks.

## CONTEXT AND CAVEATS

**Prior knowledge**

Blood transfusions can expose recipients to transmissible biologic agents that are known or suspected to be associated with cancer occurrence and may also alter recipients' immune systems, thereby placing them at increased risks of some cancers.

**Study design**

A population-based study that used computerized blood bank and health data to examine cancer occurrence among a cohort of blood transfusion recipients in Sweden and Denmark.

**Contribution**

Among blood transfusion recipients, there was a marked increase in the relative risk of most cancers and cancer overall during the first 6 months after transfusion that decreased over time. Risks of cancers that share tobacco and alcohol use as risk factors were elevated for 10–20 years after the blood transfusion.

**Implications**

The marked increase in cancer risk shortly after blood transfusion may reflect the presence of undiagnosed cancers that prompted the transfusion. The continued excess occurrence of cancers associated with tobacco and alcohol use suggests that these and other risk factors that are related to the condition that prompted the transfusion contribute to the cancer pattern observed in these blood transfusion recipients.

**Limitations**

Multiple comparisons increased the risk of chance findings. Computerized registration of blood transfusion was implemented nonuniformly. Some recipients may have received a transfusion before computerized databases were introduced.

## Subjects and Methods

### Cohort of Transfusion Recipients

Beginning in 1965 in Sweden and in 1981 in Denmark, computer systems were gradually introduced on a large scale in blood banks to monitor and improve the use of blood products. By the early 1990s, the computer systems were used in all blood banks in Sweden, while 90% and 100% coverages were achieved in Denmark in 1997 and 2002, respectively (22). These computer systems have collected information on individual blood donations and transfusions, including the dates of donations and transfusions as well as the identities of donors and recipients through their national registration numbers, which have been issued to all Swedish residents since 1947 and to all Danish residents since 1968.

The Scandinavian Donation and Transfusion (SCANDAT) database (22) was created as part of a large study on long-term health consequences of blood donation and transfusion by compiling all available computerized data from Swedish and Danish blood banks, allowing the construction of a cohort of blood transfusion recipients. We used the national registration numbers of the transfusion recipients to obtain information on their exact dates of death or emigration as of December 31, 2002, by linking the cohort with national population, death, and emigration registers. We also linked the cohort to national cancer registers (23,24) and to hospital discharge registers (25,26) to obtain information on malignant and nonmalignant diagnoses and surgical procedures.

### Follow-up

We identified all transfusion recipients who did not have a previous history of cancer at the time of their first registered blood transfusion and followed them for cancer diagnoses. For each cohort member, follow-up time began the month after the first registered transfusion of any blood product (i.e., the index transfusion) and ended on the date of the first cancer diagnosis, death, emigration, or December 31, 2002, whichever came first. For reasons related to completeness and quality of registered information in the earliest period of blood bank computerization, transfusions registered before 1968 in Sweden and before 1982 in Denmark were not considered in the analyses.

### Statistical Methods

The relative risk of cancer following blood transfusion was expressed as the standardized incidence ratio (SIR), that is, the ratio of the observed to the expected number of cancer cases in the cohort. The expected number of cancers was calculated by multiplying country-, calendar period–, age-, and sex-specific first cancer incidence rates in the general populations of Sweden and Denmark by the corresponding person-years of follow-up in the cohort and summing the products. Nonmelanoma skin cancers were included in the general population incidence rates for first cancers in Sweden but not in Denmark; therefore, only Swedish transfusion recipients were followed for the occurrence of nonmelanoma skin cancers. Analogously, general population cancer incidence rates included metastases in Denmark but not in Sweden, and, accordingly, only Danish transfusion recipients were followed for this outcome. We estimated 95% confidence intervals for the standardized incidence ratios from Wald tests by assuming a Poisson distribution of the observed cases (27). All statistical tests were two-sided.

We estimated the relative risk of cancer overall for different time intervals after the transfusion to investigate putative temporal variations in cancer risk and facilitate their interpretation (1–5 months, 6–23 months, 2–4 years, 5–9 years, 10–19 years, and ≥20 years). This was done for the entire cohort of transfusion recipients and for the strata of recipients defined by country, sex, calendar

period of first transfusion (before 1982, 1982–1991, and 1992 or later), age at first transfusion (0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥80 years), transfusion indication as approximated by discharge diagnoses (i.e., trauma, thoracic surgery for cardiovascular diseases, gastrointestinal bleeding, other defined conditions, and unknown conditions), and by the number of blood products transfused in the 30-day period following the first registered transfusion (1–2 or ≥3 products). In the calendar period-specific analyses, 1982 was chosen as a cut point because it was the first year for which Danish data were included, and 1991 was chosen because nationwide screening for hepatitis C in Denmark began in 1991 and was instituted gradually in Sweden between 1990 and 1992.

We also carried out analyses to estimate the relative risks of cancers at specific anatomic sites during the different follow-up intervals after the transfusion. In these site-specific analyses, women who had received a transfusion and who had information in the national hospital discharge registers on the surgical removal of the uterus, uterine cervix, uterine tubes (unilateral or bilateral), and/or ovaries (unilateral or bilateral) were not considered to be at risk of cancer at these specific sites and were censored on date of such surgery.

Finally, we conducted supplementary analyses to assess the relative risks of two cancers that have received particular scrutiny in previous studies of blood transfusion recipients, non-Hodgkin lymphoma and liver cancer. These analyses were stratified by country, sex, and calendar period as described above for cancer overall. In addition, for non-Hodgkin lymphoma, analyses were also stratified according to whether the index transfusion was given before or after 1985, when screening for human immunodeficiency virus (HIV) was introduced. This particular analysis was restricted to Swedish data to retain maximum comparability between the recipients transfused before and after the time point in question. Because leukocytes are believed to mediate transfusion-related immune modulation (2,28,29), we also assessed the relative risks of non-Hodgkin lymphoma in recipients whose first registered transfusion included whole blood or red blood cell products.

This study was approved by appropriate scientific ethical committees and data protection agencies in both countries.

## Results

A total of 888 843 blood transfusion recipients without a prior cancer diagnosis at the index transfusion were identified in the SCANDAT database and followed up in these analyses. Demographic characteristics of the recipients are presented in Table 1. Overall, this cohort of transfusion recipients contained more women than men (58% vs 42%). The number of transfusion recipients increased with increasing age at the index transfusion beginning with those aged 10–19 years to a peak in those aged 70–79 years. A total of 662 344 (75%) of the recipients were Swedish and 226 499 (25%) were Danish, which reflects the longer history of blood bank registration and the larger population in Sweden. Consequently, more person-years of follow-up were accumulated by Swedish transfusion recipients (4 744 992 person-years, 84% of total) than by Danish transfusion recipients (907 926 person-years, 16% of total) (Table 1).

During 5 652 918 person-years of follow-up, a total of 80 990 cancers were observed among the initially cancer-free transfusion recipients, whereas 55 788 cancers were expected (SIR = 1.45; 95% CI = 1.44 to 1.46). The increased risk of cancer overall varied widely with respect to time since the index blood transfusion (Table 2). Thus, during the first 6 months after the transfusion, transfusion recipients had a more than fivefold increase in cancer risk (SIR = 5.36; 95% CI = 5.29 to 5.43), whereas in the follow-up periods more than 2 years after the transfusion, the relative risk of cancer was increased by 10% (i.e., 1.10-fold) or less (Table 2). Similar temporal variation in relative risk of cancer overall was observed within strata of recipients defined by country, sex, calendar period, age, transfusion indication, and number of transfused blood products (Table 2). The relative risk of cancer overall declined with increasing age at first transfusion, and among the oldest recipients, statistically significantly decreased risks of cancer were observed in some follow-up periods (Table 2).

The relative risks of cancer overall also varied by transfusion indication. In particular, the relative risk of cancer was consistently less increased in those who were transfused because of trauma or thoracic surgery than in those who were transfused for other reasons. With continued follow-up, the risk of cancer in recipients transfused because of trauma or thoracic surgery did not deviate from that in the general population except for a transient but statistically significantly decreased cancer risk in the period 2–4 years after transfusion in trauma patients (Table 2).

Our analyses of the relative risks of cancers at specific sites revealed that essentially all anatomic sites contributed to the increased incidence of cancer overall that we observed during the first 6 months after the index transfusion. The risk estimates were particularly elevated for malignancies that commonly present clinically with anemia or overt bleeding, such as those of the hematopoietic system, the digestive tract, and the kidney (Table 3). More than 6 months after the index blood transfusion, the relative risk of cancer at most anatomic sites, including non-Hodgkin lymphoma, decreased to near unity (Table 3). However, for certain anatomic sites, i.e., the tongue, mouth, pharynx, esophagus, liver, and respiratory and urinary tracts, and for squamous cell carcinoma of the skin, the observed numbers of cancers continued to exceed the expected numbers even beyond the first 10–20 years after the index transfusion. In general, the risks of these cancers were increased for all types of transfusion indications, most compellingly for gastrointestinal bleeding and the least so for thoracic surgery (data not shown). Finally, a few statistically significantly decreased risks were observed in the site-specific analyses (breast cancer 2–9 years after transfusion, prostate cancer 2–4 years after transfusion, and uterine cancer 2–4 years after transfusion).

Our stratified analyses revealed that the relative risks of liver cancer were marginally higher in men than in women for all follow-up intervals; however, in general, we observed no systematic variation or notable differences in relative risk among the different strata of transfusion recipients as defined by country or calendar periods (Table 4). Except for the somewhat higher relative risks of non-Hodgkin lymphoma in Denmark than in Sweden, there was little variation in the relative risks of non-Hodgkin lymphomas among the investigated strata defined by sex, calendar periods (including before or after HIV screening), or type of transfused blood products (Table 4).

**Table 1**. Characteristics of transfusion recipients*

| Stratum | Denmark | | Sweden | | Total | |
|---|---|---|---|---|---|---|
| | No. of recipients | Person-years† | No. of recipients | Person-years† | No. of recipients | Person-years† |
| Total | 226 499 | 907 926 | 662 344 | 4 744 992 | 888 843 | 5 652 918 |
| Sex | | | | | | |
| Male | 97 423 | 364 602 | 280 308 | 1 865 542 | 377 731 | 2 230 143 |
| Female | 129 076 | 543 324 | 382 036 | 2 879 451 | 511 112 | 3 422 775 |
| Age at first transfusion, y | | | | | | |
| 0–9 | 6275 | 30 370 | 16 637 | 182 785 | 22 912 | 213 155 |
| 10–19 | 3412 | 24 551 | 14 895 | 206 046 | 18 307 | 230 597 |
| 20–29 | 11 265 | 84 281 | 45 440 | 646 520 | 56 705 | 730 801 |
| 30–39 | 13 857 | 84 229 | 48 682 | 590 709 | 62 539 | 674 938 |
| 40–49 | 17 841 | 100 720 | 50 059 | 541 237 | 67 900 | 641 957 |
| 50–59 | 26 082 | 120 348 | 73 089 | 642 479 | 99 171 | 762 827 |
| 60–69 | 38 688 | 161 708 | 113 971 | 792 631 | 152 659 | 954 339 |
| 70–79 | 55 473 | 185 091 | 161 258 | 762 124 | 216 731 | 947 215 |
| 80–89 | 43 906 | 101 830 | 115 593 | 338 626 | 159 499 | 440 456 |
| ≥90 | 9700 | 14 798 | 22 720 | 41 835 | 32 420 | 56 633 |
| Mean (SD) | 63.6 (21.4) | | 61.7 (21.9) | | 62.2 (21.8) | |
| Calendar period at first transfusion | | | | | | |
| Before 1982 | – | – | 119 222 | 1 768 405 | 119 222 | 1 768 405 |
| 1982–1991 | 35 714 | 313 262 | 152 327 | 1 537 941 | 188 041 | 1 851 203 |
| 1992–2002 | 190 785 | 594 664 | 390 795 | 1 438 646 | 581 580 | 2 033 310 |
| Transfusion indication | | | | | | |
| Trauma | 35 652 | 122 829 | 115 956 | 617 245 | 151 608 | 740 074 |
| GI bleeding | 15 903 | 53 918 | 42 849 | 263 772 | 58 752 | 317 690 |
| Thoracic surgery | 8997 | 41 158 | 53 282 | 403 009 | 62 279 | 444 167 |
| Other defined conditions‡ | 145 746 | 548 914 | 380 594 | 2 702 155 | 526 340 | 3 251 069 |
| Unclassified | 20 201 | 141 107 | 69 663 | 758 811 | 89 864 | 899 919 |
| Duration of follow-up, y | | | | | | |
| Median (IQR) | 2.8 (0.9–5.8) | | 4.7 (1.6–10.1) | | 4.1 (1.3–8.8) | |
| Longest | 20.9 | | 34.9 | | 34.9 | |

* SD = standard deviation; GI = gastrointestinal; IQR = interquartile range; – = not applicable.

† Numbers may not add up due to rounding.

‡ Includes all specific discharge diagnosis registrations that are not trauma, GI bleeding, or thoracic surgery.

## Discussion

The overall cancer incidence in this large cohort of blood transfusion recipients exceeded that of the general population. Importantly, however, the relative risk of cancer was not uniformly increased across different time windows after the index blood transfusion. Rather, for all strata of transfusion recipients and for essentially all anatomic sites, there was a marked increase in the relative risk of cancer during the first 6 months after transfusion that, with longer follow-up, decreased to approach the prevailing cancer risk in the general population.

Although the magnitude of increase in cancer risk varied considerably among groups of recipients and among different cancer types during the first 6 months after the transfusion, the relative risks followed similar temporal patterns irrespective of transfusion indication or anatomic site, suggesting shared underlying mechanisms. There has been speculation that blood transfusions could promote or facilitate tumor growth (2,28,29) and thus could precipitate incipient cancers. However, we speculate that other mechanisms unrelated to blood transfusion could account for the observed increased incidence of cancer at early times after blood transfusion. For example, selection bias (or confounding by indication) could have occurred if, as is likely, some recipients were transfused because of early symptoms [such as anemia or bleeding (30)] from occult cancers that were not diagnosed until after the transfusion. It is also possible that, in some cases, there may have been a lag between the diagnosis of a cancer and its registration in the cancer register. In addition, hospitalization, which is nearly invariably implied by the registration of a transfusion, is itself associated with an increased chance of detection and diagnosis of malignant disorders (31). Our finding of an increased incidence of squamous cell skin cancer, which rarely necessitates blood transfusion per se, may reflect such surveillance bias.

The observed increased incidence of cancer in the first 6 months of follow-up among patients transfused for trauma would be compatible with the proposed mechanisms of inclusion of patients with incipient cancer into the cohort and with increased diagnostic surveillance. It is highly likely that the prevalence of incipient cancer would be lower among transfused trauma patients or among those admitted and transfused for thoracic surgery than among patients transfused due to gastrointestinal bleeding. This prevalence difference would explain the higher relative risks of cancer in the latter group of recipients. Similarly, the higher relative risk of cancer among transfused children than among older recipients may reflect age-dependent differences in the prevalence of incipient cancer in the general population, being virtually nil among children.

**Table 2.** Standardized incidence ratios for any cancer occurrence in blood transfusion recipients by time interval after transfusion*

| | 1–5 mo | | 6–23 mo | | 2–4 y | | 5–9 y | | 10–19 y | | ≥20 y | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stratum | No. of obs | SIR (95% CI) | No. of obs | SIR (95% CI) | No. of obs | SIR (95% CI) | No. of obs | SIR (95% CI) | No. of obs | SIR (95% CI) | No. of obs | SIR (95% CI) |
| All recipients | 21935 | 5.36 (5.29 to 5.43) | 14856 | 1.34 (1.32 to 1.37) | 16744 | 1.09 (1.07 to 1.11) | 14161 | 1.08 (1.06 to 1.10) | 10500 | 1.09 (1.07 to 1.11) | 2794 | 1.10 (1.06 to 1.14) |
| Country | | | | | | | | | | | | |
| Sweden | 15995 | 5.35 (5.27 to 5.44) | 10735 | 1.30 (1.27 to 1.32) | 12752 | 1.06 (1.04 to 1.08) | 11837 | 1.07 (1.05 to 1.09) | 9695 | 1.09 (1.07 to 1.11) | 2792 | 1.10 (1.06 to 1.14) |
| Denmark | 5940 | 5.37 (5.24 to 5.51) | 4121 | 1.47 (1.43 to 1.52) | 3992 | 1.20 (1.16 to 1.24) | 2324 | 1.14 (1.09 to 1.18) | 805 | 1.14 (1.06 to1.22) | 2 | 0.58 (0.14 to 2.31) |
| Sex | | | | | | | | | | | | |
| Male | 11446 | 5.35 (5.26 to 5.45) | 7768 | 1.35 (1.32 to 1.38) | 8955 | 1.10 (1.08 to 1.13) | 7938 | 1.12 (1.09 to 1.14) | 5541 | 1.13 (1.10 to 1.16) | 1065 | 1.11 (1.05 to 1.18) |
| Female | 10489 | 5.36 (5.26 to 5.46) | 7088 | 1.34 (1.30 to 1.37) | 7789 | 1.08 (1.05 to 1.10) | 6223 | 1.04 (1.01 to 1.06) | 4959 | 1.06 (1.03 to 1.09) | 1729 | 1.08 (1.03 to 1.14) |
| Calendar period of first transfusion | | | | | | | | | | | | |
| Before 1982 | 2615 | 7.40 (7.12 to 7.69) | 1756 | 1.67 (1.59 to 1.75) | 2272 | 1.18 (1.13 to 1.23) | 3254 | 1.14 (1.10 to 1.18) | 5165 | 1.10 (1.07 to 1.13) | 2767 | 1.10 (1.06 to 1.14) |
| 1982–1991 | 4874 | 6.41 (6.23 to 6.59) | 3093 | 1.35 (1.30 to 1.40) | 4461 | 1.08 (1.05 to 1.12) | 6007 | 1.06 (1.03 to 1.08) | 5253 | 1.09 (1.06 to 1.12) | 27 | 1.05 (0.72 to 1.53) |
| 1992–2002 | 14446 | 4.85 (4.77 to 4.93) | 10007 | 1.30 (1.27 to 1.32) | 10011 | 1.07 (1.05 to 1.10) | 4900 | 1.07 (1.04 to 1.10) | 82 | 1.07 (0.86 to1.33) | 0 | – |
| Age at first transfusion, y | | | | | | | | | | | | |
| 0–9 | 171 | 86.2 (74.2 to 100) | 48 | 8.32 (6.27 to 11.0) | 25 | 2.93 (1.98 to 4.34) | 17 | 2.21 (1.37 to 3.55) | 16 | 1.25 (0.83 to 2.14) | 10 | 1.70 (0.91 to 3.16) |
| 10–19 | 92 | 62.4 (50.9 to 76.6) | 27 | 5.22 (3.58 to 7.62) | 19 | 1.74 (1.11 to 2.73) | 22 | 1.08 (0.71 to 1.64) | 66 | 1.39 (1.10 to 1.78) | 41 | 1.00 (0.73 to 1.35) |
| 20–29 | 158 | 14.4 (12.3 to 16.9) | 75 | 1.98 (1.58 to 2.48) | 96 | 1.19 (0.97 to 1.45) | 181 | 1.21 (1.05 to 1.40) | 421 | 1.08 (0.98 to 1.19) | 398 | 1.06 (0.96 to 1.17) |
| 30–39 | 365 | 13.3 (12.0 to 14.7) | 192 | 2.08 (1.81 to 2.40) | 243 | 1.27 (1.12 to 1.44) | 408 | 1.22 (1.11 to 1.34) | 838 | 1.13 (1.06 to 1.21) | 534 | 1.17 (1.08 to 1.27) |
| 40–49 | 854 | 11.3 (10.6 to 12.1) | 516 | 2.07 (1.90 to 2.25) | 668 | 1.35 (1.25 to 1.46) | 865 | 1.14 (1.07 to 1.22) | 1435 | 1.15 (1.10 to 1.22) | 681 | 1.11 (1.03 to 1.19) |
| 50–59 | 2148 | 9.31 (8.93 to 9.71) | 1335 | 1.81 (1.72 to 1.91) | 1791 | 1.32 (1.26 to 1.38) | 2256 | 1.22 (1.17 to 1.27) | 2731 | 1.14 (1.10 to 1.18) | 787 | 1.15 (1.07 to 1.23) |
| 60–69 | 4682 | 6.30 (6.12 to 6.48) | 3241 | 1.43 (1.38 to 1.48) | 4404 | 1.14 (1.11 to 1.18) | 4595 | 1.08 (1.05 to 1.11) | 3404 | 1.07 (1.04 to 1.11) | 308 | 1.01 (0.91 to 1.13) |
| 70–79 | 7743 | 4.80 (4.69 to 4.91) | 5698 | 1.28 (1.24 to 1.31) | 6470 | 1.03 (1.01 to 1.06) | 4718 | 1.04 (1.01 to 1.07) | 1458 | 1.01 (0.96 to 1.06) | 35 | 0.67 (0.48 to 0.93) |
| ≥80 | 5722 | 4.11 (4.01 to 4.22) | 3724 | 1.16 (1.13 to 1.20) | 3028 | 0.98 (0.94 to 1.01) | 1099 | 0.92 (0.87 to 0.98) | 130 | 0.79 (0.66 to 0.94) | 0 | – |
| Transfusion indication | | | | | | | | | | | | |
| Trauma | 1207 | 1.50 (1.42 to 1.59) | 2048 | 0.98 (0.94 to 1.02) | 2348 | 0.94 (0.90 to 0.98) | 1565 | 0.98 (0.94 to 1.03) | 832 | 1.02 (0.96 to 1.10) | 165 | 1.09 (0.94 to 1.27) |
| GI bleeding | 1529 | 4.74 (4.50 to 4.98) | 1263 | 1.48 (1.40 to 1.57) | 1333 | 1.20 (1.13 to 1.26) | 1110 | 1.28 (1.20 to 1.35) | 736 | 1.19 (1.11 to 1.28) | 251 | 1.28 (1.13 to 1.45) |
| Thoracic surgery | 383 | 1.25 (1.13 to 1.39) | 969 | 1.05 (0.99 to 1.12) | 1539 | 1.02 (0.97 to 1.08) | 1566 | 1.00 (0.95 to 1.05) | 1104 | 1.02 (0.96 to 1.08) | 99 | 1.05 (0.86 to 1.28) |
| Other defined† | 15815 | 6.81 (6.71 to 6.92) | 9092 | 1.46 (1.43 to 1.49) | 9753 | 1.12 (1.10 to 1.14) | 8004 | 1.09 (1.07 to 1.12) | 5736 | 1.10 (1.07 to 1.13) | 1436 | 1.12 (1.07 to 1.18) |
| Undefined | 3001 | 8.79 (8.48 to 9.11) | 1484 | 1.53 (1.46 to 1.61) | 1771 | 1.14 (1.09 to 1.19) | 1916 | 1.08 (1.04 to 1.13) | 2092 | 1.12 (1.07 to 1.17) | 843 | 1.01 (0.95 to 1.08) |
| No. of transfusion products received | | | | | | | | | | | | |
| 1–2 | 8845 | 4.40 (4.31 to 4.49) | 6953 | 1.29 (1.26 to 1.32) | 7985 | 1.08 (1.06 to 1.11) | 6538 | 1.06 (1.04 to 1.09) | 5037 | 1.09 (1.06 to 1.12) | 1610 | 1.07 (1.02 to 1.12) |
| ≥3 | 13090 | 6.28 (6.18 to 6.39) | 7903 | 1.40 (1.36 to 1.43) | 8759 | 1.10 (1.07 to 1.12) | 7623 | 1.10 (1.07 to 1.12) | 5463 | 1.09 (1.07 to 1.12) | 1184 | 1.13 (1.07 to 1.20) |

* Includes cancers that presented as metastases in Danish subjects. obs = observed; SIR = standardized incidence ratio; CI = confidence interval; – = none observed/not applicable; GI = gastrointestinal.

† Includes all specific discharge diagnosis registrations that are not trauma, GI bleeding, or thoracic surgery.

**Table 3.** Standardized incidence ratios for cancer occurrence by anatomic site in blood transfusion recipients by time interval after transfusion*

| | 1–5 mo | | 6–23 mo | | 2–4 y | | 5–9 y | | 10–19 y | | ≥20 y | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Anatomic site** | **No. of obs** | **SIR (95% CI)** | **No. of obs** | **SIR (95% CI)** | **No. of obs** | **SIR (95% CI)** | **No. of obs** | **SIR (95% CI)** | **No. of obs** | **SIR (95% CI)** | **No. of obs** | **SIR (95% CI)** |
| All malignant neoplasms† | 21 935 | 5.36 (5.29 to 5.43) | 14 856 | 1.34 (1.32 to 1.37) | 16 744 | 1.09 (1.07 to 1.11) | 14 161 | 1.08 (1.06 to 1.10) | 10 500 | 1.09 (1.07 to 1.11) | 2794 | 1.10 (1.06 to 1.14) |
| Buccal cavity and pharynx | 148 | 1.96 (1.67 to 2.31) | 307 | 1.51 (1.35 to 1.69) | 458 | 1.64 (1.49 to 1.79) | 384 | 1.62 (1.47 to 1.79) | 263 | 1.60 (1.42 to 1.81) | 54 | 1.38 (1.05 to 1.80) |
| Lip | 25 | 1.29 (0.87 to 1.91) | 45 | 0.87 (0.65 to 1.17) | 61 | 0.86 (0.67 to 1.11) | 59 | 0.98 (0.76 to 1.27) | 42 | 1.05 (0.77 to 1.42) | 7 | 0.83 (0.40 to 1.74) |
| Tongue | 23 | 2.06 (1.37 to 3.09) | 49 | 1.61 (1.22 to 2.13) | 80 | 1.89 (1.52 to 2.35) | 70 | 1.94 (1.54 to 2.45) | 58 | 2.24 (1.73 to 2.90) | 12 | 1.78 (1.01 to 3.13) |
| Salivary glands | 10 | 1.25 (0.67 to 2.32) | 25 | 1.16 (0.78 to 1.71) | 31 | 1.03 (0.73 to 1.47) | 26 | 1.01 (0.69 to 1.49) | 20 | 1.07 (0.69 to 1.66) | 5 | 1.05 (0.44 to 2.51) |
| Mouth | 37 | 1.87 (1.35 to 2.58) | 89 | 1.68 (1.36 to 2.06) | 151 | 2.08 (1.77 to 2.44) | 115 | 1.92 (1.60 to 2.30) | 67 | 1.65 (1.30 to 2.10) | 14 | 1.41 (0.84 to 2.39) |
| Pharynx | 53 | 3.10 (2.37 to 4.06) | 99 | 2.14 (1.76 to 2.61) | 138 | 2.15 (1.82 to 2.54) | 116 | 2.12 (1.76 to 2.54) | 76 | 1.95 (1.55 to 2.44) | 17 | 1.81 (1.12 to 2.90) |
| Digestive organs/peritoneum | 9800 | 9.60 (9.41 to 9.79) | 4388 | 1.61 (1.56 to 1.66) | 4123 | 1.11 (1.08 to 1.14) | 3318 | 1.08 (1.05 to 1.12) | 2255 | 1.09 (1.04 to 1.13) | 551 | 1.12 (1.03 to 1.22) |
| Esophagus | 207 | 4.84 (4.22 to 5.54) | 189 | 1.65 (1.43 to 1.91) | 234 | 1.50 (1.32 to 1.70) | 176 | 1.37 (1.18 to 1.59) | 118 | 1.41 (1.18 to 1.69) | 26 | 1.40 (0.95 to 2.06) |
| Stomach | 1647 | 11.3 (10.8 to 11.9) | 639 | 1.65 (1.53 to 1.79) | 580 | 1.09 (1.00 to 1.18) | 512 | 1.13 (1.04 to 1.24) | 285 | 0.94 (0.84 to 1.06) | 74 | 1.17 (0.93 to 1.46) |
| Small intestine | 268 | 18.4 (16.3 to 20.8) | 129 | 3.26 (2.75 to 3.88) | 98 | 1.77 (1.45 to 2.16) | 65 | 1.34 (1.05 to 1.71) | 45 | 1.25 (0.93 to 1.67) | 12 | 1.23 (0.70 to 2.17) |
| Colon‡ | 4914 | 12.9 (12.6 to 13.3) | 1836 | 1.81 (1.73 to 1.90) | 1477 | 1.07 (1.02 to 1.13) | 1145 | 1.02 (0.96 to 1.08) | 805 | 1.07 (1.00 to 1.15) | 196 | 1.05 (0.91 to 1.21) |
| Rectum§ | 975 | 4.93 (4.63 to 5.25) | 566 | 1.07 (0.98 to 1.16) | 688 | 0.94 (0.87 to 1.02) | 600 | 0.98 (0.91 to 1.06) | 430 | 1.02 (0.93 to 1.12) | 104 | 1.00 (0.83 to 1.22) |
| Liver‖ | 521 | 7.99 (7.34 to 8.71) | 354 | 2.06 (1.86 to 2.29) | 394 | 1.74 (1.58 to 1.93) | 294 | 1.66 (1.48 to 1.86) | 212 | 1.93 (1.69 to 2.21) | 46 | 2.08 (1.56 to 2.77) |
| Gallbladder, billiary passages, ampulla Vateri | 384 | 7.75 (7.01 to 8.57) | 194 | 1.46 (1.27 to 1.68) | 203 | 1.12 (0.97 to 1.28) | 176 | 1.15 (0.99 to 1.33) | 95 | 0.89 (0.73 to 1.09) | 23 | 0.92 (0.61 to 1.38) |
| Pancreas | 886 | 7.96 (7.45 to 8.50) | 484 | 1.63 (1.49 to 1.78) | 444 | 1.11 (1.01 to 1.21) | 342 | 1.04 (0.93 to 1.16) | 262 | 1.18 (1.05 to 1.33) | 67 | 1.28 (1.01 to 1.63) |
| Peritoneum and unspecified | 36 | 9.72 (7.01 to 13.4) | 9 | 0.94 (0.49 to 1.81) | 18 | 1.48 (0.93 to 2.35) | 12 | 1.40 (0.80 to 2.47) | 5 | 1.07 (0.45 to 2.57) | 4 | 3.42 (1.28 to 9.11) |
| Respiratory system | 1428 | 3.77 (3.58 to 3.97) | 1402 | 1.39 (1.32 to 1.46) | 1766 | 1.29 (1.23 to 1.35) | 1373 | 1.24 (1.18 to 1.31) | 986 | 1.35 (1.27 to 1.44) | 222 | 1.28 (1.12 to 1.46) |
| Nasal cavities and sinuses | 11 | 1.53 (0.85 to 2.76) | 36 | 1.88 (1.36 to 2.61) | 27 | 1.05 (0.72 to 1.52) | 24 | 1.13 (0.76 to 1.69) | 19 | 1.35 (0.86 to 2.11) | 3 | 0.96 (0.31 to 2.99) |
| Larynx | 38 | 1.64 (1.19 to 2.25) | 89 | 1.43 (1.17 to 1.77) | 129 | 1.53 (1.29 to 1.81) | 95 | 1.36 (1.11 to 1.66) | 60 | 1.35 (1.05 to 1.74) | 14 | 1.62 (0.96 to 2.74) |
| Lung, tracheae¶ | 1366 | 3.93 (3.73 to 4.15) | 1273 | 1.37 (1.30 to 1.45) | 1607 | 1.28 (1.22 to 1.35) | 1249 | 1.23 (1.17 to 1.30) | 903 | 1.35 (1.27 to 1.44) | 205 | 1.27 (1.11 to 1.46) |
| Mediastinum | 13 | 15.0 (8.73 to 25.8) | 4 | 1.76 (0.66 to 4.68) | 4 | 1.38 (0.52 to 3.68) | 5 | 2.36 (0.98 to 5.66) | 4 | 3.31 (1.24 to 8.81) | 0 | – |
| Breast | 666 | 1.44 (1.33 to 1.55) | 1254 | 0.99 (0.94 to 1.05) | 1629 | 0.93 (0.88 to 0.97) | 1447 | 0.95 (0.90 to 1.00) | 1399 | 1.05 (1.00 to 1.11) | 549 | 1.12 (1.03 to 1.21) |
| Female genital organs# | 983 | 3.93 (3.70 to 4.19) | 699 | 1.03 (0.95 to 1.10) | 849 | 0.90 (0.84 to 0.96) | 771 | 0.96 (0.89 to 1.03) | 601 | 0.92 (0.85 to 1.00) | 215 | 0.96 (0.84 to 1.10) |
| Cervix uteri | 127 | 3.56 (2.99 to 4.23) | 129 | 1.33 (1.12 to 1.58) | 162 | 1.19 (1.02 to 1.39) | 154 | 1.26 (1.07 to 1.47) | 110 | 1.11 (0.92 to 1.34) | 30 | 1.21 (0.85 to 1.73) |
| Corpus uteri | 192 | 1.98 (1.71 to 2.28) | 271 | 1.03 (0.91 to 1.16) | 305 | 0.85 (0.76 to 0.95) | 278 | 0.96 (0.85 to 1.08) | 218 | 1.01 (0.88 to 1.15) | 81 | 1.00 (0.81 to 1.25) |
| Uterus, other parts, and unspecified | 71 | 8.30 (6.57 to 10.4) | 27 | 1.16 (0.79 to 1.69) | 27 | 0.83 (0.57 to 1.22) | 27 | 0.96 (0.66 to 1.41) | 20 | 0.86 (0.55 to 1.33) | 15 | 1.83 (1.10 to 3.03) |
| Ovary, fallopian tube, broad ligament | 478 | 6.53 (5.97 to 7.14) | 185 | 0.93 (0.81 to 1.08) | 251 | 0.92 (0.81 to 1.04) | 230 | 0.98 (0.86 to 1.12) | 173 | 0.90 (0.78 to 1.05) | 60 | 0.95 (0.74 to 1.23) |
| Other or unspecified | 51 | 2.18 (1.66 to 2.87) | 69 | 1.10 (0.87 to 1.39) | 87 | 1.04 (0.84 to 1.28) | 66 | 0.99 (0.78 to 1.27) | 63 | 1.35 (1.05 to 1.72) | 22 | 1.52 (1.00 to 2.30) |
| Male genital organs | 1691 | 2.64 (2.52 to 2.77) | 1706 | 0.98 (0.94 to 1.03) | 2295 | 0.91 (0.88 to 0.95) | 2230 | 0.99 (0.95 to 1.03) | 1695 | 1.03 (0.99 to 1.08) | 339 | 0.99 (0.89 to 1.10) |
| Prostate | 1655 | 2.64 (2.51 to 2.77) | 1669 | 0.98 (0.93 to 1.03) | 2252 | 0.91 (0.88 to 0.95) | 2187 | 0.99 (0.94 to 1.03) | 1662 | 1.03 (0.99 to 1.09) | 328 | 0.98 (0.88 to 1.09) |
| Testis | 18 | 3.45 (2.17 to 5.48) | 20 | 1.38 (0.89 to 2.14) | 23 | 1.10 (0.73 to 1.65) | 20 | 1.00 (0.64 to 1.54) | 11 | 0.66 (0.37 to 1.19) | 3 | 0.89 (0.29 to 2.76) |
| Other or unspecified | 19 | 2.56 (1.63 to 4.01) | 18 | 0.91 (0.57 to 1.44) | 20 | 0.73 (0.47 to 1.13) | 23 | 0.98 (0.65 to 1.47) | 22 | 1.37 (0.90 to 2.08) | 8 | 2.48 (1.24 to 4.97) |
| Urinary system | 1969 | 5.82 (5.57 to 6.08) | 1222 | 1.35 (1.28 to 1.43) | 1386 | 1.12 (1.06 to 1.18) | 1224 | 1.18 (1.11 to 1.24) | 793 | 1.12 (1.05 to 1.20) | 176 | 1.11 (0.96 to 1.29) |
| Kidney | 1102 | 11.4 (10.8 to 12.1) | 383 | 1.49 (1.34 to 1.64) | 408 | 1.16 (1.05 to 1.28) | 341 | 1.15 (1.03 to 1.28) | 219 | 1.06 (0.93 to 1.21) | 58 | 1.19 (0.92 to 1.54) |
| Bladder** | 871 | 3.59 (3.36 to 3.84) | 843 | 1.30 (1.22 to 1.39) | 982 | 1.10 (1.04 to 1.17) | 885 | 1.19 (1.11 to 1.27) | 575 | 1.15 (1.06 to 1.25) | 118 | 1.08 (0.90 to 1.29) |

*(Table continues)*

**Table 3 (continued).**

| Anatomic site | 1–5 mo | | 6–23 mo | | 2–4 y | | 5–9 y | | 10–19 y | | ≥20 y | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of obs | SIR (95% CI) | No. of obs | SIR (95% CI) | No. of obs | SIR (95% CI) | No. of obs | SIR (95% CI) | No. of obs | SIR (95% CI) | No. of obs | SIR (95% CI) |
| Skin cancer | 352 | 1.24 (1.11 to 1.37) | 859 | 1.10 (1.03 to 1.17) | 1283 | 1.14 (1.08 to 1.20) | 1163 | 1.16 (1.10 to 1.23) | 909 | 1.18 (1.11 to 1.26) | 215 | 1.01 (0.88 to 1.16) |
| Malignant melanoma | 113 | 1.06 (0.88 to 1.27) | 291 | 0.99 (0.88 to 1.11) | 437 | 1.04 (0.95 to 1.15) | 359 | 0.96 (0.87 to 1.06) | 302 | 1.00 (0.89 to 1.12) | 83 | 0.96 (0.78 to 1.19) |
| Squamous cell carcinoma## | 240 | 1.35 (1.19 to 1.53) | 569 | 1.16 (1.07 to 1.26) | 847 | 1.20 (1.12 to 1.28) | 804 | 1.28 (1.20 to 1.38) | 607 | 1.29 (1.20 to 1.40) | 132 | 1.04 (0.88 to 1.24) |
| Other specified sites | 1175 | 6.95 (6.56 to 7.36) | 694 | 1.50 (1.39 to 1.61) | 818 | 1.25 (1.17 to 1.34) | 634 | 1.08 (1.00 to 1.17) | 512 | 1.06 (0.97 to 1.16) | 152 | 1.09 (0.93 to 1.28) |
| Eye | 16 | 1.76 (1.08 to 2.88) | 29 | 1.18 (0.82 to 1.70) | 26 | 0.76 (0.52 to 1.12) | 30 | 1.03 (0.72 to 1.48) | 29 | 1.35 (0.94 to 1.94) | 6 | 1.01 (0.45 to 2.24) |
| Brain and nervous system | 611 | 7.76 (7.17 to 8.40) | 273 | 1.27 (1.13 to 1.43) | 341 | 1.15 (1.03 to 1.28) | 275 | 1.06 (0.94 to 1.19) | 215 | 1.02 (0.90 to 1.17) | 65 | 1.08 (0.85 to 1.38) |
| Thyroid | 78 | 4.02 (3.22 to 5.02) | 65 | 1.21 (0.95 to 1.55) | 83 | 1.08 (0.87 to 1.33) | 65 | 0.92 (0.72 to 1.17) | 54 | 0.93 (0.71 to 1.22) | 19 | 1.21 (0.77 to 1.90) |
| Endocrinal glands | 282 | 7.46 (6.64 to 8.38) | 219 | 2.08 (1.82 to 2.37) | 246 | 1.61 (1.42 to 1.82) | 187 | 1.30 (1.13 to 1.50) | 146 | 1.13 (0.96 to 1.33) | 44 | 1.06 (0.79 to 1.42) |
| Bone | 34 | 10.2 (7.35 to 14.3) | 17 | 1.87 (1.16 to 3.01) | 19 | 1.47 (0.94 to 2.30) | 13 | 1.11 (0.64 to 1.91) | 11 | 1.22 (0.67 to 2.20) | 2 | 0.95 (0.24 to 3.78) |
| Connective tissue | 154 | 7.41 (6.32 to 8.67) | 92 | 1.62 (1.32 to 1.99) | 104 | 1.30 (1.07 to 1.57) | 65 | 0.91 (0.72 to 1.16) | 58 | 1.06 (0.82 to 1.38) | 16 | 1.15 (0.71 to 1.88) |
| Other and unspecified sites | 815 | 5.45 (5.09 to 5.84) | 589 | 1.45 (1.34 to 1.57) | 647 | 1.14 (1.06 to 1.23) | 531 | 1.10 (1.01 to 1.20) | 395 | 1.12 (1.01 to 1.23) | 129 | 1.27 (1.07 to 1.50) |
| Lymphatic and hematologic | 2884 | 9.74 (9.39 to 10.1) | 1694 | 2.12 (2.02 to 2.22) | 1432 | 1.29 (1.23 to 1.36) | 1064 | 1.14 (1.07 to 1.21) | 698 | 1.05 (0.97 to 1.13) | 194 | 1.13 (0.99 to 1.31) |
| Non-Hodgkin lymphoma†† | 882 | 7.19 (6.73 to 7.68) | 546 | 1.64 (1.51 to 1.79) | 554 | 1.20 (1.10 to 1.30) | 473 | 1.20 (1.10 to 1.31) | 305 | 1.05 (0.94 to 1.17) | 93 | 1.20 (0.98 to 1.46) |
| Hodgkin lymphoma | 93 | 9.62 (7.85 to 11.7) | 41 | 1.56 (1.15 to 2.12) | 42 | 1.14 (0.84 to 1.54) | 25 | 0.77 (0.52 to 1.14) | 24 | 1.02 (0.69 to 1.53) | 9 | 1.81 (0.94 to 3.47) |
| Multiple myeloma | 598 | 9.83 (9.07 to 10.6) | 333 | 2.03 (1.83 to 2.26) | 268 | 1.18 (1.05 to 1.33) | 201 | 1.05 (0.92 to 1.21) | 142 | 1.07 (0.90 to 1.26) | 42 | 1.28 (0.94 to 1.73) |
| All leukemias combined | 1311 | 12.8 (12.1 to 13.5) | 777 | 2.83 (2.64 to 3.03) | 569 | 1.50 (1.38 to 1.63) | 365 | 1.15 (1.04 to 1.27) | 227 | 1.03 (0.91 to 1.18) | 50 | 0.90 (0.68 to 1.19) |

* The number of outcomes may not add up to the totals for main groups and for cancer overall because patients can present with cancer at more than one site at first occurrence of cancer. obs = observed; SIR = standardized incidence ratio; CI = confidence interval.

† Includes Danish cancer patients that presented with metastases.

‡ Includes the rectosigmoid region.

§ Excludes the anus.

|| Includes primary liver cancer and liver cancer not specified as primary.

¶ Includes primary lung cancer and lung cancer not specified as primary and cancers of the pleura.

# Cases of cervical, uterus, and ovarian cancer observed following cervical resection, hysterectomy, or uni-or bilateral oopho/salpingectomy according to hospital discharge register information were not included in site-specific estimates but contributed to estimates of the combined group of cancer of the female genital organs.

** Includes bladder papilloma.

## Sweden only.

†† Includes mycosis fungoides.

**Table 4.** Standardized incidence ratios for occurrence of liver cancer and non-Hodgkin lymphoma in strata of transfusion recipients by time interval after transfusion*

| | 1–5 mo | | 6–23 mo | | 2–4 y | | 5–9 y | | 10–19 y | | ≥20 y | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cancer type** | **No. of obs** | **SIR (95% CI)** | **No. of obs** | **SIR (95% CI)** | **No. of obs** | **SIR (95% CI)** | **No. of obs** | **SIR (95% CI)** | **No. of obs** | **SIR (95% CI)** | **No. of obs** | **SIR (95% CI)** |
| Liver cancer† | | | | | | | | | | | | |
| Country | | | | | | | | | | | | |
| Sweden | 319 | 9.37 (8.39 to 10.4) | 213 | 2.28 (1.99 to 2.61) | 210 | 1.56 (1.37 to 1.79) | 203 | 1.67 (1.45 to 1.91) | 189 | 2.05 (1.77 to 2.36) | 46 | 2.08 (1.56 to 2.78) |
| Denmark | 202 | 6.49 (5.65 to 7.45) | 141 | 1.81 (1.53 to 2.13) | 184 | 2.01 (1.74 to 2.32) | 91 | 1.65 (1.35 to 2.03) | 23 | 1.31 (0.87 to 1.98) | 0 | – |
| Sex | | | | | | | | | | | | |
| Male | 339 | 9.57 (8.60 to 10.6) | 219 | 2.35 (2.05 to 2.68) | 239 | 1.89 (1.67 to 2.15) | 185 | 1.79 (1.55 to 2.06) | 135 | 2.10 (1.78 to 2.49) | 28 | 2.63 (1.82 to 3.82) |
| Female | 182 | 6.12 (5.29 to 7.08) | 135 | 1.73 (1.46 to 2.05) | 155 | 1.56 (1.33 to 1.82) | 109 | 1.49 (1.23 to 1.79) | 77 | 1.69 (1.35 to 2.11) | 18 | 1.56 (0.98 to 2.48) |
| Calendar period | | | | | | | | | | | | |
| Before 1982 | 78 | 17.4 (14.0 to 21.8) | 37 | 2.83 (2.05 to 3.90) | 47 | 2.00 (1.51 to 2.67) | 50 | 1.46 (1.10 to 1.92) | 101 | 1.96 (1.61 to 2.38) | 46 | 2.10 (1.57 to 2.80) |
| 1982–1991 | 95 | 8.21 (6.71 to 10.0) | 74 | 2.13 (1.70 to 2.68) | 92 | 1.49 (1.21 to 1.83) | 129 | 1.60 (1.34 to 1.90) | 109 | 1.90 (1.58 to 2.30) | 0 | – |
| 1992–2002 | 348 | 7.08 (6.37 to 7.87) | 243 | 1.96 (1.73 to 2.23) | 255 | 1.81 (1.60 to 2.05) | 115 | 1.86 (1.55 to 2.23) | 2 | 2.11 (0.53 to 8.43) | 0 | – |
| Non-Hodgkin lymphoma | | | | | | | | | | | | |
| Country | | | | | | | | | | | | |
| Sweden | 670 | 7.22 (6.70 to 7.79) | 392 | 1.53 (1.39 to 1.69) | 430 | 1.16 (1.05 to 1.27) | 396 | 1.17 (1.06 to 1.29) | 277 | 1.02 (0.91 to 1.15) | 93 | 1.20 (0.98 to 1.47) |
| Denmark | 212 | 7.08 (6.19 to 8.10) | 154 | 2.03 (1.73 to 2.38) | 124 | 1.37 (1.15 to 1.63) | 77 | 1.38 (1.10 to 1.73) | 28 | 1.46 (1.01 to 2.12) | 0 | – |
| Sex | | | | | | | | | | | | |
| Male | 489 | 7.87 (7.20 to 8.60) | 272 | 1.62 (1.44 to 1.82) | 299 | 1.26 (1.12 to 1.41) | 265 | 1.25 (1.11 to 1.41) | 150 | 0.99 (0.85 to 1.17) | 38 | 1.26 (0.91 to 1.73) |
| Female | 393 | 6.49 (5.88 to 7.17) | 274 | 1.67 (1.48 to 1.88) | 255 | 1.14 (1.01 to 1.29) | 208 | 1.14 (1.00 to 1.31) | 155 | 1.11 (0.95 to 1.30) | 55 | 1.16 (0.89 to 1.51) |
| Calendar period | | | | | | | | | | | | |
| Before 1982 | 76 | 8.48 (6.77 to 10.6) | 44 | 1.65 (1.23 to 2.22) | 65 | 1.34 (1.05 to 1.71) | 88 | 1.14 (0.93 to 1.41) | 143 | 1.01 (0.86 to 1.19) | 93 | 1.21 (0.98 to 1.48) |
| 1982–1991 | 171 | 7.72 (6.65 to 8.97) | 118 | 1.73 (1.44 to 2.07) | 159 | 1.26 (1.08 to 1.47) | 218 | 1.23 (1.08 to 1.40) | 159 | 1.08 (0.93 to 1.26) | 0 | – |
| 1992–2002 | 635 | 6.94 (6.42 to 7.50) | 384 | 1.62 (1.46 to 1.79) | 330 | 1.15 (1.03 to 1.28) | 167 | 1.20 (1.03 to 1.39) | 3 | 1.30 (0.42 to 4.04) | 0 | – |
| Before1985‡ | 118 | 9.38 (7.83 to 11.2) | 66 | 1.71 (1.35 to 2.18) | 93 | 1.28 (1.05 to 1.57) | 147 | 1.30 (1.10 to 1.52) | 205 | 1.05 (0.92 to 1.21) | 93 | 1.20 (0.98 to 1.47) |
| 1985–2002‡ | 552 | 6.89 (6.34 to 7.49) | 326 | 1.50 (1.34 to 1.67) | 337 | 1.13 (1.01 to 1.26) | 249 | 1.11 (0.98 to 1.26) | 72 | 0.93 (0.74 to 1.17) | 0 | – |
| Type of blood product | | | | | | | | | | | | |
| Whole blood | 50 | 6.64 (5.03 to 8.76) | 34 | 1.49 (1.07 to 2.09) | 48 | 1.13 (0.85 to 1.51) | 82 | 1.22 (0.98 to 1.51) | 127 | 1.03 (0.86 to 1.22) | 78 | 1.16 (0.93 to 1.45) |
| Red blood cells | 777 | 7.13 (6.64 to 7.64) | 476 | 1.63 (1.49 to 1.78) | 460 | 1.17 (1.06 to 1.28) | 346 | 1.14 (1.03 to 1.27) | 159 | 1.04 (0.89 to 1.21) | 15 | 1.54 (0.93 to 2.55) |

* obs = observed; SIR = standardized incidence ratio; CI = confidence interval; – = not applicable.

† Includes primary liver cancer and liver cancer not specified as primary.

‡ Restricted to Swedish data to retain maximum comparability between recipients.

With longer follow-up, the risk of cancer overall among the transfusion recipients was only slightly (less than 10%) increased compared with the matching general population. This observation is consistent with those in earlier but considerably smaller studies of overall cancer occurrence in transfusion recipients (7–10). Although cancers at most anatomic sites followed this pattern, there were a few notable exceptions. Specifically, the occurrence of cancers of the tongue, mouth, pharynx, esophagus, liver, and the respiratory and, as seen elsewhere for kidney cancer (7,8), urinary tracts remained moderately but uniformly and statistically significantly elevated for two or more decades after the index blood transfusion. All of these cancers have been associated with tobacco smoking and/or alcohol consumption (32,33). It is likely that hospitalized patients in general and transfusion recipients in particular differ from the general population with respect to a wide range of disease risk factors, such as certain potentially detrimental lifestyle habits, including tobacco smoking and alcohol consumption, as suggested by their cancer pattern (8). Such lifestyle habits presumably characterize transfusion recipients of all ages (with the likely exception of children) and transfusion indications in varying degrees. Accordingly, with continued follow-up, risks of tobacco- and/or alcohol-related cancers were generally increased for all transfusion indications except thoracic surgery (data not shown). A higher prevalence of such lifestyle factors among recipients transfused for gastrointestinal bleeding than among those transfused for other reasons would explain their higher risks of these cancers (data not shown) as well as of cancer overall with continued follow-up. Consequently, although the observed increased incidence of tobacco- and alcohol-related cancers in the context of blood transfusion should not be ignored, lifestyle factors prevalent among the recipients rather than the blood transfusion per se constitute a plausible explanation.

The observed increased occurrence of liver cancer among blood transfusion recipients must also be interpreted in light of the association between liver cancer and the transfusion-transmittable hepatitis viruses B and C (20,21). In Sweden and Denmark, screening of blood products for hepatitis B virus was introduced in the early to mid 1970s and for hepatitis C virus, in 1991 and 1992. Consequently, at the end of the study period, the estimated risk of transfusion-transmitted hepatitis C virus infection was on the order of 1 in 500 000 transfusions and the risk of hepatitis B virus infection on the order of 1 in 250 000 transfusions (34). Thus, transmission of hepatitis viruses via transfusions performed after 1992 is unlikely to have contributed materially to the observed increased occurrence of liver cancer among transfusion recipients. Moreover, regardless of the calendar period of the transfusion, an increased occurrence of liver cancer was observed in all follow-up intervals including the first decade after the transfusion, which is hardly consistent with the estimated decade-long incubation period of hepatitis virus–induced liver cancer (35). Therefore, the increase in liver cancer incidence in the first decade after transfusion should probably be attributed to the mechanisms and risk factors discussed above, and we suspect that a high prevalence of risk factors for liver cancer that are unrelated to blood transfusions continued to contribute to the increased risks observed beyond this time window. However, we cannot rule out the possibility that transfusion-transmitted hepatitis infection contributed to the increased incidence of liver cancer among recipients transfused before screening for hepatitis was in place.

Other transfusion-transmittable infectious agents that have been associated with specific cancers include HIV, human T-lymphotropic virus type I (HTLV-I) (36), and human herpes virus 8 (37,38). However, these agents are unlikely to have contributed markedly to the increased cancer occurrence in our cohort because they have a low seroprevalence in Scandinavian populations and because Scandinavian blood banks (34,39) have had strict donor deferral policies combined with HTLV-I screening since 1994 and HIV screening since 1985–1986.

Data on the association between non-Hodgkin lymphoma and blood transfusion have been conflicting. Increased risks of non-Hodgkin lymphoma after blood transfusion have been observed in cohort studies in the United States, Sweden, and the United Kingdom (7–9). By contrast, only one (12) of eight case–control or nested case–control studies (12–19) has reported an association between blood transfusions and non-Hodgkin lymphoma. In our investigation, the relative risk of non-Hodgkin lymphoma generally followed the same temporal pattern that was observed for other malignancies, i.e., it was highest immediately after the transfusion and subsequently decreased to levels similar to those in the general population at 10 or more years after transfusion. This temporal pattern was apparent in both female and male recipients, in recipients from Denmark and Sweden, in different calendar periods of transfusion, and in recipients of different types of blood products. Our analyses did not include information about lymphoma subtype, and, therefore, we cannot rule out the possibility that blood transfusions may be associated with increased risks of certain lymphoma subtypes, as has been suggested in previous investigations (12,40). Overall, however, given the temporal variation in relative risks that we observed, our results are in agreement with those of previous investigations that reported no association between blood transfusion and non-Hodgkin lymphoma (13–19).

Some of the decreased cancer risks that we observed are most likely attributable to methodologic phenomena. As previously mentioned, hospitalization is accompanied by an increased chance of cancer diagnosis. Such advanced or precipitated diagnosis of incipient cancers (referred to as lead time bias) can explain the transiently reduced risks observed for breast and prostate cancer and for cancer overall among transfused trauma patients. This mechanism may have also contributed to the decreased risk of uterine cancer that we observed 2-4 years after transfusion. In addition, although transfused women who were known to have had a hysterectomy were excluded from the analysis for uterine cancer, it is possible that this information may have been missing for some women. This potential misclassification may also have contributed to the observed decreased risk of uterine cancer. However, there is, to our knowledge, no clear biologic basis for an association of cancers of the breast, uterus, and prostate with blood transfusions.

In these analyses, we did not include information about donor health to address the possibility of transmission of cancer cells or other cancer risk factors from donors with imminent cancer to recipients (4–6,41). However, in a previous investigation based on the SCANDAT database, we found no evidence that cancer risk in

recipients of blood products from donors with incipient cancer differed from that of other recipients (42).

The strengths of this study include its population-based setting, our use of transfusion and health registers of high quality and completeness, the long-term follow-up of all recipients, and the fact that medical data collection was free of recall bias. Specifically, the cohort of transfusion recipients was constructed from meticulously managed blood bank databases that had a high degree of completeness and generally high data quality (22).

This study also has limitations that should be considered when interpreting the results. First, the large number of comparisons increased the risk of chance findings. Second, computerized blood bank databases were gradually introduced in an increasing number of geographic regions, whereas the cancer incidence data for the general population were nationwide. If cancer incidence rates varied systematically by region with regard to the presence or absence of computerized transfusion registration (43), spurious associations may have occurred. However, uniform risk estimates were observed across different calendar periods in which there were different degrees of national coverage of the transfusion database, suggesting that this potential source of error is not important. Third, we estimated the expected number of cancers in the cohort based on incidence rates in the general population. Although the majority of the cancers that contributed to these rates occurred in persons who were never exposed to a blood transfusion, cancers occurring in the identified recipients as well as cancers in persons transfused before the introduction of computerized systems would also contribute to these rates. This contribution to the expected rates would tend to attenuate any true association between blood transfusion and cancer occurrence. The precise magnitude of the effect on the risk estimates is difficult to assess, but for numerical reasons we suspect that it is likely to be of minor importance. Fourth, we defined the exposure as the first registered blood transfusion. Some of the identified transfusion recipients may have received a transfusion before the introduction of the computerized systems. We believe, however, that the similarity of the risk estimates between calendar periods indicates that this is unlikely to affect our findings materially. Fifth, our investigation did not include detailed analyses of variations in cancer risk by blood product characteristics or of dose–response relationships, whether for cancer overall or for cancer at specific anatomic sites. Thus, although the relative risk of cancer overall was only marginally increased with increasing time since blood transfusion, we cannot rule out the existence of such associations, which warrants further analyses. According to the present findings, future investigations of the association between blood transfusion and cancer risk should preferably be conducted in defined populations with complete information about transfusion history as well as, ideally, about comorbidity and other exposures relevant to cancer risk.

Our observations may be generalizable to other geographic settings that have transfusion medicine services and health care systems similar to those in Sweden and Denmark during the study period. We used data that were collected prospectively by Danish and Swedish blood banks and which, in some instances, continuously covered more than 30 years of transfusion activity. During this time, the manufacturing procedures for blood products changed from whole blood to blood components and, more recently, through the adoption of leukocyte reduction and depletion procedures. Furthermore, donor deferral policies became increasingly strict, and advanced screening techniques for infectious diseases were implemented. Nevertheless, the relative risk of cancer among the recipients and the temporal patterns remained relatively uniform throughout these years. This consistency may indicate that the cancer incidence pattern observed among the recipients relies primarily on the patterns of diseases that necessitate a blood transfusion and their respective risk factors rather than on the exposure to blood products per se. This assumption was further supported by the trivial differences in relative cancer risk by number of transfused blood products.

In summary, in this large cohort of blood transfusion recipients, the observed incidence of cancer at nearly all anatomic sites exceeded the expected incidence. However, the relative magnitude of the increased incidence decreased over time since the index transfusion resulting in an excess incidence of cancer overall of 10% or less in the time periods more than 2 years after the transfusion. The incidence of cancers of the tongue, mouth, pharynx, esophagus, liver, respiratory and urinary tracts, and skin continued to be increased for more than 10–20 years after the first transfusion. Although a causal association between blood transfusion and cancer risk cannot be ruled out, the continued excess occurrence of cancers sharing tobacco smoking or alcohol drinking as common risk factors suggests that these and other risk factors related to the conditions prompting a transfusion rather than transfusion-related exposures per se are important contributors to the cancer pattern observed in the recipients.

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