

## ➤ Risk of cancer after blood transfusion from donors with subclinical cancer: a retrospective cohort study

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### Summary

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**Background** Although mechanisms for detection of short-term complications after blood transfusions are well developed, complications with delayed onset, notably transmission of chronic diseases such as cancer, have been difficult to assess. Our aim was to investigate the possible risk of cancer transmission from blood donors to recipients through blood transfusion.

**Methods** We did a register-based retrospective cohort study of cancer incidence among patients who received blood from donors deemed to have a subclinical cancer at the time of donation. These precancerous donors were diagnosed with a cancer within 5 years of the donation. Data from all computerised blood bank registers in Sweden and Denmark gathered between 1968 and 2002 were merged into a common database. Demographic and medical data, including mortality and cancer incidence, were ascertained through linkages with nationwide, and essentially complete, population and health-care registers. The risk of cancer in exposed recipients relative to that in recipients who received blood from non-cancerous donors was estimated with multivariate Poisson regression, adjusting for potential confounding factors.

**Findings** Of the 354 094 transfusion recipients eligible for this analysis, 12 012 (3%) were exposed to blood products from precancerous donors. There was no excess risk of cancer overall (adjusted relative risk 1·00, 95% CI 0·94–1·07) or in crude anatomical subsites among recipients of blood from precancerous donors compared with recipients of blood from non-cancerous donors.

**Interpretation** Our data provide no evidence that blood transfusions from precancerous blood donors are associated with increased risk of cancer among recipients compared with transfusions from non-cancerous donors.

### Introduction

Continuous attention to transfusion safety has reduced the risk of transfusion-transmitted disease to a current record low.<sup>1</sup> However, although most infectious complications have been comparably easy to identify, possible transmission of chronic diseases with unknown causes and long induction or latency periods has been far more difficult to address.

The hypothesis that a blood transfusion can result in cancer development in the recipient has been tested by several investigators and with various study designs.<sup>2–10</sup> Some reports have described an increased risk of cancer overall<sup>2</sup> and of non-Hodgkin's lymphoma in particular,<sup>2,5,8</sup> among transfused patients compared with those who did not receive transfusions, whereas others found no such associations.<sup>7,9–12</sup> Suggested mechanisms for such an association include immune modulation, transmission of factors causally related to cancer development, and engraftment of malignant cells of donor origin.<sup>2,8,13–16</sup>

Transmission of both solid<sup>17,18</sup> and non-solid<sup>19–21</sup> malignancies, as well as oncogenic viruses such as Kaposi's sarcoma-associated herpesvirus<sup>22</sup> and Epstein-Barr virus,<sup>23</sup> from organ donors to transplant recipients has been noted repeatedly. Transmission of Kaposi's sarcoma-associated herpesvirus via blood transfusions was also recently documented.<sup>24</sup> Further, scattered reports of transmission of cancer cells from needles or surgical

instruments illustrate the ability of tumour cells to be transplanted to—and to develop in—healthy recipients.<sup>25,26</sup> The ability of tumour cells to survive in human graft recipients has also been shown in experimental settings.<sup>27</sup> However, the few studies that have addressed the issue of allotransplantation of human tumour tissue through blood transfusion or other bloodborne means have been inconclusive.<sup>14–16,28</sup>

To investigate the possible risk of cancer transmission from blood donors to recipients through blood transfusion, we did an epidemiological investigation based on a bi-national database with long-term detailed donation and transfusion histories as well as information on health outcomes among Scandinavian blood donors and recipients.

### Methods

#### Patients and procedures

We did a retrospective cohort study with data from the Scandinavian Donations and Transfusions database (SCANDAT), the assembly of which has been described in detail elsewhere.<sup>29</sup> In brief, we collected selected variables from all computerised registers of blood donations and transfusions maintained by blood banks and transfusion medicine clinics in Sweden since 1968 and in Denmark since 1982. Donor and recipient details, including dates of birth, sex, as well as types, number,

and dates of donations and transfusions, were entered into a common database. Internal codes that uniquely identified each donor, donation, blood component, and recipient enabled us to trace each transfused blood unit back to its donor(s). Before records were anonymised, the database was linked with national population and health registers, including the national registers of migration, death, cancer, and in-hospital care, using the unique personal identification number assigned to all residents of Sweden and Denmark.

We identified all individuals with no history of malignant disease who received at least one unit of whole blood, erythrocytes, plasma, or platelets between 1968 and 2002. For each recipient, we considered all transfusions that occurred during the first 30 days after the first recorded blood transfusion in our database, and identified all blood donors who contributed to these transfusions. Donors who, according to the Swedish or Danish cancer registers, were diagnosed with an incident malignancy (seventh revision of the International Classification of Disease, 140–207, excluding non-melanoma skin cancer) within 5 years of a blood donation (henceforth referred to as precancerous blood donors) were deemed to harbour a subclinical malignancy at the time of donation. Accordingly, recipients of any blood product (henceforth referred to as blood) from such a donor were thus deemed to be exposed, and correspondingly, recipients who received blood products only from donors who were not diagnosed with cancer within 5 years of the donation were deemed to be unexposed. Recipients of blood from donors with a known previous diagnosis of cancer at the time of donation were excluded from the main analyses. To ensure correct classification of exposure, all recipients who during the first 30 days received transfusions from unknown blood donors or blood donors for whom we did not have at least 5 years of follow-up were excluded from the analysis, as were recipients of autologous transfusions. The latest donations that could be included in this study were thus done in 1997. We also excluded recipients for whom the area of residence at the time of first transfusion could not be ascertained. The figure shows the study design with definitions of exposure and outcome, together with inclusion and exclusion criteria.

The recipients were followed for cancer occurrence using the Swedish and Danish cancer registers. Follow-up ended on the date of first malignant cancer diagnosis (excluding non-melanoma skin cancer), death, emigration, or on December 31, 2002. We also censored individuals who, after the initial 30-day exposure period, received a transfusion originating from a precancerous blood donor, an unknown donor, or a donor with less than 5 years of follow-up. To limit the inclusion of incipient cancers that were present in the recipient but undiagnosed at the time of the blood transfusion, we started follow-up 6 months after the first recorded

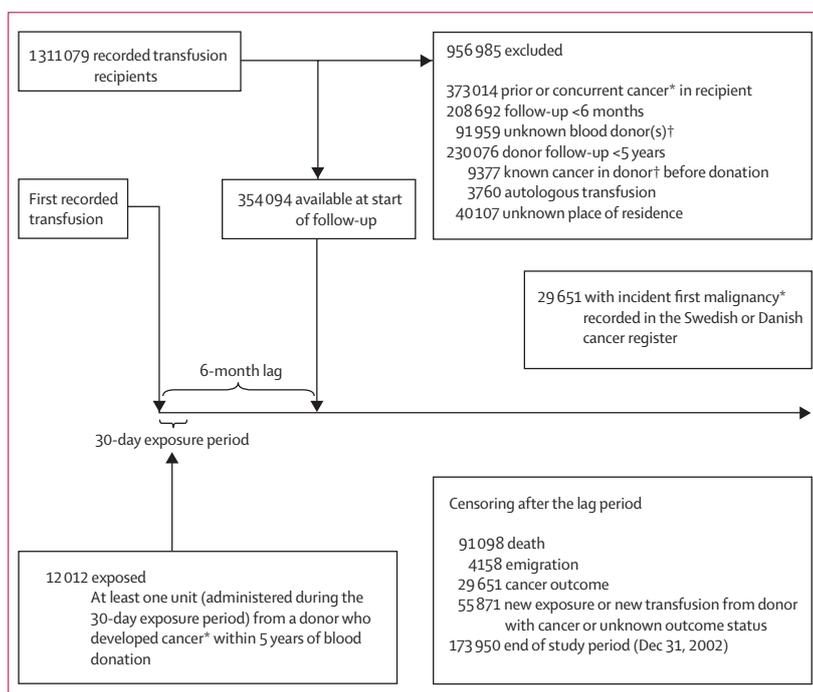
transfusion. Thus any recipients who died, emigrated, or were diagnosed with cancer within 6 months of the first recorded transfusion were not included in the analyses.

The creation of the SCANDAT database and the conduct of this study were approved by appropriate scientific ethical committees and data protection agencies in both countries.

### Statistical analysis

The relative risk of cancer after transfusion with blood from a precancerous blood donor was assessed as incidence rate ratios estimated from Poisson regression models. In addition to exposure to blood from precancerous blood donors, potential confounding factors included in the analysis were sex, attained age (categorised as <40, 40–59, 60–69, or ≥70 years), area of residence at the time of first transfusion (four Danish and five Swedish geographical regions), ABO-blood type (A, B, AB, O, or unknown), number of transfusions during the first 30 days after first transfusion (1–2, 3–4, 5–9, or ≥10 transfusions), calendar period (1968–79, 1980–89, or 1990–2002), and number of years since first transfusion (<1, 1, 2, 3–4, 5–9, 10–19, or 20–34 years). Attained age, calendar period, and time since first transfusion were treated as time-dependent covariates, allowing individuals to move between categories with time.

Since immune responses and thus the possible susceptibility to engraftment of foreign cells might vary



**Figure: Study design and inclusion criteria**

\*Code 140–207 according to the International Classification of Disease, revision 7, excluding non-melanoma skin cancer. †Donors contributing to transfusions given in the 30-day exposure period.

	Unexposed cohort	Exposed cohort	All study participants
Number of individuals	342 082	12 012	354 094
Sex			
Female	206 899	6551	213 450
Male	135 183	5461	140 644
Country			
Denmark	54 848	2686	57 534
Sweden	287 234	9326	296 560
Age at entry into cohort (years)			
0–39	81 183 (24%)	2419 (20%)	83 602 (24%)
40–59	68 199 (20%)	2444 (20%)	70 643 (20%)
60–69	55 882 (16%)	2046 (17%)	57 928 (16%)
≥70	136 818 (40%)	5103 (43%)	141 921 (40%)
Mean (SD) age at entry into cohort (years)	57.7 (22.7)	59.6 (21.4)	57.8 (22.6)
Median (range) length of follow-up (years)	7.0 (0–34)	6.2 (0–33)	7.0 (0–34)
Median (IQR) year of first recorded transfusion	1992 (1986–1995)	1993 (1989–1996)	1992 (1986–1995)
Median (range) number of transfused units*	2 (1–136)	4 (1–285)	2 (1–285)

\*During initial 30 days following first blood transfusion.

**Table 1: Characteristics of the studied recipient population**

Stratum	Number of cancers/ person-years among exposed	Number of cancers/ person-years among unexposed	Adjusted rate ratio (95% CI)*
Overall	978/90 928	28 673/3 109 872	1.00 (0.94–1.07)
Sex			
Female	425/51 298	14 290/1 991 245	0.98 (0.89–1.08)
Male	553/39 630	14 383/1 118 627	1.03 (0.94–1.12)
Age at first transfusion (years)			
0–39	64/29 040	2450/1 201 474	1.08 (0.84–1.38)
40–59	183/23 023	6589/778 005	0.91 (0.78–1.06)
60–69	267/16 028	7561/482 795	1.03 (0.91–1.16)
≥70	464/22 837	12 073/647 599	1.02 (0.93–1.12)
Calendar period of first transfusion			
1968–1979	74/14 095	4944/891 022	0.91 (0.71–1.13)
1980–1989	283/30 589	8716/1 036 966	0.96 (0.85–1.08)
1990–2002	621/46 244	15 013/1 181 885	1.03 (0.95–1.12)
Time since first transfusion (years)			
0–4	511/45 181	13 412/1 313 197	0.99 (0.90–1.08)
5–9	297/26 585	7705/877 132	1.08 (0.96–1.21)
10–19	148/16 387	5874/733 825	0.96 (0.81–1.13)
20–34	22/2775	1682/185 718	0.90 (0.59–1.38)
Number of transfusions			
1–2	258/26 845	15 765/1 851 497	1.01 (0.89–1.14)
3–4	238/21 703	6936/701 640	1.02 (0.90–1.16)
5–9	252/21 166	4244/397 543	1.05 (0.92–1.19)
≥10	230/21 215	1728/159 193	0.94 (0.81–1.07)

\*Adjusted for sex, attained age, calendar period of observation, number of transfusions, area of residence, ABO blood type, and follow-up time.

**Table 2: Adjusted rate ratios of cancer among recipients of precancerous blood, relative to recipients of non-cancerous blood**

by sex and age, and since the potential for transmission could have changed during the study period due to the use of filtered and leucocyte-depleted blood and different types of blood components, we did subanalyses stratified by recipient sex and age as well as calendar period of transfusion, number of units that were administered, and component type (ie, whether the exposure-carrying blood unit was cell-containing or plasma). In a sensitivity analysis, we varied our definition of precancerous blood, and consequentially the definition of exposure, by successively reducing the maximum time between donation and cancer diagnosis in the donor from 5 years, to 4 years, 3 years, 2 years, and 1 year. Since transfusions from donors with metastatic disease might pose a bigger threat to recipients, we did a subanalysis that took tumour stage into account. In this additional subanalysis, restricted to the Danish portion of the data (only the Danish cancer register records tumour stage), recipients of blood from donors who were diagnosed with metastatic cancer were compared with the unexposed group.

We also assessed whether time to cancer death of the donor who contributed an exposed transfusion was associated with increased cancer risk in the recipient. To test whether the risk of cancer in the recipient depended on type of cancer in the donor, we also did analyses with exposure divided into 15 broad groups of cancer in the donor. Correspondingly, we compared site-specific cancer risks among exposed and unexposed transfusion recipients. Finally, we analysed the risk of cancer of the lung, liver, skeleton, and central nervous system combined—ie, anatomical sites deemed to be at highest risk of haematogenous cancer cell transmission.<sup>30–32</sup> Although recipients of blood from donors with a previous diagnosis of cancer were excluded from the overall analyses, we investigated whether the incidence of cancer in these recipients differed from that among recipients of donors with no cancer before or within 5 years of the donation.

### Role of the funding source

The study sponsor had no role in the conduct of the study, data collection, analysis, or interpretation. O Nyrén and M Melbye had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. O Nyrén had final responsibility for the decision to submit the manuscript for publication.

### Results

Of 1 311 079 transfusion recipients in the SCANDAT database, we excluded 373 014 individuals who had a previous diagnosis of cancer and 208 692 recipients who died, emigrated, were diagnosed with cancer within 6 months of first transfusion, or for whom the start of follow-up occurred after Dec 31, 2002. We also excluded 91 959 recipients who received blood from an unknown

donor, 230076 recipients who received blood from a donor who was followed for less than 5 years, 9377 recipients who received blood from a donor with a previous diagnosis of cancer, 3760 recipients of autologous transfusions, and 40107 recipients with an unknown area of residence at the time of first transfusion. Thus, 354094 recipients remained for analysis, of whom 55871 (16%) were censored on receipt of an exposed or unknown unit outside the initial 30-day window. Table 1 shows the general characteristics of the study population. Together, these recipients contributed 3200800 person-years of follow-up, during which 29651 primary cancers occurred. 12012 (3%) recipients were exposed to blood from precancerous donors. During follow-up for a total of 90928 person-years among the exposed recipients, 978 incident cancers were recorded in the national cancer registers.

Table 2 shows the results from overall and stratified Poisson regression analyses of cancer incidence. In the adjusted analysis, we found no excess risk of cancer overall among recipients who had received one or more blood products from a precancerous blood donor, compared with recipients who had received blood only from non-cancerous donors (adjusted relative risk 1.00, 95% CI 0.94–1.07). The relative risk was not substantially affected by sex, age, calendar period, or number of transfusions. However, analyses stratified by sex and follow-up revealed a significantly increased cancer risk among exposed male recipients in the period between 5–9 years after the first transfusion (adjusted relative risk 1.19, 1.03–1.38). There was no indication of a corresponding excess risk for exposed women in the same follow-up period (adjusted relative risk 0.93, 0.76–1.12), nor was there any evidence of excess risks in any of the other follow-up intervals for either sex (data not shown).

A subanalysis on Danish data comparing recipients of blood from donors who presented with metastatic cancer within 5 years of donation to unexposed recipients produced an adjusted relative risk of 0.99 (95% CI 0.48–1.79). Analyses according to type of blood component, storage time, and time to cancer death of the donor showed no notable variation (data not shown). Also, we found no conspicuous pattern when successively reducing the maximum time allowed between donation and cancer in the donor for the blood to be considered precancerous: the adjusted relative risks were 1.00 (0.93–1.07) for 4 years, 1.00 (0.92–1.07) for 3 years, 0.93 (0.84–1.02) for 2 years, and 0.93 (0.81–1.05) for 1 year). The cancer incidence among the 9377 recipients of blood from donors with a previous diagnosis of cancer did not differ from that among recipients of blood from non-cancerous donors (adjusted relative risk 0.94, 0.86–1.02).

We found no evidence that there was any difference in potential for disease transmission when recipients of blood from donors with cancers at different anatomical

Site of donor's cancer	Number of cancers/person-years among recipients	Adjusted rate ratio (95% CI)*
No cancer (unexposed recipient)	28 673/3 109 872	1.00 (ref)
Oral cavity and upper gastrointestinal tract	37/3614	1.05 (0.75–1.43)
Lower gastrointestinal tract	76/7642	0.94 (0.74–1.17)
Liver and gallbladder	6/405	1.26 (0.50–2.56)
Respiratory organs	35/3088	1.11 (0.78–1.52)
Breast and mammary gland	160/14 857	0.98 (0.84–1.14)
Female genital organs	57/6243	0.91 (0.69–1.17)
Male genital organs, including prostate	143/12 756	1.06 (0.90–1.25)
Urinary organs	72/7458	0.91 (0.72–1.14)
Melanoma of skin	101/8387	1.13 (0.92–1.36)
Eye and nervous system	48/4092	1.07 (0.79–1.40)
Endocrinal glands	37/3515	1.20 (0.85–1.63)
Bone and connective tissue	11/1689	0.72 (0.37–1.23)
Malignant lymphomas	38/4164	0.91 (0.65–1.24)
Leukaemia and myeloma	30/3003	0.98 (0.67–1.38)
Other and unspecified	127/10 016	1.01 (0.84–1.20)

\*Adjusted for sex, attained age, calendar period of observation, number of transfusions, area of residence, ABO blood type, and follow-up time.

**Table 3: Adjusted rate ratios of cancer among recipients of precancerous blood from donors with cancers at different anatomical sites, relative to recipients of non-cancerous blood**

Site of recipient's cancer	Number of cancers among exposed	Number of cancers among unexposed	Adjusted rate ratio (95% CI)*
Oral cavity and upper gastrointestinal tract	64	1789	1.04 (0.80–1.32)
Lower gastrointestinal tract	138	3577	1.13 (0.95–1.34)
Liver and gallbladder	27	762	0.96 (0.63–1.38)
Respiratory	88	2363	1.02 (0.82–1.26)
Breast	89	3597	0.90 (0.72–1.11)
Female genital organs	49	1645	1.02 (0.76–1.34)
Male genital organs, including prostate	160	4165	1.06 (0.90–1.24)
Urinary organs	85	2240	1.07 (0.85–1.33)
Melanoma of skin	80	2418	1.04 (0.82–1.29)
Eye and nervous system	27	649	1.32 (0.87–1.92)
Endocrinal glands	14	603	0.82 (0.46–1.34)
Bone and connective tissue	9	176	1.51 (0.71–2.84)
Malignant lymphomas	30	938	0.92 (0.62–1.31)
Leukaemia and myeloma	38	1056	1.05 (0.74–1.43)
Other and unspecified	80	2695	0.78 (0.61–0.96)

\*Adjusted for sex, attained age, calendar period of observation, number of transfusions, area of residence, ABO blood type, and follow-up time.

**Table 4: Adjusted rate ratios of site-specific cancers among recipients of precancerous blood, relative to recipients of non-cancerous blood**

sites were analysed separately (table 3). Also, there was little variation in site-specific cancer risk between exposed and unexposed recipients (table 4). Finally, we detected no excess risk when the sites deemed to be at highest risk of haematogenous metastasis (lung, liver, skeleton, and central nervous system) were combined (adjusted relative risk 1.00, 95% CI 0.85–1.17).

## Discussion

In this retrospective cohort study among Scandinavian transfusion recipients, we found no evidence that blood components originating from precancerous blood donors confer an increased cancer risk on the recipients compared with blood components from non-cancerous donors. Our findings were similar, irrespective of calendar period (which could be seen as a proxy for the declining probability of receiving nucleated cells in addition to red blood cells, platelets, and plasma), the age and sex of the recipient, and the overall number of transfusions received in addition to the exposed blood component. Moreover, there was no evidence to indicate that the risk of cancer transmission varied by type of cancer in the donor, nor did we observe excess occurrences of cancers at any specific sites in the recipients.

Our data add to the sparse published works that describe the outcome, for the most part short term, after accidental<sup>33</sup> or deliberate<sup>14,15,34</sup> transfusion of blood from donors with clinically overt malignancies. Although our findings should not be over-interpreted, the overall consistency of the negative results does not support the hypothesis that allogenic transfusion of single malignant cells can lead to engraftment and subsequent development of clinical malignancies in human transfusion recipients. The plausibility of such transmission is otherwise supported by reports of long-lasting donor microchimerism after blood transfusion<sup>35–37</sup> and transmission of malignancies through organ transplantation.<sup>17–20</sup> If such transmission does occur, it is so rare that we were unable to capture it with a study that included the total blood bank experience over several years in two countries. Also, since we found no increased cancer risk associated with transfusions from an admittedly limited number of donors with a previous history of cancer, it would seem that long-term cancer survivors might be a fairly safe donor group. However, since cancer survivors normally are deferred from blood donation, we must be cautious because these post-cancerous individuals might not be representative of the total pool of cancer survivors.

A recent report from Uganda has shown the transmission of Kaposi's sarcoma-associated herpesvirus via blood transfusions.<sup>24</sup> Despite systematic exclusion of donors at increased risk of infection with HIV or AIDS-related morbidity, our database revealed 14 blood donors with a subsequent diagnosis of Kaposi's sarcoma. However, none of the 55 patients that received a blood component from these donors developed Kaposi's sarcoma during follow-up, which ranged from 0 to 26 years. Nonetheless, further follow-up might be needed. The last donation made by a donor who later developed Kaposi's sarcoma was in 1991.

The only departure from the generally inconspicuous pattern of cancer in recipients of precancerous blood components was the finding of an apparent excess risk of cancer among male transfusion recipients in the period from 5 to 9 years after the first transfusion. We cannot readily explain this finding, but the absence of a

corresponding effect among women and the large number of statistical tests done suggests that it is probably a spurious result. Also, we are not aware of any biological mechanisms by which only men should be susceptible to such transmission.

Strengths of our study include its design and large sample size. Further, the availability of nationwide population, death, migration, and cancer registers of high quality ensures that follow-up is virtually complete and unbiased. Although the geographical coverage of the computerised blood bank registration was less complete in the early years of this investigation than it was in the most recent period, there is little reason to believe that this critically affects the internal validity of our investigation. Although we have not been able to assess the validity of the SCANDAT database directly, overall data quality, internal consistency, and comparisons with official reports of annual numbers of blood donations and transfusions suggest it to be satisfactory.<sup>29</sup> Both the Swedish and Danish cancer registers are known to have a high degree of completeness.<sup>38,39</sup>

Moreover, since the impending cancer of a blood donor was unknown at the time of transfusion, the possibilities for confounding were limited. The number of transfusions administered is an important potential confounder, since it is linked to the likelihood of being exposed to precancerous blood and also possibly linked to cancer risk via the disease that prompted the transfusion. Since underlying disease in the recipient can be associated with the probability of being exposed to precancerous blood only through the number of administered transfusions, there is no need to adjust for indication in the analysis. Other conceivable confounders include cancer risk factors that act at a population level (eg, calendar time and area of residence), but might also include factors such as blood type. Hence, with proper adjustment for the number of transfusions, calendar period, area of residence, and blood type, residual confounding or confounding due to other unmeasured factors is unlikely. Although the restriction to individuals for whom we have at least 5 years of follow-up of all contributing blood donors is quite conservative and took a heavy toll on the number of study participants, it ensured that the misclassification of the exposure was kept to a minimum.

In our analyses, we restricted our transfusion information to the first 30 days of an individual's recorded transfusion history. This approach could be overly simplistic for handling the problem of widely varying transfusion histories. However, most individuals (69%) received transfusions only within such a 30-day window. Exposure could also have been misclassified by truncation of transfusion history because the introduction of computer registers was staggered; that calendar period did not modify the effect of exposure to precancerous blood is reassuring. The absence of effect modification by calendar period, despite the changing practice of transfusion medicine, is evidence against transfusion-transmitted risk via the various blood component types in use: whereas

only whole blood and other component types containing a significant concentration of leucocytes were used in the beginning of the study period, there has been a gradual shift towards blood products that are depleted of leucocytes. Since the practice of transfusion medicine differs substantially internationally—eg, with regard to donor suitability criteria and the use of blood filtering and leucocyte depletion—our findings might not be directly applicable to other settings. Nevertheless, the study encompasses more than three decades during which transfusion medicine, as a discipline, has evolved tremendously and shifted from crude whole blood transfusions to administration of specialised components.

We postulated that blood products donated more than 5 years before the cancer diagnosis in the donor would not be associated with an excess risk. If blood products were associated with risk for more than 5 years—eg, because of the presence of an oncogenic infectious agent in the donor's blood—the entailing exposure misclassification would contaminate the unexposed reference group and thus attenuate a true association. Thus, although this 5-year cutoff point is somewhat arbitrary and could potentially have masked a true association, we focused on this biologically plausible a-priori hypothesis to avoid extensive sensitivity analyses and the introduction of further multiple-testing problems. Also, we found no suspicious pattern when the 5-year exposure window was shortened.

Naturally, we cannot be certain that malignant or premalignant cells were present in the donor's blood at the time of the index blood donation, but evidence suggests that the process leading to cancer is indeed lengthy and that circulating tumour cells exist at an early stage.<sup>40</sup> We disregarded the first 6 months after the first transfusion from the analyses to exclude cancers already present at first transfusion, symptoms of which might have necessitated the transfusion. The probability that transfusion-induced cancers would become clinically evident within 6 months is deemed low, based on clinical experience with transplantation-transmitted cancers.<sup>17</sup>

Our study was not designed to address cancer risks associated with blood transfusion per se compared with no transfusion—eg, via an immunomodulating effect—but was specifically focused on the potential transmission of viable cancer cells. Accordingly, the time between exposure and clinical cancer outcome was assumed to be less than 5 years: an unrealistically short induction period if early-stage carcinogens were to be considered. Although the power to confirm excess long-term risks was limited, a point estimate of relative risk slightly below 1 with an upper 95% CI of 1.38 for the follow-up period 20–34 years after first transfusion suggests that hidden long-term excess risks are unlikely, albeit not impossible.

In conclusion, our data provide no evidence that blood transfusions from precancerous blood donors are associated with an increased risk of cancer among recipients compared with transfusions from non-cancerous donors.

#### Contributors

GE took part in procurement, management, analysis and interpretation of the data, and participated in the drafting and revision of the manuscript. MR had overall responsibility for the statistical analysis, and participated in the design of the study, interpretation of results and preparation of the manuscript. TNT took part in the study design, data analysis, and writing of the manuscript. HH and KR took part in all parts of the conception, design, planning, and execution of the study and obtained funding. AS took part in the conception, planning, and conduct of the study, interpretation of data, and commented on the manuscript. KT took part in the conception and design of the study, and participated in the revision of the manuscript. JA took part in the conception, design, planning and conduct of the study, obtained funding, and commented on the manuscript. AW took part in the collection of data and interpretation of results. CJ took part in the collection of data from Danish blood banks. GG took part in the design, conduct, and analysis, and commented on the manuscript. LW took part in the conception and design of the study, acquisition of data, analysis and interpretation of the data, critical revision of the manuscript and material support of the study. ON took part in the conception, design and conduct of the study, collection of data, analysis, interpretation of data, obtained funding, supervised the study, and participated in the drafting and revision of the manuscript. MM took part in the conception, design and conduct of the study, participated in the analysis and interpretation of the data, obtained funding, supervised the study, and contributed to the revision of the manuscript. All authors saw and approved the final version of the manuscript.

#### Conflict of interest statement

We declare that we have no conflict of interest.

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