Donation Frequency, Iron Loss, and Risk of Cancer Among Blood Donors

Gustaf Edgren, Marie Reilly, Henrik Hjalgrim, Trung Nam Tran, Klaus Rostgaard, Johanna Adami, Kjell Titlestad, Agneta Shanwell, Mads Melbye, Olof Nyrén

Background Long-term deleterious effects of repeated blood donations may be masked by the donors' healthy lifestyle. To investigate possible effects of blood donation and iron loss through blood donation on cancer incidence while minimizing "healthy donor effects," we made dose–response comparisons within a cohort of Swedish and Danish blood donors.

Methods We used a nested case–control study design, in which case patients were defined as all donors who were diagnosed with a malignancy between their first recorded blood donation and study termination (n = 10 866). Control subjects (n = 107 140) were individually matched on sex, age, and county of residence. Using conditional logistic regression, we estimated relative risks of cancer according to number of blood donations made or estimated iron loss 3–12 years before a case patient was diagnosed with cancer. All statistical tests were two-sided.

Results No clear association was observed between number of donations and risk of cancer overall. However, between the lowest (≤median, <0.75 g) and highest (>90th percentile, >2.7 g) categories of estimated iron loss, there was a trend (P_{trend} < .001) of decreasing risk for cancers of the liver, lung, colon, stomach, and esophagus, which are thought to be promoted by iron overload (combined odds ratio [OR] = 0.70, 95% confidence interval [CI] = 0.58 to 0.84), but only among men and only with a latency of 3–7 years. The risk of non-Hodgkin lymphoma was higher among frequent plasma donors (>25 vs 0 donations, OR = 2.14, 95% CI = 1.22 to 3.74).

Conclusions Repeated blood donation was not associated with increased or decreased risk of cancer overall. The lack of consistency across latency periods casts doubt on an apparent association between reduced cancer risk and iron loss in men. The positive association between frequent plasma donation and risk of non-Hodgkin lymphoma deserves further exploration.

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Although low rates of cancer incidence and all-cause mortality among blood donors (1–4) suggest that blood donation is not harmful, possible deleterious effects of repeated blood letting may be masked by the healthy lifestyle and good health of the donor population. Apart from immediate complications, such as syncope and local bleeding (5), short- and long-term health effects of repeated blood donations per se have not been thoroughly investigated.

It has been suggested that depletion of iron, which catalyzes the production of a range of reactive oxygen species and free radicals, may have beneficial health effects (2,4,6–10). Low iron stores have been associated with reduced risks of cardiovascular disease (11–15); however, most recent studies, including a clinical trial in which subjects with peripheral arterial disease were randomly assigned to reduction of stored iron through blood letting (16), did not result in the purported protection (17–20).

High levels of iron may be associated with cancers of the lung, liver, colon, stomach, and esophagus (8–10,21,22). Several reports have investigated the association between levels of stored iron, as indicated by various laboratory markers, and cancer risk, but results have varied considerably (21–24). It has been suggested that increased cell proliferation, which is itself a possible risk factor for cancer (25,26) and is stimulated by repeated removal of blood cells, may increase the risk of hematopoietic malignancies in blood

Affiliations of authors: Departments of Medical Epidemiology and Biostatistics (GE, MR, TNT, JA, ON) and Medicine, Clinical Epidemiology Unit (JA), Karolinska Institutet, Stockholm, Sweden; Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark (HH, KR, MM); Department of Epidemiology, Merck Research Laboratory, West Point, PA (TNT); Department of Clinical Immunology, Odense University Hospital, Odense, Denmark (KT); Department of Clinical Immunology and Transfusion Medicine, Karolinska University Hospital, Stockholm, Sweden (AS).

Correspondence to: Gustaf Edgren, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, SE-171 77, Stockholm, Sweden (e-mail: gustaf.edgren@ki.se).

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donors (4). Some have speculated that the immunologic effects of blood donation could also increase cancer risk (27–31).

To quantify cancer risk in relation to donation intensity and iron loss through blood donation, we conducted a case–control study nested within a large cohort of Swedish and Danish blood donors.

CONTEXT AND CAVEATS

Prior knowledge

Low rates of cancer incidence and mortality among blood donors suggest that frequent blood donation does not have long-term health risks.

Study design

Nested case–control study within a cohort of blood donors in Denmark and Sweden.

Contributions

No association between number of blood or plasma donations and overall risk of cancer was observed. A dose-dependent decreasing risk of cancers of the liver, lung, colon, stomach, and esophagus—which are suggested to be promoted by iron overload—was observed among men who donated blood 3–7 years earlier. An increased risk of non-Hodgkin lymphoma was observed among frequent plasma donors.

Implications

Risk of overall cancer is not associated with repeated blood donation.

Limitations

Factors that do or may influence cancer risk, such as smoking, alcohol consumption, diet, physical activity, anthropometric measurement, and occupational exposure to carcinogens were not available in the analysis.

Subjects and Methods

Data Sources

Starting in the mid-1960s, an increasing number of Swedish blood banks and transfusion medicine clinics began computerized registration of blood donations and transfusions (32). Similar registration had started in Denmark in the 1960s (33), but data storage on a lasting electronic medium was delayed until 1981. Near nationwide coverage was attained in Sweden by 1992 and in Denmark by 1997.

We assembled all available computerized blood donation and transfusion registers from Swedish and Danish blood banks and transfusion medicine clinics into the Scandinavian Donations and Transfusions (SCANDAT) database, which has been described in greater detail previously (34). Hemoglobin concentration was recorded for each donation, and information is also available regarding the type of donation (whole blood, plasma, platelets, or other). Using the individually unique national registration numbers that are assigned to all residents of both Sweden and Denmark, we performed record linkages with the complete and nationwide registers of total population, death, and migration, thus ensuring the correctness of the national registration numbers and correct censoring on emigration and death. Record linkages with nationwide and essentially complete Swedish and Danish cancer registers (35,36) provided diagnosis dates and anatomic sites of all malignancies. After record linkage, the database was permanently deidentified by replacing the national registration numbers with anonymous but unique identification numbers.

Study Design

From the SCANDAT database we identified all donors for whom at least one successful whole blood or plasma donation was recorded between January 1, 1968, and December 31, 2002, and who had no history of cancer at the time of the first recorded donation. We conducted a matched case–control study nested within this cohort of 1 110 212 blood donors who were followed from the date of first donation until the first cancer diagnosis, emigration, death, or December 31, 2002, whichever occurred first. Case patients were all blood donors who were diagnosed with a first primary cancer during follow-up. For each identified case patient, we used incidence density sampling to randomly select 10 control subjects from the cohort, who were alive and cancer free at the time of diagnosis of the case patient (ie, the index date). The control subjects were matched to the case patients by sex, age (±180 days), and county of residence. For meaningful comparisons, both case patients and control subjects were required to have donated blood at least once during years 3–12, counting backward from the index date.

To obtain measures of donation frequency in comparable periods, we restricted the exposure assessment to fixed exposure windows, which were predefined in terms of time before the index date (3–7, 8–12, or 3–12 years). To be eligible for the analyses that went back beyond 7 years, the case patients and control subjects had to have resided during the entire length of the time window in counties that were fully covered by the electronic registrations that were assembled in the SCANDAT database. Hence, subjects living in counties in which the registration was not in full operation from the first day of the time window or who, due to relocations, had lived in noncovered counties during parts of the time window, were not eligible. The dates of such relocations were obtained from national registers. Hence, both the case patients and control subjects had to have at least 7 years of register coverage to be eligible.

For each case patient and his or her matched control subjects, we counted the number of whole blood and plasma donations performed in the respective time windows. We estimated iron loss using the approximate volume of whole blood loss for each donation (480 mL for whole blood, 50 mL for plasma) and the hemoglobin concentration measured immediately before each donation.

Because of early symptoms, donors with an incipient malignancy are likely to donate blood less often than healthy donors, which could lead to reverse causation. We therefore carried out the following analysis to determine the point from which the case patients' donation activity first started to decline. We first divided the 5 years immediately before cancer diagnosis into 6-month segments. For each segment, we calculated the relative donation intensity of the case patients as the ratio of the observed frequency to the expected frequency (the average frequency of a randomly selected control subject from the matched set). Confidence intervals (CIs) were calculated for the relative donation intensities under the assumption that the number of donations followed a

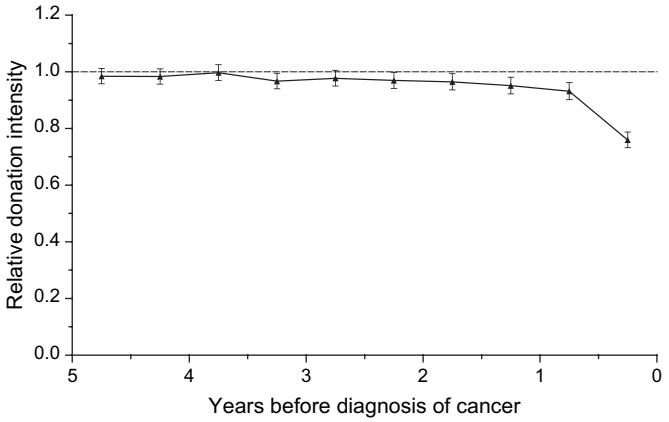

Figure 1. Donation intensity among case patients relative to control subjects presented by time to diagnosis (**triangles**). 95% confidence intervals (**error bars**) are shown.

Poisson distribution. Based on these calculations, which revealed a decreasing donation intensity among case patients starting as early as 2 years before the index date (Figure 1), we decided to exclude from the analyses the 2 years immediately before cancer diagnosis.

Statistical Analysis

We analyzed associations between cancer incidence and the number of donations (any type) in the respective exposure windows using conditional logistic regression models with the exposure variable treated as a categorical variable (to allow for nonlinear relationships) with cut points chosen at approximately the median, 75th percentile, and 90th percentile. Thus, the four categories were 1–8, 9–16, 17–25, and more than 25 donations for the 10-year window from 3–12 years before diagnosis and 0–4, 5–8, 9–12, and more than 12 donations for the shorter 5-year windows (ie, 3–8 and 8–12 years before diagnosis of the case patient). We also examined the association with the number of donations as a continuous variable to test for a linear trend. We then considered whole blood and plasma donations separately, again both as categorical and continuous variables. Both the number of whole blood and the number of plasma donations were categorized as above. Because the type of donation was recorded with less precision in the Danish data, the analyses considering whole blood and plasma donations separately were restricted to Swedish data only.

After we examined associations with overall cancer risk, we performed further analyses for three broad groups of malignancies: solid tumors (defined according to the *International Classification of Diseases, Seventh Revision* [*ICD*-7] as codes 140–199), non-Hodgkin lymphomas (including chronic lymphocytic leukemia, *ICD*-7 codes 200, 202, and 204.1), and other hematologic or lymphatic malignancies (*ICD*-7 codes 201 and 203–207 [excluding 204.1]). In a post hoc analysis, we stratified the analyses of risk of non-Hodgkin lymphoma by whether the donors performed their first donation before or after HIV screening was initiated (ie, <1986 vs ≥1986).

We also investigated the relationship between iron loss and risk of selected solid tumors (lung, liver, colon, stomach, and esophageal cancers) for which high iron levels have previously been implicated (8–10,21,22). Iron loss was categorized according to the median, 75th percentile, and 90th percentile, as less than 1.5, 1.5–3.4, 3.5–5.4, and greater than 5.4 g for the longer exposure window and as less than 0.75, 0.75–1.7, 1.8–2.7, and greater than 2.7 g for the shorter windows.

To assess the potential for confounding by lifestyle factors, we used the Swedish and Danish inpatient registers to investigate, among the control subjects only, associations between donation frequency and incidence of hospitalization for the following diseases that are associated with tobacco and alcohol use: alcoholism, alcoholic hepatitis, and chronic obstructive pulmonary disease. The control donors were followed from the index date until the first occurrence of any of these diseases, death, emigration, or December 31, 2002. Also, among all female donors who had been pregnant after 1983, whose smoking habits were recorded in the Swedish medical birth register, we calculated the number of donations during the most recent 10 years before delivery among smokers and nonsmokers.

Odds ratios (ORs) were used as estimates of relative risks. All data processing and statistical analyses were performed using SAS version 8 or higher (SAS Institute, Cary, NC). All statistical tests were two-sided. *P* values less than .05 were considered to be statistically significant. The conduct of this study was approved by all regional ethics committees in Sweden, the Danish Scientific Ethics Committee System, and the Danish Data Protection Agency.

Results

We identified a total of 30729 case patients with cancer among donors with a known area of residence. Of these, 13810 case patients had less than 7 years of donation register coverage and were consequently ineligible for the analyses. Another 6053 case patients had not donated blood in the window 3–12 years before diagnosis. For the remaining 10866 case patients, we selected a total of 107140 individually matched control subjects who had all donated blood in the window from 3–12 years before cancer diagnosis of their respective case patient and who also had at least 7 years of register coverage. A total of 4720 (43.4%) case patients were women (Table 1), and the median age at diagnosis of the case patients was 57 years (interquartile range = 48–64 years). Almost three-quarters (73%) of case patients were Swedish. The number of previous donations was similar for the case patients and control subjects (the median number of donations in the windows from 3–7 and 8–12 years before diagnosis was four and five for both case patients and control subjects, respectively). Of the 10866 case patients, 5319 (49%) had at least 12 years of blood donation register coverage.

No clear dose–response relationship was observed between the number of donations in any of the exposure windows and cancer risk overall (Table 2). However, men with at least five donations in the time window of 3–7 years were at a slightly lower risk than men with fewer donations (Table 2). This risk reduction was statistically significant among men who made 9–12 donations (Table 2).

The analyses of different groups of malignancies included a total of 10028 donors with solid cancers, 482 with non-Hodgkin lymphomas, and 356 with other hematologic or lymphatic malignancies (Table 1). The association between number of donations and risk of solid malignancies followed much the same pattern as for cancer overall, with a small but statistically significant reduction in risk for donors with 9–12 donations in the 3–7 years before

diagnosis (OR = 0.91, 95% CI = 0.85 to 0.97) (Table 3). For non-Hodgkin lymphoma, the data signaled a slightly different pattern, with a suggested but not statistically significant (P_{trend} = .07) increased risk with increasing number of donations in the time window of 3–12 years (Table 3).

The data from the Swedish component were further broken down into donations of whole blood or plasma (Table 4). Apart from a small but statistically significant reduction in risk of solid cancers with an increasing number of whole blood donations made 3–7 years before the index date (P_{trend} = .02), the analyses revealed no other associations between whole blood donations and the risk of solid cancers (Table 4). However, in the 3–12 year window, the highest category of plasma donations was associated with an increased risk of non-Hodgkin lymphoma (>25 vs 0 plasma donations, OR = 2.14, 95% CI = 1.22 to 3.74) (Table 4). Although the P_{trend} value for dose–risk was .05, the trend was erratic in all exposure windows. No consistent associations were observed between number of whole blood or plasma donations and other hematologic or lymphatic malignancies.

To further explore the association between number of plasma donations and risk of non-Hodgkin lymphoma, we stratified the analyses by whether the donors made their first donation before or after HIV screening was initiated. We found that the positive association described above was confined to those who started their donation career in the earlier period (>25 plasma donations in the 3–12 year exposure window: <1986 vs ≥1986, OR = 2.37, 95% CI = 1.20 to 4.67, vs OR = 1.29, 95% CI = 0.39 to 4.30).

We next performed analyses of iron loss in relation to risk of cancers of the liver, lung, colon, stomach, and esophagus (Table 5). In the exposure window 3–7 years before index date, we noted an inverse association between iron loss and risk with a highly statistically significant trend (P_{trend} < .001). This inverse association was seemingly driven by male donors (iron loss: >2.7 vs <0.75 g, OR = 0.70, 95% CI = 0.58 to 0.84) (Table 5). Similarly, in the exposure window 8–12 years before index date, risks were lower, especially among male donors, but none of the point estimates or tests for trend were statistically significant. In the combined exposure window (3–12 years), the point estimates for men and women in the highest donation category were statistically significant, as was the linear trend in male donors (P_{trend} = .03). In supplementary analyses, we recalculated the iron loss analyses after dividing the case patients and control subjects into three groups (cancers of the gastrointestinal tract, lung cancer, and liver cancer). These analyses revealed that the association between iron loss and reduced cancer risk was driven largely by a reduced risk of lung cancer (Supplementary Table 1, available online).

As an indirect measure of the alcohol consumption and tobacco use among blood donors with different donation activity, we calculated the incidence of alcohol- and tobacco-related diagnoses among control subjects only using the respective nations' inpatient

Table 1. Characteristics of the study subjects*

Characteristic	Cancer case patients	Matched control subjects
Total number of individuals	10866	107140
Site of cancer in case patient, No. (%)		
Solid cancers	10028 (92.3)	98871 (92.3)†
Non-Hodgkin lymphomas	482 (4.4)	4757 (4.4)†
Other hematologic/lymphatic malignancies	356 (3.3)	3512 (3.3)†
Female sex, No. (%)	4720 (43.4)	46492 (43.4)
Swedish, No. (%)	7949 (73.2)	78553 (73.3)
Age in y, median (IQR)	57 (48–64)	57 (48–64)
No. of recorded donations		
<5	2071 (19.1)	19579 (18.3)
6–15	3942 (36.3)	38232 (35.7)
16–50	3667 (33.7)	37895 (35.4)
>50	1186 (10.9)	11434 (10.7)
No. of donations, median (IQR)		
In window 3–7 y	4 (0–9)	4 (0–9)
In window 8–12 y	5 (1–9)	5 (1–10)
Iron loss in g, median (IQR)		
In window 3–7 y	0.8 (0.0–1.9)	0.8 (0.0–2.0)
In window 8–12 y	1.0 (0.2–2.1)	1.0 (0.2–2.1)

* IQR = interquartile range. Case patients and control subjects (10 per case patient, alive and free of cancer on the date of the respective case patient's cancer diagnosis) were matched on sex, age (±180 days), and county of residence. For some case patients, it was not possible to find 10 control subjects who fulfilled the eligibility and matching criteria, so the ratio of case patients to control subjects is slightly more than 0.1. Percentages may not add to 100 due to rounding.

† Cancer site in the corresponding, individually matched case patient.

Table 2. RRs, expressed as ORs, for all cancers combined in relation to number of whole blood and plasma donations, by latency and stratified by sex*

Exposure window	OR (95% CI) according to No. of donations				P_{trend}
3–12 y before diagnosis	*1–8*	*9–16*	*17–25*	*>25*	
Both sexes	1.00 (referent)	0.98 (0.91 to 1.05)	0.97 (0.89 to 1.05)	0.99 (0.90 to 1.10)	.84
Women	1.00 (referent)	0.96 (0.86 to 1.07)	0.99 (0.87 to 1.13)	0.98 (0.83 to 1.17)	.78
Men	1.00 (referent)	0.99 (0.90 to 1.09)	0.96 (0.86 to 1.07)	1.00 (0.88 to 1.13)	.68
3–7 y before diagnosis	*0–4*	*5–8*	*9–12*	*>12*	
Both sexes	1.00 (referent)	0.98 (0.93 to 1.03)	0.90 (0.85 to 0.96)	0.99 (0.93 to 1.06)	.46
Women	1.00 (referent)	1.02 (0.94 to 1.10)	0.95 (0.87 to 1.05)	1.01 (0.91 to 1.13)	.93
Men	1.00 (referent)	0.94 (0.87 to 1.01)	0.86 (0.80 to 0.94)	0.97 (0.90 to 1.05)	.39
8–12 y before diagnosis	*0–4*	*5–8*	*9–12*	*>12*	
Both sexes	1.00 (referent)	0.99 (0.92 to 1.07)	0.98 (0.90 to 1.07)	1.00 (0.91 to 1.09)	.72
Women	1.00 (referent)	0.99 (0.89 to 1.11)	1.02 (0.90 to 1.17)	0.97 (0.82 to 1.14)	.76
Men	1.00 (referent)	1.00 (0.90 to 1.10)	0.96 (0.86 to 1.07)	1.01 (0.90 to 1.13)	.82

* RR = relative risk; OR = odds ratio; CI = confidence interval. The analyses considering the two exposure windows of 3–12 and 8–12 years were restricted to the 5319 case patients and 52369 control subjects who had at least 12 years of donation register coverage.

Table 3. RRs, expressed as ORs, for solid cancers, non-Hodgkin lymphoma, and other hematologic/lymphatic malignancies in relation to number of donations, by latency*

Exposure window	OR (95% CI) according to No. of donations				P_{trend}
3–12 y before diagnosis	*1–8*	*9–16*	*17–25*	*>25*	
Solid cancer	1.00 (referent)	0.98 (0.91 to 1.06)	0.97 (0.89 to 1.06)	0.99 (0.89 to 1.10)	.73
Non-Hodgkin lymphoma	1.00 (referent)	0.92 (0.65 to 1.31)	0.89 (0.60 to 1.32)	1.27 (0.84 to 1.94)	.07
Other	1.00 (referent)	0.87 (0.57 to 1.31)	1.10 (0.68 to 1.76)	0.69 (0.35 to 1.36)	.16
3–7 y before diagnosis	*0–4*	*5–8*	*9–12*	*>12*	
Solid cancer	1.00 (referent)	0.98 (0.93 to 1.04)	0.91 (0.85 to 0.97)	0.98 (0.91 to 1.05)	.37
Non-Hodgkin lymphoma	1.00 (referent)	0.97 (0.75 to 1.25)	0.81 (0.60 to 1.10)	1.24 (0.95 to 1.62)	.16
Other	1.00 (referent)	0.93 (0.70 to 1.25)	0.80 (0.56 to 1.15)	0.99 (0.70 to 1.42)	.29
8–12 y before diagnosis	*0–4*	*5–8*	*9–12*	*>12*	
Solid cancer	1.00 (referent)	1.01 (0.94 to 1.10)	0.99 (0.90 to 1.08)	1.01 (0.91 to 1.11)	.71
Non-Hodgkin lymphoma	1.00 (referent)	0.75 (0.51 to 1.09)	0.87 (0.59 to 1.28)	1.11 (0.74 to 1.68)	.16
Other	1.00 (referent)	0.80 (0.52 to 1.25)	1.00 (0.62 to 1.62)	0.56 (0.30 to 1.03)	.09

* RR = relative risk; OR = odds ratio; CI = confidence interval. The analyses considering the two exposure windows of 3–12 and 8–12 years were restricted to the 5319 case patients and 52369 control subjects for whom we had at least 12 years of donation register coverage.

registries (Supplementary Table 2). There were only minor variations in the incidence of alcoholism and alcoholic hepatitis with donation activity. Although the incidence of chronic obstructive pulmonary disease was similar in the two lowest donation categories, the incidence in the two highest categories was nearly 50% lower (Supplementary Table 2). Among the 23471 female donors who had been pregnant in 1983 or later, those who reported being smokers had on average made 5.0 donations in the previous 10 years, compared with 6.6 among nonsmokers.

Discussion

In this case–control study nested within a large cohort of Scandinavian blood donors, we found little support for any important associations between repeated whole blood donations and cancer risk. There was some suggestion that the risk of non-Hodgkin lymphoma might be increased among frequent plasma donors who began donating before 1986, but the dose–risk trend was erratic and the data not very convincing.

Our a priori hypothesis, which was based on previously published observations (8–10,21,22), was that iron depletion may be associated with reduced risks of pulmonary, hepatic, esophageal, gastric, and colon cancer. Seemingly in support of this hypothesis, we noted that the risk of these cancers combined was 30% lower among men who fell into the 90th percentile of iron loss in the 3–7 year exposure window than men who had the smallest iron loss in the same period. The dose–risk trend among men in the 3–7 year window was monotonic and highly statistically significant. The

Table 4. RRs, expressed as ORs, for solid cancers, non-Hodgkin lymphoma, and other hematologic/lymphatic malignancies among Swedish blood donors by latency in relation to number of whole blood and plasma donations*

Exposure window	OR (95% CI) according to No. of blood donations				P_{trend}	OR (95% CI) according to No. of plasma donations			P_{trend}
3–12 y before diagnosis	*1–8*	*9–16*	*17–25*	*>25*		*0–8*	*9–25*	*>25*	
Solid cancer	1.00 (referent)	1.02 (0.93 to 1.11)	0.99 (0.89 to 1.10)	0.93 (0.81 to 1.08)	.49	1.00 (referent)	0.99 (0.83 to 1.20)	1.05 (0.90 to 1.22)	.89
Non-Hodgkin lymphoma	1.00 (referent)	0.91 (0.60 to 1.38)	1.13 (0.73 to 1.75)	1.11 (0.63 to 1.95)	.69	1.00 (referent)	0.47 (0.15 to 1.52)	2.14 (1.22 to 3.74)	.05
Other	1.00 (referent)	0.90 (0.54 to 1.50)	1.43 (0.82 to 2.50)	0.84 (0.31 to 2.22)	.85	1.00 (referent)	0.72 (0.22 to 2.37)	0.47 (0.14 to 1.57)	.18
3–7 y before diagnosis	*0–4*	*5–8*	*9–12*	*>12*		*0–4*	*5–12*	*>12*	
Solid cancer	1.00 (referent)	0.96 (0.90 to 1.03)	0.93 (0.86 to 1.00)	0.93 (0.85 to 1.01)	.02	1.00 (referent)	0.84 (0.70 to 1.01)	1.04 (0.92 to 1.17)	.99
Non-Hodgkin lymphoma	1.00 (referent)	0.85 (0.62 to 1.17)	0.99 (0.71 to 1.38)	1.04 (0.75 to 1.44)	.80	1.00 (referent)	2.19 (1.16 to 4.16)	1.42 (0.86 to 2.32)	.08
Other	1.00 (referent)	0.85 (0.58 to 1.24)	0.90 (0.58 to 1.38)	1.19 (0.76 to 1.85)	.90	1.00 (referent)	1.03 (0.48 to 2.18)	0.49 (0.22 to 1.10)	.24
8–12 y before diagnosis	*0–4*	*5–8*	*9–12*	*>12*		*0–4*	*5–12*	*>12*	
Solid cancer	1.00 (referent)	1.02 (0.93 to 1.11)	0.98 (0.88 to 1.08)	1.01 (0.90 to 1.14)	.85	1.00 (referent)	1.05 (0.83 to 1.32)	0.99 (0.84 to 1.17)	.72
Non-Hodgkin lymphoma	1.00 (referent)	0.97 (0.64 to 1.47)	0.86 (0.54 to 1.37)	1.14 (0.69 to 1.88)	.72	1.00 (referent)	0.27 (0.04 to 2.03)	1.80 (0.97 to 3.35)	.12
Other	1.00 (referent)	1.00 (0.59 to 1.69)	1.19 (0.66 to 2.14)	0.86 (0.41 to 1.80)	.95	1.00 (referent)	0.97 (0.22 to 4.32)	0.18 (0.02 to 1.32)	.15

* RR = relative risk; OR = odds ratio; CI = confidence interval. The analyses considered only the Swedish portion of the data; the analyses considering the two exposure windows of 3–12 and 8–12 years were restricted to the 3941 case patients and 38883 control subjects for whom we had at least 12 years of donation register coverage.

Table 5. RRs, expressed as ORs, for cancers of the lung, liver, esophagus, stomach, and colon in relation to iron loss, by latency and stratified by sex*

Exposure window	OR (95% CI) according to iron loss through blood donation				P_{trend}
3–12 y before diagnosis	*<1.5 g*	*1.5–3.4 g*	*3.5–5.4 g*	*>5.4 g*	
Both sexes	1.00 (referent)	0.99 (0.84 to 1.16)	0.92 (0.75 to 1.12)	0.77 (0.59 to 0.99)	.06
Women	1.00 (referent)	1.20 (0.92 to 1.56)	1.02 (0.71 to 1.45)	0.64 (0.33 to 1.26)	.99
Men	1.00 (referent)	0.88 (0.71 to 1.08)	0.86 (0.68 to 1.10)	0.76 (0.57 to 1.01)	.03
3–7 y before diagnosis	*<0.75 g*	*0.75–1.7 g*	*1.8–2.7 g*	*>2.7 g*	
Both sexes	1.00 (referent)	0.99 (0.87 to 1.12)	0.90 (0.79 to 1.04)	0.75 (0.64 to 0.88)	<.001
Women	1.00 (referent)	1.13 (0.92 to 1.39)	1.06 (0.84 to 1.35)	0.94 (0.66 to 1.32)	.87
Men	1.00 (referent)	0.92 (0.78 to 1.07)	0.83 (0.70 to 0.99)	0.70 (0.58 to 0.84)	<.001
8–12 y before diagnosis	*<0.75 g*	*0.75–1.7 g*	*1.8–2.7 g*	*>2.7 g*	
Both sexes	1.00 (referent)	0.92 (0.77 to 1.10)	1.01 (0.84 to 1.22)	0.84 (0.67 to 1.06)	.73
Women	1.00 (referent)	1.09 (0.83 to 1.44)	1.20 (0.87 to 1.66)	0.73 (0.41 to 1.28)	.53
Men	1.00 (referent)	0.82 (0.66 to 1.03)	0.92 (0.73 to 1.16)	0.83 (0.64 to 1.07)	.46

* RR = relative risk; OR = odds ratio; CI = confidence interval. The analyses considering the two exposure windows of 3–12 and 8–12 years were restricted to the 945 case patients and 9312 control subjects for whom we had at least 12 years of donation register coverage.

absence of a similar risk reduction in women in the same period may be biologically plausible because women regularly dispose of some iron through menstrual blood, and, thus, the loss through blood donation may be less important. As an estimate of the relevance of the reduced cancer risk with iron loss, we estimated the risk difference between the lowest and highest exposure groups using incidence data from the overall cohort of blood donors. We found, among male donors with an accumulated iron loss of less than 0.75 g, that the incidence of the cancers associated with high iron levels was 41.9 cases per 100 000 person-years. Thus, a relative risk estimate of 0.70, comparing the highest exposure category with the lowest, would amount to 12.6 fewer cases of the studied cancers per 100 000 person-years. The data also suggested a lower risk of cancer among male donors who had higher than the median iron loss in the period 8–12 years before the index date, but these estimates were not statistically significant and did not follow a linear trend. We postulated that any deleterious effect of iron overload would be mediated mainly through mechanisms requiring substantial induction time. Therefore, it is surprising that the association with iron depletion was stronger in the 3–7 year window than the 8–12 year window, suggesting a suspiciously short induction and latency time. Although iron has been implicated as a late-stage carcinogen (37), it is also conceivable that subtle symptoms of cancers or their precursor lesions that are associated with iron levels may develop earlier than most other malignancies and that the 2-year latency—notwithstanding our initial data exploration—might have been insufficient for excluding the possibility that developing cancers may have affected the donation activity in the latter part of the 3–7 year exposure window. It is further possible that the hemoglobin concentration, and therefore also the iron loss, among case patients was affected by the developing malignancy beyond 2 years before the diagnosis. In ad hoc analyses, we found that the association of iron loss with reduced cancer risk was driven largely by a reduced risk of lung cancers. Therefore, the possibility of residual confounding by lifestyle factors such as smoking must also be considered. In fact, a supplementary analysis revealed a small gradient of smoking- and lifestyle-related morbidity in relation to donation intensity, suggesting that some residual confounding by a "healthy donor effect" may exist despite the restriction of our analyses to donors. Furthermore, among female donors who had been pregnant after 1983 and whose smoking habits were recorded in the Swedish medical birth register, the average number of previous donations was higher among smokers than among nonsmokers. The magnitude of confounding by lifestyle, however, is likely to be small and would hardly explain the difference by sex.

To our knowledge, only three studies of cancer occurrence among blood donors have been published previously (1,4,30). They all compared donors with nondonors, and their results mainly reflected the healthy donor effect. None appropriately addressed dose–response relationships between number of donations and cancer risk within a donor cohort. Hence, our study is not readily comparable with previous studies.

A noteworthy strength of this study is the well-defined cohort, which includes the majority of blood donors in recent years in Sweden and Denmark (essentially all donors after the register coverage became complete). Virtually complete high-quality population and health registers ensured essentially complete follow-up, and the large sample size allowed us to precisely characterize the overall cancer risk profile of both male and female blood donors. However, the statistical power was clearly insufficient to detect small effects in site-specific analyses. To limit the scope for both type I and type II errors, we restricted our analyses to a limited number of outcome categories that were defined a priori.

Although the blood donation registers were introduced gradually, typically one county at a time, the availability of data on internal migration allowed us to overcome exposure misclassification due to left truncation by considering only individuals who were fully covered by the donation registers throughout the full exposure window. The restriction to individuals who had donated blood at least once in the most recent 12 years reduced the number of study participants considerably, but in this way the reference group included only active donors. Accordingly, the effect of recently introduced screening tests and eligibility criteria, which may otherwise have contaminated the lowest exposure category with former donors who were no longer eligible for donation, was minimized.

Although the median follow-up time exceeded 10 years in the cohort within which this case–control study was nested (1), an insufficient number of donors were covered by the SCANDAT

database for a meaningful assessment of relative risks associated with exposure in a third 5-year window (13–17 years before the index date). Therefore, it must be pointed out that our results do not rule out the possibility of associations with a longer latency than 12 years.

An important limitation of this study is the lack of information about possibly important confounding factors, such as smoking, alcohol consumption, diet, physical activity, anthropometric measures, and occupational exposures. Although the restriction of our study to donors only with internal comparisons across strata that were defined by donation activity should have limited the scope for important confounding by lifestyle factors, the analyses among the control subjects suggested an association between donation frequency and alcohol- and tobacco-related diseases. However, we cannot directly quantify the impact of the suspected confounding.

Given international differences in blood collection practices, involving maximum permitted blood donations annually and iron substitution use, the results from this study may not be entirely generalizable to other settings. Donors in the most heavily exposed group in this study made more than two donations per year and often approached the maximum of three or four for women and men, respectively. It is unknown to what extent these blood donors experienced mitotic stress or depletion of stored iron, but considering that the iron loss in the highest exposure category, which corresponds to an average daily iron loss of at least 1.4 mg, exceeds the normal average daily iron uptake, some level of iron depletion is likely to have occurred (38–41). Our database did not contain information about whether or not iron supplementation pills were dispensed, let alone whether they were taken. Although iron supplementation might have partly masked a biologic effect, it seems unlikely to have totally canceled or reversed it (42).

Although whole blood donation has been found to cause a transient, yet noticeable, immunomodulation (27–29,31), the risk elevation we observed for non-Hodgkin lymphoma among frequent plasma donors cannot be readily explained. From the cohort within which the study was nested, we calculated an incidence of 9.4 cases of non-Hodgkin lymphoma per 100 000 person-years among donors with fewer than nine plasma donations. Given a relative risk of 2.14, the incidence rate theoretically translates into an additional 10.7 cases per 100 000 person-years of follow-up. Because this association seemed to be confined to those who began donating before 1986, a time when donor selection underwent major changes due to the risk of HIV transmission, and there was generally a stronger economic incentive for plasma donations than whole blood donations, the finding could conceivably be confounded by some lifestyle-related risk factors. However, if the induction and latency time for non-Hodgkin lymphoma is long, the follow-up period among plasma donors who started donating after 1986 may not yet have been sufficient. The possible link between blood donation and risk of non-Hodgkin lymphoma was one of few a priori hypotheses, but because chance cannot confidently be ruled out in view of multiple testing and the small number of case patients, more studies of the association may be warranted. Our finding might constitute one of few clues to the etiology of this rapidly increasing malignancy.

In conclusion, we found that repeated blood donation was not associated with risk of cancer overall. The overriding hypothesis of a positive association between iron stores and risk of a number of cancers that have previously been associated with iron loss (8–10,21,22) gets at least some support from our data; however, residual confounding from unmeasured health-promoting factors that are related to donation activity remains a possibility. A positive association between frequent plasma donation and risk of non-Hodgkin lymphoma must be interpreted cautiously, and further exploration might generate new insights about factors involved in the etiology of this malignancy.

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