Reproductive history, as measured by parity, age at first birth and sex of offspring, and cancer-specific survival after a haematological malignancy

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ABSTRACT

Background: Overall, women have better cancer-specific survival than men following haematological malignancies. The effect of reproductive factors on prognosis in women remains unknown and population-based studies are needed.

Material and methods: A nationwide cohort of 21,237 Swedish women with a recorded haematological malignancy at ages 18–69 years was identified in the Swedish Cancer Register 1970–2018. Pre-diagnosis childbirths for each woman were linked to the Swedish Multigeneration Register. Net survival and excess hazard ratios for parity, age at first birth, time since the latest birth, and sex of offspring were estimated using flexible parametric models adjusted for age, year, and educational level.

Results: In unadjusted analyses, parity ($p = 0.0012$) and high age at first birth ($p < 0.0001$) were associated with better survival. After co-adjustments for reproductive factors and confounders, the associations were attenuated. The adjusted association with parity was mainly observed among women aged above 40 years at diagnosis ($p = 0.0033$). The associations with reproductive factors were non-significant across subtypes of haematological malignancy. There was a tendency of higher excess mortality for an increasing number of boys compared to girls, although only significant for women with three or more children ($p = 0.0126$).

Conclusion: Reproductive factors were in part associated with survival following diagnosis of a haematological malignancy. However, the effect sizes were small with inconsistent association patterns, and thus reproductive factors may only partly contribute to the survival advantage of women over men.

Background

Overall, women have a better cancer-specific survival following a haematological malignancy compared to men, and the sex difference varies by haematological subtype [1–4]. Moreover, it has been reported that young girls have better survival than boys after childhood acute lymphoblastic leukaemia (ALL) [5]. There is a growing body of evidence for sex-related differences in cancer genomics including differences in oncogenic mutational processes [6–8]. In addition, women experience more chemotherapy-induced haematotoxicity than men mainly due to reduced drug metabolism, which in turn may lead to greater anti-tumoural efficacy in women [9,10]. Genetic polymorphisms that influence tumorigenesis and chemo-intolerance could potentially be affected by or interact with other biological factors, such as hormonal activity [7,9].

Reproductive history as a proxy for hormonal load in women could thus contribute to the observed female cancer-specific survival advantage after a haematological malignancy and has not been studied in detail. Parity has been associated with a better prognosis after Hodgkin lymphoma (HL), however, this was found for both women and men [11]. In young women, an HL diagnosis shortly after pregnancy does not confer a worse prognosis compared to women who are not diagnosed near pregnancy [12,13]. Neither does pregnancy trigger relapse in women of reproductive age with HL [14].

The sex difference in prognosis following a haematological malignancy varies by haematological subtype with the strongest female survival advantage for chronic lymphocytic leukaemia (CLL), ALL, HL, and follicular lymphoma (FL), while the male disadvantage has been less pronounced for acute myeloid leukaemia (AML) [3,15,16]. The reasons for these differences across subtypes are largely unknown. Pregnancy has profound local and systemic effects on the female body, including the increased proliferation of haematopoietic stem cells and T-cell mediated immuno-deficiency, but the long-lasting effects of childbirth on the haematopoiesis and immune function are not well-described in the

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/0284186X.2022.2064726.
logical malignancy. The maternal immune system modulation during pregnancy has been shown to be more complex than previously described [20].

Foetal microchimerism from male offspring in female cancer patients has been suggested to positively influence prognosis after malignancy by increased tolerance for cancer therapy and an immunologically mediated anti-tumour effect [21–23]. This suggests that the sex of the offspring could potentially influence the mother's prognosis.

To our knowledge, no comprehensive overview of the effect of reproductive factors on cancer survival in women with a haematological malignancy exists. Using the strength of Swedish national registers, we, therefore, aimed to assess if parity, age at first birth, and time since the latest birth are associated with the prognosis following a haematological malignancy. We included all haematological malignancies in combination and by subtypes. As a secondary aim, we assessed if the number of boy deliveries influences the maternal prognosis following diagnosis of a haematological malignancy.

**Material and methods**

**Study population**

Using several Swedish population-based registers, we created a cohort of women diagnosed with a haematological malignancy between 1970 and 2018 in Sweden. The registers were linked on an individual level using the 10-digit Swedish National Registration Number assigned to all Swedish residents. The Swedish Cancer Register (SCR) includes all malignancies diagnosed in Sweden from 1958 and onwards, and is deemed to have high validity [24,25]. For each tumour, the date of diagnosis, hospital, diagnosis code, and morphology are recorded. The register uses the current International Classification of Diseases (ICD) system, but all tumours are also coded in ICD version 7 across all years to enable comparisons over calendar time.

In the Swedish Cancer Register, we identified women aged 18–69 years and with a primary diagnosis of a haematological malignancy from 1 January 1970 until 31 December 2018. Only women without a previous malignant cancer diagnosis were included, i.e., the haematological malignancy was the first-ever malignant cancer in the woman. We restricted the analysis to women diagnosed after 1970 due to the introduction of curative treatments for several haematological cancers and the improved subtype classification of haematological malignancy in the mid-70s. The following diagnoses were included: B-cell lymphoma (BCL, ICD-7 code 200), HL (ICD-7: 201), other lymphomas (ICD-7: 202), multiple myeloma (MM)/plasmocytoma (ICD-7: 203), ALL (ICD-7: 204.0), CLL (ICD-7: 204.1), AML (ICD-7: 205.0, 205.9, 206.0, 206.9), chronic myeloid leukaemia (CML, ICD-7: 205.1), other and unspecified leukaemia (ICD-7: 204.9, 206.1, 207), essential thrombocytopenia (ET, ICD-7: 207.9, pathoanatomical code 293), polycythaemia vera (PV, ICD-7: 208) and myelofibrosis (MF, ICD-7: 209) (Supplemental Table S1).

Lymphoid malignancies were categorised as BCL, HL, other lymphomas, myeloma, ALL, and CLL, while myeloid malignancies were AML, CML, ET, PV, and MF (Supplemental Table S1). Patients with myelodysplastic syndromes (MDS, ICD-7: 205.9), which have been reported to the cancer registry since 1993, were included in the AML and myeloid groups.

To obtain information on liveborn childbirths for each woman, the cohort was individually linked to the Swedish Multigeneration Register (MGR) at Statistics Sweden [26]. The MGR includes all Swedish residents born in 1932 or later and alive in 1961 with links to their parents, and can therefore be used to identify mothers and offspring. For each woman, we identified her number of children, the number of boys and girls, age at first birth, and time since the latest birth before the diagnosis of haematological malignancy. In women of reproductive age, we only included children born before the diagnosis of haematological malignancy. For women born outside Sweden (15.6%), those children who never resided in Sweden are not included in the MGR and were thus not counted in the reproductive variables. For immigrant women, those children who immigrated before age 18 are more likely to be included in the MGR than children who immigrated as adults.

Information on death was linked to the cohort from the Total Population Register (TPR) and the Swedish Cause of Death Register (CDR). The CDR includes information on all deaths in Sweden including the date of death and underlying cause of death. If the date of death was incomplete in CDR, date information from TPR was used. Date of the first emigration after cancer was also included in TPR. Highest attained education level one year before diagnosis was obtained from the census 1970 and from the Education register at Statistics Sweden, with annual information from 1990 and onwards. Of the included women, 4.1% had missing information on education level.

**Statistical analysis**

Time at risk was defined from the date of diagnosis until the date of death, first emigration, or end of study (31 December 2018), whichever occurred first. Follow-up was also censored at 15 years since diagnosis. We used the relative survival framework to estimate net survival from cancer using a model-based approach [27]. Net survival is a measure of the excess mortality in the patients caused by the disease and can be estimated without requiring information on the cause of death. The primary endpoint was death due to any cause, which was then compared to the expected all-cause mortality rates in a comparable (age- and year-matched) Swedish female population. Net survival curves were estimated by age of diagnosis and parity, and by age of diagnosis and age at first birth, and as a supplementary result standardised using the education distribution within each age group. To assess the association between reproductive factors and excess mortality, we estimated excess hazard ratios (EHR) with 95% confidence intervals (CI) using the flexible parametric survival model (FPM) with time-since-diagnosis as the
Table 1. Age and year of diagnosis and reproductive factors by subtype of haematological malignancy. Sweden 1970–2018, 18–69 years.

| Subtype | N (%) | BCL | N (%) | HL | N (%) | Other Lymphoma | N (%) | ALL | N (%) | CLL | N (%) | AML | N (%) | CML | N (%) | Other Leukaemia | ET, PV, MF | N (%) |
|---------|-------|-----|-------|----|------|----------------|------|-----|-------|-----|-------|-----|-------|-----|--------|-----------------|-----------|------|
| Total   | 21237 (100) | 7695 (100) | 2166 (100) | 514 (100) | 21237 (100) | 7695 (100) | 2166 (100) | 514 (100) | 2562 (100) | 496 (100) | 1766 (100) | 2481 (100) | 845 (100) | 330 (100) | 2382 (100) |

**Age at diagnosis**

- **18–29**: 2054 (10) 369 (5) 1010 (47) 31 (6) 6 (0) 141 (28) 9 (1) 256 (10) 100 (12) 45 (14) 87 (4)
- **30–39**: 2249 (11) 706 (9) 355 (25) 57 (11) 62 (2) 79 (16) 47 (3) 357 (14) 150 (18) 47 (14) 209 (9)
- **40–49**: 3575 (17) 1362 (18) 274 (13) 111 (22) 363 (14) 106 (21) 190 (11) 461 (15) 199 (24) 59 (18) 459 (19)
- **50–59**: 5656 (27) 2282 (30) 189 (9) 133 (26) 856 (33) 81 (16) 569 (32) 571 (23) 229 (27) 67 (20) 688 (29)
- **60–69**: 7694 (36) 2976 (39) 158 (7) 182 (35) 1275 (50) 89 (18) 951 (54) 836 (34) 167 (20) 112 (34) 948 (40)

**Year at diagnosis**

- **1970–79**: 784 (4) 183 (2) 252 (12) 9 (2) 23 (1) 31 (6) 32 (2) 124 (5) 59 (7) 50 (15) 21 (1)
- **1980–89**: 1777 (8) 658 (9) 339 (16) 25 (5) 124 (5) 70 (14) 64 (4) 257 (10) 98 (12) 34 (10) 108 (5)
- **1990–99**: 3988 (19) 1555 (20) 440 (20) 82 (16) 465 (18) 116 (23) 291 (17) 470 (19) 163 (19) 35 (11) 371 (16)
- **2000–09**: 7201 (34) 2652 (35) 568 (26) 179 (35) 954 (37) 135 (27) 712 (40) 786 (32) 261 (31) 101 (31) 853 (36)
- **2010–18**: 7487 (35) 2647 (34) 567 (26) 219 (43) 996 (39) 144 (29) 667 (38) 844 (34) 264 (31) 110 (33) 1029 (43)

**Parity**

- **0**: 4347 (21) 1315 (17) 1000 (46) 92 (18) 348 (14) 158 (32) 255 (14) 500 (20) 166 (20) 69 (21) 444 (19)
- **1**: 3516 (17) 1298 (17) 362 (17) 74 (11) 318 (15) 98 (19) 293 (17) 419 (17) 154 (18) 60 (18) 378 (16)
- **2+**: 8014 (38) 3040 (40) 519 (24) 223 (43) 1063 (42) 146 (29) 733 (42) 918 (37) 320 (38) 130 (39) 922 (39)
- **3+**: 5360 (25) 2042 (27) 285 (13) 125 (24) 770 (30) 95 (19) 485 (24) 668 (26) 205 (24) 71 (22) 638 (27)

**Age at first birth**

- **No children**: 4347 (21) 1315 (17) 1000 (46) 92 (18) 348 (14) 158 (32) 255 (14) 500 (20) 166 (20) 69 (21) 444 (19)
- **13–19**: 2843 (13) 1115 (15) 187 (9) 57 (11) 391 (15) 50 (10) 230 (13) 342 (14) 125 (15) 45 (14) 301 (13)
- **20–24**: 8084 (38) 3209 (43) 472 (17) 723 (14) 890 (35) 142 (29) 637 (36) 801 (32) 247 (29) 100 (30) 731 (31)
- **25–29**: 4733 (22) 1748 (23) 316 (13) 126 (25) 619 (24) 94 (19) 418 (24) 537 (22) 198 (23) 80 (24) 597 (25)
- **30–34**: 1840 (9) 675 (9) 157 (7) 48 (9) 233 (9) 35 (7) 152 (9) 217 (9) 80 (10) 23 (7) 220 (9)
- **35–49**: 670 (3) 233 (3) 34 (2) 16 (3) 81 (3) 17 (3) 74 (4) 84 (3) 29 (3) 13 (4) 89 (4)

**Time-since-latest-birth, years**

- **No children**: 4347 (21) 1315 (17) 1000 (46) 92 (18) 348 (14) 158 (32) 255 (14) 500 (20) 166 (20) 57 (17) 224 (9)
- **0–9**: 2659 (13) 772 (10) 670 (31) 68 (13) 103 (4) 114 (23) 61 (4) 415 (17) 175 (21) 50 (15) 368 (15)
- **10–19**: 3007 (14) 1150 (15) 198 (9) 87 (17) 341 (13) 85 (17) 192 (11) 377 (15) 159 (19) 62 (19) 559 (24)
- **20–29**: 4662 (22) 1868 (24) 160 (7) 114 (22) 686 (27) 72 (15) 473 (27) 478 (19) 190 (23) 92 (28) 787 (33)
- **30+**: 6562 (31) 2590 (34) 138 (6) 153 (30) 1084 (42) 67 (14) 785 (45) 711 (29) 155 (18) 69 (21) 444 (19)

Parity variables include only childbirths occurring before diagnosis of haematological malignancy.
across levels of parity and age at first birth, indicating some confounding by education (Supplemental Figure S2).

Associations between reproductive factors and excess mortality for all haematological subtypes combined are shown in Table 2. When assessing the reproductive factors separately (model 1), parity \( p = 0.0012 \), age at first birth \( p < 0.0001 \), and time since the latest childbirth \( p < 0.0001 \) were all associated with survival. After co-adjustments for all reproductive factors, age and year of diagnosis, and education, nulliparity at diagnosis was not associated with excess mortality compared to women with one child (EHR = 1.02, 95% CI 0.88–1.17) (Model 2). Moreover, having two children (vs. one child) before cancer was significantly associated with lower excess mortality (0.90, 0.83–0.97), while having three children was not (0.96, 0.88–1.04). However, no association with parity was observed in women aged 18–39 at diagnosis (Model 3), but only in women aged 40–69 years at diagnosis (Model 4). Increasing age at first birth was associated with lower excess mortality (Model 2) but in the separate analyses of ages 18–39 and 40–69 years the association was no longer significant (Models 3 and 4). Short (0–9 years) and a long time since the latest pregnancy (30 or more years) was associated with increased excess mortality, the latter in particular if haematological malignancy was diagnosed at age 40–69 years. There was no indication of non-proportional excess hazards for parity, while for age at first birth the association with low age at first birth appeared stronger at 5 and 10 years after diagnosis, while the protective effect of high age at first birth became significant 15 years after diagnosis.
**Table 2.** Associations between reproductive factors and excess mortality for all haematological malignancies combined and by lymphoid and myeloid subtypes. Sweden 1970–2018, 18–69 years.

| Parity | Patients | Deaths within 15y | All subtypes | All subtypes | All subtypes | All subtypes | Lymphoid subtypes | Myeloid subtypes |
|--------|----------|------------------|--------------|--------------|--------------|--------------|-------------------|-----------------|
|        | N = 20,367 | N = 7576 | Model (1) | Model (2) | Model (3) | Model (4) | Model (5) | Model (6) |
| Parous | 16530 | 6370 | N/A | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] |
| Parousc | 16530 | 6370 | N/A | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] |
|        | 3837 1206 N/A 1.02 [0.88, 1.17] | 1.04 [0.93, 1.18] | 0.94 | 1.30 | 1.08 | 0.83 |
|        | 3837 1206 | 1.06 [0.97, 1.16] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] |
| Parity | 0 | 3368 1290 | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] |
|        | 2 | 7879 2928 | 0.92 [0.86, 0.99] | 0.90 [0.83, 0.97] | 1.03 | 0.89 | 0.94 | 0.85 |
|        | 3+ | 5283 2152 | 1.00 [0.93, 1.08] | 0.96 [0.88, 1.04] | 0.95 | 0.98 | 1.02 | 0.87 |
|        | p = 0.0012 | p = 0.0125 | 0.7437 | 0.0033 | 0.0678 | 0.0808 |
|        | 3837 1206 | 1.09 [1.01, 1.18] | 1.09 | 1.07 | 1.09 | 1.08 |
|        | 13–19 | 2780 1284 | 1.15 [1.06, 1.24] | 1.08 [1.00, 1.17] | 1.09 | 1.07 | 1.09 | 1.08 |
|        | 20–24 | 6651 2691 | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] |
|        | 25–29 | 4644 1679 | 0.93 [0.87, 1.00] | 0.99 [0.92, 1.07] | 0.93 | 1.01 | 1.00 | 0.90 |
|        | 30–34 | 1807 549 | 0.87 [0.79, 0.97] | 0.95 [0.85, 1.07] | 1.07 | 0.97 | 0.98 | 0.89 |
|        | 35–49 | 648 167 | 0.74 [0.61, 0.88] | 0.80 [0.66, 0.97] | 1.06 | 0.84 | 0.80 | 0.70 |
|        | p < 0.0001 | p = 0.0343 | 0.7340 | 0.0262 | 0.1514 | 0.0841 |
| Time-since-latest-birth, years | No children | 3837 1206 | 1.25 [1.13, 1.38] | 1.13 [1.01, 1.27] | 1.22 | 0.95 | 1.12 | 1.14 |
|        | 0–9 | 2442 729 | 1.11 [0.99, 1.24] | 1.13 [1.01, 1.27] | 1.22 | 0.95 | 1.12 | 1.14 |
|        | 0.0014 | 0.0126 | 0.94 | 0.0676 | 0.0070 | 0.0001 |
|        | 10–19 | 2941 1018 | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] |
|        | 20–29 | 4622 1742 | 1.06 [0.97, 1.17] | 1.02 [0.92, 1.12] | 0.59 | 1.05 | 1.06 | 0.90 |
|        | 30+ | 6525 2881 | 1.29 [1.16, 1.43] | 1.15 [1.03, 1.29] | N/A | 1.21 | 1.23 | 0.92 |
|        | p < 0.0001 | p = 0.0055 | 0.1924 | 0.0049 | 0.0070 | 0.1967 |

EHR: excess hazard ratio. N/A: Not available.

Model 1 for each reproductive variable separately and adjusted for age and year (interaction) and haematological subtype (stratified with separate baselines).

Models 2–6 adjusted for age and year (interaction), haematological subtype (stratified with separate baselines), education and all reproductive variables in the table.

p-Values from Wald tests.

Lymphoid: BCL, HL, Other lymphoma, MM, ALL, and CLL (Supplemental Table S1).

Myeloid: AML, CML, ET, PV, and MF (Supplemental Table S1).

The reference group ‘parous’ corresponds to women with one child (parity = 1), age at first birth 20–24 years and 10–19 years since latest birth. Effect of nulliparous group estimated separately to avoid collinearity between reproductive variables for models 2–6.

Age at first birth was mainly at 1 year after diagnosis (Supplemental Table S3). Having boys was not associated with lower excess mortality in women with 1 or 2 children, however, among women with ≥3 children higher excess mortality with more boys was observed (p = 0.0126) (Figure 2). When assessing the order of girl/boy deliveries, there was no clear pattern of association though the overall association was significant (p = 0.0062) (Supplemental Table S4).

In the second step, associations between reproductive factors and excess mortality were estimated separately by subtype of haematological malignancy. There was no association between parity and excess mortality in women with lymphoid malignancies, whereas for myeloid malignancies higher parity was modestly associated with lower excess mortality (Table 2, models 5 and 6). Increasing age at first birth was no longer significantly associated with lower excess mortality for both lymphoid and myeloid malignancies, whereas a long time since the latest birth (>30 years) was associated...
### Table 3. Associations between reproductive factors and excess mortality by haematological subtype. Sweden 1970–2018, 18–69 years.

|              | BCL | HL | Other Lymphoma | Myeloma | ALL | CLL | AML | CML | Other Leukaemia | ET, PV, MF |
|--------------|-----|----|----------------|---------|-----|-----|-----|-----|----------------|------------|
|              | N  = 7460 | N  = 1904 | N  = 496 | N  = 2506 | N  = 436 | N  = 1743 | N  = 2367 | N  = 815 | N  = 307 | N  = 2333 |
| Parous       | EHR [95% CI] | EHR [95% CI] | EHR [95% CI] | EHR [95% CI] | EHR [95% CI] | EHR [95% CI] | EHR [95% CI] | EHR [95% CI] | EHR [95% CI] | EHR [95% CI] |
| Nulliparous  | 1.06 [0.82, 1.39] | 0.88 [0.51, 1.51] | 1.77 [0.47, 6.69] | 0.98 [0.61, 1.57] | 1.46 [0.79, 2.71] | 1.88 [0.82, 4.35] | 0.83 [0.62, 1.10] | 1.16 [0.65, 2.05] | 1.87 [0.79, 4.42] | 2.55 [0.84, 7.77] |
| Parous*      | p = 0.6431 | p = 0.6431 | p = 0.3987 | p = 0.9336 | p = 0.2319 | p = 0.1382 | p = 0.1848 | p = 0.6182 | p = 0.1549 | p = 0.0991 |
| Parity       | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] |
|              | 2     | 0.91 [0.80, 1.05] | 0.87 [0.57, 1.34] | 1.76 [0.83, 3.74] | 0.82 [0.69, 0.97] | 1.22 [0.83, 1.77] | 1.07 [0.75, 1.54] | 0.92 [0.78, 1.08] | 0.93 [0.63, 1.39] | 0.86 [0.48, 1.54] |
|              | 3+    | 0.96 [0.82, 1.12] | 0.71 [0.42, 1.20] | 2.08 [0.90, 4.81] | 0.96 [0.79, 1.16] | 1.27 [0.81, 1.97] | 1.34 [0.89, 2.02] | 0.82 [0.68, 0.98] | 1.48 [0.94, 2.34] | 1.00 [0.54, 1.86] |
|              | p = 0.3771 | p = 0.4384 | p = 0.2309 | p = 0.0186 | p = 0.5143 | p = 0.2617 | p = 0.0861 | p = 0.0461 | p = 0.7777 | p = 0.0453 |
| Age at first birth | 13–19 | 1.03 [0.90, 1.18] | 1.75 [1.14, 2.69] | 1.05 [0.58, 1.88] | 1.10 [0.94, 1.29] | 0.78 [0.49, 1.24] | 1.30 [0.94, 1.80] | 1.07 [0.91, 1.27] | 0.81 [0.54, 1.21] | 1.30 [0.76, 2.22] |
|              | 20–24 | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] |
|              | 25–29 | 0.98 [0.86, 1.11] | 0.89 [0.56, 1.41] | 0.91 [0.54, 1.55] | 0.98 [0.85, 1.14] | 1.09 [0.74, 1.60] | 1.15 [0.83, 1.60] | 0.94 [0.80, 1.10] | 1.04 [0.72, 1.52] | 1.22 [0.75, 2.01] |
|              | 30–34 | 1.00 [0.82, 1.22] | 0.91 [0.47, 1.79] | 0.98 [0.44, 2.22] | 0.87 [0.68, 1.11] | 1.37 [0.78, 2.43] | 1.08 [0.60, 1.93] | 0.87 [0.69, 1.10] | 0.78 [0.37, 1.68] | 0.88 [0.32, 2.43] |
|              | 35–49 | 0.73 [0.50, 1.07] | 1.06 [0.31, 3.62] | 0.00 [0.00, 1] | 1.03 [0.68, 1.57] | 0.92 [0.41, 2.09] | 1.12 [0.47, 2.68] | 0.79 [0.53, 1.15] | 0.39 [0.08, 1.93] | 1.72 [0.54, 5.50] |
|              | p = 0.5475 | p = 0.0704 | p = 0.9677 | p = 0.4932 | p = 0.5603 | p = 0.5986 | p = 0.4292 | p = 0.5423 | p = 0.7181 | p = 0.6416 |
| Time-since-latest-birth, years | 0–9 | 1.22 [0.99, 1.51] | 1.63 [0.95, 2.79] | 0.82 [0.33, 2.05] | 1.14 [0.77, 1.67] | 0.94 [0.57, 1.54] | 1.06 [0.53, 2.13] | 1.02 [0.81, 1.27] | 1.14 [0.73, 1.78] | 0.90 [0.45, 1.83] |
|              | 10–19 | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] | 1.00 [ref] |
|              | 20–29 | 1.09 [0.93, 1.29] | 1.44 [0.78, 2.69] | 0.76 [0.34, 1.73] | 1.11 [0.89, 1.39] | 1.14 [0.69, 1.87] | 1.27 [0.79, 2.04] | 0.84 [0.68, 1.03] | 1.13 [0.69, 1.85] | 0.63 [0.30, 1.33] |
|              | 30+   | 1.34 [1.10, 1.64] | 1.00 [0.44, 2.25] | 0.91 [0.35, 2.36] | 1.17 [0.90, 1.51] | 1.23 [0.64, 2.36] | 1.88 [1.10, 3.20] | 0.84 [0.65, 1.08] | 0.98 [0.48, 2.00] | 1.14 [0.48, 2.70] |
|              | p = 0.0072 | p = 0.2353 | p = 0.8855 | p = 0.6535 | p = 0.8968 | p = 0.0694 | p = 0.3400 | p = 0.8876 | p = 0.3511 | p = 0.1368 |

EHR: excess hazard ratio.  
*p-values from Wald tests.  
*Adjusted for age and year (interaction), education, haematological subtype (stratified with separate baselines) and all reproductive variables in the table; except for CML and ET/PV/MF where model is adjusted for age and year without interaction due to power. Effect of nulliparous group estimated separately to avoid collinearity between reproductive variables.  
*The reference group 'parous' corresponds to women with one child (parity = 1), age at first birth 20–24 years and 10–19 years since latest birth. Effect of nulliparous group estimated separately to avoid collinearity between reproductive variables.
with increased excess mortality among lymphoid malignancies only.

When subdividing subtypes further, the associations were attenuated and non-significant with the following exceptions: high parity was associated with lower excess mortality for MM, CML, and the combined group ET, PV, and MF, and time-since-latest birth was associated with excess mortality for BCL without a clear dose-response effect (Table 3). Low age at first birth was associated with increased excess mortality in HL (EHR = 1.75, 1.14–2.69).

Discussion
In this large nationwide cohort study, we found that parity and high age at first birth were to some extent associated with survival after a haematological malignancy. This suggests that childbearing could, in part, contribute to superior survival among women compared to men. The associations were attenuated after adjustments for confounders, and there was no clear dose-response pattern for parity, where women with two children had the best survival. The association with parity was mainly observed among women above 40 years at diagnosis, which indicates that the underlying mechanisms may vary for pre- and post-menopausal women. The findings were not driven by a specific subtype of haematological malignancy, and subtypes with a large female survival advantage did not show a larger protective effect of reproductive factors. There was a tendency towards increased mortality in women with boy offspring, although the patterns of association were inconsistent.

Reproductive factors are proxies for hormonal exposure levels during a woman’s life and are known to affect the female physiology and disease risk both during pregnancy and throughout life [30–32]. Except for one earlier study on HL [11], this is the first comprehensive overview of the effects of reproductive factors on prognosis following a haematological malignancy.

We conclude that reproductive factors could only partly explain the better survival among women with haematological malignancies, as no strong associations were observed. Assuming that nulliparous women would have a prognosis similar to men, or at least in-between men and parous women, we would expect that high parity and young age at first birth among parous women to be protective for cancer death [33]. We found that parous women had some protection from an increasing number of children, while, in contrast, low age at first birth was associated with lower survival. This indicates that the underlying mechanisms may vary with age, and indeed, the association with high parity was observed only in women above 40 years at diagnosis. The significant findings among women above 40 years at diagnosis are interesting, and could in theory be due to long-term and permanent changes in the haematopoietic immunological systems after childbirth [34,35]. Interestingly, the poorer prognosis in women with low age at first birth occurred at 5 and 10 years after diagnosis, while the protective effect of high age at first birth was restricted to the first year after diagnosis. The majority of women in this study had finished childbearing at diagnosis of haematological malignancy. Among pre-menopausal women, we only counted childbirths before cancer, however, findings are unlikely to be confounded by pregnancy events after cancer diagnosis [14]. Mortality was higher for women diagnosed within 10 years of delivery or more than 30 years after the latest childbirth, of which both findings could reflect age effects rather than direct effects of childbearing. In a previous large study, no increased mortality in HL patients diagnosed closed to pregnancy was observed [12].

When subdividing malignancies into lymphoid and myeloid subtypes, we found somewhat diverging results for parity and time-since-latest-birth, but a similar protective effect of high age at first birth. If reproductive factors had a major impact on haematological cancer survival, we would expect a larger protective effect in subtypes where the male-to-female survival difference is the greatest. However, we found no specific subtype driving the associations, and among the subtypes with the largest male-to-female survival differences (e.g., ALL, CLL, and HL), reproductive factors did not confer a better survival for women. The lack of association for a specific subtype could also be an issue of power and a few exposed events. Reproductive events may also be proxies for other underlying factors, such as comorbidity or socioeconomic status. Studies have shown that women with haematological malignancies have less comorbidity than men, which in turn could influence the cancer-specific survival advantage [9]. Low socioeconomic status has been associated with lower survival for several haematological malignancies, in particular non-Hodgkin lymphoma (NHL), HL, MM, and AML [36–38]. In a large study from England, the authors found a significant survival difference between the most deprived compared to most affluent women with NHL, although less so for HL and leukaemia after the implementations of national cancer plans [38]. However, among men, the survival disadvantage was even larger and more persistent over time for NHL, MM, and leukaemia. Adjustment for education attenuated the findings in our study, which suggests that underlying factors may play a role. Another explanation would be if childbearing influences the risk of haematological malignancy, and that malignancies in parous women represent a subgroup of malignancies that are different from non-parous women with respect to biology and prognosis (e.g., ‘healthy mother effect’). However, no association has been found between parity and the risk for NHL or leukaemia [39,40].

Treatment decisions for haematological malignancies in Sweden follow national guidelines, where the sex of the patient is taken into account in HL but no other subtypes [41]. Studies have indicated slower elimination of chemotherapeutic agents leading to more haematotoxicity and thus a greater efficacy of chemotherapy in women with lymphoma [9,10,42,43]. Long-term sex differences in treatment response could indicate a long-lasting effect of reproductive factors, such as accumulating effects of repeated pregnancies on lifelong epi-genetic changes [35].

We found no strong associations between having boy offspring, and if anything results indicated that boy pregnancies
may be associated with a poorer prognosis. This is in contrast to the hypothesis of a protective effect of male microchimerism in mothers with haematological malignancies [21–23]. The number of boy pregnancies is not an ideal proxy for male microchimerism, as it may be mixed with the overall effect of parity. We tried to circumvent this issue by comparing women of the same parity, and still found no effect. However, women with boy pregnancies are also a mixture of women with and without male microchimerism/allogeneic foetal cells, which may have diluted the effect. Male microchimerism has in one small, yet important, Danish study been associated with reduced cancer mortality in women [23]. The authors speculate that microchimerism is beneficial for cancer prognosis either via increased immune surveillance or a general enhancement in tissue repair. Such an effect would in theory be most prominent in patients with CML, where the graft vs. leukaemia effect after allogeneic stem cell transplantation is most pronounced [44]. However, no such effect was observed in our analyses, neither when assessing lymphoid vs. myeloid subtypes separately, nor for CML alone.

The recently discovered molecular differences in tumorigenesis in women and men indicate that hormonal activity and reproductive factors could interact with both the onset and progression of malignant disease [7]. This study reported a potential sex bias in genome instability for B-cell NHL and CLL, but not for myeloid subtypes. However, there is also evidence that girls with childhood ALL may have better survival than boys, indicating that effects of sex could also be present in the period before puberty [5].

The strengths of our study include the population-based setting with nearly complete information on cancer and childbearing for nearly 50 years. The Swedish Cancer Registry has routine follow-up and has been validated to be highly complete for haematological malignancies [24,25]. Childbearing information from Statistics Sweden was obtained from the Multigeneration Register with linkages via the personal identification number that enabled longitudinal follow-up. We were thus able to also include children born outside Sweden and who immigrated together with their mothers to Sweden, which is more complete than the Medical Birth Register that only covers children born in Sweden. We applied relative survival methods that also take deaths due to other causes into account and therefore accommodate treatment-related deaths.

A limitation of the study was the lack of information on treatments for haematological malignancies. However, national treatment guidelines were introduced in the late 1970s in Sweden. We had no detailed clinical information about the patient or the malignancy. For lymphoid malignancies, the lack of detailed histopathological codes in the Swedish cancer register prevented us from separating low and high-grade lymphomas, and from investigating more specific NHL subtypes. The MGR only includes liveborn children, and we were thus unable to include spontaneous or elective abortions and stillbirths in the reproductive history. The subtype-specific analyses were hampered by low power, where several of the findings in the all-malignancies combined analysis did not remain when stratified by haematological subtype. Although some raised point estimates for specific subtypes were interesting, it is important not to over-interpret non-significant findings.

In conclusion, reproductive factors are modestly associated with prognosis after a haematological malignancy in women, but they are unlikely to explain why women have better survival than men. The explanation is likely multifactorial, where reproductive history may partly contribute. This is the first large-scale study evaluating, in a comprehensive way, the role of reproductive factors in the female survival advantage after haematological malignancies.

Ethical approval

The study was approved by the Ethical Review Authority in Stockholm (2010-1950-31/4, amendment 2018-1293-32). The data were obtained without informed consent. Registration in the national health and population registers is mandatory by law without consent. The use of the data for research purposes is governed by the General Data Protection Regulation (GDPR) of the European Union and the Swedish Ethics Review Act (2003:460). All analyses were performed on pseudonymized data with a study-specific random patient id number and without directly identifiable information on patients or children available to the authors.

Disclosure statement

ALJV, PWD, and MB declare no conflicts of interest. SE is part of an industry-academia partnership between Karolinska Institutet and Janssen Pharmaceutica NV for which Karolinska Institutet receives grant support.

Funding

This work was supported by the Swedish Research Council under Grant 2019-00227, the Swedish Cancer Society under Grant 19-0325 Pj01H, and Karolinska Institutet Foundations and Funds under Grant 2020-01405.

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Data availability statement

The data underlying this study are available at the National Board of Health and Welfare, Sweden, and Statistics Sweden for investigators with the appropriate approvals, but restrictions apply. However, data can be made available from the authors upon reasonable request for meta-analyses, and with the appropriate approvals of the Swedish Ethical Review Authority (https://etikprovningsmyndigheten.se).

References

[1] Cook MB, McGlynn KA, Devesa SS, et al. Sex disparities in cancer mortality and survival. Cancer Epidemiol Biomarkers Prev. 2011; 20(8):1629–1637.
[2] Micheli A, Ciampichini R, Obenraigner W, et al. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. Eur J Cancer. 2009;45(6):1017–1027.
[3] Radkiewicz C, Johansson ALV, Dickman PW, et al. Sex differences in cancer risk and survival: a Swedish cohort study. Eur J Cancer. 2017;84:130–140.

[4] Hedstrom G, Peterson S, Berglund M, et al. Male gender is an adverse risk factor only in young patients with diffuse large B-cell lymphoma – a Swedish population-based study. Acta Oncol. 2015;54(6):924–932.

[5] Holmes L Jr, Hossain J, Desvignes-Kendrick M, et al. Sex variability in pediatric leukemia survival: large cohort evidence. ISRN Oncol. 2012;2012:1–9.

[6] Dunford A, Weinstock DM, Savova V, et al. Tumor-suppressor genes that escape from X-inactivation contribute to cancer sex bias. Nat Genet. 2017;49(1):10–16.

[7] Li CH, Prokopek SD, Sun RX, et al. Sex differences in oncogenic mutational processes. Nat Commun. 2020;11(1):4330.

[8] Yuan Y, Liu L, Chen H, et al. Comprehensive characterization of molecular differences in cancer between male and female patients. Cancer Cell. 2016;29(5):711–722.

[9] Klimm B, Engert A. Differences in hematotoxicity between male and female patients with Hodgkin lymphoma and other malignancies. Nat Clin Pract Oncol. 2008;5(6):316–323.

[10] Klimm B, Reineke T, Havenerkamp H, et al. Role of hematotoxicity and sex in patients with Hodgkin’s lymphoma: an analysis from the German Hodgkin study group. J Clin Oncol. 2005;23(31):8003–8011.

[11] Kravdal O, Hansen S. The importance of childbearing for Hodgkin’s disease: new evidence from incidence and mortality models. Int J Epidemiol. 1996;25(4):737–743.

[12] Møller H, Purushotham A, Linklater KM, et al. Recent childbirth is an adverse prognostic factor in breast cancer and melanoma, but not in Hodgkin lymphoma [research support, Non-U]. Eur J Cancer. 2008;44(14):2058–2073.

[13] Johansson ALV, Fredriksson I, Mellemkjaer L, et al. Cancer survival and female patients with hodgkin lymphoma and other malignancies. Nat Clin Pract Oncol. 2008;5(6):316–323.

[14] Ellingjord-Dale M, Vos L, Tretli S, et al. Parity, hormones and breast cancer subtypes – results from a large nested case-control study in a national screening program. Breast Cancer Res. 2017;19(1):10.

[15] Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48(1):27–33.

[16] Muir C, Murawski N, Wiesen MH, et al. The role of sex and hormone status: a meta-analysis of epidemiological studies. Breast Cancer Res. 2006;8(4):R43.

[17] Biasoli I, Castro N, Delamain M, et al. Lower socioeconomic status is independently associated with shorter survival in Hodgkin lymphoma patients – an analysis from the Brazilian Hodgkin lymphoma registry. Int J Cancer. 2018;142(5):883–890.

[18] Roos-Hesselink JW. Pregnancy and hematopoietic stem-cell self-renewal in females and during pregnancy. Blood. 2009;113(16):3666–3672.

[19] Jorgensen N, Persson G, Hvid TFV. The tolerogenic function of regulatory T cells in pregnancy and cancer. Front Immunol. 2019;10:911.

[20] Nakada D, Oguro H, Levi BP, et al. Oestrogen increases haematopoietic stem-cell self-renewal in females and during pregnancy. Nature. 2014;505(7484):555–558.

[21] Sridama V, Pacini F, Yang SL, et al. Decreased levels of helper T cells: a possible cause of immunodeficiency in pregnancy. N Engl J Med. 1982;307(6):352–356.

[22] Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol. 2010;63(6):425–433.

[23] Bryan JN. Fetal microchimerism in cancer protection and promotion: current understanding in dogs and the implications for human health. Aaps J. 2015;17(3):506–512.

[24] Gilmore GL, Haq B, Shadduck RK, et al. Fetal-maternal microchimerism in normal parous females and parous female cancer patients. Exp Hematol. 2008;36(9):1073–1077.

[25] Kamper-Jorgensen M, Hjalgrim H, Andersen AM, et al. Male microchimerism and survival among women. Int J Epidemiol. 2014;43(1):168–173.

[26] Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48(1):27–33.

[27] Roos-Hesselink JW. Pregnancy and hematopoietic stem-cell self-renewal in females and during pregnancy. Blood. 2009;113(16):3666–3672.

[28] Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol. 2010;63(6):425–433.

[29] Bryan JN. Fetal microchimerism in cancer protection and promotion: current understanding in dogs and the implications for human health. Aaps J. 2015;17(3):506–512.

[30] Gilmore GL, Haq B, Shadduck RK, et al. Fetal-maternal microchimerism in normal parous females and parous female cancer patients. Exp Hematol. 2008;36(9):1073–1077.

[31] Kamper-Jorgensen M, Hjalgrim H, Andersen AM, et al. Male microchimerism and survival among women. Int J Epidemiol. 2014;43(1):168–173.

[32] Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48(1):27–33.

[33] Roos-Hesselink JW. Pregnancy and hematopoietic stem-cell self-renewal in females and during pregnancy. Blood. 2009;113(16):3666–3672.

[34] Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol. 2010;63(6):425–433.

[35] Bryan JN. Fetal microchimerism in cancer protection and promotion: current understanding in dogs and the implications for human health. Aaps J. 2015;17(3):506–512.