Gestational age and cancer risk up to young adulthood in Swedish population born 1974 to 2013: A population-based cohort study

Monica S. M. Persson1,2 | Weiyao Yin1,2,3,4 | Nora Döring1 | Kari Risnes3 | Elisabete Weiderpass4,5,6 | Eva Steliarova-Foucher4 | Sven Sandin1,5,6

1Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
2Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, China
3NTNU, Trondheim, Norway
4International Agency for Research on Cancer, Lyon, France
5Department of Psychiatry, Ichan School of Medicine at Mount Sinai, New York, USA
6Seaver Autism Center for Research and Treatment at Mount Sinai, New York, USA

Correspondence
Weiyao Yin, Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels väg 12A, SE-171 77 Stockholm, Sweden. Email: weiyao.yin.2@ki.se

Abstract
We examined the association between gestational age and risk of any primary cancer and observed whether the risk patterns differed by sex, birth weight for gestational age categories, cancer site and age of onset. All people live-born in Sweden 1974 to 2013 were prospectively followed up from birth until 2016 using national registers. Gestational age was extracted from the Medical Birth Register and primary malignant cancer diagnoses were from the Swedish cancer register. The adjusted hazard ratios (aHR) for any primary cancer according to weekly gestational age and gestational age categories were determined using cox proportional hazards models adjusted for birth year and parental age. The study included 3,137,691 people; 180,363 (5.8%) born preterm and 254,790 (8.1%) born postterm. They were followed up for 71,691,112 person-years, to a maximum of 43 years and recorded 22,604 new cancers. Although aHRs for the predefined GA categories were only increased for moderate to late preterm delivery (aHR 1.07, 95% CI 1.01-1.14), gestational week-specific aHRs were increased for gestational weeks 30 to 35, with greatest aHR observed for 31 weeks (aHR 1.18, 95% CI 1.05-1.32). Increased cancer risk related to shorter gestational ages were observed particularly for women, those born small for gestational age, childhood cancers and for cancers originating at certain sites (e.g., testicular and liver cancer). We provide the first evidence that those born between 30 and 35 weeks gestation may have increased risk of any primary malignant cancer up to young adulthood. Additionally, increasing gestational ages may reduce the risk of testicular and liver cancer.

Keywords
Cancer, epidemiology, gestational age, population-based, preterm birth

Abbreviations: aHR, adjusted HR; AYA, adolescent and young adult; GA, gestational age; HR, hazard ratios; ICD, International Classification of Diseases; LISA, Longitudinal Integrated Database for Health Insurance; MBR, Medical Birth Register; OR, odds ratio; RECAP, Research on Children and Adults Born Preterm.
What's new?
Possible links between gestational age and risk of cancer in both childhood and adulthood need to be clarified. This study of more than 3 million people up to young adulthood found that individuals born between 30 and 35 weeks of gestation may have an increased risk of developing any primary malignant cancer compared to individuals born at term. The risk was highest in females and in people born small for their gestational age. Furthermore, the risk was highest for cancers presenting in childhood or affecting certain organs like the testes and the liver.

1 | INTRODUCTION

Preterm births account for approximately 11% of all births globally, and are considered the leading cause of childhood deaths.1 Previous work has indicated that preterm births may be associated with an increased risk of certain childhood cancers, such as hepatoblastomas, compared to being born at term.2 Preterm births may also influence cancer risk beyond childhood. There is conflicting evidence regarding whether those born preterm have increased risks of breast and testicular cancer.3-5 Increased risks of testicular cancer could be driven by altered sex hormone levels in the pre- and postnatal periods of individuals that are born prematurely.5 Exposure to oxidative stress due to immature antioxidant defense systems may also play a role.2 It may also be that preterm birth and cancer share genetic risk factors.

Cancer accounts for approximately 15% of deaths globally,6 and is a major cause of death in childhood.7 It is now also the leading cause of death for middle-aged adults in high-income countries.8 Although many etiologic factors for cancer are well recognized, the contribution of preterm birth to cancer risk is uncertain. Previous work has shown that gestational age at birth is inversely correlated with cancer-related mortality earlier in life (<30 years).9 A modest (albeit nonsignificant) increase in cancer mortality was observed for shorter gestational age categories up to the age of 50.10 Further work is required to expand upon these findings. Earlier studies of cancer risks have been hampered by small sample sizes, the categorization of gestational ages, lack of adjustment for potential confounding (including unmeasured familial confounding) and, importantly, have not considered the risk across the full range of gestational ages (including postterm births).

Our study aimed to examine the association between gestational age and risk of any primary cancer and to determine whether the risk patterns differed by sex, birth weight for gestational age, family history of cancer, age of onset, cancer site and accounting for unmeasured familial confounding.

2 | METHODS

2.1 | Study design

The association between gestational age and cancer risk was determined using a population-based cohort. The work is descriptive in nature and reported using the RECORD guidelines for the reporting of studies conducted using observational routinely collected health data.11

2.2 | Study population

The population consisted of individuals live-born in Sweden between January 1, 1974 and December 31, 2013. To ensure greater coverage of confounding factors and to reduce the potential effects of changing immigration patterns throughout the observation period, only people with Swedish-born parents (mother and father) were included. People with missing information on gestational age, sex or with implausible death/emigration dates were excluded.

2.3 | Exposure

Gestational age in weeks was extracted from the Medical Birth Register12 (MBR) where it is determined from routine ultrasound examinations (routine practice since the mid-1990s) or the date of the last menstrual period. Gestational age was primarily analyzed as weeks. In addition, it was categorized as extremely preterm (<27 6/7 weeks gestation), very preterm (28 0/7-31 6/7 weeks gestation), moderate to late preterm (32 0/7-36 6/7 weeks gestation), term (37 0/7-41 6/7 weeks gestation) and postterm (≥42 0/7 weeks gestation).13,14

2.4 | Outcome

The primary outcome was any primary cancer reported to the Swedish Cancer Register.15 Over 96% of newly detected cancer cases in Sweden are captured within the Cancer Register and the reporting has been mandatory since 1958.16 Cancers at any site were considered and identified using ICD-7 codes17 140-209, except 156, 163 and 199, as these indicate possible secondary malignancies. Only cancers with malignant behavior were included. We also performed analysis by cancer sites classified according to ICD-7 codes (Table S1).

2.5 | Covariates

Covariates potentially informative for confounding or risk modification were extracted from the MBR,12 including sex, birth weight and birth year. The MBR contains data on all births in Sweden since 1973. Birth weight for gestational age categories were calculated according to sex-specific birth weight distributions per 5-year birth brackets and categorized as small for gestational age (≤10th percentile of
population), appropriate for gestational age (11-89th percentile population) and large for gestational age (≥90th percentile of population). Maternal smoking during pregnancy, which has been recorded since 1983 and is available for almost all births from 1990 onwards, was classified as smoker or nonsmoker.

The Multi-Generation Register was used to obtain information about the fathers of the study population. Through linkage using patient identification numbers, data on the parents’ cancer history and highest level of education at the date of delivery were extracted. Family history of any primary, malignant cancer in either parent, occurring before or on the date of birth of the index child, was determined and classified as present or absent. Educational level was determined from the Longitudinal Integrated Database for Health Insurance (LISA), which contains data on the educational level of all individuals aged ≥16 years from 1990 onwards and aged ≥15 years from 2010 onwards. Highest parental education measured as years of formal education, available only for the study population born 1990 or later, was categorized as low (≤9 years), medium (10-14 years) and high (≥15 years).

2.6 | Observation period

The population was followed from date of birth to the earliest occurrence of one of the following events: (a) first cancer, (b) death, (c) emigration or (d) December 31, 2016. Dates of death and emigration were gathered from the Total Population Register. Because the main outcome considered was any cancer, including those developing in utero and presenting at birth, cancers recorded as early as day 0 (ie, date of birth) were included. For individuals with cancer at birth to be included in the analyses, 1 day was added to the event date. Similarly, where death or emigration occurred on the date of birth, it was assumed that the neonates were alive at birth (hence registered as live-born), and 1 day was added to the censoring date.

2.7 | Statistical analysis

We first calculated crude cancer rates per 100 000 person-years for any primary malignant cancer. Follow-up was calculated from birth to censoring date. Next, we examined the association between gestational age and any primary malignant cancer. Using Cox proportional hazards models with attained age as the underlying time scale, we calculated hazard ratios (HRs) and 95% Wald type confidence intervals (CIs) for the cancer outcome. Gestational age was analyzed as gestational age in weeks (continuous) and by categories. In addition, we determined the change in risk (slope) within each gestational age category. To avoid making any assumptions about the form of the association, natural cubic splines with four equally placed knots were applied for gestational age in weeks and continuous covariates. In a first “crude” model, we adjusted only for birth year using splines. In the second model, considered the adjusted HR (aHR), we additionally adjusted for potential confounding by maternal and paternal age at birth using splines. Unless otherwise specified, all data presented are aHR.

To better understand the relationship between cancer and gestational age, we examined the risk separately for males and females, by birth weight for gestational age category, by family history of cancer, by childhood or adolescent and young adult (AYA) cancers and by cancer site. In addition, we analyzed for a potential interaction between sex and gestational age through the inclusion of a sex-by-gestational age interaction term to the model.

When examining childhood cancers, patients were followed up from birth through 14 years of age or censoring. For AYA cancers, the observation period commenced on the 15th birthday. On examination of individual cancer sites, a person was not considered censored by the occurrence of a cancer at a different site, and each person could therefore contribute a cancer event across multiple cancer sites. The study population was restricted only to females for the examination of breast, cervical, uterine and ovarian cancer. Conversely, only males formed the population for the examination of testicular cancer.

Sensitivity analyses were conducted to examine potential confounding. For this purpose, gestational age was analyzed as categories. The population was restricted to full siblings discordant for gestational age category and familial confounding was examined by stratifying analyses by siblings. This approach allows unmeasured confounders shared by full siblings, such as childhood environmental exposures, pregnancy-related factors and lifestyle factors, to be accounted for. Further sensitivity analyses were conducted to determine the potential confounding effect of smoking and parental education using change-in-estimate methods for live births from 1990 onwards.

Additional sensitivity analyses were conducted by excluding cancers reported in the first 28 days or 6 months after birth. For these analyses, the observation time was started at 28 days or 6 months. Finally, the impact of congenital malformations was examined through sensitivity analyses (a) restricted to people with a congenital malformation, (b) restricted to people without a congenital malformation and (c) adjusting for the presence of congenital malformations in the full population.

All tests of statistical hypotheses were performed on the two-sided 5% level of confidence corresponding to two-sided 95% CIs for the HR not overlapping unity. No adjustment for multiplicity of statistical tests was performed. The proportional hazards assumption was examined using Schoenfeld residuals. The SAS software 9.4 (proc phreg) was used for all analyses.

3 | RESULTS

3.1 | Study population

Exactly, 4 063 803 individuals were live-born in Sweden between January 1, 1974 and December 31, 2013 (Figure S1). Of these, 3 144 742 were born to Swedish-born parents. Following the exclusion of 7051 people with missing gestational age or sex, or with implausible death/emigration dates (eg, death prior to birth date), the final cohort consisted of 3 137 691 live births.
| Characteristic                       | Extremely preterm (<28 weeks) | Very preterm (28-31 weeks) | Moderate to late preterm (32–36 weeks) | All preterm (<37 weeks) | Term (37-41 weeks) | Postterm (42-45 weeks) | All N (%) |
|-------------------------------------|-------------------------------|-----------------------------|----------------------------------------|-------------------------|--------------------|-----------------------|-----------|
| No. individuals (% of total)        | 5846 (0.2)                   | 17 014 (0.5)                | 157 503 (5.0)                          | 180 363 (5.8)           | 2 702 538 (86.1)   | 254 790 (8.1)         | 3 137 691 |
| No. males                           | 3133 (53.6)                  | 9253 (54.4)                 | 85 227 (54.1)                          | 97 613 (54.1)           | 1 377 161 (51.0)   | 138 616 (54.4)        | 1 613 390 |
| Birth year                          |                               |                             |                                        |                         |                    |                       |           |
| 1974-1979                           | 423 (7.2)                    | 1979 (11.6)                 | 20 734 (13.2)                          | 23 136 (12.8)           | 404 676 (15.0)     | 62 278 (24.4)         | 490 090 |
| 1980-1984                           | 476 (8.1)                    | 1760 (10.3)                 | 19 222 (12.2)                          | 21 458 (11.9)           | 323 127 (12.0)     | 33 351 (13.1)         | 377 936 |
| 1985-1989                           | 637 (10.9)                   | 2276 (13.4)                 | 23 039 (14.6)                          | 25 952 (14.4)           | 374 526 (13.9)     | 29 529 (11.6)         | 430 007 |
| 1990-1994                           | 915 (15.7)                   | 2779 (16.3)                 | 23 743 (15.1)                          | 27 437 (15.2)           | 406 439 (15.0)     | 32 781 (12.9)         | 466 657 |
| 1995-1999                           | 770 (13.2)                   | 2081 (12.2)                 | 18 099 (11.5)                          | 20 950 (11.6)           | 299 853 (11.1)     | 24 747 (9.7)          | 345 550 |
| 2000-2004                           | 874 (15.0)                   | 2194 (12.9)                 | 18 790 (11.9)                          | 21 858 (12.1)           | 303 746 (11.2)     | 26 811 (10.5)         | 352 415 |
| 2005-2009                           | 972 (16.6)                   | 2232 (13.1)                 | 19 004 (12.1)                          | 22 208 (12.3)           | 326 337 (12.1)     | 25 559 (10.0)         | 374 104 |
| 2010-2013                           | 779 (13.3)                   | 1713 (10.1)                 | 14 872 (9.4)                           | 17 364 (9.6)            | 263 834 (9.8)      | 19 734 (7.8)          | 300 932 |
| Birth weight for gestational age    |                               |                             |                                        |                         |                    |                       |           |
| Small                               | 617 (10.6)                   | 1719 (10.1)                 | 15 788 (10.0)                          | 18 124 (10.1)           | 273 401 (10.1)     | 25 766 (10.1)         | 317 291 |
| Appropriate                         | 4420 (75.6)                  | 13 239 (77.8)               | 124 837 (79.3)                         | 142 496 (79.0)          | 2 150 524 (79.6)   | 202 661 (79.5)        | 2 495 681|
| Large                               | 619 (10.6)                   | 1719 (10.1)                 | 15 834 (10.1)                          | 18 172 (12.1)           | 272 839 (10.1)     | 25 805 (10.1)         | 316 816 |
| Missing                             | 190 (3.3)                    | 337 (2.0)                   | 1044 (0.7)                             | 1571 (0.9)              | 5774 (0.2)         | 558 (0.2)             | 7903 (0.3)|
| Maternal age                        |                               |                             |                                        |                         |                    |                       |           |
| <20 years                           | 150 (2.6)                    | 434 (2.6)                   | 3773 (2.4)                             | 4357 (2.4)              | 46 961 (1.7)       | 5966 (2.4)            | 57 314 |
| 20-24 years                         | 865 (14.8)                   | 2795 (16.4)                 | 27 414 (17.4)                          | 31 074 (17.2)           | 448 735 (16.6)     | 48 234 (18.9)         | 528 043 |
| 25-29 years                         | 1719 (29.4)                  | 5126 (30.1)                 | 51 160 (32.5)                          | 58 005 (32.2)           | 929 382 (34.4)     | 88 994 (34.9)         | 1 076 381|
| 30-34 years                         | 1829 (31.3)                  | 5219 (30.7)                 | 46 381 (29.5)                          | 53 429 (29.6)           | 840 326 (31.1)     | 75 181 (29.5)         | 968 936 |
| 35-39 years                         | 1005 (17.2)                  | 2785 (16.4)                 | 23 326 (14.8)                          | 27 116 (15.0)           | 362 985 (13.4)     | 30 892 (12.1)         | 420 993 |
| ≥40 years                           | 278 (4.8)                    | 655 (3.9)                   | 5449 (3.5)                             | 6382 (3.5)              | 74 149 (2.7)       | 5493 (2.2)            | 86 024 |
| Paternal age                        |                               |                             |                                        |                         |                    |                       |           |
| <20 years                           | 44 (0.8)                     | 130 (0.8)                   | 948 (0.6)                              | 1122 (0.6)              | 10 703 (0.4)       | 1257 (0.5)            | 13 082 |
| 20-24 years                         | 485 (8.3)                    | 1556 (9.2)                  | 14 747 (9.4)                           | 16 788 (9.3)            | 221 316 (8.2)      | 24 338 (9.6)          | 262 442 |
| 25-29 years                         | 1473 (25.2)                  | 4424 (26.0)                 | 43 336 (27.5)                          | 49 233 (27.3)           | 754 083 (27.9)     | 76 046 (29.9)         | 879 362 |
| 30-34 years                         | 1854 (31.7)                  | 5419 (31.9)                 | 50 793 (32.3)                          | 58 066 (32.2)           | 925 773 (34.3)     | 85 058 (33.4)         | 1 068 897|
| 35-39 years                         | 1230 (21.0)                  | 3486 (20.5)                 | 30 743 (19.5)                          | 35 459 (19.7)           | 534 228 (19.8)     | 45 966 (18.0)         | 615 653 |
| ≥40 years                           | 760 (13.0)                   | 1999 (11.8)                 | 16 936 (10.8)                          | 19 695 (10.9)           | 256 435 (9.5)      | 22 125 (8.7)          | 298 255 |
3.2 | Population characteristics

The characteristics of the 3 137 691 males and females live-born between 1974 and 2013 are outlined in Table 1. They were followed up to a median attained age of 23 years, reached a maximum attained age of 43 years and totaled 71 691 112 person-years of follow-up. Of the births, 2 702 538 (86.1%) occurred at term, 180 363 (5.8%) were born preterm and 254 790 (8.1%) were born postterm. Overall, 1 613 390 (51.4%) of the population were male and 1 524 301 (48.6%) were female.

3.3 | Any primary malignant cancer

A total of 22 604 primary malignant cancers were recorded during the follow-up period, equating to an overall cancer rate of 31.5 (95% CI 31.1-31.9) per 100 000 person-years. Crude rates were highest in the postterm group and lowest in the preterm group (Table 2). After adjusting for birth year, maternal age and paternal age a higher risk of any primary malignant cancer was observed in those born moderate to late preterm (32-36 weeks) compared to those born at term (aHR 1.07, 95% CI 1.01-1.14). Relative to week 40, this increased risk was observed specifically for those born at weeks 30 to 35 (Figure 1). Although not supported by our statistical inference, elevated aHR point estimates, but not lower confidence limits, were also observed for weeks 29 and 36. The risk was highest for births at 31 weeks (aHR 1.18, 95% CI 1.05-1.32) (Figure 2, Table 2). No difference in risk was observed for postterm compared to term births.

3.4 | Subgroup analysis

Shorter gestation was associated with the highest cancer risk in females, those born small for gestational age, and in childhood (Figure 2). For these subgroups, an increased risk of any cancer was observed for those born around weeks 30 to 35 compared to those born at term. A statistically significant interaction was found between sex and gestational age (P = .002). The aHR was highest for females born at 31 weeks gestation (aHR females: 1.31, 95% CI 1.11-1.53; males 1.07, 95% CI 0.90-1.27). At 36 to 39 weeks gestation, males had a higher risk of cancer than females (aHR at week 37 weeks males: 1.04, 95% CI 1.01-1.08; females: 1.00, 95% CI 0.97-1.04), while risks were higher for females again for postterm births (aHR at week 44 females: 1.05, 95% CI 0.99-1.11; males: 0.94, 95% CI 0.88-1.00). Moderate to late preterm was associated with increased risk for childhood (aHR at week 31:1.18, 95% CI 1.05-1.32), but not AYA cancers (aHR at week 31:1.09, 95% CI 0.94-1.26).

The association between gestational age and cancer was examined by cancer site (Figure 3, Tables S2 and S3). Large uncertainty in the estimate at shorter gestation was observed due to the low number of cancer cases in each category, which hampers firm conclusions. Compared to births at 40 weeks, preterm birth conferred an increased risk of acute lymphocytic leukemia and Central nervous system (CNS),
| Gestational age | Week | Cancer events | Person-years | Rate (95% CI) | Model 1 HR (95% CI) | Change in risk per week (95% CI) | Model 2 HR (95% CI) | Change in risk per week (95% CI) |
|----------------|------|---------------|--------------|--------------|---------------------|---------------------------------|---------------------|---------------------------------|
| All births     | 23-45 | 22 604        | 71 691 112   | 31.5 (31.1-31.9) | 1.00 (0.64-1.54) | 0.80 (0.43-1.48) | 0.88 (0.61-1.26) | 1.00 (0.64-1.54) | 0.80 (0.43-1.48) | 0.87 (0.61-1.24) |
| Extremely      | 23   | 20            | 78 292.4     | 25.6 (16.5-39.6) | 0.85 (0.50-1.44) | 0.90 (0.58-1.40) | 0.95 (0.66-1.37) | 1.01 (0.76-1.34) |                     |                     |
| preterm        | 24   |               |              |              |                     | 0.85 (0.50-1.44) | 0.90 (0.58-1.40) | 0.95 (0.66-1.37) | 1.01 (0.76-1.34) |                     |                     |
|                | 25   |               |              |              |                     | 0.85 (0.50-1.44) | 0.90 (0.58-1.40) | 0.95 (0.66-1.37) | 1.01 (0.76-1.34) |                     |                     |
|                | 26   |               |              |              |                     | 0.85 (0.50-1.44) | 0.90 (0.58-1.40) | 0.95 (0.66-1.37) | 1.01 (0.76-1.34) |                     |                     |
|                | 27   |               |              |              |                     | 0.85 (0.50-1.44) | 0.90 (0.58-1.40) | 0.95 (0.66-1.37) | 1.01 (0.76-1.34) |                     |                     |
| Very preterm   | 28   | 105           | 335 483.1    | 31.3 (25.9-37.9) | 1.08 (0.89-1.31) | 1.06 (0.86-1.31) | 1.04 (0.87-1.24) | 1.08 (0.89-1.31) | 1.06 (0.86-1.31) | 1.03 (0.86-1.24) |
|                | 29   |               |              |              |                     | 1.12 (0.95-1.30) | 1.16 (1.02-1.31) | 1.17 (1.05-1.32) |                     |                     |
|                | 30   |               |              |              |                     | 1.12 (0.95-1.30) | 1.16 (1.02-1.31) | 1.17 (1.05-1.32) |                     |                     |
|                | 31   |               |              |              |                     | 1.12 (0.95-1.30) | 1.16 (1.02-1.31) | 1.17 (1.05-1.32) |                     |                     |
| Moderate to     | 32   | 1143          | 3 495 387.8  | 32.7 (30.9-34.7) | 1.17 (1.05-1.30) | 1.14 (1.04-1.25) | 1.11 (1.03-1.18) | 1.17 (1.05-1.30) | 1.14 (1.04-1.25) | 1.10 (1.03-1.18) |
| late           | 33   |               |              |              |                     | 1.17 (1.05-1.30) | 1.14 (1.04-1.25) | 1.11 (1.03-1.18) | 1.17 (1.05-1.30) | 1.14 (1.04-1.25) | 1.10 (1.03-1.18) |
| preterm        | 34   |               |              |              |                     | 1.17 (1.05-1.30) | 1.14 (1.04-1.25) | 1.11 (1.03-1.18) | 1.17 (1.05-1.30) | 1.14 (1.04-1.25) | 1.10 (1.03-1.18) |
|                | 35   |               |              |              |                     | 1.17 (1.05-1.30) | 1.14 (1.04-1.25) | 1.11 (1.03-1.18) | 1.17 (1.05-1.30) | 1.14 (1.04-1.25) | 1.10 (1.03-1.18) |
|                | 36   |               |              |              |                     | 1.17 (1.05-1.30) | 1.14 (1.04-1.25) | 1.11 (1.03-1.18) | 1.17 (1.05-1.30) | 1.14 (1.04-1.25) | 1.10 (1.03-1.18) |
| Term           | 37   | 19 142        | 61 423 085.2 | 31.2 (30.7-31.6) | Ref                 | 1.02 (0.99-1.04) | 1.00 (0.99-1.01) | Ref                 | 1.01 (0.99-1.04) | 1.00 (0.99-1.01) |
|                | 38   |               |              |              |                     | 1.00 (0.99-1.02) | 1.00 (0.99-1.01) |                     | 1.00 (0.99-1.02) | 1.00 (0.99-1.01) |
|                | 39   |               |              |              |                     | 1.00 (0.99-1.02) | 1.00 (0.99-1.01) |                     | 1.00 (0.99-1.02) | 1.00 (0.99-1.01) |
|                | 40   |               |              |              |                     | 1.00 (0.99-1.02) | 1.00 (0.99-1.01) |                     | 1.00 (0.99-1.02) | 1.00 (0.99-1.01) |
|                | 41   |               |              |              |                     | 1.00 (0.99-1.02) | 1.00 (0.99-1.01) |                     | 1.00 (0.99-1.02) | 1.00 (0.99-1.01) |
| Postterm       | 42   | 2194          | 6 358 864.1  | 34.5 (33.1-36.0) | 1.00 (0.96-1.04) | 1.00 (0.98-1.02) | 1.04 (0.95-1.12) | 1.00 (0.96-1.04) | 1.00 (0.98-1.02) | 1.03 (0.95-1.12) |
|                | 43   |               |              |              |                     | 1.00 (0.97-1.03) | 1.00 (0.96-1.05) |                     | 1.00 (0.97-1.04) | 1.00 (0.96-1.05) |
|                | 44   |               |              |              |                     | 1.00 (0.97-1.03) | 1.00 (0.96-1.05) |                     | 1.00 (0.97-1.04) | 1.00 (0.96-1.05) |
|                | 45   |               |              |              |                     | 1.00 (0.97-1.03) | 1.00 (0.96-1.05) |                     | 1.00 (0.97-1.04) | 1.00 (0.96-1.05) |

*a* Model 1 is adjusted for birth year.

*b* Model 2 is adjusted for birth year, maternal age and paternal age.
connective tissue, eye, kidney, testicle, uterus, small intestine and liver cancers. Preterm birth associated with increased risks of cancer of the testes (weeks 35-39 vs 40) and liver (weeks 37-39 vs 40), while post-term birth conferred a statistically significant decreased risk of these cancers. For the other cancer sites, the differences were not suggestive of a dose response as there was no trend in risk by gestational age on visual inspection. Increased risk of cancers at different sites were found for specific gestational ages: small intestine at weeks 32-33 vs 40, uterus at weeks 29-31 vs 40, CNS at weeks 29-31 vs 40 and connective tissue at weeks 28-30 vs 40. The risk was highest for small intestinal cancer at 32 weeks (HR 6.21, 95% CI 1.14-33.84) and uterine cancer at 29 weeks (HR 17.13, 95% CI 1.46-201.44).

3.5 | Sensitivity analysis

The potential impact of familial confounding was examined in a population of 597,387 full siblings with discordant gestational ages (Table S4). On stratifying according to full siblings, the moderate to
FIGURE 3  Adjusted hazard ratio (HR) for individual cancer sites according to gestational age, adjusted for birth year, maternal age and paternal age [Color figure can be viewed at wileyonlinelibrary.com]
late preterm born (32-36 weeks) were more likely to develop cancer than their term-born siblings.

There was no evidence of confounding due to smoking or parental education (indicator of socioeconomic status) in the population of 1 756 124 people born after 1990 with smoking and parental education data (n = 83 534 with missing data excluded), as the aHRs remained unchanged following adjustment for these factors (Table S5).

The association between gestational age and cancer did not substantially change when excluding cancers in the first 28 days (population = 3 131 370) or 6 months (population = 3 126 765) after birth (Table S6).

The association between gestational age and cancer was not substantially altered by adjusting for congenital malformations (Table S7). However, examination of the 84 719 people with congenital malformations found that those born moderate to late preterm had a statistically significantly increased risk of developing cancer (aHR 1.79, 95% CI 1.29-2.49).

Finally, inspection of the Schoenfeld residuals did not suggest any violation of the proportional hazards assumption (Figure S2).
4 | DISCUSSION

4.1 | Main findings

In the largest and most detailed study to date, we provide the first evidence for the association between gestational age and cancer up to young adulthood. Using national registers in Sweden, we have observed that people born between 30 and 35 weeks gestation have increased risk of any primary malignant cancer compared to those born at 40 weeks. The risk was highest in females, individuals of both sexes born small for gestational age and for cancers presenting in childhood. Those born preterm may be at higher risk of developing cancers of the small intestine, liver, uterus, testicle, CNS and connective tissue. Conversely, postterm birth may lower the risk of developing liver and testicular cancer. Sensitivity analyses suggest that congenital malformations may influence the observed association. Further examination and elucidation of the mechanism is warranted.

4.2 | Comparability with other studies

Earlier work by Spector et al examined the association between preterm births and cancer in childhood. They found a small, albeit nonsignificant, difference in cancer rates for those born <32 weeks (OR 1.13, 95% CI 0.92-1.40) and 32-36 weeks (OR 1.07, 95% CI 0.99-1.1) compared to those born ≥37 weeks. Also utilizing gestational age categories, Risnes et al determined that cancer mortality up to midadulthood was modestly increased for moderately preterm and earlier births. Despite pooling data from four Nordic national registers, precision was low and the difference was not statistically significant. Finally, Crump et al showed that those born preterm were at increased risk of cancer-related mortality up to midadulthood compared to those born at term. For each week increase in gestational age up to full term, the hazard of cancer-related mortality increased by 4% (HR 0.96, 95% CI 0.94-0.97). In contrast to previous work, we examined gestational age in weeks using splines, thus removing the assumption of a linear relationship between gestational age and cancer risk and avoiding the need to categorize the outcome. Indeed, in our study the association between gestational age and any primary cancer does not appear linear but varies with the highest risk observed for those born at 31 weeks and a lower risk for earlier and later births.

Consistent with other studies we showed that longer gestation is associated with decreased risk of testicular and liver cancer. In a previous meta-analysis based on eight studies increased gestational age in weeks associated with decreased risk of testicular cancer (effect size 0.95, 95% CI 0.92-0.99). This is in line with our findings, which show that those born preterm have increased risk of testicular cancer compared to term-born males. This risk was further reduced with increasing gestational age, so that the risk was lower in those born postterm than in those born at term. Postterm gestational age was also associated with decreased risks of liver cancer. Previous evidence of the association of preterm birth with an increased risk of hepatoblastomas in childhood was confirmed in our study.

In contrast to our work, a meta-analysis of five studies did not find a difference in CNS cancer risk between preterm and term births. However, the underlying case-control studies examined only childhood CNS cancers (up to a maximum of 15 years) and, unlike our work, gestational age was only categorized as preterm vs term.

4.3 | Strengths and limitations

Strengths include a large population-based sample which allowed examination of risks by week, instead of reducing the information to preterm vs term. Inclusion of essentially all eligible births in the study period, prospective follow-up of patients through national health registries, and outcome ascertainment through the Cancer Register where malignant cancer reporting is required by law minimized the risk of biases. Finally, the use of multigeneration data allowed us to adjust for familial confounding, thereby automatically adjusting for unmeasured confounding common to full siblings.

Despite the large sample size, lack of granularity in the data and insufficient number of events meant that we could not go into more detail regarding cancer types (eg, type of liver cancer) or examine cancer types in childhood vs AYA separately. In addition, low number of events at extremely and very low gestational ages resulted in wide confidence intervals that limited interpretation of the association at short gestations. Also, absence of information on the reason for preterm birth hinders further interpretation on the mechanism whereby gestational age and cancer are associated. Gestational age was measured using different methods and its accuracy may have impacted the results. However, we do not expect that inaccuracies in the estimation of gestation age would be systematically different across the gestational age spectrum. Finally, we were only able to adjust for smoking and parental education (indicator of socioeconomic status) for a part of the population. However, data for births from 1990-onwards indicates that these factors were not important confounders of the association.

4.4 | Possible explanations for findings

The observed associations may be due to (a) differences in the prenatal environment, (b) postpartum differences in the management of individuals born at different gestational ages, (c) physiological differences relating to different gestational ages, (d) factors, often genetic, that are related to both preterm birth and cancer, (e) unmeasured confounders or (f) by chance. First, prenatal conditions indicative of a “toxic environment”, such as hypoxia, inflammation and maternal medications/nutrition, may not only lead to preterm birth, but also influence cancer risk later in life. Second, those born prematurely are more likely to be exposed to ionizing radiation during stays at neonatal intensive care units and in the year following discharge. Such early carcinogenic exposures may explain the increased risks of cancer
in organs that are particularly sensitive, such as the CNS and testes. Third, physiological differences may arise due to the introduction to the extraterine environment prior to the completion of maturation or may simply reflect the different levels of maturation at which birth occurs. Increase in hormone-sensitive cancers, such as testicular cancer, could be due to altered levels of sex hormones in those born prematurely. This may also explain the increased risk of uterine cancer, likely an important factor behind the raised risk of cancers observed in females. Preterm birth is associated with cryptorchidism or undescended testis in males which, in turn, confers a 3- to 4-fold increased risk for testicular cancer. When born preterm and small for gestational age, it is likely that both the prenatal environment, postnatal management and physiology (eg, altered endocrine systems) deviate from the norm, thus explaining the higher risks observed for this subgroup. Smaller, albeit statistically nonsignificant and therefore speculative, increases in estimated aHR were observed at 29 and 36 weeks; however, it remains unclear why the highest risks were observed particularly for births at 30 to 35 weeks gestation. Fourth, the association observed may be due to genetic factors influencing both gestational age and cancer risk, which may also manifest as congenital malformations. A higher proportion of people with congenital malformations were born moderate to late preterm, compared to those without. It was this group in particular that had substantially increased risks of any cancer, which may be representative of the known association between Down’s syndrome and acute myeloid leukemia.

Fifth, the statistically nonsignificant reductions in cancer risk in those born prior to 27 weeks gestation may be due to unmeasured factors that ensure that a person is able to survive following such a short gestational period. These underlying characteristics may confound the observed association between early gestational ages and cancer risk. However, the small numbers on which these observations are based require interpretation to be done with caution. Finally, the lack of a clear dose-response relationship between gestational age and risk of any cancer may indicate that the findings have arisen by chance. However, this is less likely to be the case for testicular and liver cancer where the presence of a dose-response relationship warrants further examination.

5 | CONCLUSION

We provide the first evidence that those born between 30 and 35 weeks gestation may have increased risk of any primary malignant cancer up to young adulthood. Increasing gestational ages appear to associate with reductions in the risk of testicular and liver cancer.

CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

AUTHOR CONTRIBUTIONS

Kari Risnes and Sven Sandin conceived the study. Monica S. M. Persson planned and performed the analysis and wrote the article. Weiyao Yin, Nora Döring, Elisabete Weiderpass, Eva Stelianova-Foucher and Kari Risnes provided expertise and feedback. All authors critically revised the article and approved the final version. Sven Sandin is the guarantor.

DATA AVAILABILITY STATEMENT

Data are available from the Swedish registers (online via bestalladata.socialstyrelsen.se) upon request. Further details and other data that support the findings of our study are available from the corresponding author upon request.

ETHICS STATEMENT

The study was approved by the Swedish Ethical Review Board Stockholm (2017/1875-31/12). Informed consent was not sought as it is assumed that patients do not object to registry-based research provided that the research is deemed ethical by the Ethical Review Board.

ORCID

Monica S. M. Persson https://orcid.org/0000-0002-8532-3006
Weiyao Yin https://orcid.org/0000-0002-9534-8207
Elisabete Weiderpass https://orcid.org/0000-0003-2237-0128

REFERENCES

1. Harrison MS, Goldenberg RL. Global burden of prematurity. Semin Fetal Neonatal Med. 2016;21:74-79.
2. Paquette K, Coltin H, Boivin A, Amre D, Nuyt A-M, Luu TM. Cancer risk in children and young adults born preterm: a systematic review and meta-analysis. PLoS One. 2019;14:e0210366.
3. Crump C, Sundquist K, Winkleby MA, Sieh W, Sundquist J. Gestational age at birth and risk of testicular cancer. Int J Cancer. 2012;131:446-451.
4. Ekbom A, Erlandsson G, Hsieh C, Trichopoulos D, Adami H-O, Cnattingius S. Risk of breast cancer in prematurely born women. J Natl Cancer Inst. 2000;92:840-841.
5. Kaijser M, Akre O, Cnattingius S, Ekbom A. Preterm birth, birth weight, and subsequent risk of female breast cancer. Br J Cancer. 2003;89:1664-1666.
6. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
7. Pritchard-Jones K, Pieters R, Reaman GH, et al. Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries. Lancet Oncol. 2013;14:e95-e103.
8. Dagenais GR, Leong DP, Rangarajan S, et al. Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study. Lancet. 2020;395:785-794.
9. Crump C, Sundquist J, Winkleby MA, Sundquist J. Gestational age at birth and mortality from infancy into mid-adulthood: a national cohort study. Lancet Child Adolesc Health. 2019;3:408-417.
10. Risnes K, Bilsteen JF, Brown P, et al. Mortality among young adults born preterm and early term in 4 nordic nations. JAMA Netw Open. 2021;4:e2032779.
11. Benchimol EI, Smeeth L, Guttmann A, et al. The reporting of studies conducted using observational routinely-collected health data (RECORD) statement. PLoS Med. 2015;12:e1001885.
12. Cnattingius S, Ericson A, Gunnarskog J, Källén B. A quality study of a medical birth registry. Scand J Soc Med. 1990;18:143-148.
13. Preterm Birth [Internet]. https://www.who.int/news-room/factsheets/detail/preterm-birth. Accessed October 2, 2020.
14. Quinn J-A, Munoz FM, Gonik B, et al. Preterm birth: case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. Vaccine. 2016;34:6047-6056.
15. The Swedish Cancer Register [Internet]. Socialstyrelsen. https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/swedish-cancer-register/. Accessed October 2, 2020.
16. Barlow L, Westergren K, Holmberg L, Talbäck M. The completeness of the Swedish cancer register—a sample survey for year 1998. Acta Oncol. 2009;48:27-33.
17. Smedby B, Schiøler G, Nordisk Medicinal-Statistisk Komité. Health Classifications in the Nordic Countries: Historic Development in a National and International Perspective 2006 00 = Hälsoklassifikationer i de nordiska länderna. Kbh.; Albertslund: Nordic Medico Statistical Committee; Kan bestilles hos: Schultz Information; 2006.
18. Ananth CV, Vintzileos AM. Distinguishing pathological from constitutional small for gestational age births in population-based studies. Early Hum Dev. 2009;85:653-658.
19. Ludvigsson JF, Almqvist C, Bonamy A-KE, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31:125-136.
20. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol. 2019;34:423-437.
21. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol. 1997;145:72-80.
22. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81:515-526.
23. Chen X. Score Test of Proportionality Assumption for Cox Models. 2008. Los Angeles, CA: Statistical Consulting Group, UCLA; http://www.ats.ucla.edu/stat/.
24. Spector LG, Puumala SE, Carozza SE, et al. Cancer risk among children with very low birth weight. Pediatrics. 2009;124:96-104.
25. Cook MB, Akre O, Forman D, Madigan MP, Richiardi L, McGlynn KA. A systematic review and meta-analysis of perinatal variables in relation to the risk of testicular cancer—experiences of the son. Int J Epidemiol. 2010;39:1605-1618.
26. Hogan AH, Bellin E, Douglas L, Levin TL, Esteban-Cruciani N. Radiation exposure of premature infants beyond the perinatal period. Hosp Pediatr. 2018;8:672-678.
27. Gurney JK, McGlynn KA, Stanley J, et al. Risk factors for cryptorchidism. Nat Rev Urol. 2017;14:534-548.
28. Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. J Clin Endocrinol Metab. 2007;92:804-810.
29. Marlow EC, Ducore J, Kwan ML, et al. Leukemia risk in a cohort of 3.9 million children with and without Down syndrome. J Pediatr. 2021;234:172-180.e3.

SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Persson MSM, Yin W, Döring N, et al. Gestational age and cancer risk up to young adulthood in Swedish population born 1974 to 2013: A population-based cohort study. Int. J. Cancer. 2022;150(8):1269-1280. doi:10.1002/ijc.33886