

# Risk of Subsequent Bone Cancers Among 69 460 Five-Year Survivors of Childhood and Adolescent Cancer in Europe.

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## Abstract

### Introduction

We investigate the risks of subsequent primary bone cancers after childhood and adolescent cancer in 12 European countries. For the first time, we satisfactorily address the risks beyond 40 years from diagnosis and beyond 40 years of age among all survivors.

### Methods

This largest-ever assembled cohort comprises 69 460 five-year survivors of cancer diagnosed before age 20 years. Standardized incidence ratios, absolute excess risks, and multivariable-adjusted relative risks and relative excess risks were calculated. All statistical tests were two-sided.

### Results

Overall, survivors were 21.65 times (95% confidence interval = 18.97 to 24.60 times) more likely to be diagnosed with a subsequent primary bone cancer than expected from the general population. The greatest excess numbers of bone cancers were observed after retinoblastoma, bone sarcoma, and soft tissue sarcoma. The excess number of bone cancers declined linearly with both years since diagnosis and attained age (all  $P < .05$ ). Beyond 40 years from diagnosis and age 40 years, there were at most 0.45 excess bone cancers among all survivors per 10 000 person-years at risk; beyond 30 years from diagnosis and age 30 years, there were at most 5.02 excess bone cancers after each of retinoblastoma, bone sarcoma, and soft tissue sarcoma, per 10 000 person-years at risk.

### Conclusions

For all survivors combined and the cancer groups with the greatest excess number of bone cancers, the excess numbers observed declined with both age and years from diagnosis. These results provide novel, reliable, and unbiased information about risks and risk factors among long-term survivors of childhood and adolescent cancer.

**Topic:**

- osteosarcoma
- cancer
- adolescent
- child
- pulmonary coin lesion
- retinoblastoma
- sarcoma
- survivors
- diagnosis
- malignant bone neoplasms
- immature bone
- cancer survivors

**Issue Section:**

Survival after childhood and adolescent cancer has improved substantially, with approximately 80% of those diagnosed surviving at least five years (1). As a result, there are now an estimated 300 000 to 500 000 survivors of childhood and adolescent cancer in Europe (2). However, increased survival comes at a cost because the treatments utilized to achieve such successful survival rates are also associated with adverse health outcomes. One of the most serious such outcomes concerns subsequent primary neoplasms (SPNs), with reports on cancer-related or treatment-induced SPNs first being published in the 1970s (3). Since then, numerous studies have demonstrated that there are substantially higher risks of SPNs among the overall population of childhood and adolescent cancer survivors compared with that expected from the general population (4–9), with risks ranging from three- to sixfold that expected (4–12). In particular, when assessed by the SPN site, several reports have indicated that, of all SPNs, subsequent primary bone cancers have the greatest multiplicative excess risk (5,6), ranging from 10-fold to 45-fold that expected (4–6,8,13,14). However, the previous literature has generally been limited by a small number of bone SPNs, and apart from European cohorts based on patients diagnosed before 1970 in France (14), the Nordic countries (4), and the United Kingdom (5), the interval of follow-up from diagnosis has been limited in other previous studies.

Thus, we sought to understand the risks of bone SPNs, both overall and for specific morphological subtypes, using the PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup), the largest cohort of childhood and adolescent cancer survivors currently available. With nearly 70 000 five-year survivors of cancer diagnosed before the age of 20 and 235 observed bone SPNs, the latter being 2.5 times more than in the largest previous report (5), the PanCareSurFup SPN cohort gives an unrivaled opportunity to assess the long-term risks of bone SPNs. In particular, our aims for this study were to determine the risks and risk factors for bone SPNs in this Europe-wide cohort and, in particular, to assess the risks among survivors followed beyond 40 years from diagnosis or to attained ages beyond 40 years.

## **Methods**

### **PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies**

PanCareSurFup (15) is a pan-European project within the larger PanCare initiative (16) that seeks to better understand the frequency, severity, and impact of late effects of childhood and adolescent cancer. For this study, 13 population-based and hospital-based cohorts of childhood and adolescent cancer survivors from the following 12 European countries were pooled to assess the risk of bone SPNs: Denmark, Finland, France, Hungary, Iceland, Italy, the Netherlands, Norway, Slovenia, Sweden, Switzerland, and the United Kingdom. Ethical approval was obtained separately within each participating country, observing all relevant national laws and requirements. The larger European cohorts relating to specific countries included here have been described in detail in a separate publication, together with an overview of PanCareSurFup (17).

## **Cohort Ascertainment**

All childhood and adolescent diagnoses within each of the 13 participating cohorts were pooled ( $n = 105015$ ). In order to classify the first primary neoplasms (FPNs) of each survivor according to the International Classification of Childhood Tumors (ICCC), third edition (18), all first primary neoplasms (FPNs) were coded using the third revision of the International Classification of Disease Oncology (ICD-O) with the aid of the International Agency for Research on Cancer (IARC)/International Association of Cancer Registries Check and Conversion Program (19). As only typography data were available for Slovenian diagnoses before 1983, these survivors could not be classified according to the ICCC (typography and morphology required); these individuals were not excluded from the study, but rather grouped into a “not classifiable” FPN type. All remaining diagnoses that did not conform to the ICCC were excluded. Furthermore, FPN diagnoses that did not have a malignant behavior were excluded, except for intracranial tumors where benign and unspecified behaviors were included. To ensure consistency between cohorts, survivors diagnosed with Langerhans cell histiocytosis, myelodysplastic syndromes, chronic myeloproliferative, lymphoproliferative disorders, or immunoproliferative diseases were excluded. Finally, only those surviving at least five years after an initial diagnosis before age 20 years were included. Ultimately, 69460 five-year survivors of childhood and adolescent cancer, diagnosed between 1940 and 2008, were included in this study (Supplementary Figure 1, available online).

## **Subsequent Primary Neoplasm Ascertainment**

The ascertainment method for SPNs varied by country (Supplementary Table 1, available online), but the following sources were utilized: population-based cancer registries, late effect clinics, questionnaires, medical records and hospital data, national mortality records, and health insurance registries. Validation of all SPNs was undertaken principally using pathology reports, although occasionally other definitive diagnostic reports were used. To be included, SPNs had to be histologically different from the FPN and have a malignant behavior code. For this study, all bone SPNs occurred in a bone site and were classified according to the following morphological groups: osteosarcoma, chondrosarcoma, Ewing sarcoma, and all other bone SPNs (Supplementary Table 2, available online).

## **General Population Cancer Rates**

General population cancer rates were obtained from the IARC’s *Cancer Incidence in Five Continents Time Trends* (20). Country-specific rates for bone cancer overall were available for all countries, except Hungary. Morphology-specific bone cancer rates were available for all countries, except Hungary, Slovenia, Sweden, Norway, and Finland. To estimate missing rates, we utilized the Italian general population rates for Hungary and Slovenia and Danish general population rates for

Finland, Norway, and Sweden; Italy and Denmark were selected due to their relatively close geographical proximity to the corresponding countries with missing general population data. If the range of calendar years for the general population rates did not cover the ascertainment period of the SPNs for a country, rates from the closest available year were used.

## **Statistical Analyses**

Follow-up for a bone SPN began five years after the FPN diagnosis date and ended at the first occurrence of loss to follow-up, death, or the study exit date (Supplementary Table 1, available online). Standardized incidence ratios were calculated as the observed divided by the expected number of bone cancers. Absolute excess risks per 10000 person-years were calculated as the observed minus the expected number of bone cancers, divided by person-years at risk and multiplied by 10000. For both the standardized incidence ratio and absolute excess risk calculations, multiple SPNs were included to avoid bias. We concentrate on absolute excess risks rather than standardized incidence ratios because of their direct and clear interpretation as the excess numbers of SPNs beyond that expected per 10000 person-years. The expected number of bone cancers was calculated by multiplying the person-years for each sex-, age (five-year)-, and calendar year (one-year)-specific stratum by the corresponding general population cancer rate and then summing across the strata. Using multivariable Poisson regression models, we also provide relative risks (RRs) and relative excess risks (RERs), which can be interpreted as the ratios of standardized incidence ratios and absolute excess risks, respectively, with respect to a specified reference category having adjusted for all other explanatory factors included within the model. The following explanatory factors were adjusted for within the models: sex, cohort, FPN diagnosis, age at diagnosis, treatment era, and years since diagnosis or attained age; years since diagnosis and attained age were not included in the same model due to collinearity. Likelihood ratio tests were utilized to test for heterogeneity and linear trends.

The cumulative probability of bone SPNs, in relation to years since diagnosis, was calculated including the first bone SPN only, where death was treated as a competing risk. All statistical analyses were conducted using Stata 13.1 (21), where the criterion for statistical significance was a two-sided *P* value of less than .05.

## **Data Availability**

The data are not publicly available due to them containing semi-identifiable information that could compromise research participant privacy. Nonetheless, additional summary tables of count data or person-years are available from the corresponding author upon request.

## **Results**

### **Study Characteristics**

Individuals in the cohort were followed-up for a total of 1 126424 person-years. The median follow-up time from FPN diagnosis was 21.4 years (range = 5.0–66.6 years), and the median attained age was 29.7 years (range = 5.0–79.4 years) at study exit. Among the 69460 cancer survivors included in the cohort, 235 bone SPNs were observed among 230 survivors (Table 1). Bone SPNs were most frequently observed among survivors of retinoblastoma (73 SPNs), bone sarcoma (37 SPNs), and

soft tissue sarcoma (STS) (37 SPNs), which when combined accounted for nearly two-thirds of all bone SPNs observed.

## **Risks and Risk Factors of Bone SPNs Overall**

Overall, survivors were 21.65 times (95% CI = 18.97 to 24.60 times) more likely to experience a bone SPN than expected, which equated to 1.99 (95% CI = 1.72 to 2.26) excess bone cancers per 10 000 person-years (Tables 2). When the risk of a bone SPN was assessed by FPN diagnosis, all diagnostic groups were found to have at least a fivefold increased risk compared with that expected (Table 3). Retinoblastoma survivors were found to have the greatest excess risks both in multiplicative and absolute terms, with a standardized incidence ratio of 134.91 (95% CI = 105.74 to 169.62) and 12.03 (95% CI = 9.25 to 14.81) excess bone cancers per 10000 person-years. Bone sarcoma and STS survivors had the next greatest excess risks at 78.18-fold (95% CI = 55.04 to 107.75) and 46.77-fold (95% CI=32.93 to 64.47) that expected, respectively. After all FPNs combined, there was not a statistically significant linear trend in excess risks (RRs or RERs) of bone SPN with either age at diagnosis of FPN or treatment era of FPN when adjusted, but as years since diagnosis and attained age increased, both the relative risks and relative excess risks statistically significantly declined (all  $P_{\text{trend}} < .001$ ). Specifically, from the age range of five to 19 years to 40+ years of age, the standardized incidence ratio declined from 28.98 (95% CI=24.62 to 33.88) to 6.96 (95% CI=2.55 to 15.14). Beyond 40 years from diagnosis and age 40 years, there were at most 0.45 excess bone SPNs per 10000 person-years. At 45 years since diagnosis, the cumulative incidence of a bone SPN was 0.6% compared with 0.03% of the expected (Figure 1A).

## **Risks and Risk Factors of Bone SPNs by FPN**

As retinoblastoma, bone sarcoma, and STS survivors experienced the greatest risks of developing a bone SPN, these three groups were explored in more detail. When explanatory factors were assessed, male retinoblastoma survivors were found to have a statistically significantly greater absolute excess risk than female retinoblastoma survivors after adjustment for potential confounders ( $P_{\text{heterogeneity}} = .04$ ) (Table 4); no statistically significant effects were observed for the sex of bone sarcoma or STS survivors. There was no evidence of a relationship between excess risks (RRs or RERs) for bone SPNs and age at diagnosis, after adjustment, for bone sarcoma or STS survivors; age at diagnosis was not assessed as a risk factor for retinoblastoma survivors as 95.3% of these survivors were diagnosed at zero to four years. There was also no evidence of an increasing or decreasing linear trend in the excess risks (RRs or RERs) for bone SPNs among survivors of retinoblastoma, bone sarcoma, or STS treated in more recent eras. For retinoblastoma, bone sarcoma, and STS survivors, as years since diagnosis and attained age increased, the RERs declined linearly (all  $P_{\text{trend}} < .05$ ). Beyond 30 years from diagnosis and age 30 years, there were at most 5.02 excess bone cancers per 10000 person-years among survivors of each of retinoblastoma, bone sarcoma, and STS. In Table 4, we also provide the excess numbers of bone SPNs after all FPNs except retinoblastoma, bone sarcoma, and STS. Overall, 0.85 (95% CI=0.65 to 1.04) excess bone SPNs were experienced per 10000 person-years. This excess number declined (all  $P_{\text{trend}} < .05$ )

linearly with increased years from diagnosis and attained age. When the cumulative probability was assessed by FPN type, the risk was greatest for retinoblastoma survivors, reaching 3.2% at 25 years from diagnosis, while the corresponding cumulative probabilities for bone sarcoma, STS, all other FPNs, and that expected from the general population were 1.4%, 0.9%, 0.2%, and 0.02%, respectively (Figure 1B).

## **Risks and Risk Factors of Morphology-Specific Bone SPNs**

When assessed by morphological subtype, 179 osteosarcoma, 14 Ewing sarcoma, 21 chondrosarcoma, and 21 other bone SPNs were observed (Table 2); the corresponding standardized incidence ratios were 41.37 (95% CI=35.53 to 47.90), 5.71 (95% CI=3.12 to 9.58), 11.39 (95% CI =7.05 to 17.41), and 9.37 (95% CI=5.80 to 14.32). At 30 years from the FPN diagnosis, the cumulative probabilities for osteosarcoma, chondrosarcoma, and other bone SPNs were approximately 70 times (0.3%), 40 times (0.04%), and 50 times (0.05%) that expected for each respective morphological subtype; the cumulative probability for Ewing sarcoma SPNs at 20 years was 20 times (0.02%) that expected (Figure 1C).

As 76.2% of the bone SPNs observed were osteosarcomas, potential explanatory factors were investigated only for this group (Table 3). Although both standardized incidence ratios and absolute excess risks were generally numerically greater for osteosarcoma than for bone SPNs overall, the pattern of relationships with explanatory factors was very similar to those seen for bone SPNs overall.

## **Discussion**

Our study is the largest ever to assess the risk of bone SPNs among childhood and adolescent cancer survivors, with 69 460 five-year survivors, 1 126 424 person-years at risk, and 235 observed bone SPNs. There were more than 100 000 and 30 000 person-years accrued among survivors beyond age 40 years and beyond 40 years from diagnosis, respectively, enabling satisfactory assessment of excess risks for these groups of survivors for the first time. Among all five-year survivors, as years from diagnosis and attained age increased, both multiplicative and absolute excess risks declined linearly; among those surviving beyond 40 years from diagnosis and beyond 40 years of age, the excess number of bone cancers did not exceed 0.5 per 10 000 persons per year. After each of retinoblastoma, bone sarcoma, and STS, the excess number of bone cancers also declined linearly with both increased years from diagnosis and increased attained age; beyond 30 years from diagnosis and age 30 years, there were at most five excess bone cancers observed per 10 000 person-years for each FPN type. Finally, there was no evidence of a relationship between excess risks (RRs or RERs) for bone SPNs and either age at diagnosis or treatment era, after taking into account confounding.

Overall, the risk of a bone SPN was 22 times that expected from the general population, which is consistent with previous studies (4–6,8,13). The risk of a bone SPN was observed to vary by morphological subtype, with the multiplicative excess risks ranging from six times that expected from the general population for Ewing sarcoma SPNs to 41 times that expected from the general population for osteosarcoma SPNs.

Survivors of retinoblastoma, bone sarcoma, and STS were observed to have the greatest risks of a bone SPNs, with risks of 135, 78, and 47 times that expected, respectively; these results are consistent with previous reports (6,13,22–30). The large increased risk observed in retinoblastoma survivors likely corresponds to the fact that heritable retinoblastoma survivors develop bone SPNs, particularly osteosarcomas, at substantially greater frequencies than the general population due to a genetic predisposition (13,28,30), in addition to the increased risk resulting from radiotherapy and chemotherapy experienced by both heritable and nonheritable survivors. For bone sarcoma and STS survivors, exposure to radiation and chemotherapy, specifically alkylating agents, has been previously shown to increase the risk of bone SPNs (13,22,26,28). Previous reports have also found increased risks of bone SPNs among bone sarcoma and STS survivors independent of treatment, which suggests potential genetic predisposition as well (6,28).

Previous studies have suggested that bone SPNs after childhood and adolescent cancer largely occur in the short term following the original cancer, but these reports were based on limited follow-up (10,22). Our findings indicate for the first time that the excess number of bone cancers decline with both years from diagnosis and attained age to beyond 40 years in each timescale. It is important to remember, however, that the current survivors living beyond 40 years from diagnosis or attaining ages beyond 40 years may not be representative of future survivors reaching these milestones.

Therefore, the presented findings are only applicable to survivors who have at least 40 years since diagnosis or 40 years' attained age at the time of the study, which largely comprises survivors of central nervous system neoplasms, Hodgkin lymphoma, retinoblastoma, and Wilms tumors. It will be important to reassess our findings with additional follow-up in order to determine whether the risks of bone SPNs remain low among more recently treated survivors reaching mature adulthood.

Finally, the excess number of bone cancers observed did not vary with more recent treatment era after all cancers, retinoblastoma, bone sarcoma, or STS, whereas five-year survival has improved substantially over the recent treatment eras covered by our data. For example, in Britain, five-year survival after all childhood cancers diagnosed in 1966–1970 and 1996–2000 increased from 28% to 77%; corresponding figures after retinoblastoma, bone sarcoma, and STS were 86% to 96%, 23% to 64%, and 32% to 66%, respectively (31). As treatment intensity generally increased in order to achieve such substantial improvements in five-year survival over the treatment eras covered by our data, it is very reassuring that the excess numbers of bone SPNs have not increased following treatment from 1940–1969 to beyond 2000.

A potential limitation of our study is the statistically significant heterogeneity in bone SPN risks between cohorts. The most likely explanation of this heterogeneity relates to different cumulative levels of exposure to radiation (from radiotherapy) and cytotoxic drugs carcinogenic to bone between countries, resulting from differences in treatment practices over time (32). Although we were not able to find evidence of this in the literature for the at-risk groups identified in this study, variations in British, German, and Nordic treatment regimens were clearly documented for acute myeloid leukemia patients (33–35), and thus our explanation seems plausible. As detailed treatment information was unavailable in this study, we were not able to investigate further this hypothesis within our data, nor calculate dose-response relationships between the risk of development of bone SPNs and cumulative doses of radiotherapy and chemotherapy. Also, information on cancer-predisposing genetic conditions was lacking, and therefore it was not possible to stratify results by, for example, heritability status for retinoblastoma survivors. However, as we are undertaking nested case-control studies as a part of PanCareSurFup, we shall overcome each of these limitations in the future, particularly in regards to whether there is evidence of variation in dose responses between cohorts.

This largest-ever investigation into the risk of bone SPNs after childhood and adolescent cancers has provided strong evidence that the excess number of bone SPNs observed after all childhood cancer, retinoblastoma, bone sarcomas, and STS declines linearly with both increased years since diagnosis and attained age. Beyond 40 years from diagnosis and age 40 years, there were at most 0.45 excess bone SPNs among all survivors per 10000 person-years at risk; beyond 30 years from diagnosis and age 30 years, there were at most 5.02 excess bone SPNs after each of retinoblastoma, bone sarcoma, and STS per 10000 person-years at risk. Despite the substantial improvement in five-year survival after each of these cancer groups since 1940 and the associated more intensive treatment, the excess number of bone SPNs observed has not increased among survivors of more recent treatments. The evidence assembled in this study provides reliable and unbiased information about risks and risk factors among long-term survivors not previously available, which is likely to be helpful to both survivors and health care professionals.

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## Notes

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#### References

1. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999-2007: Results of EUROCORE-5—a population-based study. *Lancet Oncol.* 2014;15(1):35–47.
2. European Commission. Improving healthcare for young cancer survivors. <http://ec.europa.eu/programmes/horizon2020/en/news/improving-healthcareyoung-cancer-survivors>. Accessed January 9, 2017.
3. Li FP, Cassady JR, Jaffe N. Risk of second tumors in survivors of childhood cancer. *Cancer.* 1975;35(4):1230–1235.
4. Olsen JH, Mo' ller T, Anderson H, et al. Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. *J Natl Cancer Inst.* 2009;101(11):806–813.
5. Reulen RC, Frobisher C, Winter DL, et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. *JAMA.* 2011;305(22): 2311–2319.
6. Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: Childhood cancer survivor study. *J Natl Cancer Inst.* 2001;93(8):618–629.
7. Magnani C, Terracini B, Cordero Di Montezemolo L, et al. Incidence of second primary malignancies after a malignant tumor in childhood: A population-based survey in Piedmont (Italy). *Int J Cancer.* 1996;67(1):6–10.
8. Cardous-Ubbink MC, Heinen RC, Bakker PJM, et al. Risk of second malignancies in long-term survivors of childhood cancer. *Eur J Cancer.* 2007;43(2): 351–362.
9. Inskip PD, Curtis RE. New malignancies following childhood cancer in the United States, 1973-2002. *Int J Cancer.* 2007;121(10):2233–2240.

10. Friedman DL, Whitton J, Leisenring W, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: The Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2010;102(14):1083–1095.
11. Jenkinson HC, Hawkins MM, Stiller CA, Winter DL, Marsden HB, Stevens MCG. Long-term population-based risks of second malignant neoplasms after childhood cancer in Britain. *Br J Cancer.* 2004;91(11):1905–1910.
12. Wilson CL, Cohn RJ, Johnston KA, Ashton LJ. Late mortality and second cancers in an Australian cohort of childhood cancer survivors. *Med J Aust.* 2010; 193(5):258–261.
13. Hawkins MM, Kinnier Wilson LM, Burton HS, et al. Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. *J Natl Cancer Inst.* 1996; 88(5):270–278.
14. Schwartz B, Benadjaoud MA, Cle´ro E, et al. Risk of second bone sarcoma following childhood cancer: Role of radiation therapy treatment. *Radiat Environ Biophys.* 2014;53(2):381–390.
15. PanCareSurFup. <http://www.pancaresurfup.eu/>. Accessed December 6, 2015.
16. Hjorth L, Haupt R, Skinner R, et al. Survivorship after childhood cancer: PanCare: A European Network to promote optimal long-term care. *Eur J Cancer.* 2015;51(10):1203–1211.
17. Winther JF, Kenborg L, Byrne J, et al. Childhood cancer survivor cohorts in Europe. *Acta Oncol (Madr).* 2015;54(5):655–668.
18. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. *Cancer.* 2005;103(7):1457–1467.
19. International Association of Cancer Registries. Check and conversion program. [http://www.iacr.com.fr/index.php?option¼com\\_content&view¼article&id¼72:iaccrgtools&catid¼68&Itemid¼445](http://www.iacr.com.fr/index.php?option¼com_content&view¼article&id¼72:iaccrgtools&catid¼68&Itemid¼445). Accessed December 6, 2015.
20. International Agency for Research on Cancer. CI5plus: Cancer incidence in five continents time trends. 2016. <http://ci5.iarc.fr/CI5plus/Default.aspx>. Accessed January 9, 2017.
21. StatCorp. Stata Statistical Software: Release 13. 2013. <http://www.stata.com/>. Accessed December 6, 2015.
22. Henderson TO, Whitton J, Stovall M, et al. Secondary sarcomas in childhood cancer survivors: A report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2007;99(4):300–308.
23. Fidler MMM, Frobisher C, Guha J, et al. Long-term adverse outcomes in survivors of childhood bone sarcoma: The British Childhood Cancer Survivor Study. *Br J Cancer.* 2015;112(12):1857–1865.
24. Moll AC, Imhof SM, Bouter LM, Tan KE. Second primary tumors in patients with retinoblastoma. A review of the literature. *Ophthalmic Genet.* 1997;18(1):27–34.
25. Woo KI, Harbour JW. Review of 676 second primary tumors in patients with retinoblastoma: Association between age at onset and tumor type. *Arch Ophthalmol (Chicago, Ill 1960).* 2010;128(7):865–870.
26. Tucker MA, D’Angio GJ, Boice JD, et al. Bone sarcomas linked to radiotherapy and chemotherapy in children. *N Engl J Med.* 1987;317(10):588–593.
27. Newton WA, Meadows AT, Shimada H, Bunin GR, Vawter GF. Bone sarcomas as second malignant neoplasms following childhood cancer. *Cancer.* 1991; 67(1):193–201.
28. Le Vu B, de Vathaire F, Shamsaldin A, et al. Radiation dose, chemotherapy and risk of osteosarcoma after solid tumours during childhood. *Int J Cancer.* 1998;77(3):370–377.
29. Garwicz S, Anderson H, Olsen JH, et al. Second malignant neoplasms after cancer in childhood and adolescence: A population-based case-control study in the 5 Nordic countries. The Nordic Society for Pediatric Hematology and Oncology. The Association of the Nordic Cancer Registries. *Int J Cancer.* 2000; 88(4):672–678.
30. Hansen MF, Koufos A, Gallie BL, et al. Osteosarcoma and retinoblastoma: A shared chromosomal mechanism revealing recessive predisposition. *Proc Natl Acad Sci U S A.* 1985;82(18):6216–6220.
31. Stiller C. *Childhood Cancer in Britain.* Oxford: Oxford University Press; 2007.
32. Turcotte LM, Liu Q, Yasui Y, et al. Temporal trends in treatment and subsequent neoplasm risk among 5-year survivors of childhood cancer, 1970–2015. *JAMA.* 2017;317(8):814.
33. Creutzig U, Ritter J, Zimmermann M, et al. Improved treatment results in high-risk pediatric acute myeloid leukemia patients after intensification with high-dose cytarabine and mitoxantrone: Results of Study Acute Myeloid Leukemia–Berlin-Frankfurt-Mu¨nster 93. *J Clin Oncol.* 2001;19(10):2705–2713.
34. Stevens RF, Hann IM, Wheatley K, Gray RG. Marked improvements in outcome with chemotherapy alone in paediatric acute myeloid leukemia: Results of the United Kingdom Medical Research Council’s 10th AML trial. MRC Childhood Leukaemia Working Party. *Br J Haematol.* 1998;101(1):130–140.
35. Lie SO, Abrahamsson J, Clausen N, et al. Long-term results in children with AML: NOPHO-AML Study Group–report of three consecutive trials. *Leukemia.* 2005;19(12):2090–2100.