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Pregnancy and the Risk for Cancer in Neurofibromatosis 1

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ABSTRACT

Background: Neurofibromatosis type 1 (NF1) is associated with a high risk for cancer. Benign cutaneous neurofibromas of women with NF1 may increase in size and number during pregnancy. However, it is not known whether pregnancy affects the risk for cancer in NF1.

Methods: We retrieved the pregnancies of women in the Finnish NF1 cohort and in a 10-fold control cohort from the Finnish Medical Birth Register. Cancers occurring during or after pregnancy were obtained from the Finnish Cancer Registry and summarized using standardized incidence ratio (SIR). The cancer incidence of nonNF1 mothers of individuals with NF1 was also estimated.

Results: Totals of 263 pregnancies in 136 women with NF1 and 3176 pregnancies in 1720 controls were observed. In the NF1 group, two cancers were identified during pregnancy and the year following the delivery (SIR 6.44, 95% CI 1.07–19.89). Among controls, the SIR was markedly lower (0.25, 95% CI 0.01–1.08). Within 1–10 years after pregnancy, the SIR of women with NF1 was 7.54 (95% CI 4.15–12.41). The SIR of women with NF1 aged 20–49 years, and without a known history of deliveries was 8.63 (95% CI 6.08–11.81). The nonNF1 mothers displayed a SIR of 0.81 (95% CI 0.66–1.00) after giving birth to a child with NF1.

Conclusions: The pregnancy-related cancer incidence in women with NF1 is similar to women with NF1 aged 20–49 years overall, although notably higher than in the general population. Giving birth to a child with NF1 does not affect the risk for cancer in women without NF1.

1 | Introduction

Neurofibromatosis type 1 (NF1; OMIM #162200) is a tumor predisposition syndrome caused by pathogenic variants of the *NF1* gene that encodes the tumor suppressor protein neurofibromin [1–3]. Our earlier findings indicate that the birth incidence of NF1 can be as high as 1/2000 in the Finnish population [4]. However, due to excess mortality throughout the lifetime, the prevalence of NF1 decreases significantly in older age groups, leading to an average prevalence of 1/4500–1/2000 [5–7]. While the inheritance of NF1 follows a dominant trait, approximately half of the children born with NF1 have no family history of NF1 [5, 6, 8]. NF1 can be reliably diagnosed based on its clinical manifestations [9, 10].

The hallmark tumors of NF1 include benign cutaneous and plexiform neurofibromas, the latter of which may turn into a malignant peripheral nerve sheath tumor (MPNST) [3, 11, 12].

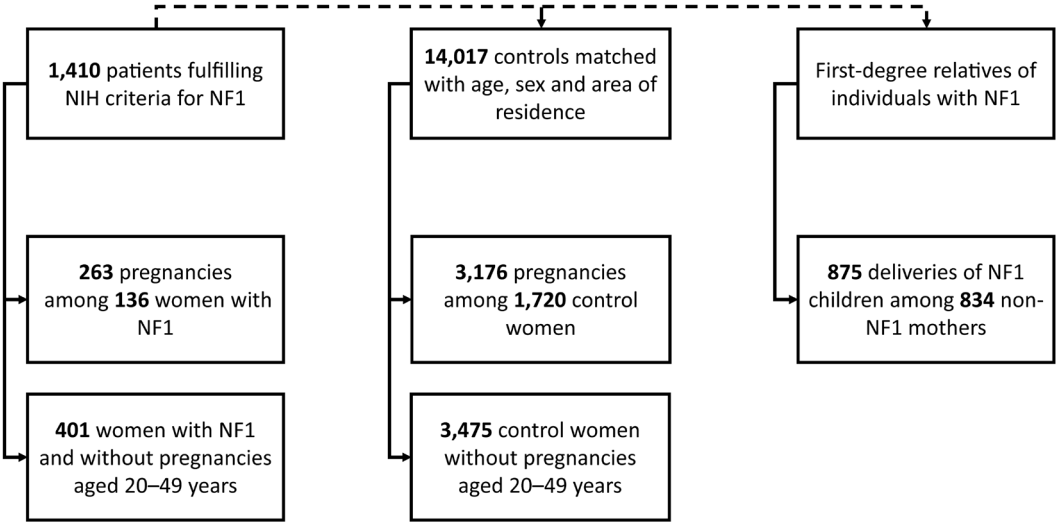

FIGURE 1 | The cohorts included in the study.

Other tumors associated with NF1 include, for example, breast cancer [13–19], gastrointestinal stromal tumor [17, 20–22], and tumors of the central nervous system [17, 22–25]. The estimates of overall cancer incidence in NF1 range from 2.7- to 9.5-fold compared to the nonNF1 population [17, 22–24], and a standardized incidence ratio (SIR) of 5.0 for any cancer in NF1 was reported in a large population-based Finnish study [17]. However, the incidence of MPNST can be as high as ~2000-fold in NF1 compared to the general population [17, 24, 26]. The NF1-related excess of cancers is especially high among young individuals [17, 23]. NF1-related cancers may show characteristics specific to the syndrome. For example, NF1-associated breast cancers are more frequently hormone receptor negative and harbor *ERBB2* amplifications than breast cancers in the general population [18, 19, 22, 27, 28].

Pregnancy is known to modulate the maternal risk for cancer in the general population. Specifically, parity is associated with a reduced risk for breast, ovarian, and endometrial cancer [29]. Moreover, experiencing the first birth at a young age can further decrease the risk for breast cancer [29, 30]. However, the risk for breast cancer initially increases during or after pregnancy [29–32], and breast cancer is one of the most common cancers diagnosed in association with pregnancy [33, 34]. Breast cancers observed in close association with pregnancy are more often hormone receptor negative than young women's breast cancers that are unrelated to pregnancy [35]. One large study reported that the risk for breast cancer was increased for 24 years after pregnancy, after which parous women had a lower risk than nulliparous women [32]. However, the effect of pregnancy on cancer risk depends on, for example, maternal age [32, 34]. Conflicting results have been published regarding the role of family history of breast cancer in predicting the risk for breast cancer during or after pregnancy [29, 31, 32].

The hormonal changes occurring during pregnancy and lactation, and the resulting development of mammary glands have been suggested as the underlying mechanism of pregnancy-induced changes in the risk for breast cancer [29, 30]. Pregnancy also modulates the maternal immune system to allow tolerance to the fetus while maintaining protection against infections [36, 37]. Moreover, fetal cells may reach the maternal circulation [38], and fetomaternal microchimerism can modulate the maternal risk for cancer [39]. This raises the question whether giving birth to a child with NF1 could induce immune tolerance to dysfunctional neurofibromin in nonNF1 mothers, or leave *NF1* deficient cells in the mother's body, which could later lead to cancer.

Cutaneous neurofibromas of women with NF1 typically increase in size and number during puberty, which suggests hormone-induced growth [40, 41]. Women with NF1 frequently report growth of cutaneous neurofibromas and the occurrence of new tumors during pregnancy [40, 42–45], yet no consistent growth of all neurofibromas has been documented during pregnancy [45]. While hormonal contraceptives in general have not been associated with the growth of cutaneous neurofibromas, certain progestin depot formulations have been suggested to have an effect [46], which further points to hormone-induced growth of neurofibromas. Neurofibromas and MPNSTs harbor a clonal population of cells of the Schwann cell lineage [47, 48]. Neurofibromin deficiency potentiates the response of Schwann cells to hormonal stimulation [43, 49–52]. Neurofibromin has been suggested to act as a negative regulator of the estrogen receptor [53], which could partly explain the findings. However, it seems that only a subset of neurofibromas expresses hormone receptors and responds to hormone stimulation in vitro [43, 50, 51].

Based on the prior studies of pregnancies of women with NF1, the average duration of pregnancy is shorter among individuals with NF1 than in the general population, and cesarean sections are more frequent [54, 55]. However, there are no studies regarding the effect of pregnancy on cancer risk in NF1. Considering the high cancer risk inherent to NF1 overall and especially at the fertile age, the NF1-related increased risk for breast cancer, and the potential for hormone-induced growth of neurofibromas, the estimation of the pregnancy-related cancer incidence in NF1 is highly relevant. This assessment is needed not only for the clinical management of individuals with NF1 but also for informing the decisions of women with NF1 who are considering pregnancy.

2 | Materials and Methods

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland. Research permits were secured from the Finnish Institute for Health and Welfare, the Finnish Population Register Centre, and all participating hospitals.

2.1 | Study Population

The study was based on the Finnish NF1 cohort of 1410 individuals with NF1 and a 10-fold control cohort of 14 017 individuals matched with individuals with NF1 based on age, sex, and area of residence (Figure 1). The Finnish NF1 cohort has been collected by searching all central and university hospitals of mainland Finland for NF1-related hospital visits in 1987–2011, as previously described [4]. The medical records of each individual were reviewed to confirm the fulfillment of the National Institutes of Health diagnostic criteria for NF1 [9]. The first-degree relatives of individuals with NF1 were retrieved from the Finnish Population Register Centre and excluded from the control cohort. For the present study, only females were included. In addition to the NF1 and control cohorts, the nonNF1 mothers of individuals with NF1 were analyzed. For this analysis, the medical records of the women with a cancer and a child with NF1 were specifically screened for manifestations of NF1, and those with any symptoms of NF1 were excluded. The group of non-NF1 mothers included 38 women with multiple children with NF1. The father was known to have NF1 in 33/38 (87%) of the families, including all the three families with three children with NF1.

2.2 | Data Sources

Information on pregnancies occurring in 1987–2013 was retrieved from the Medical Birth Register maintained by the Finnish Institute for Health and Welfare. The register includes all live births and fetuses with a birth weight ≥ 500 g or a gestational age ≥ 22 weeks. The register contains information on, for example, the date of delivery, the number of previous pregnancies, and the duration of the pregnancy. Information on cancer diagnoses was obtained from the Finnish Cancer Registry that covers the whole Finland. The registration of cancers diagnosed in Finland has been compulsory since 1961. The Finnish Cancer Registry also provided the rates of cancer incidence in the general population stratified by age, sex, and calendar year. Dates of death and emigration were from the Finnish Population Register Centre. For women with NF1, also information on children born after 2013 were available based on the data of the Finnish Population Register Centre.

2.3 | Data Analysis

Cancer incidence of women with NF1 and controls was studied (1) during pregnancy and within 1 year postpartum; (2) within 1–5 years postpartum; and (3) within 5–10 years postpartum. Pregnancy and the year following its end were combined, since cancers that manifest during the pregnancy may be registered after the childbirth [31, 34]. During pregnancy, the symptoms of cancer may be considered pregnancy-related, or diagnostic procedures may be avoided to prevent harm to the child, leading to a delay in cancer diagnosis [34]. Cancer incidence was also computed among NF1 and control women aged 20–49 years to provide a point of comparison. Based on the Medical Birth Register, parous women were excluded from this analysis, yet the group likely included women who had given birth before 1987. To study the effect of giving birth to a child with NF1, cancer incidence of the nonNF1 mothers of individuals with NF1 was studied during pregnancy and after giving birth to a child later diagnosed with NF1. The follow-up for cancers was terminated at the age of 80 years or, in another analysis, restricted to pregnancy and the 10 years following the birth of a child with NF1.

Only one cancer per individual was counted in the primary analyses, yet all cancers observed during the follow-up time were included in a sensitivity analysis. In each analysis, SIR was computed as a ratio of observed to expected cancers during the follow-up. The 95% confidence interval (CI) was obtained based on the Poisson distribution. The number of cancer diagnoses expected during the follow-up was computed by multiplying the person-years observed in the cohort with the general population cancer incidence rate stratified by calendar year and 10-year categories of age. Standard likelihood ratio test was used to compare SIRs in the Poisson regression model between women with NF1 and controls. In addition, women with a history of pregnancy and women aged 20–49 years without a known history of pregnancy were separately compared within the NF1 and control groups.

Women with NF1 entered the study on the date of their cohort entry, that is, their first NF1-related hospital visit during the ascertainment period. Controls entered the study on the cohort entry date of the respective individual with NF1. In the analysis of women aged 20–49 years, the follow-up for cancers started at the cohort entry or the 20th birthday, whichever was later, and ended on the date of death, emigration, 50th birthday, start of a pregnancy, cancer diagnosis, or censoring due to the end of data availability. When multiple cancers per individual were counted, the cancer diagnosis did not lead to the end of the follow-up.

The pregnancy-related analyses of individuals with NF1 and controls started at the latter of cohort entry or the start of the pregnancy. For analyses of cancer incidence 1–5 or 5–10 years postpartum, the start of follow-up was delayed accordingly. The start of the pregnancy was computed based on the total duration of pregnancy recorded in the Medical Birth Register. Because of the availability of the Medical Birth Register data, the start of follow-up for the NF1, and control cohorts was always in 1987–2013. The follow-up of the nonNF1 mothers of the individuals with NF1 started at the latter of the beginning of a pregnancy with a child with NF1, or January 1st, 1961, which marked the beginning of the full coverage of Finnish cancer registration. In all cohorts, the follow-up ended on the date of death, emigration, start of a new pregnancy, cancer diagnosis, or censoring due to the end of data availability. In the analyses including multiple cancers per individual, the follow-up was continued beyond the first cancer diagnosis. In the case of multiple pregnancies during the study period, each pregnancy was included as a separate case and the follow-up related to the previous pregnancy was censored at the start of the new pregnancy.

The follow-up data were available for individuals with NF1 until May 2nd, 2017, and for controls until December 31st, 2013. To exclude the possibility of ongoing pregnancies at the end of data availability, the data were censored 9 months earlier, that is, August 2nd, 2016 for individuals with NF1 and March 31st, 2013 for controls. The nonNF1 mothers of individuals with NF1 were followed up until December 31st, 2014.

All statistical analyses were performed using the R software for statistical computing, version 4.0.0 and packages survival, version 3.1–12, and lubridate, version 1.8.0.

3 | Results

3.1 | Cancer Incidence During Pregnancy and the Year Following Delivery

A total of 136 women with NF1 contributed follow-up time from 263 different pregnancies (Figure 1; Table 1). The cancer incidence of women with NF1 was not increased during or shortly after pregnancy compared with the baseline level of nulliparous women with NF1 at the fertile age. Two cancers were diagnosed in women with NF1 during pregnancy or the year following delivery. Compared with the general population of similar age, individuals with NF1 had a significantly increased incidence of cancer with a SIR of 6.44 (95% CI 1.07–19.89). However, a SIR of 8.63 (95% CI 6.08–11.81) was observed in the 401 women with NF1 and without known history of pregnancies who contributed follow-up time during the ages of 20–49 years ($p = 0.690$ for the comparison of pregnancy-associated SIR vs. SIR among nulliparous women aged 20–49 years). The average age at delivery was 29.2 (standard deviation [SD] 5.2) years in the NF1 group.

The cancer incidence during and shortly after pregnancy was significantly higher in the NF1 than in the control group ($p = 0.008$). The SIR was 0.25 (95% CI 0.01–1.08) in the control cohort during pregnancy and 1 year postpartum. Only one cancer was observed in association with the 3176 pregnancies of 1720 control women with a mean age of 29.5 (SD 5.2) years at delivery. The cancer incidence of the controls was smaller during pregnancy and the year following delivery compared with the cancer incidence of the 3475 nulliparous control women aged 20–49 years ($p = 0.038$).

The SIR estimates and the comparisons between groups remained essentially unchanged when allowing for multiple cancers per individual. No individual had two cancers diagnosed during or shortly after pregnancy.

3.2 | Cancer Incidence 1–10 Years Postpartum

Altogether, 15 cancers in 13 women with NF1 were diagnosed 1–10 years postpartum. Out of the 15 tumors, five (33%) were breast cancers and three (20%) were MPNSTs. As expected given the overall high cancer incidence associated with NF1, the cancer incidence of women with NF1 was above the general population level 1–5 years and 5–10 years postpartum with SIRs of 6.80 (95% CI 2.44–14.61) and 7.88 (95% CI 3.60–14.67), respectively (Table 1). The combined SIR for 1–10 years after delivery was 7.54 (95% CI 4.15–12.41) in women with NF1. The SIRs observed 1–5 and 5–10 years after delivery were not significantly different compared with the women with NF1 aged 20–49 years and without a known history of deliveries ($p = 0.610$ and $p = 0.809$, respectively). Allowing for multiple cancers per individual, the SIR for 1–10 years after delivery was 8.35 (95% CI 4.80–13.31), which did not significantly differ from the SIR of 8.73 (95% CI 6.27–11.76) among the nulliparous women with NF1 at ages 20–49 years ($p = 0.880$). Moreover, the incidence of breast cancer did not significantly differ between women with NF1 1–10 years postpartum (SIR 7.12, 95% CI 2.55–15.29) and the nulliparous women with NF1 aged 20–49 years (SIR 4.13, 95% CI 1.77–7.98; $p = 0.347$). In the control cohort, the cancer incidence 1–5 and 5–10 years postpartum was at the general population level (Table 1).

3.3 | Cancer Incidence of the NonNF1 Mothers of Individuals With NF1

Giving birth to a child with NF1 did not modify the maternal risk for cancer. A total of 834 women without NF1 gave birth to 875 children with NF1 during the follow-up time (Figure 1). Within the total follow-up time of 25 033 person-years, 95 cancers in 88 women were diagnosed. When only the first cancers were considered, the overall SIR for cancer was 0.81 (95% CI 0.66–1.00) among the nonNF1 mothers of individuals with NF1. Allowing for multiple cancers, the SIR remained essentially unchanged (0.84, 95% CI 0.69–1.03).

Eight cancers and 7401 person-years of follow-up occurred within 10 years of a pregnancy with a child with NF1. Six of the eight cancers were breast cancers. During the 10 years following the delivery, a SIR of 0.89 (95% CI 0.41–1.66) was observed for first cancers only, and 0.89 (95% CI 0.41–1.65) for any cancers. None of the cancers occurred during pregnancy.

4 | Discussion

Pregnancy and breastfeeding are recognized factors that can alter the maternal risk for cancer [29]. Given that neurofibromas may grow in response to hormonal stimulation, there has been a concern regarding cancer risk associated with pregnancy in NF1. For example, a case report described a fatal MPNST that started to grow during pregnancy and recurred during another pregnancy [56]. However, our systematic analysis of the pregnancies in the Finnish NF1 cohort suggests that pregnancy may not increase the cancer risk of women with NF1 above their baseline risk. Nevertheless, the high baseline risk for cancer in NF1 mandates vigilance for symptoms of cancer also during pregnancy.

Observing two cancers in close association with pregnancy in a relatively small set of 263 pregnancies is a marked number, and the SIR of 6.44 during pregnancy and the year following delivery indicates a substantial risk compared to the general population. Yet, these observations may merely represent the overall high cancer incidence of individuals with NF1. The SIR estimate even seems modest compared with our previously published estimates of SIR 30.8 in women with NF1 aged 15–29 years and

TABLE 1 | Cancer incidence in women with neurofibromatosis 1 (NF1) and control women in relation to pregnancy and delivery.

	NF1 cohort						Control cohort					
	Women	Pregnancies	Observed cancers[a]	Expected cancers	Person-years	SIR (95% CI)	Women	Pregnancies	Observed cancers[a]	Expected cancers	Person-years	SIR (95% CI)
Presumably nulliparous women aged 20–49 years[b]	401	—	35	4.06	2986	8.63 (6.08 to 11.81)	3475	—	68	34.14	25 792	1.99 (1.56 to 2.50)
During pregnancy and within 1 year postpartum	136	263	2	0.31	412	6.44 (1.07 to 19.89)	1720	3176	1	4.06	5107	0.25 (0.01 to 1.08)
Within 1–5 years postpartum	149	251	5	0.74	653	6.80 (2.44 to 14.61)	1768	2844	10	7.95	7110	1.26 (0.63 to 2.21)
Within 5–10 years postpartum	127	137	8	1.02	525	7.88 (3.60 to 14.67)	1423	1548	11	10.84	5808	1.01 (0.53 to 1.74)

Abbreviations: CI: confidence interval; SIR: standardized incidence ratio.
[a]Only the first cancers observed during the follow-up were considered.
[b]Based on the information of the Finnish Medical Birth Register, parous women were excluded. However, the register data is only available since 1987 and the group likely includes women with children born before 1987.

SIR 9.50 in women with NF1 aged 30–44 years [17]. However, since the 95% CI of the SIR estimate for cancer during or shortly after pregnancy was wide, 1.07–19.89, we cannot rule out an interaction between NF1 and pregnancy that could influence cancer risk.

Breast cancer is one of the cancers most commonly diagnosed in association with pregnancy in the general population [33, 34]. Even though we did not observe any breast cancers during pregnancy or shortly after delivery, five breast cancers were seen in women with NF1 within 1–10 years after delivery, representing one third of all cancers observed in this analysis. However, this is in line with the high overall incidence of breast cancer among women with NF1 since 30 years of age [13–15, 18, 23]. Again, despite being high compared to the general population or the control cohort, the incidence of cancer overall, or breast cancer specifically was not significantly different among women with NF1 within 1–10 years after delivery than the baseline incidence among women with NF1 aged 20–49 years nor the previously published NF1-related estimates in this age group [17, 18]. Pregnancy-associated breast cancers are often hormone receptor negative [35], and the interaction of pregnancy and genetic predisposition primarily modifies the risk for estrogen receptor negative breast cancer [57]. We could not assess the estrogen receptor status of the five breast cancers observed 1–10 years postpartum, yet NF1 is known to be associated with an increased frequency of estrogen receptor negativity in breast cancer [18]. The examination of hormone receptor status in relation to the history of pregnancies can yield novel insights into the NF1-associated breast cancer predisposition in future studies.

Pregnancy represents a period when even healthy women get close medical attention. This may increase the probability of detecting cancer, leading to an accumulation of cancer diagnoses close to pregnancy. It can be hypothesized that since women with NF1 already have frequent contacts with health care because of their NF1, pregnancy may not cause a major increase in the diagnostic sensitivity. Such a difference in the diagnostic sensitivity between individuals with NF1 and the general population could hinder the detection of minor increases in the cancer incidence of women with NF1.

While previous studies have reported that pregnancy and breastfeeding affect the risk for cancer in the general population [29–32], we did not observe a significant effect of pregnancy in the control cohort compared with the general population. The population figures of cancer incidence naturally involve a large proportion of parous women, thereby diminishing the difference between parous women and the average population. Moreover, the limited size of the cohort likely contributes to the lack of significant difference between the parous controls and the general population, since cancer during pregnancy is rather uncommon in the general population. In line with the protective effect of parity, the cancer incidence among the control women aged 20–49 years without known history of deliveries was higher than that of the general population. In addition to the protective effect of parity, a selection bias could also affect the increased SIR: the exclusion of parous women may lead to a higher likelihood of including women who have not become pregnant because of their prior morbidity, which could also be related to a higher future risk for cancer. This could also be the case in the NF1 group. For example, microdeletions of the *NF1* gene are known to be associated with a more severe phenotype, including an increased risk for MPNST [58]. Consequently, cancer incidence figures for women aged 20–49 years who have no known history of childbirth should be interpreted with caution.

We also studied the risk for cancer among the nonNF1 mothers of individuals with NF1. The analysis aimed to explore whether giving birth to a child with NF1 could increase the mother's risk for cancer via, for example, fetomaternal microchimerism, or immune tolerance to dysfunctional neurofibromin. However, the cancer incidence of the nonNF1 mothers of individuals with NF1 was nonsignificantly below the general population level. This result suggests that giving birth to a child with NF1 does not confer an additional risk for maternal cancer. The SIR for cancer was below the general population level partly because we specifically searched for symptoms of NF1 among the women with a cancer and a child with NF1, and excluded all women with any signs suggestive of NF1. However, even if no such exclusions had been made, the SIR estimate would suggest a cancer incidence below the general population level.

The Finnish NF1 cohort is relatively large with over 1400 individuals with NF1. However, the number of women at the fertile age is obviously much lower, which limits our ability to study uncommon phenomena, such as cancer associated with pregnancy. It is therefore clear that more studies are needed to assess the association of pregnancy and cancer in NF1. The Finnish Medical Birth Register provides highly comprehensive information on pregnancies and their duration, the Finnish Cancer Registry covers practically all cancers diagnosed in Finland, and these sources can be reliably linked using the Finnish personal identity code as a key. While the source data are reliable, we had limited access to records of deliveries prior to 1987. Therefore, the women included in the present analyses may have already given births prior to the study period. Moreover, the Finnish Medical Birth Register only covers pregnancies with duration of at least 22 weeks, and we have no information on pregnancies that terminated earlier.

While the size of the present cohort is insufficient to completely exclude an excess risk for cancer associated with pregnancy in NF1, it is reassuring that at least the risk does not seem to be extremely high. Given the current lack of conclusive evidence, the association between pregnancy and the development of NF1-related tumors—both benign and malignant—remains a potential topic to be discussed when counseling women with NF1 considering pregnancy. Regardless of the existence of an association between pregnancy and cancer risk in NF1, the notably high cancer incidence among women with NF1 at the fertile age needs to be considered in the counseling and clinical care of these individuals.

Author Contributions

Roope A. Kallionpää, Juha Määttänen, Jussi Leppävirta, Sirkku Peltonen, and Juha Peltonen: conceptualization, data curation, and investigation. **Roope A. Kallionpää and Juha Määttänen:** formal analysis. **Roope A. Kallionpää, Sirkku Peltonen, and Juha Peltonen:** funding acquisition. **Roope A. Kallionpää:** writing – original draft. **Roope A. Kallionpää, Juha Määttänen, Jussi**

Leppävirta, Sirkku Peltonen, and Juha Peltonen: writing – review and editing.

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Ethics Statement

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (66/180/2012). Research permits were secured from the Finnish Institute for Health and Welfare, the Finnish Population Register Centre, and all participating hospitals. The study followed the principles of the Declaration of Helsinki. The study was register-based and retrospective and therefore exempt from obtaining informed consent from the participants.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available upon request for researchers though data access is restricted. Please contact the Finnish Institute for Health and Welfare for permission.

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