Temporal changes of the incidence of childhood cancer in Germany during the COVID-19 pandemic: Updated analyses from the German Childhood Cancer Registry

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In a previous study from Germany[1] we provided the first comprehensive assessment of the impact of the COVID-19 pandemic on paediatric cancer diagnoses and provision of healthcare covering an entire country. It has now been two years since the outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and its first COVID-19 lockdowns with extensive social distancing policies, stay-at-home orders and other societal restrictions imposed across Germany and worldwide in March 2020. Since then, several virus variants and pandemic waves have led to enduring societal restrictions and temporarily overwhelmed intensive care units in numerous countries over the past two years.

Our previously reported incidence estimates had some uncertainties because of unknown additional cases due to late reporting to the German Childhood Cancer Registry (GCCR) (cases diagnosed in 2020 but reported only later in 2021; assumed completeness of data at time of analysis: 92–97%[1]). Based on the most up-to-date database of the GCCR, including eventually all late reports received throughout the year 2021, and newly available official population demographics for 2020, we are now able to complement our previous publication by the most accurate incidence estimates for the year 2020. In addition, we are able provide preliminary estimates for the incidence in 2021 (database as of 15 March 2022) for a continued evaluation of temporal changes of the incidence of childhood cancer in Germany during the COVID-19 pandemic. We calculated age-standardised incidence rates (ASR), using the weights of the SEGI 1960 Standard World Population.[2] Since a comparison between the preliminary ASR for 2020 as presented in our previous publication and the definitive incidence data shown here indicates that timeliness of reporting for cases diagnosed in 2020 had markedly improved, we estimated ASR for 2021 by applying the following three hypothetical scenarios of late reporting: (i) considering no additional cases due to late reporting after 15 March 2022,(ii) adding the minimum proportion of additional cases due to late reporting (specific to diagnostic group) observed for diagnoses in 2015-2019, and (iii) adding the proportion of additional cases due to late reporting (specific to diagnostic group) observed for diagnoses in 2020 (defined as main scenario).

In line with our previous estimates, we found a remarkable increase in incidence rates of childhood cancer overall and across diagnostic groups for 2020 compared to the incidence rates of the previous five years (Table 1). ASRs for cancer in 0 to 14 year olds were elevated by 10%, ranging from 8 to 12% across diagnostic groups. For cancer at ages 0 to 17 years, ASRs were similarly increased, varying between 10 and 15% higher rates than in 2015–2019. The percentage increase was

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	0-14 years					0-17 years				
	ASR[1] per 1,000,000 [95% CI]					ASR[1] per 1,000,000 [95% CI]				
ICCC-3 diagnostic group[2]	**2015-2019[2]**	**2020[3]**	**2021 (SI)[4]**	**2021 (SII)[5]**	**2021 (SIII)[6]**	**2015-2019[2]**	**2020[3]**	**2021 (SI)[4]**	**2021 (SII)[5]**	**2021 (SIII)[6]**
All cancers	172.8 [169.3-176.4]	190.5 [182.4-198.7]	168.2 [160.7-175.9]	175.5 [167.8-183.4]	175.4 [167.6-183.3]	171.3 [168.1-174.5]	191.0 [183.6-198.5]	169.2 [162.3-176.3]	176.7 [169.7-184.0]	176.2 [169.1-183.4]
Leukaemias	55.2 [53.2-57.2]	61.2 [56.7-65.9]	57.9 [53.4-62.5]	58.0 [53.6-62.6]	57.7 [53.2-62.3]	51.5 [49.8-53.3]	56.9 [52.9-61.1]	54.9 [51.0-59.0]	55.1 [51.1-59.2]	54.7 [50.8-58.8]
Lymphoid leukaemia	43.1 [41.3-44.9]	47.6 [43.6-51.7]	44.9 [41.0-48.9]	44.2 [40.4-48.3]	44.6 [40.7-48.7]	39.2 [37.7-40.7]	43.2 [39.7-46.8]	40.9 [37.5-44.5]	40.5 [37.1-44.0]	40.7 [37.3-44.3]
Acute myeloid leukaemia	7.3 [6.6-8.1]	7.8 [6.2-9.6]	8.1 [6.5-9.9]	8.2 [6.6-10.0]	8.3 [6.7-10.1]	7.3 [6.6-7.9]	7.7 [6.2-9.3]	8.5 [7.0-10.1]	8.5 [7.0-10.2]	8.6 [7.1-10.3]
Lymphomas	21.2 [20.0-22.4]	23.7 [21.0-26.6]	18.2 [15.9-20.7]	18.4 [16.0-20.9]	19.2 [16.8-21.8]	26.1 [24.9-27.3]	30.0 [27.2-32.9]	24.4 [22.0-27.1]	24.4 [21.9-27.0]	25.4 [22.9-28.1]
Hodgkin lymphoma	6.7 [6.1-7.4]	6.7 [5.3-8.2]	6.8 [5.4-8.3]	6.7 [5.3-8.2]	6.9 [5.5-8.4]	11.1 [10.4-11.9]	12.5 [10.8-14.4]	11.9 [10.2-13.7]	11.9 [10.2-13.7]	12.2 [10.5-14.1]
Non-Hodgkin lymphoma	6.5 [5.9-7.2]	7.1 [5.6-8.7]	5.2 [4.0-6.6]	5.0 [3.8-6.4]	5.4 [4.2-6.8]	7.7 [7.0-8.3]	8.2 [6.7-9.7]	6.3 [5.1-7.7]	6.1 [4.9-7.5]	6.4 [5.2-7.8]
CNS tumours	41.2 [39.6-43.0]	46.2 [42.3-50.3]	42.0 [38.3-45.9]	46.9 [43.0-51.0]	45.7 [41.9-49.8]	39.3 [37.8-40.8]	44.5 [41.0-48.2]	40.1 [36.8-43.5]	45.2 [41.7-48.8]	43.8 [40.3-47.4]
Malignant	24.3 [23.0-25.6]	24.8 [21.9-27.8]	23.2 [20.5-26.1]	25.9 [23.0-29.0]	25.5 [22.6-28.5]	22.7 [21.6-23.9]	23.2 [20.7-25.9]	22.0 [19.6-24.6]	24.5 [21.9-27.2]	23.9 [21.3-26.6]
Non-malignant	16.9 [15.9-18.1]	21.4 [18.8-24.2]	18.8 [16.3-21.4]	20.6 [18.1-23.3]	20.3 [17.8-23.0]	16.6 [15.6-17.5]	21.3 [18.9-23.8]	18.1 [15.9-20.4]	20.7 [18.4-23.2]	19.9 [17.6-22.3]
Non-CNS solid tumours	55.2 [53.2-57.2]	59.3 [54.8-64.0]	50.1 [46.0-54.4]	51.4 [47.3-55.8]	52.6 [48.4-57.0]	54.3 [52.5-56.1]	59.5 [55.4-63.8]	49.8 [46.0-53.7]	51.4 [47.6-55.4]	52.1 [48.3-56.2]

***Table 1*: Estimated age-standardised incidence rates of childhood cancer (ages 0−14 years and 0−17 years) in Germany in 2015−2019, 2020 and 2021. The incidence rates for 2021 were estimated by applying different hypothetical scenarios of additional cases due to late reporting.**

[1] ASR: age-standardized incidence rate (using Segi World Standard Population; Ref: Segi M. Cancer mortality for selected sites in 24 countries (1950-57): Sendai, Japan Tohoku University of medicine, 1960) per 1,000,000 person-years.

[2] Age-standardized incidence rate per 1,000,000 person-years in 2015-2019. Incidence rates for 2015-2019 included all cases reported in the respective year or the subsequent year, cases reported only after the subsequent calendar year were neglected.

[3] Age-standardized incidence rate per 1,000,000 person-years in 2020. Incidence rates included all cases reported in 2020 or the subsequent year, cases reported only after the subsequent calendar year were neglected.

[4] Scenario I: estimated age-standardized incidence rate per 1,000,000 person-years in 2021, considering no additional cases due to late reporting after 15 March 2022.

[5] Scenario II: estimated age-standardized incidence rate per 1,000,000 person-years in 2021, considering the minimum proportion of additional cases due to late reporting (by diagnostic group) observed for diagnoses in 2015-2019. The minimum proportion of additional cases due to late reporting for childhood cancer at ages 0-14 years amounted to 12·5% for all cancers combined, 6·1% for leukaemias, 3·3% for lymphoid leukaemias, 5·6% for acute myeloid leukaemias, 10·4% for lymphomas, 7·2% for Hodgkin lymphomas, 3·0% for Non-Hodgkin lymphomas, 20·1% for CNS tumours, 21·0% for malignant CNS tumours, 16·9% for non-malignant CNS tumours and 12·7% for non-CNS solid tumours. The minimum proportion of additional cases due to late reporting for childhood cancer at ages 0-17 years amounted to 12·5% for all cancers combined, 6·1% for leukaemias, 3·3% for lymphoid leukaemias, 4·7% for acute myeloid leukaemias, 8·8% for lymphomas, 7·3% for Hodgkin lymphomas, 5·6% for Non-Hodgkin lymphomas, 21·1% for CNS tumours, 20·7% for malignant CNS tumours, 21·8% for non-malignant CNS tumours and 13·0% for non-CNS solid tumours.

[6] Scenario III: estimated age-standardized incidence rate per 1,000,000 person-years in 2021, considering the proportion of additional cases due to late reporting (by diagnostic group) observed for diagnoses in 2020. The proportion of additional cases due to late reporting for childhood cancer at ages 0-14 years amounted to 12·4% for all cancers combined, 5·5% for leukaemias, 4·2% for lymphoid leukaemias, 6·3% for acute myeloid leukaemias, 15·4% for lymphomas, 10·7% for Hodgkin lymphomas, 10·7% for Non-Hodgkin lymphomas, 17·1% for CNS tumours, 19·0% for malignant CNS tumours, 15·1% for non-malignant CNS tumours and 15·2% for non-CNS solid tumours. The proportion of additional cases due to late reporting for childhood cancer at ages 0-17 years amounted to 12·2% for all cancers combined, 5·5% for leukaemias, 4·0% for lymphoid leukaemias, 6·4% for acute myeloid leukaemias, 13·3% for lymphomas, 10·1% for Hodgkin lymphomas, 10·5% for Non-Hodgkin lymphomas, 17·4% for CNS tumours, 17·9% for malignant CNS tumours, 16·9% for non-malignant CNS tumours and 14·6% for non-CNS solid tumours.

highest for lymphomas and tumours of the central nervous system (CNS) (primarily driven by CNS tumours with non-malignant behaviour). All estimates however involve some degree of uncertainty because childhood cancers are rare disorders.

Estimating the ASRs in 2021 (Table 1), suggested a decline in ASRs for 2021 compared to 2020. This applied to both ages 0 to 14 years and 0 to 17 years, and across diagnostic groups, with the exception of acute myeloid leukaemia, Hodgkin lymphoma and CNS tumours for which the ASR remained on the level of 2020. Estimated ASRs of childhood cancer overall, leukaemia overall and lymphoid leukaemia for 2021 were still elevated compared to those in the five years before the pandemic. ASRs estimated for lymphomas overall and non-CNS solid tumours however have dropped so drastically that they fell below the respective ASRs from 2015 to2019.

Internationally, a growing number of institutional observations and scientific assessments confirm unprecedented detrimental consequences of the COVID-19 pandemic on several areas of healthcare, including cancer care. A remarkable decline in new cancer diagnoses as well as evidence for missed and delayed diagnoses, delayed treatment and rises in cancer deaths have been noted.[3,4] Disruptions to diagnostic and therapeutic services and a decline in new cancer diagnoses have also specifically reported for childhood cancer[5,6] and are of major public health concern.

We previously speculated that the unexpected increase in childhood cancer incidence rates in Germany in 2020 might be the consequence of greater parental attention to early disease symptoms in their child and possibly also doctor's awareness during the COVID-19 pandemic and hence more timely healthcare consultations and referral to tertiary facilities. Since many childhood cancers tend to present with non-specific symptoms that mimic those of infectious including COVID-19, increased parental and physician's awareness and earlier presentation might have indeed led to a shorter diagnostic process and thereby earlier diagnoses. The GCCR lacks regrettably information about disease stage at diagnosis. Analyses by stage might have given indications whether, for example, the observed increase in some cancer types was due to more diagnoses of early stages. That we did observe indications of a potential rebound effect in the 2021 incidence estimates for lymphoma (lymphomas overall, others than Hodgkin lymphoma) and non-CNS solid tumours but not for other diagnostic groups, speaks however against this explanation as being the only cause for the increase. Although it is reassuring that we found no signs of missed or delayed childhood cancer diagnoses in Germany throughout 2020 and 2021, the underlying reasons for the marked increase in incidence rates in 2020 remain largely unclear. Especially the continuing increase in the incidence of CNS tumours in 2021 is noteworthy, as this is the diagnostic group where complete registration has traditionally been a challenge. A possible explanation of the increase relates to improvements in completeness of reporting. During the COVID-19 pandemic waves, children with a CNS tumour might have been less frequently treated in adult neuro-oncology or neurology departments than before but more often in paediatric haematology-oncology units, where reporting to the GCCR is an established routine. An actual increase in risk for childhood cancer overall in direct or indirect response to the COVID-19 pandemic appears highly unlikely according to the current scientific knowledge, but seems conceivable for lymphoid leukaemias[7] and in particular its major subtype B-precursor acute lymphoblastic leukaemia[8,9].

Declaration of interests

The authors declare that the research was conducted in the absence of any commercial, personal or financial relationships with other people or organisations that could be construed as a potential conflict of interest.

Authors' contributions

Conceptualisation, FE, JS; methodology, FE, formal analysis, FE, JS, CS; data curation, FE, CS; writing – original draft preparation, FE; writing – review and editing, JS, CS, MS, AB; project administration, FE.

FE and CS had full access to all data and verified the data reported in the study. All authors approved the final manuscript as submitted, agreed to be accountable for all aspects of the work and had the final responsibility for the decision to submit for publication.

Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/ World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/ World Health Organization.

Ethics committee approval and consent to participate

No ethics approval and consent was required for this study. This research was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Consent for publication

Not applicable, since no individual person's data was used.

Data sharing

Under the permission that national data protection requirements are fully met, access to aggregated or pseudonymised individual-level data may be made available upon reasonable request. All data access requests should be directed to the corresponding author.

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