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Evaluation of spatiotemporal associations between the COVID-19 pandemic and the incidence of cancer diagnoses in Bavaria, Germany: A registry-based study (PanSCan)

Statistical analysis plan for the PanSCan study – **Pan**demic and **S**patiotemporal **Can**cer Analysis (SAP)

Version 1.0 of 28st of May 2025

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Abbreviations

ASR	Age-standardized Incidence Rate
CAR	Conditional autoregressive
COVID-19	Coronavirus disease 2019
GISD	German Index of Socioeconomic Deprivation
ICU	Intensive Care Unit
LGL	Bavarian Health and Food Safety Authority (Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit)
PanSCan	Pandemic and Spatiotemporal Cancer Analysis
PCR	Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

1. Background

The COVID-19 pandemic has severely disrupted healthcare systems worldwide, particularly affecting the diagnosis and treatment of non-communicable diseases such as cancer (1). Numerous studies have consistently reported a decline in newly diagnosed cancer cases (2–5), likely due to delays in early detection and restricted access to medical services during the pandemic (6–8).

In Germany, these effects were particularly evident in cancer screening and treatment. Hospitals postponed elective procedures to prioritize COVID-19 care, and cancer screening programs were temporarily put on hold. The number of screenings declined significantly by 21.46% during the COVID-19 pandemic, with mammography screenings showing a particularly sharp reduction of 98.71% in April 2020 (9). The provision of cancer care was also affected, with reductions of 21% in follow-up care, 12% in psycho-oncological support, and 9% in tumor surgeries (10,11). During the initial pandemic wave (March–April 2020), even greater declines were observed, with follow-up care decreasing by 70%, psycho-oncological support by 32%, and tumor surgeries by 20% (10,11).

Studies indicate that the decline in cancer diagnoses during the COVID-19 pandemic, particularly during the first lockdown phase (April–May 2020), varied across tumor sites and demographic groups (12,13). Colorectal cancer diagnoses, for instance, decreased by up to 17% in 2021 compared to 2019, while reductions in breast cancer diagnoses were primarily observed among women over 75 years of age (14). Findings on tumor stage at diagnosis also show regional discrepancies within Germany. While the Cancer Registry of Schleswig-Holstein reported no significant shift in tumor stages in 2020 (15), data from Lower Saxony indicated a redistribution of lung cancer stages in the same year, with an increased proportion of T1 and T4 diagnoses and fewer T2 and T3 cases compared to 2015 to 2019 (16). As these findings are based on relative stage proportions rather than absolute case numbers, they do not necessarily indicate a true stage shift. However, in the context of declining incident cancer cases and reduced treatments these observations may still reflect disruptions in early cancer detection during the COVID-19 pandemic. This highlights the potential for delayed diagnoses to disproportionately affect specific tumor stages and subgroups.

Delays in cancer diagnosis and treatment have critical consequences for patient outcomes. Hanna et al. (2020) found that a four-week treatment delay increased mortality risk (17). In the UK, delays in cancer diagnosis during the COVID-19 lockdown were projected to result in 3,291 to 3,621 avoidable deaths. The increase in cancer deaths ranged from 4.8% for lung cancer to 16.6% for colorectal cancer, highlighting the severe impact of diagnostic delays on long-term survival (18).

An analysis by the Bavarian Cancer Registry, based on a sample covering approximately half of all pathology departments in Bavaria, revealed a 6.7% decline in cancer diagnoses during the first year of the pandemic (March 2020–February 2021) compared to the pre-pandemic period (March 2019 to February 2020). The number of diagnoses decreased from 42,857 to 39,980 (19), coinciding with lockdown periods and restrictions on public life. However, it remains unclear whether this decline reflects temporary diagnostic delays or results in changing cancer incidence and survival patterns.

Beyond the indirect effects of the pandemic, socioeconomic disparities have been shown to influence cancer incidence. Studies in Germany indicate that cancer incidence is higher in socioeconomically deprived areas and that these disparities have widened over time. Between 2007 and 2018, age-standardized cancer incidence declined across all deprivation quintiles;

however, this decline was less pronounced in the most deprived regions for certain cancers, such as colorectal cancer and male lung cancer (20). This suggests that socioeconomic inequalities in cancer incidence may have persisted or even worsened during the pandemic.

The COVID-19 pandemic has had a significant impact on healthcare systems, including cancer diagnostics and treatment. In this context, it is particularly relevant to examine how incident cancer cases have evolved during the pandemic and whether these changes varied across regions and population subgroups.

1.1 Objectives

This study aims to investigate how the COVID-19 pandemic – and its severity at the regional level – affected incident cancer cases in Bavaria. Particular attention will be given to regional differences, sociodemographic factors, socioeconomic status, and tumor characteristics. To this end, we will model monthly incident cancer cases at the district level using a spatiotemporal statistical model and compare trends between the pre-pandemic and pandemic periods. This approach allows for the identification of spatially and demographically heterogeneous effects, providing insights into the potential long-term impact of the pandemic on cancer detection and healthcare access.

1.2 Study design

This study is a registry-based study using data from the Bavarian Cancer Registry (2018–2023). The analysis applies a spatiotemporal approach to assess changes in cancer incidence before (2018 to February 2020) and during the pandemic (March 2020 to May 2023).

1.3 Hypotheses

The COVID-19 pandemic led to significant reductions in cancer diagnoses in Bavaria, with variations across geographic regions.

Geographic regions exhibit different patterns of delayed diagnoses due to differences in healthcare access and pandemic-related restrictions.

Certain tumor sites, tumor stages, and demographic subgroups (e.g., elderly, high-risk groups) experienced greater declines in diagnoses.

1.4 Participants

Inclusion criteria:

All incident cancer cases among individuals aged 18 years and older, including carcinoma in situ, diagnosed between 2018 and 2023 within Bavaria and recorded in the Bavarian Cancer Registry.

Exclusion criteria:

Death Certificate Only (DCO) cases as they lack essential clinical information and the recorded date of diagnosis is in most cases the date of death, leading to temporal distortions in incidence estimates.

2. Analysis sets

Full analysis set includes all incident cancer cases diagnosed during the study period.

3. Analysis variables

3.1 Outcome / primary endpoint

The primary endpoint is the number of incident cancer cases per district $_i$ and month $_t$.

Bavarian wide data on newly diagnosed cancer cases are obtained for the period from 2018 to 2023 from the Bavarian Cancer Registry (26). The cancer cases are aggregated by district (*Landkreise und kreisfreie Städte*). Stratification variables include month, year, sex, and age at diagnosis (e.g., age groups 18-49, 50-64, 65-74, ≥75 years).

3.2 Explanatory variables / confounders at the time of diagnosis

Individual level data (assigned to a person):

- **Socioeconomic data:**
  - Age
  - Sex (male, female)
- **Spatial data:**
  - District of residence
- **Tumor-specific data:**
  - Tumor site (based on ICD-10, for instance, breast, colon, cervix uteri, pancreas, prostate, lung, leukemia, skin/melanoma, liver, sarcoma)

    The selection is based on its diagnostic challenges and the potential impact of the COVID-19 pandemic:

    - Screening availability: Tumors with established screening programs that may have been disrupted during the COVID-19 pandemic (e.g., breast (C50, D05), colon (C18-C21), and cervical cancer (C53-C55, D06)) (21).
    - Aggressiveness: Rapidly growing tumors with high mortality that require early diagnosis (e.g., pancreatic cancer (C25)) versus slow-growing tumors that remain treatable even at later stages (e.g., prostate cancer (C61)) (22).
    - Symptom presentation: Tumors that become symptomatic only in advanced stages, leading to late diagnoses (e.g., lung cancer (C33-C34)), versus tumors that present with early but nonspecific symptoms, allowing for potentially earlier detection (e.g., leukemia (C91-C95), skin/melanoma (C43)).
    - Incidence and rarity: Frequent tumors (e.g. colorectal cancer (C18-C21)) are more resistant to fluctuations in diagnostic rates due to their regular and high-frequency diagnosis. They could allow for the identification of general care gaps caused by the pandemic, while rare tumors (e.g. liver (C22), sarcomas (C40-C41, C47, C49)), which often lack standardized diagnostic processes and require access to specialized centers (23), could highlight specific care gaps.
  - Grading

- Tumor malignancy/behaviour code
  - Stage of diagnosis according to the TNM classification

Regional level data:

- **Socioeconomic data:**
  - Deprivation (German Index of Socioeconomic Deprivation (GISD) (24)
- **Settlement structure:**
  - Urban-rural typology data

3.3 Explanatory variables / confounders between baseline and study end

SARS-CoV-2 Incidence

Regional level data:

- **SARS-CoV-2 Incidence:**
  - Daily, district-level Bavarian wide data on newly reported SARS-CoV-2 infections confirmed by polymerase chain reaction (PCR) are collected for the period from March 2020 to May 2023 and aggregated into calendar months and years.
- **Intensive care unit (ICU) capacities** / COVID-19 ICU bed occupancy by district as a proxy for the severity of the COVID-19 pandemic (25).

4. Handling of missing values and outliers

4.1 Missing values

In case of missing values, imputation will be considered.

5. Statistical analyses / methods

5.1 Descriptive analysis

Summary statistics (mean, standard deviation, interquartile range) for age, sex, and tumor site.

Descriptive analyses will characterize the data structure and identify regional and temporal patterns, including annual age-standardized incidence rates (ASR) at the district level for the total population and by age group.

ASR is calculated by adjusting observed incidence rates to the age distribution of a reference population (old European standard population / WHO 1976 version), ensuring comparability across districts and over time. Cancer cases in individuals aged 18 and older will be obtained from the Bavarian Cancer Registry and aggregated by district, time, sex, and age at diagnosis.

By eliminating age distribution effects, ASR allows for standardized comparisons. It is determined by weighting observed incidence rates in each age group according to the reference population, summing the results, and normalizing by the total weight of the standard population.

The descriptive analyses can help explore data structure, detect biases and heterogeneities, and provide a basis for subsequent inferential statistical models.

5.2 Primary inferential analysis

To investigate spatiotemporal trends in incident cancer cases and assess potential effects of the COVID-19 pandemic, a Bayesian spatiotemporal Poisson model with a Conditional Autoregressive (CAR) structure will be applied.(27) This model is appropriate under the assumption that the variance of the outcome is proportional to the mean; however, in the presence of overdispersion, a negative binomial variant will be considered to ensure robust inference.

The outcome variable is the count of newly diagnosed cancer cases per district and month. Modeling raw counts allows for direct incorporation of the data's discrete nature and avoids potential instability introduced by rate standardization in small populations. This approach facilitates the use of flexible count-based models that can accommodate overdispersion, enables smoothing across space and time, and allows for adjustment of relevant covariates—ultimately enhancing the accuracy and interpretability of temporal trend estimates.

The CAR approach introduces a spatially structured random effect that borrows strength from neighboring districts by assuming that geographically adjacent areas are more likely to have similar incidence patterns. This allows for explicit modeling of spatial autocorrelation and helps to stabilize estimates in regions with small case numbers.

The model will be applied across all districts and stratified by tumor type and age group to identify heterogeneous temporal trends across population subgroups. Covariates such as the GISD, urban-rural district typology, and geographic characteristics will be included to adjust for confounding and potential effect modification.

Statistical analyses will be conducted in *R* using Bayesian modeling. Poisson regression will be implemented with the *rstanarm* and *cor.test* packages, while geographic visualizations illustrating regional differences in cancer incidence will be created using *ggplot2* and the *sf* package.

6. Planned subgroup analyses

- Stratification by

  (1) Tumor characteristics:
    a. Tumor site (ICD-10: e.g. breast, colon, cervix uteri, pancreas, prostate, lung, leukemia, skin/melanoma, colon, liver, sarcoma,...),
    b. Tumor stage,
    c. Behaviour code (malignant, in situ),
  (2) Sex (male, female), and
  (3) Age group (18-49, 50-64, 65-74, ≥75 years).

- Regional analysis by regional districts (*Landkreise und kreisfreie Städte*).

7. Interpretation of results

The results will be interpreted in the context of district-level variation in both cancer cases and COVID-19 incidence. By incorporating COVID-19 incidence as a time-varying covariate, the analysis allows for interpretation of how pandemic-related disruptions may have influenced cancer reporting. Spatial and temporal trends will be considered in light of local pandemic severity, socioeconomic deprivation, and urban-rural differences, enabling identification of population subgroups and regions most affected. Geospatial visualizations will support interpretation by highlighting spatial heterogeneity and shifts in cancer incidence before and

during the pandemic. Caution will be applied in interpreting potential associations, acknowledging the observational nature of the data and residual confounding.

8. Data problems

Possible underreporting in certain regions or time periods (completeness).

Delays in data entry due to pandemic disruptions.

In-situ cases and invasive cancers were previously reported separately, but recent reporting methodology has led to their combined reporting, potentially affecting data consistency across periods.

9. Software

In general, the software for analysis will be the open-source programming language *R* and *RStudio* (latest version) (28). Additional GIS software tools, such as *QGIS* (29) or *ArcGIS* (30) may be used for spatio-temporal analyses if necessary.

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