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LETTER TO THE EDITOR

Cancer diagnosis is one quarter lower than the expected cancer incidence in the first year of COVID-19 pandemic in Germany: A retrospective register-based cohort study

Dear Editor,

The coronavirus disease of 2019 (COVID-19) pandemic has necessitated that semi-urgent and elective medical cases, including cancer screenings, are postponed in hospitals worldwide to accommodate the increasing number of patients with severe COVID-19 symptoms [1–4]. Consequently, several reports from the first COVID-19 wave in spring 2020 showed a significant decrease in new cancer diagnoses as well as cancer therapy and screenings [5, 6]. We aimed to investigate this further by performing a novel registry-based analysis of insurance claim data from BARMER, Germany's second largest health insurance provider. Detailed descriptions of the study can be found in the Supplementary Materials and Methods.

A total of 33,810,604 person-years were analyzed. This included a reference period from January 2017 to December 2019 covering 25,614,919 person-years and the first year of COVID-19 from April 2020 to March 2021, covering 8,195,685 person-years. One hundred sixty-one thousand and fifty individual patients with newly encoded malignant diagnoses (ICD-GM codes: C00-C26, C30-41, C43-58, C60-97) or benign neoplasms (ICD-GM codes: D00-48) were identified (Supplementary Table S1). The median age was 66 years, and 58.6% were female. At the time of data analysis, there were 696 patients with incomplete information (0.4% of all cases). These cases were not considered.

The overall incidence of benign and malignant neoplasms encoded by ICD C00 to D48 decreased by 23.06% (-11.63[95%CI: -11.13 to -12.14] per 10,000 insurance holders [IH]; $P < 0.001$).The most prominent decrease in benign and malignant neoplasms was in the age group 18-49 years with 26.98% (95%CI: -5.69[-5.15 to -6.23] per 10,000 IH; $P < 0.001$) and in females with 24.18% (95%CI: -12.54[-11.86 to -13.21] per 10,000 IH; $P < 0.001$) (Figure 1A, Supplementary Table S2). The number of newly diagnosed malignant neoplasms (C-diagnoses) decreased by 19.9% (95%CI: -6,59[-6.18 to -7.01] per 10,000 IH; $P < 0.001$), the diagnosis of benign and in situ neoplasia (D-diagnoses) decreased by 66.46% (95%CI: -7,74[-7.55 to -7.93] per 10,000 IH; $P < 0.001$). The respective fractions of cancerous and benign lesions, however, remained stable (Supplementary Table S3).

When analyzing entity-specific changes, a clear difference in the decrease of diagnoses which ranged from a non-significant decrease of 5.77% (95%CI: -0.03[0.03 to -0.09] per 10,000 IH; not significant) for brain and eye tumors (C69-C72) to a decrease of more than 30% for breast cancer (-1.35[95%CI: -1.21 to -1.5] per 10,000 IH; $P < 0.001$) and for melanoma (-1.06[95%CI: -0.94 to -1.19] per 10,000 IH; $P < 0.001$) was found (Figure 1B; Supplementary Table S4). When analyzing the number of affected patients, the largest decrease was observed for breast, gastrointestinal cancer and melanoma (Figure 1B; Supplementary Table S4). From March 2020 to March 2021, three further waves of COVID-19 hit Germany. We could not show seasonality or catch-up effects between the first and the second COVID-19 wave even when lockdown measures were lifted during the summer months of 2020 (Figure 1C).

There was also a decrease in invasive interventions, chemo- and radiation therapies for tumors. Specifically, 26.28% less tumor-related invasive interventions (-10.42[95%CI: -10.0 to -10.86] per 10,000 IH; $P < 0.001$) (Supplementary Table S5), 19.05% less chemotherapies (-1.16[95%CI: -0.98 to -1.34] per 10,000 IH; $P < 0.001$) (Supplementary Table S6) and 28.04% less radiation therapies (-0.83[95%CI: -0.71 to -0.95] per 10,000 IH; $P < 0.001$) (Supplementary Table S7) were observed. The relative decrease in surgical and other invasive interventions was most prominent for lesions of unclear identity (-41.58%; -0.86[95%CI: -0.77 to -0.95] per 10,000 IH; $P < 0.001$) and

Abbreviations: CI, confidence interval; CNS, central nervous system; COVID-19, coronavirus disease of 2019; ICD-10 GM, German modification of the 10th revision of the International Classification of Diseases; IH, insurance holders.

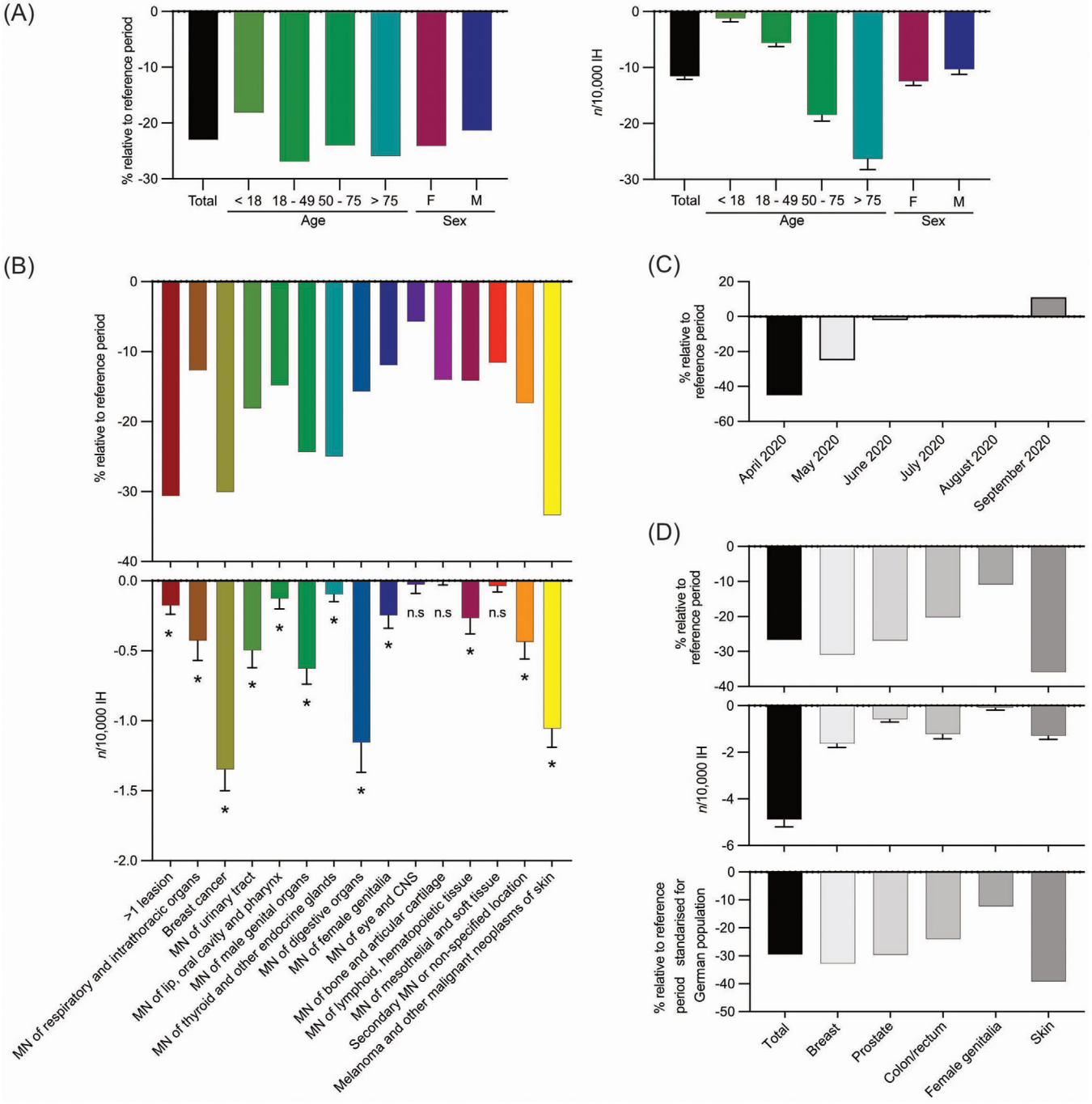

FIGURE 1 Relative and absolute changes in cancer incidence in the first year of COVID-19. (A) according to age and gender; (B) according to cancer location; (C) relative changes per month; (D) relative and absolute change of incidence of benign, pre-malignant and malignant lesions according to organ screening program.Abbreviations: IH – Insurance holders; MN – malignant neoplasm; CNS – central nervous system

benign neoplasms (-35.09%; -3.35[95%CI: -3.14 to -3.56] per 10,000 IH; $P < 0.001$) followed by melanoma resection (-34%; -1.06[95%CI: -0.94 to -1.18]; $P < 0.001$) and breast cancer resections (-31.97%; -1.32 [95%CI: -1.18 to -1.46] per 10,000 IH; $P < 0.001$) (Supplementary Table S5). Regarding chemotherapies and immunotherapies, we observed the strongest relative decrease by 60.14% (-0.34[95%CI: -0.29 to -0.38] per 10,000 IH; $P < 0.001$) in patients with an ICD-GM code for metastatic disease with an unknown primary tumor. Chemotherapy for breast cancer (-37.25%; -0.11[95%CI: -0.08 to -0.15] per 10,000 IH; $P < 0.001$) and cancer of the gastrointestinal-tract (-13.45%; -0.16[95%CI: -0.08 to -0.24] per 10,000 IH; $P <$

0.001) were also substantially reduced (Supplementary Table S6).

In Germany, five routine cancer-screening programs were available (breast, melanoma, colorectal, cervical and prostate cancer, Supplementary Table S8) in which benign, pre-neoplastic and neoplastic lesions of the screened organs are detected. A 26.83% (-4.90[95%CI: -4.6 to -5.2] per 10,000 IH; $P < 0.001$) decrease for all newly diagnosed malignant, benign, or precancerous lesions usually detected by these screening programs was observed. The detection of skin lesions decreased by 36.01% (-1.31[95%CI: -1.18 to -1.44] per 10,000 IH; $P < 0.001$), followed by breast cancer/adenoma detection with a 31.05% decrease (-1.64[95%CI: -1.48 to -1.8] per 10,000 IH; $P < 0.001$) (Figure 1D). Among malignancies, the number of potentially missed or undiagnosed cases was most pronounced for breast cancer patients (-1.35/10,000 IH) and melanoma (-1.06/10,000 IH). Even after age- and sex standardization, we still observed the most striking decrease in incidence in these potentially preventable tumors (-38.4% for melanoma, -33.3% for breast cancer and -30.0% for prostate cancer) (Figure 1D).

While several reports have demonstrated a strong decrease in new cancer diagnoses during the first months of the COVID-19 pandemic (March-June 2020), to our knowledge, there currently exist no large-scale follow-up studies available. The present study is the first large register-based cohort study addressing this issue in Germany which includes not only inpatients but also outpatients data.

We found that cancers that typically manifest with severe symptoms, such as brain tumors, had only a slight and non-significant decrease in incidence. In contrast, more common cancer types mainly diagnosed by screening programs such as melanoma, breast cancer, prostate cancer (the latter being the most frequent cancers in women and men respectively in Germany) and colorectal cancers, which is the second most frequent type of cancer, showed decreased in incidence. The temporary stop of the respective screening programs can partially explain this effect. However, the observed decrease in colorectal cancers was greater than the numbers usually diagnosed by screening colonoscopies. This may be due to patients avoiding medical consultation for symptoms perceived as less severe during the COVID-19 pandemic. This hypothesis is further corroborated by the sharp decrease in cancer diagnoses in people aged >75 years who are no longer the main target of screening programs. For other cancers, such as gastric cancer, avoidance of potential aerosol-producing procedures like gastroscopies may explain why their incidence decreased.

Our findings align with a recent study from England showing that a 3- or 6-month delay in oncological surgeries decreases the 5-year survival rate by up to 35% for certain cancers [7]. In combination, these data suggest that there could be a secondary increase in cancer mortality to COVID-19 becoming evident in several years. A French study further showed worse survival rates of patients with metastatic colon cancer diagnosed during the first lockdown, presumably due to a higher tumor burden [8]. On the other hand, two recent database analyses for breast and prostate cancer could not confirm the reduced prognosis for delayed treatment in early-stage cancer [9, 10]. Both studies, however, analyzed data from patients who were already diagnosed and may thus not be directly comparable.

This study had several limitations. The BARMER statutory health insurance includes approximately 10% of the German population. There may, however, have been a selection bias as socio-economic factors may have influenced insurance status. Further, the available data does not include the cancer stage at the time of diagnosis. In addition to the overall decrease in cases, the tumor stage at the time of diagnosis could potentially also be more advanced. Lastly, due to our study's retrospective nature, no direct causal inference between the COVID-19 pandemic and the decrease in newly diagnosed cancerous and precancerous lesions could be made.

In conclusion, besides the direct impact of COVID 19 on health, there seems to be major collateral damage associated with the under-diagnosis of other medical conditions. The incidence of cancerous and precancerous lesions is 23.3% lower than expected. This mainly affects precancerous lesions and cancer types with an overall good prognosis if diagnosed early and for which screening programs have been implemented.

DECLARATIONS

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CONFLICT OF INTEREST

All Authors declare that he/she has no conflict of interest.

ETHICAL APPROVAL

Not applicable

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Writing - review & editing. All authors

CONSENT FOR PUBLICATION

All authors have consent for publication.

AVAILABILITY OF DATA AND MATERIALS

Data is available upon request from the "Institut fuer Gesundheitssystemforschung", BARMER (U Marschall).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.