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Heterogeneous impact of the COVID-19 pandemic on lung, colorectal and breast cancer incidence in Hungary: results from time series and panel data models

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Heterogeneous impact of the COVID-19 pandemic on lung, colorectal and breast cancer incidence in Hungary: results from time series and panel data models

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Abstract

Objective

During the COVID-19 pandemic, health system capacities and resources were reallocated to provide sufficient care for COVID patients, limiting access for others. Patients themselves also constrained their visits to healthcare providers. In this study we analysed the heterogeneous effects of the pandemic on the new diagnoses of lung, colorectal and breast cancer in Hungary.

Design

Time series and panel models of quarterly administrative data, disaggregated by gender, age group and district of residence.

Participants and setting

Data for the whole population of Hungary between 2017q1 and 2021q2.

Main outcome measures

Number of newly diagnosed lung, colorectal and breast cancer patients, defined as those who were hospitalised with the appropriate primary ICD-10 diagnosis code but had not had hospital encounters with such a code within the previous five years.

Results

We found that the incidence of the three types of cancer decreased by 15-20% during the examined period of the pandemic, with different time patterns across cancer types. Heterogeneity by gender was not statistically significant (p>0.1), and the incidence decreased more in percentage terms among people at least 65 years old than among the younger (p<0.05 for lung cancer and p<0.1 for colorectal cancer). At the district level, both the previously negative income gap in lung cancer incidence and the previously positive income gap in breast cancer incidence significantly narrowed during the pandemic (p<0.05).

Conclusions

The decline in new cancer diagnoses, caused by a combination of supply- and demand-side factors, highlights the fact that some cancer cases have remained hidden. It calls for action by policy makers to engage individuals with high risk of cancer more in accessing healthcare services, to diagnose the disease early and to prepare for effective management of patient pathways from diagnosis to survival or end-of-life care.

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Strengths and limitations of this study

- The effect of the COVID-19 pandemic on the three most common types of cancer was examined in Hungary based on nationwide administrative data until 2021q2.
- Heterogeneous effects by age group and the income level of the district of residence were found.
- Time series and panel data models were used.
- The potential supply- and demand-side mechanisms were outlined.
- Causal effects of these mechanisms could not be separated.

Word count: 3447

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1. Introduction

The COVID-19 pandemic is a huge challenge for healthcare systems and requires the highest level of resilience in health policy decision making. It is a learning process with countless pandemic-related issues to be addressed, very often involving trade-offs coupled with high-level of uncertainty [1]. It may come to the point, for example, where, at least temporarily, a choice has to be made between treating COVID or non-COVID patients, because the overburdened healthcare systems do not have the capacity to do both [2]. Effectively managing the pandemic requires thinking in terms of a complex system, with a high number of factors that are not linearly linked [3]. For example, preventive measures (wearing a mask, isolation, quarantine) and the proportion of the population vaccinated can affect the number of COVID patients, which then affects the necessary administrative restrictions on healthcare, which in turn can influence the availability and quality of services for non-COVID patients. In this indirect context, reserving inpatient capacity to treat COVID patients, which was a policy tool in many countries, and self-limiting patients' access to healthcare providers play an important role. To make the impact of such decisions clearer, ex post analyses of the consequences can provide a scientific basis to the management of the crisis in the future [1].

Lessons learned are of paramount importance in the case of serious chronic diseases such as cancer, which cannot be lumped together with other deferred care because of health priorities. Cancer is a complex disease that requires patients to undergo different types of procedures and laboratory or imaging tests to be diagnosed and staged. To achieve the maximum benefit for patients, these services must work in a coordinated manner, with a high level of patient engagement and compliance. Cancer survival can be increased by detecting tumours in the asymptomatic state, i.e. by screening programmes, and by rapid and effective investigation of suspected tumours, which can be enhanced by effective management of the cancer patient pathways [4]–[6]. Failure to do so can lead to lower quality of care and poorer outcomes for patients [7]. Due to the control measures of the COVID-19 pandemic [8], putative new cancer patients are exposed to a range of harms, including suspension of screening and prevention efforts, delays in timely diagnosis and staging of new patients, and delays in initiation of therapy [9].

According to a recent study, the impact of the COVID-19 pandemic on cancer care has been varying across countries [10]. In New Zealand, for example, the number of cancer diagnoses fell by 40% compared to previous years during the national shutdown in March-April 2020, before returning to pre-shutdown levels in the following months [11]. In contrast, in Catalonia, Spain, and in Belgium, where reductions of similar magnitude occured, the historical figures were not reached after the end

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of the lockdown [12, 13]. In Poland, unlike in other countries, a recent study showed no decline in the number of oncological diagnoses at hospitals during the first wave [14].

In Hungary, a European country with 9.7 million inhabitants, cancer incidence (623 new cases per 100,000 people) is 10% higher, and cancer mortality (330 deaths per 100,000 people) is 25% higher than the European Union average. The three most common types are lung, colorectal and breast cancer [15]. After a relatively mild first wave, the country was hit particularly hard – in international comparison – by the second (2020q4) and the third (2021q1-2021q2) waves of the COVID-19 pandemic, resulting in the death of 30,000 people (0.3% of the population) until June 2021 [16]. The aims of the corresponding health policy measures were to contain the spread of the virus and to reallocate resources to COVID-19 care. These included the suspension of population-level cancer screening programmes altogether for about three months (between 16 March – 1 June 2020 and between 9 April – 29 April 2021) and of elective and one-day surgeries for even longer periods, although oncological diagnostic and curative services were exempt from the suspensions. Despite the large direct and indirect effects on the healthcare system, no systematic mapping has taken place yet on how the diagnosis and care of cancer patients evolved during the pandemic in Hungary. (For a specific analysis of the effect of lower screening activity on breast cancer incidence, total and partial mastectomy rates see [17].) To understand the impact of the COVID-19 pandemic on cancer care, it is important to examine the trends in the number of newly diagnosed cases and the areas where health policy interventions may be needed.

The aim of our study was to analyse the heterogeneous effects of the COVID-19 pandemic on the new diagnoses of lung, colorectal and breast cancer until June 2021 in Hungary by gender, age group and district-level income.

2. Materials and Methods

Data

We used administrative inpatient care data that were collected by the National Health Insurance Fund Administration (NHIFA [NEAK]), the single payer of the Hungarian healthcare system, covering the whole population of the country (9.7 million people). We defined the number of newly diagnosed cancer patients as those who were hospitalised with the appropriate primary ICD-10 diagnosis code (C34 for lung cancer, C18-C21 for colorectal cancer and C50 for breast cancer) but had not had hospital encounters with such a code within the previous five years. The data were obtained by quarter (between 2017q1–2021q2), disaggregated by gender, five-year age group and district of residence.

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Hungary is composed of 197 districts, with an average population of about 50,000 people. (Specifically, Budapest, the capital consists of 23 districts.) For the district-level analysis, the data were merged to the year 2017 value of annual per capita taxable income of the district, which was obtained from the National Regional Development and Spatial Planning Information System (TeIR).

Beyond the crude incidence values in the aggregate as well as the gender- and age-specific analyses, we used the gender- and age-standardized incidence (with the 2017 population structure of Hungary as the baseline) in the district-level estimations. The (calendar year specific) size of the population of the corresponding gender, five-year age group and district was available from the TeIR system.

Statistical analysis

First, we performed time series modelling of the number of newly diagnosed lung, colorectal and breast cancer cases by estimating

(1) $\log y_t = \alpha + \beta t + \sum_{j=2}^{4} \gamma_j q_j + \sum_{k=2020Q1}^{2021Q2} \delta_k D_k + \varepsilon_t$

where t denotes time (quarter), y_t is the number of new cases, q_j $(j = 2,3,4)$ is the j-th calendar quarter (the first quarter being the baseline) and D_k $(k = 2020q1, ..., 2021q2)$ are dummy variables for the quarters of the pandemic. The parameters δ_k show the quarter-specific deviation from the usual trend and seasonality during the pandemic. Finally, ε_t is the error term. The models were estimated with ordinary least squares (OLS) as the error terms turned out to be serially uncorrelated in each model.

Second, we investigated heterogeneous effects by gender and age group by estimating equations

(2) $\log y_{gt} = \alpha_g + \beta_g t + \sum_{j=2}^{4} \gamma_{gj} q_j + \rho_g \sum_{k=2020Q2}^{2021Q2} D_k + \varepsilon_{gt},$

where g denotes gender (male or female) or age group (45-64 or 65+ years), hence ρ_g measures the overall change of the number of new cases by group during the five quarters of the pandemic. We also estimated $\rho_{male} - \rho_{female}$ and $\rho_{45-64\,years} - \rho_{65+\,years}$ in difference-in-difference specifications and evaluated their statistical significance (i.e. whether the effects are the same across gender or age group).

Third, to investigate how the effect of the pandemic varies by district-level income, we classified the districts into three income quantiles (tertiles) and showed the time series of the age- and gender-adjusted incidences by tertile. Afterwards, to formally estimate the heterogeneous effect by district-level income, we fitted the following models on district-quarter panel data:

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$$(3) \quad s_{it} = \alpha + \beta_0 t + \sum_{j=2}^{4} \gamma_{j0} q_j + \log I_i * \left(\beta_1 t + \sum_{j=2}^{4} \gamma_{j1} q_j \right) + \sum_{k=2020Q1}^{2021Q2} \delta_{k0} D_k + \log I_i * \theta * \sum_{k=2020Q2}^{2021Q2} D_k + c_i + \varepsilon_{it}$$

where i is district, t is time (quarter), and beyond the notations of equation (1), s_{it} is the adjusted incidence (per 100,000 inhabitants), $\log I_i$ is the year 2017 logarithmic district-level per capita income and c_i are district fixed effects.[1] (Hence we estimated a standard fixed-effects panel model [18].) The parameter of interest is $\theta/100$, which shows the relative effect of the pandemic in a better-off district compared to a worse-off one, i.e. how a 1% larger average income of the district affected the change of the incidence during the pandemic.

Patient and public involvement

Due to the nature of the study, patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3. Results

Aggregate, age- and gender-specific effects

According to the upper panel of Figure 1, the quarterly number of new cases of the three major types of cancer was between 1800–2400 before the pandemic, corresponding to annual unadjusted incidence rates of 78–92 per 100,000 inhabitants. The lower panel of the Figure shows the changes of the new case numbers in 2020–2021 compared to the trend and seasonality of the preceding three years (i.e. the parameter estimates of the pandemic dummies from equation (1)), with 95% confidence intervals. (Details of the estimated models are given in Appendix Table A1.) The incidence of colorectal and breast cancer decreased by 25–30% in 2020q2 and remained below the historical trend by about 10% in 2020q3. Afterwards, breast cancer incidence reached its usual level in 2020q4, but colorectal cancer incidence still remained significantly lower. Then, the incidence of both types of cancer fell short of the historical trend by 20–25% in the first half of 2021. Meanwhile, the decline of lung cancer incidence was more flat, being below the historical trend by 10–16% during each quarter. Overall, the incidence of the three major types of cancer decreased by 15–20% in the first five quarters of the pandemic, between 2020q2 and 2021q2.

Figure 2 shows the cumulative number of new cases between 2020q1–2021q2, compared to two earlier periods (2017q1–2018q2 and 2018q1–2019q2). During this time, around 5,000 fewer people

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[1] Here we used s_{it} instead of $\log s_{it}$ because of zeros in some district-quarter observations.

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than usual (around 50 fewer per 100,000 inhabitants) were diagnosed with the three major types of cancer combined.

According to Figure 3, the number of new cases declined more substantially for the 65+ years old than for the 45–64 years old population; according to the upper panel of Table 1, the difference was 10–16 percentage points and was statistically significant for lung cancer (p<0.05) and colorectal cancer (p<0.1). On the other hand, the middle panel of Table 1 shows that there was no statistically significant difference across genders in the decrease of cancer incidence.

Table 1: Regression results for the heterogeneity of the change of incidence during the pandemic by gender, age group and district-level income

	Lung cancer		Colorectal cancer		Breast cancer	
Effect of 2020q2-2021q2 on new case numbers (in %) by age group						
-64 years	-8.5**	(3.0)	-12.3**	(4.4)	-7.9	(7.0)
65+ years	-18.1***	(2.6)	-23.4***	(3.8)	-22.6***	(5.9)
Difference	-10.4**	(4.1)	-12.6*	(6.2)	-15.9	(9.0)
Effect of 2020q2-2021q2 on new case numbers (in %) by gender						
Females	-15.8***	(1.9)	-20.7***	(3.8)		
Males	-13.2***	(2.0)	-19.4***	(3.9)		
Difference	3.1	(3.4)	1.7	(7.0)		
Effect of district-level income on the change of incidence (per 100,000 people) in 2020q2-2021q1						
Log income * Dummy (2020q2-2021q2)	4.4**	(2.0)	-1.6	(1.8)	-4.5**	(2.1)
Note: Mean dependent variable	20.9		22.8		19.4	

*** p<0.01, ** p<0.05, * p<0.1. Standard errors in parentheses.
Upper two parts: estimated ρ_g-s from the logarithmic model (2), transformed to the percentage scale. The estimated differences ($\rho_{male} - \rho_{female}$ and $\rho_{65 + years} - \rho_{45 - 64 years}$), transformed to the percentage scale, are also shown. Gender and age group specific time series models. Controls: linear trend and seasonal dummies. Period: 2017q1–2021q2. Number of quarters: 18.
Lower part: estimated θ-s from equation (3) are shown. District-quarter panel. Number of districts: 197. Period: 2017q1–2021q2. Number of quarters: 18. Controls: district fixed effects; and linear trend, seasonal dummies and dummy of the pandemic, each interacted with log district-level per capita income. The mean of the adjusted incidence per 100,000 inhabitants is shown as a note.

District-level effects

In Hungary, average income differences across districts are substantial, with a 2.6–fold difference between the richest vs. the poorest district, and a 1.8–fold difference between the 95% and 5% quantile in terms of district-level taxable income. Figure 4 shows the time series of gender- and age-standardized cancer incidence in three quantiles (tertiles) defined by district-level income. Before the pandemic, lung cancer incidence was higher and breast cancer incidence was lower in the worse-off districts compared to the better-off ones. However, during the pandemic, lung cancer incidence decreased to a greater extent and breast cancer incidence to a smaller extent in the worse-off districts (compared to the better-off ones), hence the income gradient (which was negative for lung cancer and

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positive for breast cancer) narrowed for both types of cancer. According to the lower panel of Table 1, a 1% higher district-level income was associated with a 0.044 smaller decrease for lung cancer (95% confidence interval: 0.005–0.083) and a 0.045 larger decrease for breast cancer (95% CI: 0.004–0.086) quarterly incidence per 100,000 inhabitants during the pandemic. (For comparison, the average quarterly incidence was 19–21 per 100,000 inhabitants.) Meanwhile, no clear pattern (and no statistically significant association) emerged for colorectal cancer.

4. Discussion

Our study provided a detailed analysis of the number of diagnoses of the three most common types of cancer in Hungary during the COVID-19 pandemic and considered the changes by age, gender and income level of the district of residence.

Overall, we found a 15-20% decrease in the number of cases between 2020q2 and 2021q2. While in principle it is possible that the true cancer incidence also decreased somewhat due to COVID-19, we conclude, in line with the experience of several other countries [10], that the significant drop in the number of diagnoses is mostly due to undiagnosed cases. Indeed, in the first five quarters of the pandemic, only around 0.5 percentage point of the decrease of observed case numbers could be explained with COVID-19 mortality even in the 65+ years old age group (and a negligible share in the younger population).[2] Although we acknowledge that, beyond age, some other variables such as lifestyle or comorbidities may simultaneously increase the risk of cancer and COVID-19 death, these background factors may explain only a minor additional part of the decrease of cancer incidence. For instance, smoking, which drastically increases the risk of lung cancer, increases the COVID-19 mortality rate only moderately (OR=1.35) [19].

The drop in newly diagnosed cancer cases was less than what was observed with comparable methods in Catalonia, a region that took a worse hit from COVID-19 than Hungary during the first wave (11–15% in Hungary vs. 34% in Catalonia in March-September of 2020 [12]) but was larger than in Belgium (7–14% vs. 6% in 2020 [13]). What is even more troubling from a health policy point of view is the fact that, unlike in New Zealand [11], at least during the period under scrutiny, with the exception of breast cancer in 2020q4, we did not observe the health system catching up fully in diagnosing putative undiagnosed cancers in the breaks between the pandemic waves. Instead, cancer incidence remained below its historical average up until 2021q2, the end of our observation period.

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[2] Between 2020q2–2021q2, less than 0.1% of the 0–64 years old and around 1.4% of the 65+ years old population of Hungary died from COVID-19, but two-thirds of these deaths occurred in 2021, which cannot explain the drop in diagnoses in the earlier quarters.

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This is all the more of concern because the contraction of cancer diagnosis or treatment was never among the stated health policy measures meant to free up capacity to deal with the pandemic. Thus we conclude that the mechanisms by which COVID-19 has had this adverse effect on cancer diagnoses must be different. In what follows we present some possible causes – both on the supply and the demand side of health care – that can explain the decrease and the lack of subsequent rebound in cancer diagnosis and therapy.

First, on the supply side, as already mentioned above, organized breast cancer screening was suspended twice during the pandemic (specifically for its effects see [17]), and the nationwide colorectal cancer screening programme has not yet been effectively implemented after successful regional pilots in previous years [20, 21].

Second, the reallocation of healthcare provider capacities to COVID-related care (i.e. the involvement of medical personnel and equipment in COVID intensive care units, vaccination, etc.) may have had an indirect impact on the number of interventions performed as the workload due to COVID-19 might have taken capacity away from cancer care.

Third, the performance-based reimbursement techniques for specialist outpatient and inpatient care that are normally linked to patient visits and providers' activities (procedure codes in outpatient care and diagnosis related groups in inpatient care) were suspended at the very beginning of the pandemic in March 2020 and since then have remained so. Instead, new prospective budgets were assigned to all providers based on the performance of previous years. Hence, the financial incentives [22] for providers' performance (higher patient numbers and cases leading to more revenues) disappeared. Understandably, such a change in financial incentives may have had a negative effect on the activity of healthcare providers.

Fourth, a new law on employment conditions of healthcare personnel has been in force since March 2021. Several provisions of this new regulation, which was a crucial step regarding the modernization of the healthcare sector in Hungary, have an effect on healthcare delivery, e.g. rules on incompatibility between private and public sector employment and penalization of informal out-of-pocket payments. The ban on informal payments was accompanied by a one-off, substantial wage increase, but no performance incentive scheme was introduced to motivate more efficient care. During the third pandemic wave, this may have negatively affected finding cancer patients who had been undiagnosed.

Fifth, on the demand side of the healthcare system, patients' readiness to visit a doctor could also decrease. Indeed, there is evidence that symptomatic patients have avoided healthcare providers due to fear of COVID-19 infection, leading to increased morbidity and mortality [23]. A recent study showed

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that the most significant concern expressed by oncology patients about the COVID-19 pandemic was fear [24].

We note that although the second and the third waves of the pandemic resulted in significantly more COVID-19 cases and deaths in Hungary, the decline in the new diagnoses (at least in breast and colorectal cancer) was more significant during the first wave. We could clearly see a learning curve: both patients and providers learned to live and act in the given pandemic situation meaning also that skyrocketing numbers of COVID-19 cases in the second or the third wave did not lead to larger patient withdrawal than in the first wave. The effect of the pandemic on cancer incidence is heterogeneous over time and thus it may be difficult to extrapolate the short- and medium-term observations into the future.

We consider it a particular strength of our paper that we could use a large set of administrative data covering the period until June 2021 – a more extended interval than used in the international papers reviewed above or made publicly available specifically for Hungary.[3] Also, based on these data, we could examine heterogeneities by age group, gender and the income level of the district of residence. The estimated larger decrease for the older than for the younger population is in line with other papers [12, 13] and show that the combined effect of the mechanisms outlined above was stronger there.

Our district-level analysis gives a more nuanced picture on socioeconomic heterogeneity than a previous study did [12] because, having had access to data on 197 districts with vastly different average incomes and a population of 50,000 people on average, we had enough statistical power to estimate the effect on different cancer types separately. We found that breast cancer incidence, which is detected with screening in the majority of cases [26], dropped statistically significantly more in the better-off than in the worse-off districts, while the number of new lung cancer cases, for which no population-level screening programme exists in Hungary, decreased more in the worse-off districts. There was no statistically significant relationship for colorectal cancer. We note that district-level analyses have already proved fruitful for establishing socioeconomic heterogeneities in other COVID-related outcomes as well in Hungary [27].

Our study also has some limitations. First, the causal effects of the aforementioned mechanisms could not be separated based on the available semiaggregate data, and second, longer-term outcome

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[3] The aggregate number of new cancer patients in Hungary, calculated with a slightly different methodology than ours, is available from the National Cancer Register for 2020 [25]. According to those data, the total number of new cancer diagnoses decreased by 13% in 2020 (compared to 2019), while in our calculation the combined number of the three most frequent cancer types decreased by 12% in that year.

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measures such as mortality could not be examined because of the limited time span since the outbreak of the pandemic.

Turning to policy conclusions, the decline in the number of newly diagnosed patients due to delayed or unavailable care is a risk for public healthcare systems as the global cancer burden is rising [28]. Our findings can inform health policy actors about the projected excess cancer cases, expected interventions hence increased morbidity and mortality in the years to come due to delayed diagnosis during the pandemic. Also, when facing the subsequent waves of the pandemic, we are more capable of describing the mechanisms, forecasting the consequences of a new wave and evaluating the trade-offs associated with various policy interventions.

As during the early waves of the pandemic numerous policy decisions had to be made uninformed, "in the fog of war", the impact of these decisions on patient care and outcomes deserves further investigation to develop an evidence-based policy approach for the future. On the other hand, the fact that patients themselves have restricted their visits to healthcare providers out of fear calls for action by policy makers to engage potential cancer patients in accessing healthcare services, to diagnose the disease early and to prepare for effective management of patient pathways from diagnosis to survival or end-of-life care.

5. Statements

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Figure legends

Figure 1: Number of new cancer cases (2017q1–2021q2) and deviation from the trend and
seasonality (2020q1–2021q2)

Note: The lower panel shows the parameter estimates of the dummies for 2020q1–2021q2 from the logarithmic
model (1) (displayed in Appendix Table A1), transformed to the percentage scale, with 95% confidence intervals.
Controls: linear trend and seasonal dummies. Period: 2017q1–2021q2. Number of quarters: 18

Figure 2: Cumulative number of new cancer cases during the pandemic and in previous periods

Figure 3: Number of new cancer cases by age group (2017q1–2021q2)

Figure 4: Gender- and age-adjusted incidence (per 100,000 inhabitants) by district-level income
tertile for lung, colorectal and breast cancer (2017q1–2021q2)

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Figure 1: Number of new cancer cases (2017q1–2021q2) and deviation from the trend and seasonality (2020q1–2021q2)

Note: The lower panel shows the parameter estimates of the dummies for 2020q1–2021q2 from the logarithmic model (1) (displayed in Appendix Table A1), transformed to the percentage scale, with 95% confidence intervals. Controls: linear trend and seasonal dummies. Period: 2017q1–2021q2. Number of quarters: 18

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Figure 2: Cumulative number of new cancer cases during the pandemic and in previous periods

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Figure 3: Number of new cancer cases by age group (2017q1–2021q2)

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Figure 4: Gender- and age-adjusted incidence (per 100,000 inhabitants) by district-level income tertile for lung, colorectal and breast cancer (2017q1–2021q2)
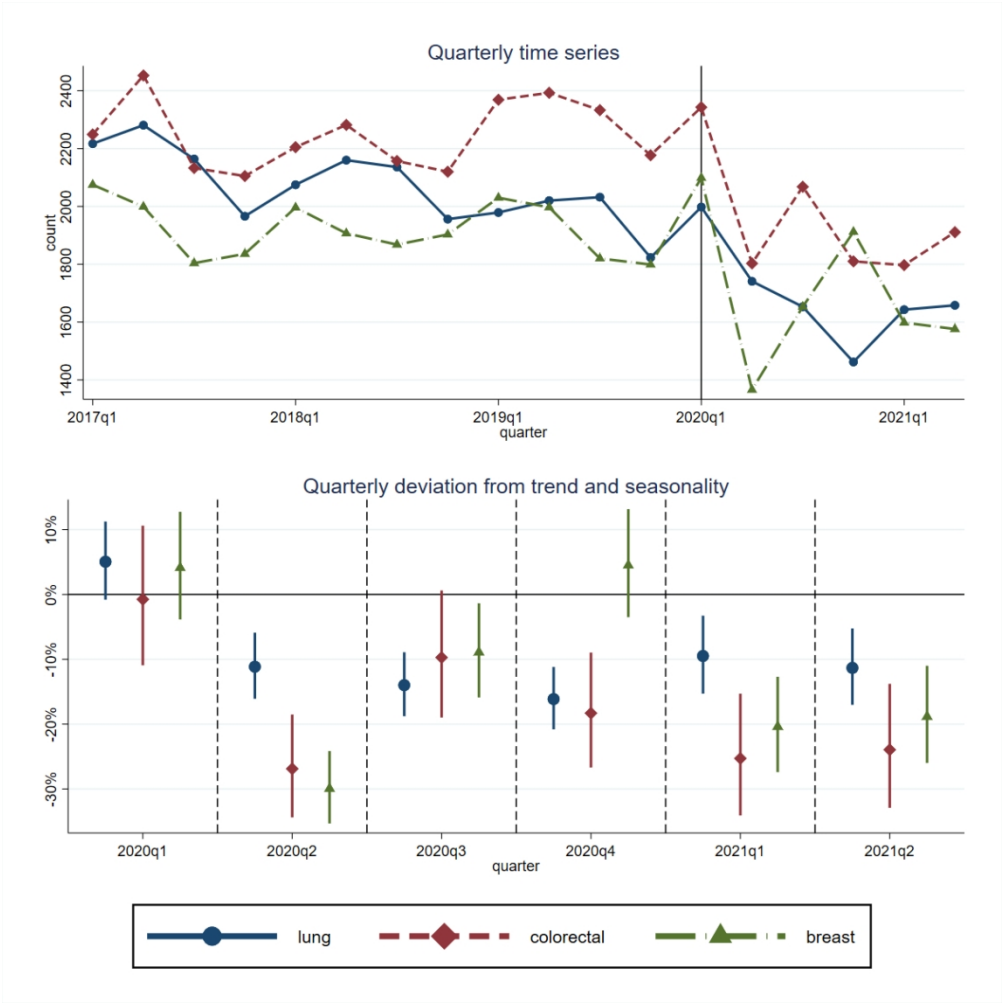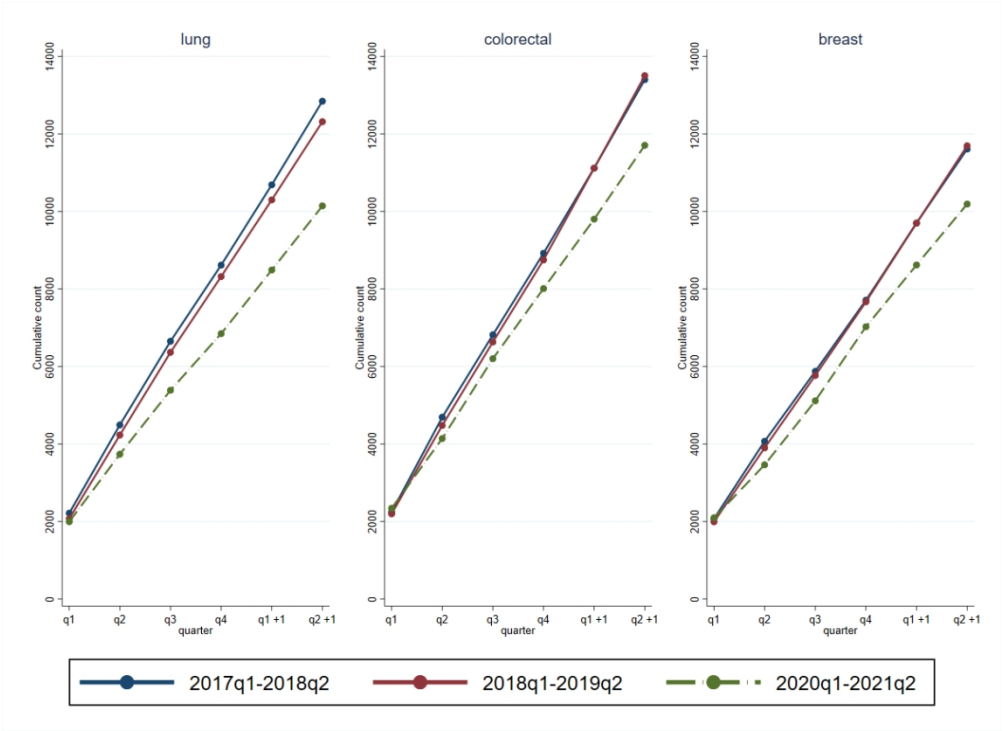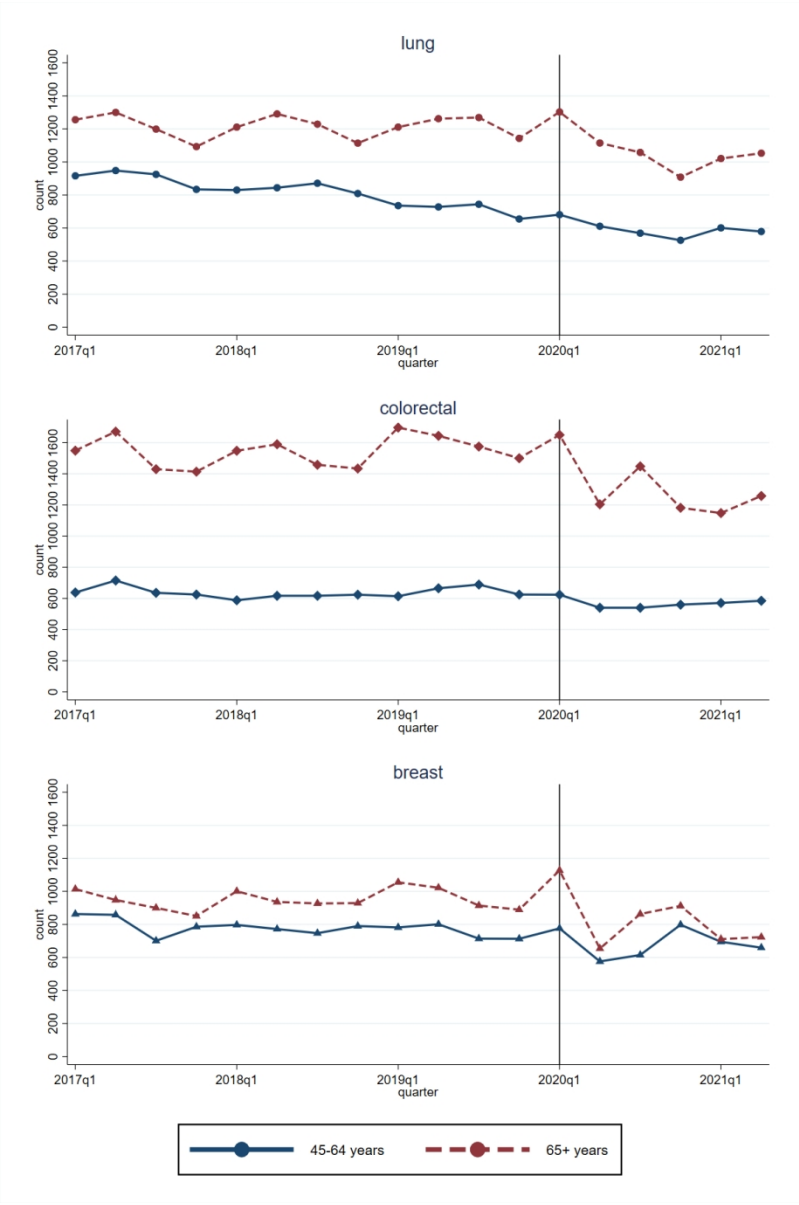
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Appendix Table A1: Details of the time series models

	log new lung cancer		log new colorectal cancer		log new breast cancer	
Quarterly trend	-0.0117***	(0.0016)	0.0047	(0.0030)	-0.0011	(0.0022)
Seasonal dummies (baseline = q1)						
q2	0.041**	(0.015)	0.039	(0.028)	-0.032	(0.020)
q3	0.0337*	(0.015)	-0.040	(0.028)	-0.103***	(0.021)
q4	-0.052**	(0.015)	-0.078**	(0.029)	-0.094***	(0.021)
Dummies between 2020q1 – 2021q2						
2020q1	0.049*	(0.024)	-0.0074	(0.046)	0.040	(0.034)
2020q2	-0.118***	(0.024)	-0.313***	(0.046)	-0.356***	(0.034)
2020q3	-0.151***	(0.024)	-0.102*	(0.046)	-0.093**	(0.034)
2020q4	-0.176***	(0.024)	-0.202***	(0.046)	0.044	(0.034)
2021q1	-0.100***	(0.028)	-0.292***	(0.053)	-0.228***	(0.039)
2021q2	-0.120***	(0.028)	-0.274***	(0.053)	-0.209***	(0.039)
Constant	10.35***	(0.367)	6.64***	(0.694)	7.87***	(0.510)

*** $p<0.01$, ** $p<0.05$, * $p<0.1$. Standard errors in parentheses.
Quarterly time series between 2017q1–2021q2. Number of quarters: 18.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	5-6
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		7-9
		(*b*) Report category boundaries when continuous variables were categorized		6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		8-9
Discussion				
Key results	18	Summarise key results with reference to study objectives		9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results		11
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Heterogeneous impact of the COVID-19 pandemic on lung, colorectal and breast cancer incidence in Hungary: results from time series and panel data models

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Heterogeneous impact of the COVID-19 pandemic on lung, colorectal and breast cancer incidence in Hungary: results from time series and panel data models

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1

Abstract

Objective

During the COVID-19 pandemic, health system resources were reallocated to provide care for COVID-19 patients, limiting access for others. Patients themselves also constrained their visits to healthcare providers. In this study we analysed the heterogeneous effects of the pandemic on the new diagnoses of lung, colorectal and breast cancer in Hungary.

Design

Time series and panel models of quarterly administrative data, disaggregated by gender, age group and district of residence.

Participants

Data for the whole population of Hungary between the first quarter of 2017 and the second quarter of 2021.

Main outcome measures

Number of newly diagnosed lung, colorectal and breast cancer patients, defined as those who were hospitalised with the appropriate primary ICD-10 diagnosis code but had not had hospital encounters with such a code within the previous five years.

Results

The incidence of lung, colorectal and breast cancer decreased by 14.4% (95% CI 10.8% to 17.8%), 19.9% (95% CI 12.2% to 26.9%) and 15.5% (95% CI 2.5% to 27.0%), respectively, during the examined period of the pandemic, with different time patterns across cancer types. The incidence decreased more among people at least 65 years old than among the younger (p<0.05 for lung and p<0.1 for colorectal cancer). At the district level, both the previously negative income gap in lung cancer incidence and the previously positive income gap in breast cancer incidence significantly narrowed during the pandemic (p<0.05).

Conclusions

The decline in new cancer diagnoses, caused by a combination of supply- and demand-side factors, suggests that some cancer cases have remained hidden. It calls for action by policy makers to engage individuals with high risk of cancer more in accessing healthcare services, to diagnose the disease early and to prepare for effective management of patient pathways from diagnosis to survival or end-of-life care.

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Keywords: cancer incidence, COVID-19, time series, panel data

Strengths and limitations of this study

- The effect of the COVID-19 pandemic on the incidence of the three most common types of cancer was examined in Hungary based on nationwide administrative data until the second quarter of 2021.
- The aggregate effect was estimated with time series models to control for previous trend and seasonality, while the heterogeneous effects by gender, age group and the income level of the district of residence were estimated with panel data models.
- Causal effects of the potential supply- and demand-side mechanisms (that are outlined in the paper) could not be established.
- Disease stages and longer-term outcomes such as mortality could not be examined because of the lack of data.

Word count: 4004

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1. Introduction

The COVID-19 pandemic is a huge challenge for healthcare systems and requires the highest level of resilience in health policy decision making. It is a learning process with countless pandemic-related issues to be addressed, very often involving trade-offs coupled with high-level of uncertainty [1]. For example, it had gotten to the point where, at least temporarily, a choice had to be made between treating COVID-19 or non-COVID-19 patients, because the overburdened healthcare systems did not have the capacity to do both [2]. Effectively managing the pandemic requires thinking in terms of a complex system, with a high number of factors that are not linearly linked [3]. For example, preventive measures (wearing a mask, isolation, quarantine) and the proportion of the population vaccinated can affect the number of COVID-19 patients, which then affects the necessary administrative restrictions on healthcare, which in turn can influence the availability and quality of services for non-COVID-19 patients. In this indirect context, reserving inpatient capacity to treat COVID-19 patients, which was a policy tool in many countries, and self-limiting patients' access to healthcare providers play an important role. To make the impact of such decisions clearer, ex post analyses of the consequences can provide a scientific basis to the management of the crisis in the future [1].

Lessons learned are of paramount importance in the case of serious chronic diseases such as cancer, which cannot be lumped together with other deferred care because of health priorities. Cancer is a complex disease that requires patients to undergo different types of procedures and laboratory or imaging tests to be diagnosed and staged. To achieve the maximum benefit for patients, these services must work in a coordinated manner, with a high level of patient engagement and compliance. Cancer survival can be increased by detecting tumours in the asymptomatic state, i.e. by screening programmes, and by rapid and effective investigation of suspected tumours, which can be enhanced by effective management of the cancer patient pathways [4]–[6]. Failure to do so can lead to lower quality of care and poorer outcomes for patients [7]. Due to the control measures of the COVID-19 pandemic [8], putative new cancer patients are exposed to a range of harms, including suspension of screening and prevention efforts, delays in timely diagnosis and staging of new patients, and delays in initiation of therapy [9].

According to a recent study, the impact of the COVID-19 pandemic on cancer care has been varying across countries [10]. In New Zealand, for example, the number of cancer diagnoses fell by 40% compared to previous years during the national shutdown in March-April 2020, before returning to pre-shutdown levels in the following months [11]. In contrast, in Catalonia, Spain, and in Belgium, where reductions of similar magnitude occurred, the historical figures were not reached after the end

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of the lockdown [12, 13]. In Poland, unlike in other countries, a recent study showed no decline in the number of oncological diagnoses at hospitals during the first wave [14].

In Hungary, a European country with 9.7 million inhabitants, cancer incidence (623 new cases per 100,000 people) is 10% higher, and cancer mortality (330 deaths per 100,000 people) is 25% higher than the European Union average. The three most common types are lung, colorectal and breast cancer [15]. Population-level breast cancer screening has been available for women aged 45-64 since 2002 [16], while colorectal cancer screening was initiated for people aged 50-70 in 2018 [17].

The Hungarian healthcare system is highly centralised. The state has exclusive powers to set the strategic direction, control funding, define the benefits package, and issue and implement regulations. The country has a single health insurance fund. Public outpatient and inpatient services are formally free of charge at the point of care, although – as in other Central and Eastern European countries [18] – informal payments had been a constant challenge before they were made illegal and sanctioned in 2021. There is a growing private outpatient care sector as well [15].

After a relatively mild first wave, Hungary was hit particularly hard – in international comparison – by the second (2020q4) and the third (2021q1-2021q2) waves of the COVID-19 pandemic, resulting in the death of 30,000 people (0.3% of the population) until June 2021 [19].[1] The aims of the corresponding health policy measures were to contain the spread of the virus and to reallocate resources to COVID-19 care. These included the suspension of population-level cancer screening programmes (such as breast and colorectal screening) altogether for about three months (between 16 March – 1 June 2020 and between 9 April – 29 April 2021) and of elective and one-day surgeries for even longer periods, although oncological diagnostic and curative services were exempt from the suspensions. Other important policy measures included the replacement of performance-based reimbursement with global budgets during the whole pandemic to maintain the financial sustainability and solvency of healthcare providers. In 2021, beyond the already mentioned ban on informal payments, significant increases in physicians' salaries were introduced [20].

Despite the large direct and indirect effects on the healthcare system, no systematic mapping has taken place yet on how the diagnosis and care of cancer patients evolved during the pandemic in Hungary. (For a specific analysis of the effect of lower screening activity on breast cancer incidence, total and partial mastectomy rates see [21].) To understand the impact of the COVID-19 pandemic on cancer care, it is important to examine the trends in the number of newly diagnosed cases and the areas where health policy interventions may be needed.

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[1] Throughout the paper, qi denotes the i-th calendar quarter of a year.

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The aim of our study was to analyse the heterogeneous effects of the COVID-19 pandemic on the new diagnoses of lung, colorectal and breast cancer until June 2021 in Hungary by gender, age group and district-level income.

2. Materials and Methods

Data

We used administrative inpatient care data that were collected by the National Health Insurance Fund Administration (NHIFA [NEAK]), the single payer of the Hungarian healthcare system, covering the whole population of the country (9.7 million people). We defined the number of newly diagnosed cancer patients as those who were hospitalised with the appropriate primary ICD-10 diagnosis code (C34 for lung cancer, C18-C21 for colorectal cancer and C50 for breast cancer) but had not had hospital encounters with such a code within the previous five years.[2] The data were obtained by quarter (between 2017q1–2021q2), disaggregated by gender, five-year age group and district of residence.

Hungary is composed of 197 districts, with an average population of about 50,000 people. (Specifically, Budapest, the capital consists of 23 districts.) For the district-level analysis, the data were merged to the year 2017 value of annual per capita taxable income of the district, which was obtained from the National Regional Development and Spatial Planning Information System (TeIR).

Beyond the crude incidence values in the aggregate as well as the gender- and age-specific analyses, we used the gender- and age-standardized incidence (with the 2017 population structure of Hungary as the baseline) in the district-level estimations. The (calendar year specific) size of the population of the corresponding gender, five-year age group and district was available from the TeIR system.

Statistical analysis

First, we performed time series modelling of the number of newly diagnosed lung, colorectal and breast cancer cases by estimating

(1) $\log y_t = \alpha + \beta t + \sum_{j=2}^{4} \gamma_j q_j + \sum_{k=2020Q1}^{2021Q2} \delta_k D_k + \varepsilon_t$

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[2] In this study we used financing, and not register data, and did not have more detailed information such as disease stage or subtype within the major groups of lung, colorectal or breast cancer. However, similar NHIFA data were applied in the past fruitfully to estimate cancer incidence in Hungary (see e.g. [22] for lung cancer). Also, we note that although cancer screening and diagnostic procedures are practiced in the private sector as well, essentially all of the main oncological treatment modalities (surgery, chemotherapy, radiation therapy) is carried out in the public sector and coded as inpatient data. Hence patients who were diagnosed in the private sector appear in our definition when they first undergo treatment in the public sector.

where t denotes time (quarter), y_t is the number of new cases, q_j ($j = 2,3,4$) is the j-th calendar quarter (the first quarter being the baseline) and D_k ($k = 2020q1, ..., 2021q2$) are dummy variables for the quarters of the pandemic. The parameters δ_k show the quarter-specific deviation from the usual trend and seasonality during the pandemic. Finally, ε_t is the error term. The models were estimated with ordinary least squares (OLS) as the error terms turned out to be serially uncorrelated in each model. Then, OLS provides unbiased estimates of the parameters (with appropriate standard errors).

Second, we estimated the following equations, where ρ measures the overall effect during the first five quarters of the pandemic, between 2020q2 and 2021q2:

(2) $\log y_t = \alpha + \beta t + \sum_{j=2}^{4} \gamma_j q_j + \rho \sum_{k=2020Q2}^{2021Q2} D_k + \varepsilon_t.$

Third, we investigated heterogeneous effects by gender and age group by estimating equations

(3) $\log y_{gt} = \alpha_g + \beta_g t + \sum_{j=2}^{4} \gamma_{gj} q_j + \rho_g \sum_{k=2020Q2}^{2021Q2} D_k + \varepsilon_{gt},$

where g denotes gender (male or female) or age group (45-64 or 65+ years), hence ρ_g measures the overall change of the number of new cases by group during the five quarters of the pandemic.[3] We also estimated $\rho_{male} - \rho_{female}$ and $\rho_{45-64\ years} - \rho_{65+years}$ in difference-in-difference specifications and evaluated their statistical significance (i.e. whether the effects are the same across gender or age group).

Fourth, to investigate how the effect of the pandemic varies by district-level income, we classified the districts into three income quantiles (tertiles) and showed the time series of the age- and gender-adjusted incidences by tertile. Afterwards, to formally estimate the heterogeneous effect by district-level income, we fitted the following models on district-quarter panel data:

(4) $s_{it} = \alpha + \beta_0 t + \sum_{j=2}^{4} \gamma_{j0} q_j + \log I_i * \left(\beta_1 t + \sum_{j=2}^{4} \gamma_{j1} q_j \right) + \sum_{k=2020Q1}^{2021Q2} \delta_{k0} D_k + \log I_i * \theta * \sum_{k=2020Q2}^{2021Q2} D_k + c_i + \varepsilon_{it}$

where i is district, t is time (quarter), and beyond the notations of equation (1), s_{it} is the adjusted incidence (per 100,000 inhabitants), $\log I_i$ is the year 2017 logarithmic district-level per capita income

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[3] We did not examine the 0-44 years old age group specifically because of the small sample size (only 1.8%, 3.4% and 11.7% of new lung, colorectal and breast cancer patients, respectively, were below 45 years between 2017-2019). The aggregate analysis contains these patients as well.

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and c_i are district fixed effects.[4] (Hence we estimated a standard fixed-effects panel model [23].) The parameter of interest is $\theta/100$, which shows the relative effect of the pandemic in a higher-income district compared to a lower-income one, i.e. how a 1% larger average income of the district affected the change of the incidence during the pandemic.

Patient and public involvement

Due to the nature of the study, patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3. Results

Aggregate, age- and gender-specific effects

According to the upper panel of Figure 1, the quarterly number of new cases of the three major types of cancer was between 1800–2400 before the pandemic, corresponding to annual unadjusted incidence rates of 78–92 per 100,000 inhabitants. The lower panel of the Figure shows the changes of the new case numbers in 2020–2021 compared to the trend and seasonality of the preceding three years (i.e. the parameter estimates of the pandemic dummies from equation (1)), with 95% confidence intervals. (Details of the estimated models are given in Appendix Table A1.) The incidence of colorectal and breast cancer decreased by 26.9% (95% CI 18.5% to 34.4%) and by 30.0% (95% CI 24.1% to 35.4%), respectively, in 2020q2 and remained only slightly below the historical trend in 2020q3. Afterwards, breast cancer incidence reached its usual level in 2020q4, but colorectal cancer incidence still remained significantly lower. Then, the incidence of both types of cancer fell short of the historical trend by 20–25% in the first half of 2021. Meanwhile, the decline of lung cancer incidence was more flat, being below the historical trend by 10–16% during each quarter.

Overall, as the upper panel of Table 1 shows, the incidence of lung, colorectal and breast cancer decreased by 14.4% (95% CI 10.8% to 17.8%), 19.9% (95% CI 12.2% to 26.9%) and 15.5% (95% CI 2.5% to 27.0%), respectively, in the first five quarters of the pandemic, between 2020q2 and 2021q2.

Figure 2 shows the cumulative number of new cases between 2020q1–2021q2, compared to two earlier periods (2017q1–2018q2 and 2018q1–2019q2). During this time, around 5,000 fewer people than usual (around 50 fewer per 100,000 inhabitants) were diagnosed with the three major types of cancer combined.

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[4] Here we used s_{it} instead of $\log s_{it}$ because of zeros in some district-quarter observations.

According to Figure 3, the number of new cases declined more substantially for the 65+ years old than for the 45–64 years old population; according to the second panel of Table 1, the difference was 10–16 percentage points and was statistically significant for lung cancer (p<0.05) and colorectal cancer (p<0.1). On the other hand, the third panel of Table 1 shows that there was no statistically significant difference across genders in the decrease of cancer incidence.

Table 1: Regression results for the the change of incidence during the pandemic aggregately and by gender, age group and district-level income

	Lung cancer		Colorectal cancer		Breast cancer	
Effect of 2020q2-2021q2 on new case numbers (in %)	-14.4***	(1.6)	-19.9***	(3.4)	-15.5**	(5.6)
Effect of 2020q2-2021q2 on new case numbers (in %) by age group						
-64 years	-8.5**	(3.0)	-12.3**	(4.4)	-7.9	(7.0)
65+ years	-18.1***	(2.6)	-23.4***	(3.8)	-22.6***	(5.9)
Difference	-10.4**	(4.1)	-12.6*	(6.2)	-15.9	(9.0)
Effect of 2020q2-2021q2 on new case numbers (in %) by gender						
Females	-15.8***	(1.9)	-20.7***	(3.8)		
Males	-13.2***	(2.0)	-19.4***	(3.9)		
Difference	3.1	(3.4)	1.7	(7.0)		
Effect of district-level income on the change of incidence (per 100,000 people) in 2020q2-2021q1						
Log income * Dummy (2020q2-2021q2)	4.4**	(2.0)	-1.6	(1.8)	-4.5**	(2.1)
Note: Mean dependent variable	20.9		22.8		19.4	

*** p<0.01, ** p<0.05, * p<0.1. Standard errors in parentheses.
Upper part: estimated ρ from the logarithmic model (2), second and third parts: estimated ρ_g-s from the logarithmic model (3), each transformed to the percentage scale. The estimated differences ($\rho_{male} - \rho_{female}$ and $\rho_{65 + years} - \rho_{45 - 64 years}$), transformed to the percentage scale, are also shown. Gender and age group specific time series models. Controls: linear trend and seasonal dummies. Period: 2017q1–2021q2. Number of quarters: 18.
Lower part: estimated θ-s from equation (4) are shown. District-quarter panel. Number of districts: 197. Period: 2017q1–2021q2. Number of quarters: 18. Controls: district fixed effects; and linear trend, seasonal dummies and dummy of the pandemic, each interacted with log district-level per capita income. The mean of the adjusted incidence per 100,000 inhabitants is shown as a note.

District-level effects

In Hungary, average income differences across districts are substantial, with a 2.6–fold difference between the richest vs. the poorest district, and a 1.8–fold difference between the 95% and 5% quantile in terms of district-level taxable income. Figure 4 shows the time series of gender- and age-standardized cancer incidence in three quantiles (tertiles) defined by district-level income. Before the pandemic, lung cancer incidence was higher and breast cancer incidence was lower in the lower-income districts compared to the higher-income ones. However, during the pandemic, lung cancer incidence decreased to a greater extent and breast cancer incidence to a smaller extent in the lower-income districts (compared to the higher-income ones), hence the income gradient (which was negative for lung cancer and positive for breast cancer) narrowed for both types of cancer. According

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to the lower panel of Table 1, a 1% higher district-level income was associated with a 0.044 smaller decrease for lung cancer (95% CI 0.005 to 0.083) and a 0.045 larger decrease for breast cancer (95% CI 0.004 to 0.086) quarterly incidence per 100,000 inhabitants during the pandemic. (For comparison, the average quarterly incidence was 19–21 per 100,000 inhabitants.) Meanwhile, no clear pattern (and no statistically significant association) emerged for colorectal cancer.

4. Discussion

Our study provided a detailed analysis of the number of diagnoses of the three most common types of cancer in Hungary during the COVID-19 pandemic and considered the changes by age, gender and income level of the district of residence.

Overall, we found a 15-20% decrease in the number of cases between 2020q2 and 2021q2. While in principle it is possible that the true cancer incidence also decreased somewhat due to COVID-19, we conclude, in line with the experience of several other countries [10], that the significant drop in the number of diagnoses is mostly due to undiagnosed cases. Indeed, in the first five quarters of the pandemic, only around 0.5 percentage point of the decrease of observed case numbers could be explained with COVID-19 mortality even in the 65+ years old age group (and a negligible share in the younger population).[5] Although we acknowledge that, beyond age, some other variables such as lifestyle or comorbidities may simultaneously increase the risk of cancer and COVID-19 death, these background factors may explain only a minor additional part of the decrease of cancer incidence. For instance, smoking, which drastically increases the risk of lung cancer, increases the COVID-19 mortality rate only moderately (OR=1.35) [24].

The drop in newly diagnosed cancer cases was less than what was observed with comparable methods in Catalonia, a region that took a worse hit from COVID-19 than Hungary during the first wave (11–15% in Hungary vs. 34% in Catalonia in March-September of 2020 [12]) but was larger than in Belgium (7–14% vs. 6% in 2020 [13]). What is even more troubling from a health policy point of view is the fact that, unlike in New Zealand [11], at least during the period under scrutiny, with the exception of breast cancer in 2020q4, we did not observe the health system catching up fully in diagnosing putative undiagnosed cancers in the breaks between the pandemic waves. Instead, cancer incidence remained below its historical average up until 2021q2, the end of our observation period.

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[5] Between 2020q2–2021q2, less than 0.1% of the 0–64 years old and around 1.4% of the 65+ years old population of Hungary died from COVID-19, but two-thirds of these deaths occurred in 2021, which cannot explain the drop in diagnoses in the earlier quarters.

This is all the more of concern because it did not happen on purpose. While some health policy measures were taken to free up capacity to deal with the pandemic, cancer diagnosis and care was not among them. So what can have been the causal explanatory mechanisms at play? In what follows we present some possible causes – both on the supply and the demand side of healthcare – that can explain the decrease and the lack of subsequent rebound in cancer diagnosis and therapy.

First, on the supply side, as already mentioned above, organized breast cancer screening was suspended twice during the pandemic. As a result the number of mammography examinations decreased by 68% in 2020q2, was around the normal level in 2020q3 and then decreased by 20-35% between 2020q4-2021q2, which contributed to the reduction in new breast cancer diagnoses and mastectomy surgeries [21]. (Specifically, [21] estimated the causal effects of lower screening activity during the pandemic on breast cancer patient pathways in a regression discontinuity framework.)

Second, the reallocation of healthcare provider capacities to COVID-19-related care (i.e. the involvement of medical personnel and equipment in COVID-19 intensive care units, vaccination, etc.) may have had an indirect impact on the number of interventions performed. A proportion of the physicians who carried out diagnostic procedures was assigned to other COVID-19 related care. The workload for radiologists was particularly heavy during COVID-19 diagnostics, for which CT was used, so this may have resulted in limited access to imaging in other areas of care. Staff availability was further limited by COVID-19 diagnosis or quarantine among healthcare workers.

Third, the performance-based reimbursement techniques for specialist outpatient and inpatient care that are normally linked to patient visits and providers' activities (procedure codes within the German point system in outpatient care and diagnosis related groups in inpatient care) were suspended at the very beginning of the pandemic in March 2020 and since then have remained so. Instead, in order to maintain financial sustainability and the solvency, new prospective budgets were assigned to all providers based on the performance of previous years. Hence, the financial incentives [25] for providers' performance (higher patient and case numbers, more reported interventions, surgeries and DRGs result in more revenues) have literally disappeared. Understandably, such a change in financial incentives on its own may have had a negative effect on the activity of healthcare providers.

Fourth, a new law on employment conditions of healthcare personnel has been in force since March 2021 [20]. Several provisions of this new regulation, which was a crucial step regarding the modernization of the healthcare sector in Hungary, have an effect on healthcare delivery, e.g. rules on incompatibility between private and public sector employment and penalization of informal out-of-pocket payments, which had previously had a major impact on the organisation of patient pathways

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and caused inequality in the access to high-quality care [18]. The ban on informal payments was accompanied by a one-off, substantial wage increase, but no performance incentive scheme was introduced to motivate more efficient care. During the third pandemic wave, this may have negatively affected finding cancer patients who had been undiagnosed.

Fifth, on the demand side of the healthcare system, patients' readiness to visit a doctor could also decrease. Indeed, there is evidence that symptomatic patients have avoided healthcare providers due to fear of COVID-19 infection, leading to increased morbidity and mortality [26]. A recent study showed that the most significant concern expressed by oncology patients about the COVID-19 pandemic was fear [27].

We note that although the second and the third waves of the pandemic resulted in significantly more COVID-19 cases and deaths in Hungary, the decline in the new diagnoses (at least in breast and colorectal cancer) was more significant during the first wave. We could clearly see a learning curve: both patients and providers adapted to the given pandemic situation meaning also that skyrocketing numbers of COVID-19 cases in the second or the third wave did not lead to larger patient withdrawal than in the first wave. The effect of the pandemic on cancer incidence is heterogeneous over time and thus it may be difficult to extrapolate the short- and medium-term observations into the future.

We consider it a particular strength of our paper that we could use a large set of administrative data covering the period until June 2021 – a more extended interval than used in the international papers reviewed above or made publicly available specifically for Hungary.[6] Also, based on these data, we could examine heterogeneities by age group, gender and the income level of the district of residence. The estimated larger decrease for the older than for the younger population is in line with other papers [12, 13] and show that the combined effect of the mechanisms outlined above was stronger there.

Our district-level analysis gives a more nuanced picture on socioeconomic heterogeneity than a previous study did [12] because, having had access to data on 197 districts with vastly different average incomes and a population of 50,000 people on average, we had enough statistical power to estimate the effect on different cancer types separately. We note that district-level analyses have already proved fruitful for establishing socioeconomic heterogeneities in other COVID-19-related outcomes as well in Hungary [29].

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[6] The aggregate number of new cancer patients in Hungary, calculated with a slightly different methodology than ours, is available from the National Cancer Register for 2020 [28]. According to those data, the total number of new cancer diagnoses decreased by 13% in 2020 (compared to 2019), while in our calculation the combined number of the three most frequent cancer types decreased by 12% in that year.

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Time series data on cancer incidence trends show that lung cancer incidence was already declining before the pandemic, which might be explained by the fact that smoking among men has decreased in recent decades in Hungary (while smoking among women has stagnated or slightly increased) [30].

Our study also has some limitations. First, the causal effects of the aforementioned mechanisms could not be separated based on the available semiaggregate data. Second, disease stages and subtypes within the main groups of lung, colorectal and breast cancer were not available because of the ICD-based data and definitions. Third, longer-term outcome measures such as mortality could not be examined because of the limited time span since the outbreak of the pandemic. Finally, the uncertainty of the parameter estimates are sometimes too large to draw strong conclusions about the relative magnitude of the effects.

Turning to policy conclusions, the decline in the number of newly diagnosed patients due to delayed or unavailable care is a risk for public healthcare systems as the global cancer burden is rising [31]. Our findings can inform health policy actors about the projected excess cancer cases, expected interventions hence increased morbidity and mortality in the years to come due to delayed diagnosis during the pandemic. Also, when facing the subsequent waves of the pandemic, we are more capable of describing the mechanisms, forecasting the consequences of a new wave and evaluating the trade-offs associated with various policy interventions.

As during the early waves of the pandemic numerous policy decisions had to be made uninformed, "in the fog of war", the impact of these decisions on patient care and outcomes deserves further investigation to develop an evidence-based policy approach for the future. On the other hand, the fact that patients themselves have restricted their visits to healthcare providers out of fear calls for action by policy makers to engage potential cancer patients in accessing healthcare services, to diagnose the disease early and to prepare for effective management of patient pathways from diagnosis to survival or end-of-life care.

5. Statements

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compiled the first draft of the manuscript, with contributions from the other authors. All authors critically revised the manuscript and approved its current version.

Conflict of interest: None declared.

Data availability statement: The administrative inpatient care data on the quarter – gender – age group – district level were obtained from the National Health Insurance Fund Administration (NEAK). District-level income was available from the National Regional Development and Spatial Planning Information System (TeIR) through the Databank of the Centre for Economic and Regional Studies (KRTK). The authors do not have permission to share the data to third parties.

Ethics approval statement: The study is a secondary analysis of (semi)aggregate administrative data so ethics approval was not required.

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Figure legends

Figure 1: Number of new cancer cases (2017q1–2021q2) and deviation from the trend and seasonality (2020q1–2021q2)

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Note: The lower panel shows the parameter estimates of the dummies for 2020q1–2021q2 from the logarithmic model (1) (displayed in Appendix Table A1), transformed to the percentage scale, with 95% confidence intervals. Controls: linear trend and seasonal dummies. Period: 2017q1–2021q2. Number of quarters: 18

Figure 2: Cumulative number of new cancer cases during the pandemic and in previous periods

Figure 3: Number of new cancer cases by age group (2017q1–2021q2)

Figure 4: Gender- and age-adjusted incidence (per 100,000 inhabitants) by district-level income tertile for lung, colorectal and breast cancer (2017q1–2021q2)
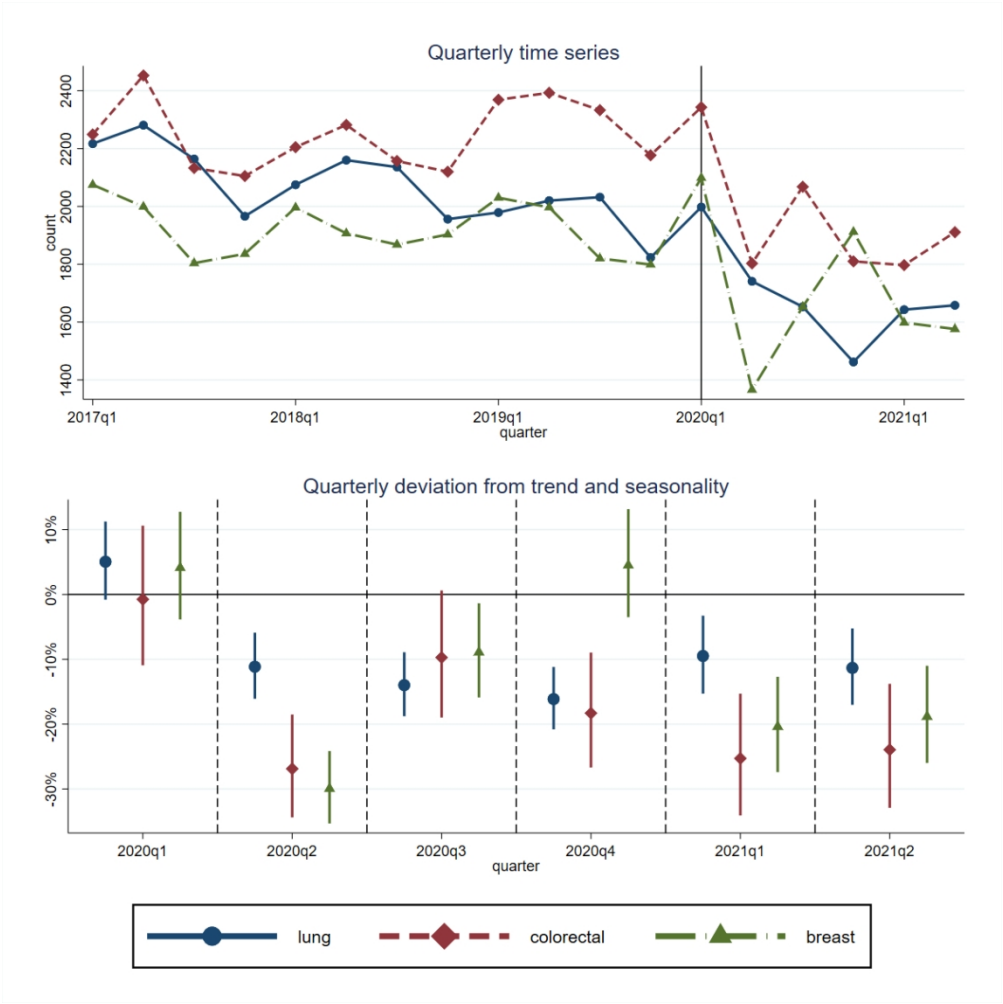
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Figure 1: Number of new cancer cases (2017q1–2021q2) and deviation from the trend and seasonality (2020q1–2021q2)

Note: The lower panel shows the parameter estimates of the dummies for 2020q1–2021q2 from the logarithmic model (1) (displayed in Appendix Table A1), transformed to the percentage scale, with 95% confidence intervals. Controls: linear trend and seasonal dummies. Period: 2017q1–2021q2. Number of quarters: 18

101x101mm (300 x 300 DPI)

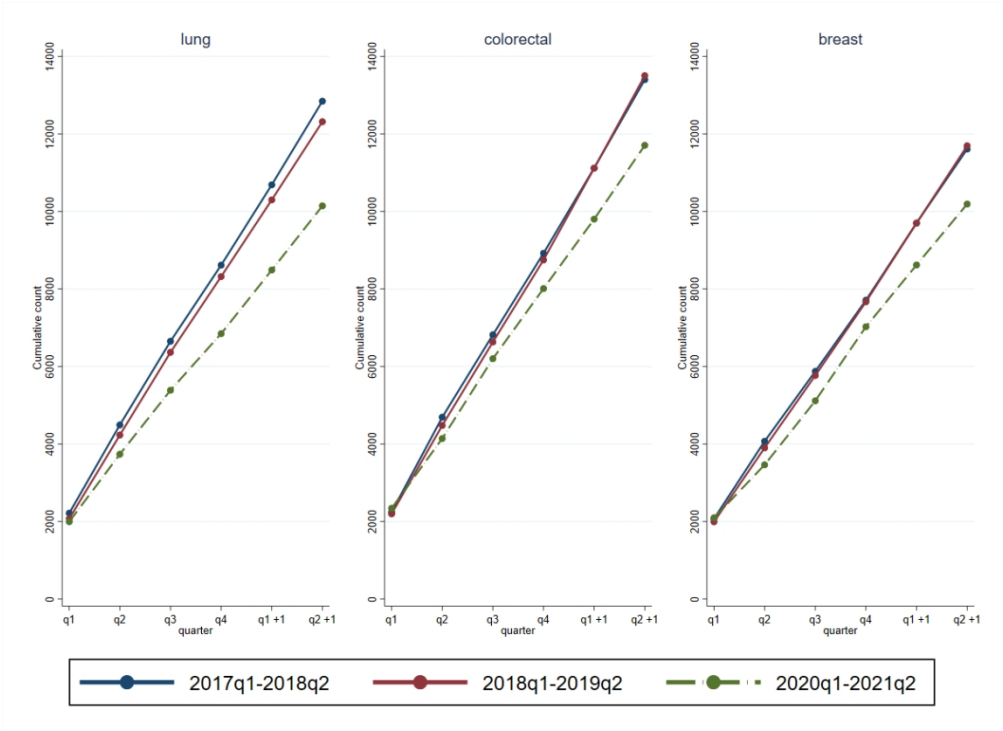Figure 2: Cumulative number of new cancer cases during the pandemic and in previous periods
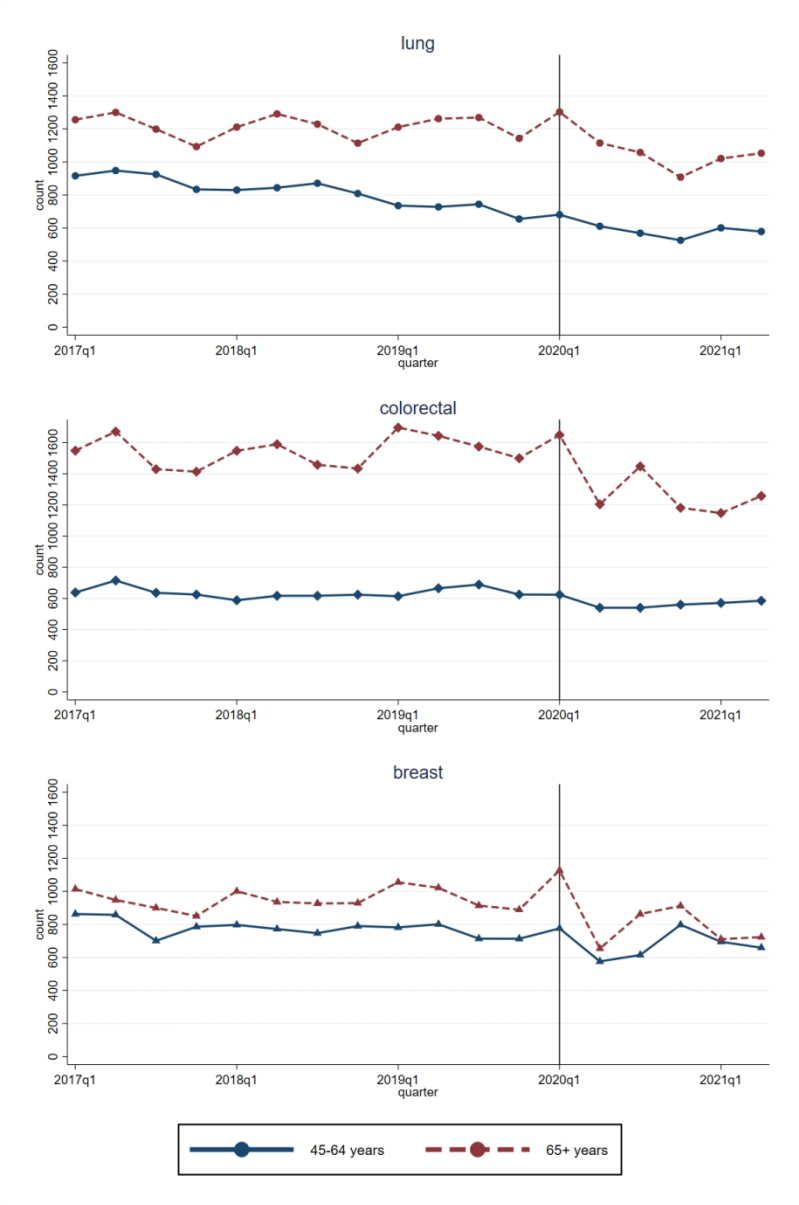
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Figure 3: Number of new cancer cases by age group (2017q1–2021q2)
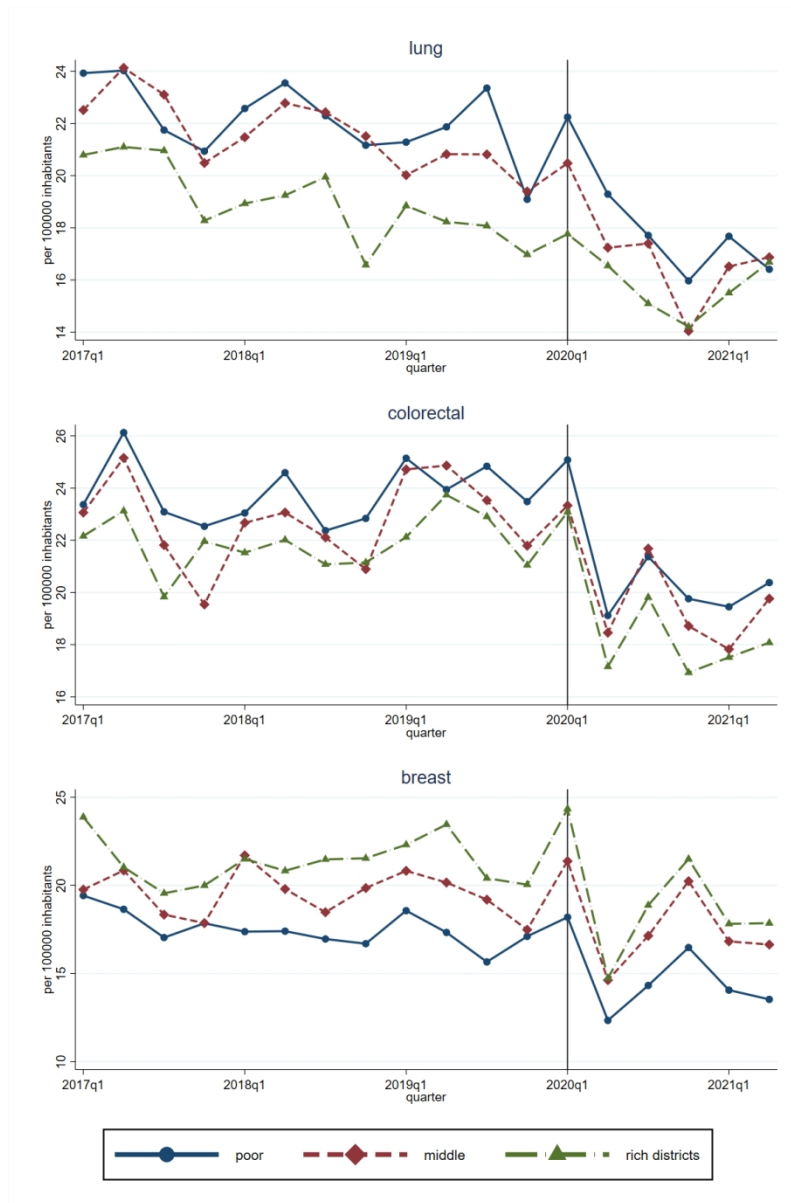
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Figure 4: Gender- and age-adjusted incidence (per 100,000 inhabitants) by district-level income tertile for lung, colorectal and breast cancer (2017q1–2021q2)

101x152mm (300 x 300 DPI)

Appendix Table A1: Details of the time series models

	log new lung cancer		log new colorectal cancer		log new breast cancer	
Quarterly trend	-0.0117***	(0.0016)	0.0047	(0.0030)	-0.0011	(0.0022)
Seasonal dummies (baseline = q1)						
q2	0.041**	(0.015)	0.039	(0.028)	-0.032	(0.020)
q3	0.0337*	(0.015)	-0.040	(0.028)	-0.103***	(0.021)
q4	-0.052**	(0.015)	-0.078**	(0.029)	-0.094***	(0.021)
Dummies between 2020q1 – 2021q2						
2020q1	0.049*	(0.024)	-0.0074	(0.046)	0.040	(0.034)
2020q2	-0.118***	(0.024)	-0.313***	(0.046)	-0.356***	(0.034)
2020q3	-0.151***	(0.024)	-0.102*	(0.046)	-0.093**	(0.034)
2020q4	-0.176***	(0.024)	-0.202***	(0.046)	0.044	(0.034)
2021q1	-0.100***	(0.028)	-0.292***	(0.053)	-0.228***	(0.039)
2021q2	-0.120***	(0.028)	-0.274***	(0.053)	-0.209***	(0.039)
Constant	10.35***	(0.367)	6.64***	(0.694)	7.87***	(0.510)

*** $p<0.01$, ** $p<0.05$, * $p<0.1$. Standard errors in parentheses.
Quarterly time series between 2017q1–2021q2. Number of quarters: 18.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	5-6
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Heterogeneous impact of the COVID-19 pandemic on lung, colorectal and breast cancer incidence in Hungary: results from time series and panel data models

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Heterogeneous impact of the COVID-19 pandemic on lung, colorectal and breast cancer incidence in Hungary: results from time series and panel data models

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Abstract

Objective

During the COVID-19 pandemic, health system resources were reallocated to provide care for COVID-19 patients, limiting access for others. Patients themselves also constrained their visits to healthcare providers. In this study we analysed the heterogeneous effects of the pandemic on the new diagnoses of lung, colorectal and breast cancer in Hungary.

Design

Time series and panel models of quarterly administrative data, disaggregated by gender, age group and district of residence.

Participants

Data for the whole population of Hungary between the first quarter of 2017 and the second quarter of 2021.

Main outcome measures

Number of newly diagnosed lung, colorectal and breast cancer patients, defined as those who were hospitalised with the appropriate primary ICD-10 diagnosis code but had not had hospital encounters with such a code within the previous five years.

Results

The incidence of lung, colorectal and breast cancer decreased by 14.4% (95% CI 10.8% to 17.8%), 19.9% (95% CI 12.2% to 26.9%) and 15.5% (95% CI 2.5% to 27.0%), respectively, during the examined period of the pandemic, with different time patterns across cancer types. The incidence decreased more among people at least 65 years old than among the younger ($p<0.05$ for lung and $p<0.1$ for colorectal cancer). At the district level, both the previously negative income gap in lung cancer incidence and the previously positive income gap in breast cancer incidence significantly narrowed during the pandemic ($p<0.05$).

Conclusions

The decline in new cancer diagnoses, caused by a combination of supply- and demand-side factors, suggests that some cancer cases have remained hidden. It calls for action by policy makers to engage individuals with high risk of cancer more in accessing healthcare services, to diagnose the disease early and to prepare for effective management of patient pathways from diagnosis to survival or end-of-life care.

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Keywords: cancer incidence, COVID-19, time series, panel data

Strengths and limitations of this study

- The effect of the COVID-19 pandemic on the incidence of the three most common types of cancer was examined in Hungary based on nationwide administrative data until June 2021.

- The aggregate effect was estimated with time series models to control for previous trend and seasonality, while the heterogeneous effects by gender, age group and the income level of the district of residence were estimated with panel data models.

- Causal effects of the potential supply- and demand-side mechanisms (that are outlined in the paper) could not be established.

- Disease stages and longer-term outcomes such as mortality could not be examined because of the lack of data.

Word count: 3929

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1. Introduction

The COVID-19 pandemic is a huge challenge for healthcare systems and requires the highest level of resilience in health policy decision making. It is a learning process with countless pandemic-related issues to be addressed, very often involving trade-offs coupled with high-level of uncertainty [1]. For example, it had gotten to the point where, at least temporarily, a choice had to be made between treating COVID-19 or non-COVID-19 patients, because the overburdened healthcare systems did not have the capacity to do both [2]. Effectively managing the pandemic requires thinking in terms of a complex system, with a high number of factors that are not linearly linked [3]. For example, preventive measures (wearing a mask, isolation, quarantine) and the proportion of the population vaccinated can affect the number of COVID-19 patients, which then affects the necessary administrative restrictions on healthcare, which in turn can influence the availability and quality of services for non-COVID-19 patients. In this indirect context, reserving inpatient capacity to treat COVID-19 patients, which was a policy tool in many countries, and self-limiting patients' access to healthcare providers play an important role. To make the impact of such decisions clearer, ex post analyses of the consequences can provide a scientific basis to the management of the crisis in the future [1].

Lessons learned are of paramount importance in the case of serious chronic diseases such as cancer, which cannot be lumped together with other deferred care because of health priorities. Cancer is a complex disease that requires patients to undergo different types of procedures and laboratory or imaging tests to be diagnosed and staged. To achieve the maximum benefit for patients, these services must work in a coordinated manner, with a high level of patient engagement and compliance. Cancer survival can be increased by detecting tumours in the asymptomatic state, i.e. by screening programmes, and by rapid and effective investigation of suspected tumours, which can be enhanced by effective management of the cancer patient pathways [4]–[6]. Failure to do so can lead to lower quality of care and poorer outcomes for patients [7]. Due to the control measures of the COVID-19 pandemic [8], putative new cancer patients are exposed to a range of harms, including suspension of screening and prevention efforts, delays in timely diagnosis and staging of new patients, and delays in initiation of therapy [9].

According to a recent study, the impact of the COVID-19 pandemic on cancer care has been varying across countries [10]. In New Zealand, for example, the number of cancer diagnoses fell by 40% compared to previous years during the national shutdown in March-April 2020, before returning to pre-shutdown levels in the following months [11]. In contrast, in Catalonia, Spain, and in Belgium, where reductions of similar magnitude occurred, the historical figures were not reached after the end

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of the lockdown [12, 13]. In Poland, unlike in other countries, a recent study showed no decline in the number of oncological diagnoses at hospitals during the first wave [14].

In Hungary, a European country with 9.7 million inhabitants, cancer incidence (623 new cases per 100,000 people) is 10% higher, and cancer mortality (330 deaths per 100,000 people) is 25% higher than the European Union average. The three most common types are lung, colorectal and breast cancer [15]. Population-level breast cancer screening has been available for women aged 45-64 since 2002 [16], while colorectal cancer screening was initiated for people aged 50-70 in 2018 [17].

The Hungarian healthcare system is highly centralised. The state has exclusive powers to set the strategic direction, control funding, define the benefits package, and issue and implement regulations. The country has a single health insurance fund. Public outpatient and inpatient services are formally free of charge at the point of care, although – as in other Central and Eastern European countries [18] – informal payments had been a constant challenge before they were made illegal and sanctioned in 2021. There is a growing private outpatient care sector as well [15].

After a relatively mild first wave, Hungary was hit particularly hard – in international comparison – by the second (2020q4) and the third (2021q1-2021q2) waves of the COVID-19 pandemic, resulting in the death of 30,000 people (0.3% of the population) until June 2021 [19].[1] The aims of the corresponding health policy measures were to contain the spread of the virus and to reallocate resources to COVID-19 care. These included the suspension of population-level cancer screening programmes (such as breast and colorectal screening) altogether for about three months (between 16 March – 1 June 2020 and between 9 April – 29 April 2021) and of elective and one-day surgeries for even longer periods, although oncological diagnostic and curative services were exempt from the suspensions. Other important policy measures included the replacement of performance-based reimbursement with global budgets during the whole pandemic to maintain the financial sustainability and solvency of healthcare providers. In 2021, beyond the already mentioned ban on informal payments, significant increases in physicians' salaries were introduced [20].

Despite the large direct and indirect effects on the healthcare system, no systematic mapping has taken place yet on how the diagnosis and care of cancer patients evolved during the pandemic in Hungary. (For a specific analysis of the effect of lower screening activity on breast cancer incidence, total and partial mastectomy rates see [21].) To understand the impact of the COVID-19 pandemic on

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[1] Throughout the paper, q1, q2, q3 and q4 stand for the first, second, third and fourth calendar quarters of the year, respectively.

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cancer care, it is important to examine the trends in the number of newly diagnosed cases and the areas where health policy interventions may be needed.

The aim of our study was to analyse the heterogeneous effects of the COVID-19 pandemic on the new diagnoses of lung, colorectal and breast cancer until June 2021 in Hungary by gender, age group and district-level income.

2. Materials and Methods

Data

We used administrative inpatient care data that were collected by the National Health Insurance Fund Administration (NHIFA [NEAK]), the single payer of the Hungarian healthcare system, covering the whole population of the country (9.7 million people). We defined the number of newly diagnosed cancer patients as those who were hospitalised with the appropriate primary ICD-10 diagnosis code (C34 for lung cancer, C18-C21 for colorectal cancer and C50 for breast cancer) but had not had hospital encounters with such a code within the previous five years. The data were obtained by quarter (between 2017q1–2021q2), disaggregated by gender, five-year age group and district of residence.

We note that the financing (and not register) data at hand did not provide more detailed information such as disease stage or subtype within the major groups of lung, colorectal or breast cancer. However, similar NHIFA data were applied in the past fruitfully to estimate cancer incidence in Hungary (see e.g. [22] for lung cancer). Also, we note that although cancer screening and diagnostic procedures are practiced in the private sector as well, essentially all of the main oncological treatment modalities (surgery, chemotherapy, radiation therapy) is carried out in the public sector and coded as inpatient data. Hence patients who were diagnosed in the private sector appear in our definition when they first undergo treatment in the public sector.

Hungary is composed of 197 districts, with an average population of about 50,000 people. (Specifically, Budapest, the capital consists of 23 districts.) For the district-level analysis, the data were merged to the year 2017 value of annual per capita taxable income of the district, which was obtained from the National Regional Development and Spatial Planning Information System (TeIR).

Beyond the crude incidence values in the aggregate as well as the gender- and age-specific analyses, we used the gender- and age-standardized incidence (with the 2017 population structure of Hungary as the baseline) in the district-level estimations. The (calendar year specific) size of the population of the corresponding gender, five-year age group and district was available from the TeIR system.

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Statistical analysis

First, we performed time series modelling of the number of newly diagnosed lung, colorectal and breast cancer cases by estimating

$$(1) \quad \log y_t = \alpha + \beta t + \sum_{j=2}^{4} \gamma_j q_j + \sum_{k=2020Q1}^{2021Q2} \delta_k D_k + \varepsilon_t$$

where t denotes time (quarter), y_t is the number of new cases, q_j ($j = 2,3,4$) is the j-th calendar quarter (the first quarter being the baseline) and D_k ($k = 2020q1, ..., 2021q2$) are dummy variables for the quarters of the pandemic. The parameters δ_k show the quarter-specific deviation from the usual trend and seasonality during the pandemic. Finally, ε_t is the error term. The models were estimated with ordinary least squares (OLS) as the error terms turned out to be serially uncorrelated in each model. Then, OLS provides unbiased estimates of the parameters (with appropriate standard errors).

Second, we estimated the following equations, where ρ measures the overall effect during the first five quarters of the pandemic, between 2020q2 and 2021q2:

$$(2) \quad \log y_t = \alpha + \beta t + \sum_{j=2}^{4} \gamma_j q_j + \rho \sum_{k=2020Q2}^{2021Q2} D_k + \varepsilon_t.$$

Third, we investigated heterogeneous effects by gender and age group by estimating equations

$$(3) \quad \log y_{gt} = \alpha_g + \beta_g t + \sum_{j=2}^{4} \gamma_{gj} q_j + \rho_g \sum_{k=2020Q2}^{2021Q2} D_k + \varepsilon_{gt},$$

where g denotes gender (male or female) or age group (45-64 or 65+ years), hence ρ_g measures the overall change of the number of new cases by group during the five quarters of the pandemic.[2] We also estimated $\rho_{male} - \rho_{female}$ and $\rho_{45-64\ years} - \rho_{65+years}$ in difference-in-difference specifications and evaluated their statistical significance (i.e. whether the effects are the same across gender or age group).

Fourth, to investigate how the effect of the pandemic varies by district-level income, we classified the districts into three income quantiles (tertiles) and showed the time series of the age- and gender-adjusted incidences by tertile. Afterwards, to formally estimate the heterogeneous effect by district-level income, we fitted the following models on district-quarter panel data:

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[2] We did not examine the 0-44 years old age group specifically because of the small sample size (only 1.8%, 3.4% and 11.7% of new lung, colorectal and breast cancer patients, respectively, were below 45 years between 2017-2019). The aggregate analysis contains these patients as well.

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$$(4) \quad s_{it} = \alpha + \beta_0 t + \sum_{j=2}^{4} \gamma_{j0} q_j + \log I_i * \left(\beta_1 t + \sum_{j=2}^{4} \gamma_{j1} q_j \right) + \sum_{k=2020Q1}^{2021Q2} \delta_{k0} D_k + \log I_i * \theta *$$
$$\sum_{k=2020Q2}^{2021Q2} D_k + c_i + \varepsilon_{it}$$

where i is district, t is time (quarter), and beyond the notations of equation (1), s_{it} is the adjusted incidence (per 100,000 inhabitants), $\log I_i$ is the year 2017 logarithmic district-level per capita income and c_i are district fixed effects.[3] (Hence we estimated a standard fixed-effects panel model [23].) The parameter of interest is $\theta/100$, which shows the relative effect of the pandemic in a higher-income district compared to a lower-income one, i.e. how a 1% larger average income of the district affected the change of the incidence during the pandemic.

Patient and public involvement

Due to the nature of the study, patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3. Results

Aggregate, age- and gender-specific effects

According to the upper panel of Figure 1, the quarterly number of new cases of the three major types of cancer was between 1800–2400 before the pandemic, corresponding to annual unadjusted incidence rates of 78–92 per 100,000 inhabitants. The lower panel of the Figure shows the changes of the new case numbers in 2020–2021 compared to the trend and seasonality of the preceding three years (i.e. the parameter estimates of the pandemic dummies from equation (1)), with 95% confidence intervals. (Details of the estimated models are given in Appendix Table A1.) The incidence of colorectal and breast cancer decreased by 26.9% (95% CI 18.5% to 34.4%) and by 30.0% (95% CI 24.1% to 35.4%), respectively, in 2020q2 and remained only slightly below the historical trend in 2020q3. Afterwards, breast cancer incidence reached its usual level in 2020q4, but colorectal cancer incidence still remained significantly lower. Then, the incidence of both types of cancer fell short of the historical trend by 20–25% in the first half of 2021. Meanwhile, the decline of lung cancer incidence was more flat, being below the historical trend by 10–16% during each quarter.

Overall, as the upper panel of Table 1 shows, the incidence of lung, colorectal and breast cancer decreased by 14.4% (95% CI 10.8% to 17.8%), 19.9% (95% CI 12.2% to 26.9%) and 15.5% (95% CI 2.5% to 27.0%), respectively, in the first five quarters of the pandemic, between 2020q2 and 2021q2.

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[3] Here we used s_{it} instead of $\log s_{it}$ because of zeros in some district-quarter observations.

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Figure 2 shows the cumulative number of new cases between 2020q1–2021q2, compared to two earlier periods (2017q1–2018q2 and 2018q1–2019q2). During this time, around 5,000 fewer people than usual (around 50 fewer per 100,000 inhabitants) were diagnosed with the three major types of cancer combined.

According to Figure 3, the number of new cases declined more substantially for the 65+ years old than for the 45–64 years old population; according to the second panel of Table 1, the difference was 10–16 percentage points and was statistically significant for lung cancer (p<0.05) and colorectal cancer (p<0.1). On the other hand, the third panel of Table 1 shows that there was no statistically significant difference across genders in the decrease of cancer incidence.

Table 1: Regression results for the the change of incidence during the pandemic aggregately and by gender, age group and district-level income

	Lung cancer		Colorectal cancer		Breast cancer	
Effect of 2020q2-2021q2 on new case numbers (in %)	-14.4***	(1.6)	-19.9***	(3.4)	-15.5**	(5.6)
Effect of 2020q2-2021q2 on new case numbers (in %) by age group						
-64 years	-8.5**	(3.0)	-12.3**	(4.4)	-7.9	(7.0)
65+ years	-18.1***	(2.6)	-23.4***	(3.8)	-22.6***	(5.9)
Difference	-10.4**	(4.1)	-12.6*	(6.2)	-15.9	(9.0)
Effect of 2020q2-2021q2 on new case numbers (in %) by gender						
Females	-15.8***	(1.9)	-20.7***	(3.8)		
Males	-13.2***	(2.0)	-19.4***	(3.9)		
Difference	3.1	(3.4)	1.7	(7.0)		
Effect of district-level income on the change of incidence (per 100,000 people) in 2020q2-2021q1						
Log income * Dummy (2020q2-2021q2)	4.4**	(2.0)	-1.6	(1.8)	-4.5**	(2.1)
Note: Mean dependent variable	20.9		22.8		19.4	

*** p<0.01, ** p<0.05, * p<0.1. Standard errors in parentheses.

Upper part: estimated ρ from the logarithmic model (2), second and third parts: estimated ρ_g-s from the logarithmic model (3), each transformed to the percentage scale. The estimated differences ($\rho_{male} - \rho_{female}$ and $\rho_{65+\ years} - \rho_{45-64\ years}$), transformed to the percentage scale, are also shown. Gender and age group specific time series models. Controls: linear trend and seasonal dummies. Period: 2017q1–2021q2. Number of quarters: 18.

Lower part: estimated θ-s from equation (4) are shown. District-quarter panel. Number of districts: 197. Period: 2017q1–2021q2. Number of quarters: 18. Controls: district fixed effects; and linear trend, seasonal dummies and dummy of the pandemic, each interacted with log district-level per capita income. The mean of the adjusted incidence per 100,000 inhabitants is shown as a note.

District-level effects

In Hungary, average income differences across districts are substantial, with a 2.6–fold difference between the richest vs. the poorest district, and a 1.8–fold difference between the 95% and 5% quantile in terms of district-level taxable income. Figure 4 shows the time series of gender- and age-standardized cancer incidence in three quantiles (tertiles) defined by district-level income. Before the

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pandemic, lung cancer incidence was higher and breast cancer incidence was lower in the lower-income districts compared to the higher-income ones. However, during the pandemic, lung cancer incidence decreased to a greater extent and breast cancer incidence to a smaller extent in the lower-income districts (compared to the higher-income ones), hence the income gradient (which was negative for lung cancer and positive for breast cancer) narrowed for both types of cancer. According to the lower panel of Table 1, a 1% higher district-level income was associated with a 0.044 smaller decrease for lung cancer (95% CI 0.005 to 0.083) and a 0.045 larger decrease for breast cancer (95% CI 0.004 to 0.086) quarterly incidence per 100,000 inhabitants during the pandemic. (For comparison, the average quarterly incidence was 19–21 per 100,000 inhabitants.) Meanwhile, no clear pattern (and no statistically significant association) emerged for colorectal cancer.

4. Discussion

Our study provided a detailed analysis of the number of diagnoses of the three most common types of cancer in Hungary during the COVID-19 pandemic and considered the changes by age, gender and income level of the district of residence.

Overall, we found a 15-20% decrease in the number of cases between 2020q2 and 2021q2. While in principle it is possible that the true cancer incidence also decreased somewhat due to COVID-19, we conclude, in line with the experience of several other countries [10], that the significant drop in the number of diagnoses is mostly due to undiagnosed cases. Indeed, in the first five quarters of the pandemic, only around 0.5 percentage point of the decrease of observed case numbers could be explained with COVID-19 mortality even in the 65+ years old age group (and a negligible share in the younger population).[4] Although we acknowledge that, beyond age, some other variables such as lifestyle or comorbidities may simultaneously increase the risk of cancer and COVID-19 death, these background factors may explain only a minor additional part of the decrease of cancer incidence. For instance, smoking, which drastically increases the risk of lung cancer, increases the COVID-19 mortality rate only moderately (OR=1.35) [24].

The drop in newly diagnosed cancer cases was less than what was observed with comparable methods in Catalonia, a region that took a worse hit from COVID-19 than Hungary during the first wave (11–15% in Hungary vs. 34% in Catalonia in March-September of 2020 [12]) but was larger than in Belgium (7–14% vs. 6% in 2020 [13]). What is even more troubling from a health policy point of view is the fact

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[4] Between 2020q2–2021q2, less than 0.1% of the 0–64 years old and around 1.4% of the 65+ years old population of Hungary died from COVID-19, but two-thirds of these deaths occurred in 2021, which cannot explain the drop in diagnoses in the earlier quarters.

that, unlike in New Zealand [11], at least during the period under scrutiny, with the exception of breast cancer in 2020q4, we did not observe the health system catching up fully in diagnosing putative undiagnosed cancers in the breaks between the pandemic waves. Instead, cancer incidence remained below its historical average up until 2021q2, the end of our observation period.

This is all the more of concern because it did not happen on purpose. While some health policy measures were taken to free up capacity to deal with the pandemic, cancer diagnosis and care were not among them. In what follows we present some possible causal mechanisms – both on the supply and the demand side of healthcare – that can explain the decrease and the lack of subsequent rebound in cancer diagnosis and therapy.

First, on the supply side, as already mentioned above, organized breast cancer screening was suspended twice during the pandemic. As a result the number of mammography examinations decreased by 68% in 2020q2, was around the normal level in 2020q3 and then decreased by 20-35% between 2020q4-2021q2, which contributed to the reduction in new breast cancer diagnoses and mastectomy surgeries [21]. (Specifically, [21] estimated the causal effects of lower screening activity during the pandemic on breast cancer patient pathways in a regression discontinuity framework.)

Second, the reallocation of healthcare provider capacities to COVID-19-related care (i.e. the involvement of medical personnel and equipment in COVID-19 intensive care units, vaccination, etc.) may have had an indirect impact on the number of interventions performed. A proportion of the physicians who carried out diagnostic procedures was assigned to other COVID-19 related care. The workload for radiologists was particularly heavy during COVID-19 diagnostics, for which CT was used, so this may have resulted in limited access to imaging in other areas of care. Staff availability was further limited by COVID-19 diagnosis or quarantine among healthcare workers.

Third, the performance-based reimbursement techniques for specialist outpatient and inpatient care that are normally linked to patient visits and providers' activities (procedure codes within the German point system in outpatient care and diagnosis related groups in inpatient care) were suspended at the very beginning of the pandemic in March 2020 and since then have remained so. Instead, in order to maintain financial sustainability and the solvency, new prospective budgets were assigned to all providers based on the performance of previous years. Hence, the financial incentives [25] for providers' performance (higher patient and case numbers, more reported interventions, surgeries and DRGs result in more revenues) have literally disappeared. Understandably, such a change in financial incentives on its own may have had a negative effect on the activity of healthcare providers.

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Fourth, a new law on employment conditions of healthcare personnel has been in force since March 2021 [20]. Several provisions of this new regulation, which was a crucial step regarding the modernization of the healthcare sector in Hungary, have an effect on healthcare delivery, e.g. rules on incompatibility between private and public sector employment and penalization of informal out-of-pocket payments, which had previously had a major impact on the organisation of patient pathways and caused inequality in the access to high-quality care [18]. The ban on informal payments was accompanied by a one-off, substantial wage increase, but no performance incentive scheme was introduced to motivate more efficient care. During the third pandemic wave, this may have negatively affected finding cancer patients who had been undiagnosed.

Fifth, on the demand side of the healthcare system, patients' readiness to visit a doctor could also decrease. Indeed, there is evidence that symptomatic patients have avoided healthcare providers due to fear of COVID-19 infection, leading to increased morbidity and mortality [26]. A recent study showed that the most significant concern expressed by oncology patients about the COVID-19 pandemic was fear [27].

We note that although the second and the third waves of the pandemic resulted in significantly more COVID-19 cases and deaths in Hungary, the decline in the new diagnoses (at least in breast and colorectal cancer) was more significant during the first wave. Hence the effect of the pandemic on cancer incidence is heterogeneous over time and thus it may be difficult to extrapolate the short- and medium-term observations into the future.

We consider it a particular strength of our paper that we could use a large set of administrative data covering the period until June 2021 – a more extended interval than used in the international papers reviewed above or made publicly available specifically for Hungary.[5] Also, based on these data, we could examine heterogeneities by age group, gender and the income level of the district of residence. The estimated larger decrease for the older than for the younger population is in line with other papers [12, 13] and show that the combined effect of the mechanisms outlined above was stronger there.

Our district-level analysis gives a more nuanced picture on socioeconomic heterogeneity than a previous study did [12] because, having had access to data on 197 districts with vastly different average incomes and a population of 50,000 people on average, we had enough statistical power to estimate the effect on different cancer types separately. We note that district-level analyses have already

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[5] The aggregate number of new cancer patients in Hungary, calculated with a slightly different methodology than ours, is available from the National Cancer Register for 2020 [28]. According to those data, the total number of new cancer diagnoses decreased by 13% in 2020 (compared to 2019), while in our calculation the combined number of the three most frequent cancer types decreased by 12% in that year.

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proved fruitful for establishing socioeconomic heterogeneities in other COVID-19-related outcomes as well in Hungary [29].

Time series data on cancer incidence trends show that lung cancer incidence was already declining before the pandemic, which might be explained by the fact that smoking among men has decreased in recent decades in Hungary (while smoking among women has stagnated or slightly increased) [30].

Our study also has some limitations. First, the causal effects of the aforementioned mechanisms could not be separated based on the available semiaggregate data. Second, disease stages and subtypes within the main groups of lung, colorectal and breast cancer were not available because of the ICD-based data and definitions. Third, longer-term outcome measures such as mortality could not be examined because of the limited time span since the outbreak of the pandemic. Finally, the uncertainty of the parameter estimates are sometimes too large to draw strong conclusions about the relative magnitude of the effects.

Turning to policy conclusions, the decline in the number of newly diagnosed patients due to delayed or unavailable care is a risk for public healthcare systems as the global cancer burden is rising [31]. Our findings can inform health policy actors about the projected excess cancer cases, expected interventions hence increased morbidity and mortality in the years to come due to delayed diagnosis during the pandemic.

As during the early waves of the pandemic numerous policy decisions had to be made uninformed, "in the fog of war", the impact of these decisions on patient care and outcomes deserves further investigation to develop an evidence-based policy approach for the future. On the other hand, the fact that patients themselves have restricted their visits to healthcare providers out of fear calls for action by policy makers to engage potential cancer patients in accessing healthcare services, to diagnose the disease early and to prepare for effective management of patient pathways from diagnosis to survival or end-of-life care.

5. Statements

Author contributions: All authors contributed to the design of the study and the interpretation of the results. P.E., P.F-F. and M.T. had access to the data and performed the statistical analysis. M.Cs., N.G.,

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R.O-B., B.Sz-N., B.V. and A.Z. drew the policy conclusions from the results. P.E., M.Cs., B.V. and A.Z. compiled the first draft of the manuscript, with contributions from the other authors. All authors critically revised the manuscript and approved its current version.

Conflict of interest: None declared.

Data availability statement: The administrative inpatient care data on the quarter – gender – age group – district level were obtained from the National Health Insurance Fund Administration (NEAK). District-level income was available from the National Regional Development and Spatial Planning Information System (TeIR) through the Databank of the Centre for Economic and Regional Studies (KRTK). The authors do not have permission to share the data to third parties.

Ethics approval statement: The study is a secondary analysis of (semi)aggregate administrative data so ethics approval was not required.

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Figure legends

Figure 1: Number of new cancer cases (2017q1–2021q2) and deviation from the trend and seasonality (2020q1–2021q2)

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Note: The lower panel shows the parameter estimates of the dummies for 2020q1–2021q2 from the logarithmic model (1) (displayed in Appendix Table A1), transformed to the percentage scale, with 95% confidence intervals. Controls: linear trend and seasonal dummies. Period: 2017q1–2021q2. Number of quarters: 18

Figure 2: Cumulative number of new cancer cases during the pandemic and in previous periods

Figure 3: Number of new cancer cases by age group (2017q1–2021q2)

Figure 4: Gender- and age-adjusted incidence (per 100,000 inhabitants) by district-level income tertile for lung, colorectal and breast cancer (2017q1–2021q2)
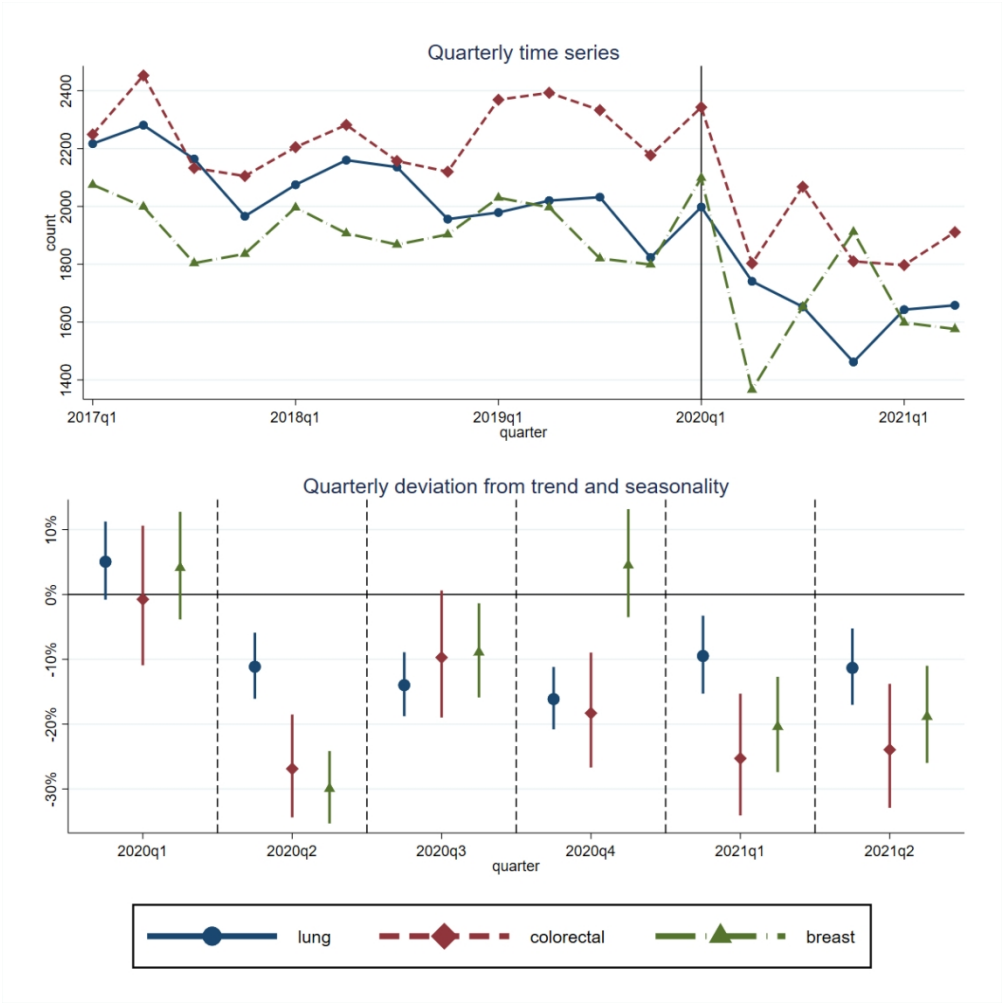
17

Figure 1: Number of new cancer cases (2017q1–2021q2) and deviation from the trend and seasonality (2020q1–2021q2)

Note: The lower panel shows the parameter estimates of the dummies for 2020q1–2021q2 from the logarithmic model (1) (displayed in Appendix Table A1), transformed to the percentage scale, with 95% confidence intervals. Controls: linear trend and seasonal dummies. Period: 2017q1–2021q2. Number of quarters: 18
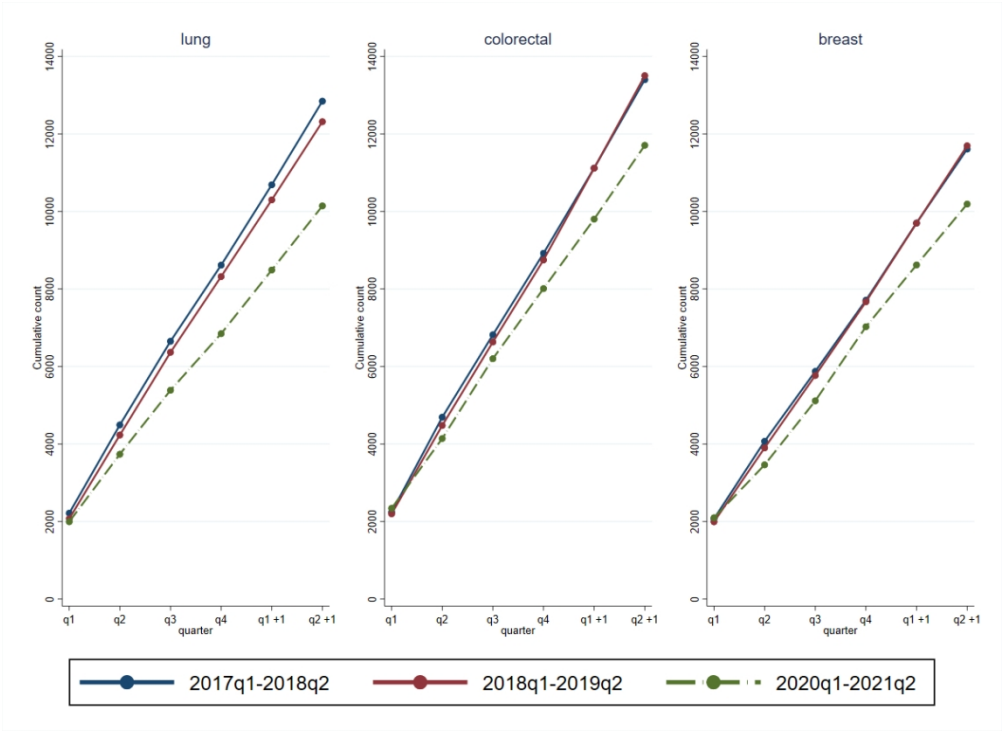
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Figure 2: Cumulative number of new cancer cases during the pandemic and in previous periods
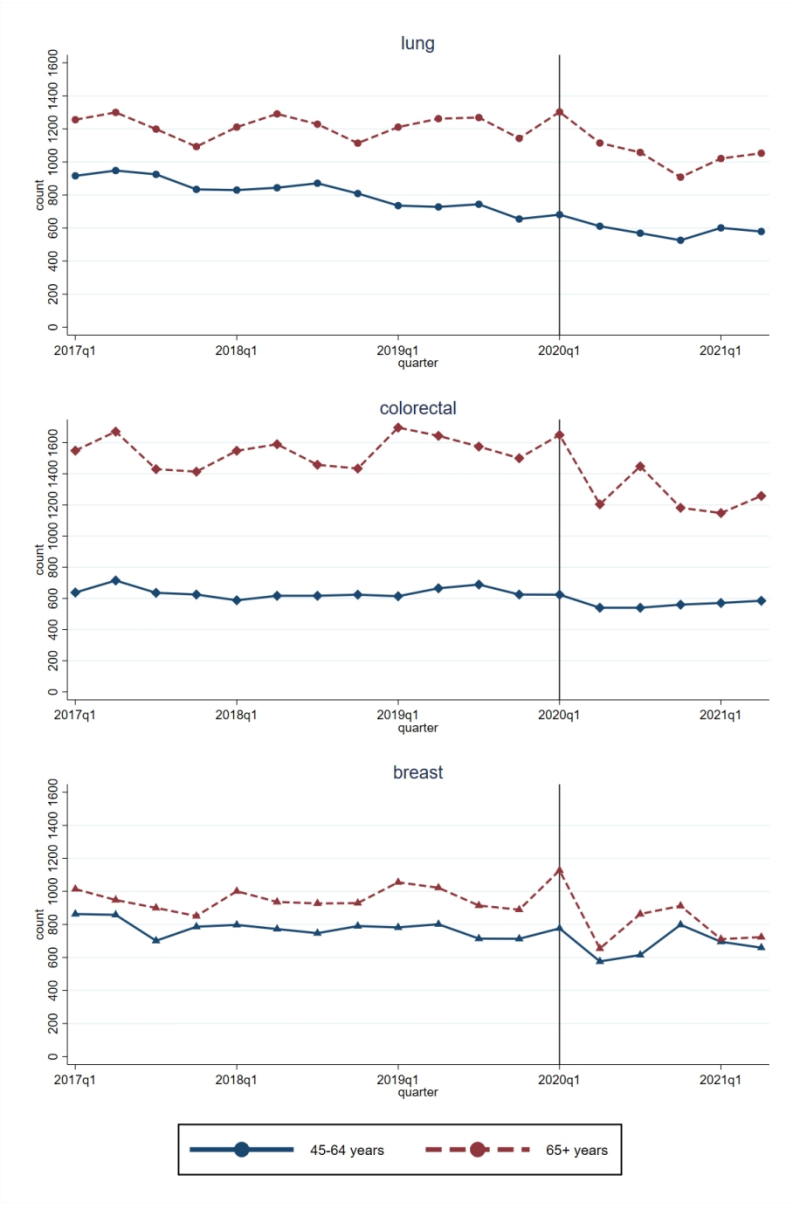
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Figure 3: Number of new cancer cases by age group (2017q1–2021q2)
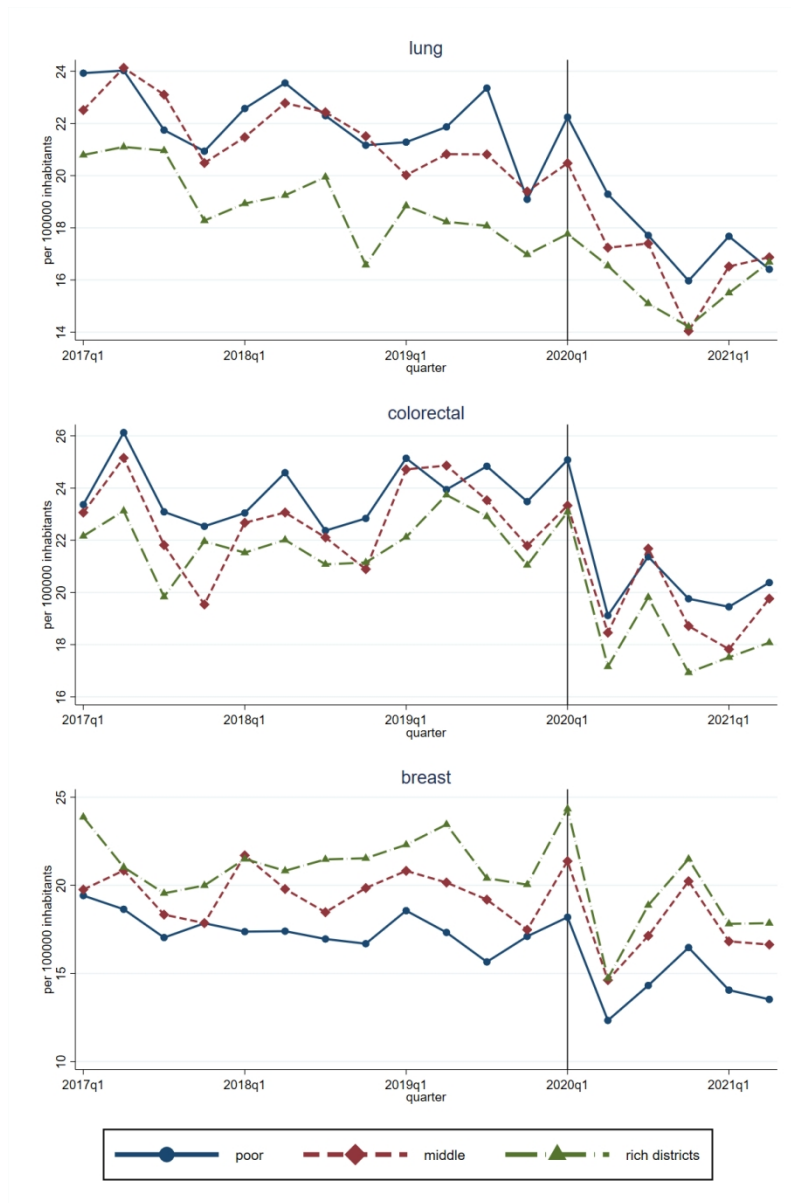
101x152mm (300 x 300 DPI)

Figure 4: Gender- and age-adjusted incidence (per 100,000 inhabitants) by district-level income tertile for lung, colorectal and breast cancer (2017q1–2021q2)

101x152mm (300 x 300 DPI)

Appendix Table A1: Details of the time series models

	log new lung cancer		log new colorectal cancer		log new breast cancer	
Quarterly trend	-0.0117***	(0.0016)	0.0047	(0.0030)	-0.0011	(0.0022)
Seasonal dummies (baseline = q1)						
q2	0.041**	(0.015)	0.039	(0.028)	-0.032	(0.020)
q3	0.0337*	(0.015)	-0.040	(0.028)	-0.103***	(0.021)
q4	-0.052**	(0.015)	-0.078**	(0.029)	-0.094***	(0.021)
Dummies between 2020q1 – 2021q2						
2020q1	0.049*	(0.024)	-0.0074	(0.046)	0.040	(0.034)
2020q2	-0.118***	(0.024)	-0.313***	(0.046)	-0.356***	(0.034)
2020q3	-0.151***	(0.024)	-0.102*	(0.046)	-0.093**	(0.034)
2020q4	-0.176***	(0.024)	-0.202***	(0.046)	0.044	(0.034)
2021q1	-0.100***	(0.028)	-0.292***	(0.053)	-0.228***	(0.039)
2021q2	-0.120***	(0.028)	-0.274***	(0.053)	-0.209***	(0.039)
Constant	10.35***	(0.367)	6.64***	(0.694)	7.87***	(0.510)

*** $p<0.01$, ** $p<0.05$, * $p<0.1$. Standard errors in parentheses.
Quarterly time series between 2017q1–2021q2. Number of quarters: 18.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	5-6
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9

Discussion

Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.