

ORIGINAL RESEARCH

Cancer diagnosis in Catalonia (Spain) after two years of COVID-19 pandemic: an incomplete recovery

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Background: This study aimed to estimate potential undetected cancers over the first 2 years of the COVID-19 pandemic in Catalonia.

Methods: Cancer incidence was compared between pre-pandemic (2019) and pandemic (March 2020-January 2022) periods in the Catalan Pathology Registry (CPR) according to sex, age, and tumor site. The correlation between cancer diagnosis and COVID-19 health care workload was also evaluated by means of the Pearson's correlation coefficient (R). The expected incident cancers (E) during the pandemic were estimated by applying 2019 CPR cancer incidence specific rates by sex and 5-year age groups to the 2020 and 2021 Catalan population pyramids. CPR incident cancers were considered observed (O). Standardized incidence ratios (SIR) and 95% confidence intervals (CIs) were calculated using the O/E ratio.

Results: After two pandemic years, cancer diagnosis decreased by 12% (SIR 0.88, 95% CI 0.87-0.89), or ~7700 undetected cancers (13 000 with nonmelanoma skin cancer). Without nonmelanoma skin cancer, 72% of the cancer underdiagnosis was generated in 2020. Diagnoses decreased more in men (whole pandemic -14%; 2020 -21%; 2021 -8%) than in women (-9%, -19%, -3%, respectively), dropping significantly overall in all pandemic waves but the fifth (first -37%, second -16%, third -8%, fourth -6%, fifth -2%, sixth -6%), and across all adult age groups. In the first wave, CPR cancer diagnosis was inversely correlated with COVID-19 caseload in primary care (R -0.91, 95% CI -0.97 to -0.75) and occupancy in conventional hospital wards (R -0.91, 95% CI -0.99 to -0.48) and intensive care (R -0.91, 95% CI 95% -0.98 to -0.70).

Conclusions: Our study evaluated the overall pandemic impact on cancer diagnosis on a large scale and with minimal selection bias, showing that as of February 2022, cancer detection in Catalonia had not yet recovered to pre-pandemic levels. Pending cancer incidence data from population-based cancer registries, early CPR data could inform the development of Spanish cancer control plans.

Key words: COVID-19, SARS-CoV-2, pandemic, cancer diagnosis, undetected cancers

INTRODUCTION

Cancer is one of the leading causes of disease worldwide. At least 19 million new cancers were expected in 2020,¹ although this estimate did not take into account the impact of the COVID-19 pandemic and the major challenges it has entailed for protecting public health and maintaining routine medical care. In the first pandemic wave, health systems were

subjected to sudden and overwhelming pressure.^{2,3} In cancer, this meant delaying diagnoses⁴⁻⁴¹ and altering treatment regimens.^{30-31,42-47} Subsequent pandemic waves, including the one linked to the omicron variant, have triggered new health crises.⁴⁸ Worldwide, uneven implementation of testing, contact tracing, social restrictions, health system capacity, and COVID-19 vaccine coverage has driven the inequitable impact of the pandemic between countries.³ Four large, nationwide European studies have consistently reported decreases in the overall cancer diagnosis during the first pandemic wave,⁴⁻⁸ and two have described an incomplete recovery after the first pandemic year.^{5,7}

Following the first confirmed COVID-19 case in Spain on 31 January 2020, the country became one of the hardest hit

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in Europe during the spring of 2020.⁴⁹ A strict nationwide lockdown was in effect from 14 March to 11 May 2020, with restrictions gradually lifting to June 20. During the lockdown, telemedicine was expanded, cancer protocols modified, and organized cancer screening programs and non-essential surgery temporarily suspended.³⁷ In the five successive waves (with the last beginning in November 2021), less restrictive measures were established based on health care pressure and vaccination coverage in each Spanish region. Single-center and multicenter hospital-based studies have estimated an overall decrease in cancer diagnosis of 21% to 37% in the first wave,^{33-34,36-37} and 17% in the first pandemic year.³⁵ The heterogeneous methods and hospital biases inherent to this type of study, however, make it difficult to precisely estimate potential undetected cancers during the pandemic.

In Catalonia, a region in northeast Spain with 7.7 million inhabitants, the first case of COVID-19 was confirmed on 25 February 2020. During the first wave, the lockdown was the same as in the rest of Spain, but in the following waves, social restrictions have been tailored to regional epidemiological indicators.⁵⁰ As elsewhere, studies evaluating the impact of the pandemic on cancer diagnosis in Catalonia have described heterogeneous methods and results. One large population-based study carried out in primary care estimated an overall 34% drop in cancer diagnoses in patients older than 14 years up to September 2020.³⁸ Meanwhile, a study based on two hospital pathology laboratories reported a decrease of 6% to 20% until December 2020.⁴⁰

Our study assessed incident cancers from January 2019 to January 2022 in the Catalan Pathology Registry (CPR), which covers ~90% of all pathological diagnoses in the Catalan public health system (71 high-tech and general hospitals, plus 212 primary care centers that have generated pathological specimens). We aimed to estimate the potential number of undetected cancers in Catalonia according to sex, age, tumor site, pandemic waves, and COVID-19 health care workload over two pandemic years.

MATERIAL AND METHODS

Since 2015, pathology laboratories have generated structured reports on all specimens originating in publicly funded hospitals and primary care centers, resulting in the identification of >610 000 neoplastic specimens in the CPR. Before the pandemic, an average of 3500 specimens coded with SNOMED CT terminology were sent to CPR every working day (around 900 000 specimens/year).⁵¹ Specimens include cytologies, biopsies, and necropsies. To ensure cancer identification according to international rules of population-based cancer registries,⁵²⁻⁵³ neoplastic diagnoses are systematically assigned to the International Classification of Diseases for Oncology, 2nd revision (ICD-O-3.2)⁵⁴ Neoplastic reports include topography, histology, and tumor behaviors.

The present study included all incident malignancies registered from January 2019 to January 2022, along with

benign and uncertain cases in the nervous system (Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmoop.2022.100486>). Pseudonymized specimen data were pooled and ordered chronologically by patient. If a patient had different neoplastic morphologies in a single organ, multiple tumors were considered, and topography, morphology, and the date of first neoplastic specimen were collected for each tumor. If specimens came from different organs and with different morphologies, multiple tumors were also considered, and the topography (in this case different), morphology, and date of first neoplastic specimen were recorded for each tumor.⁵³ Date of cancer incidence was defined as the date of the first neoplastic specimen. Finally, after identifying all cancers, previously validated algorithms were applied based on the date of cancer incidence, location, and morphology of tumors to exclude prevalent tumors and ensure that only annual incident cancers from January 2019 to January 2022 were included in the study.⁵⁵

Incident cancers were classified according to ICD-O-3.2 topography: lip, oral cavity, pharynx (C00-C14); esophagus (C15); stomach (C16); colorectal, anus (C18-C21); liver, gallbladder, extrahepatic bile ducts (C22-C24); pancreas (C25); larynx (C32); lung (C34), thymus, heart, mediastinum, pleura (C37-C39); bones (C40-C41); soft tissues, peritoneum, retroperitoneum (C47-C49); breast (C50); vulva, vagina (C51-C52); cervix (C53); endometrium (C54); ovary (C56.9); prostate (C61.9); testis (C62); kidney (C64.9); urinary tract (C66.9-C68.0); brain, meninges, spinal cord (C70-C72); thyroid (C73.9); other tumor sites (C17 small intestine, C58.9 placenta, C60 penis, C69 eye, C74.9-C75 endocrine glands); and unknown primary site (C26.9, C39.9, C57.9, C63.9, C68.9, C76, C80.9). Skin melanoma was identified by topography (C44) and specific ICD-O-3.2 morphologies (M87203-M87803). The rest of the skin tumors were considered nonmelanoma skin cancer (mostly basal and squamous cell cancers). Lymphoid and myeloid malignancies were identified by topography (C42, C77) and morphology (lymphoid: M95903-M97383, M97493-M97691, M98113-M98373, M99403, M99483, M99703-M99713, M97283-M99713; myeloid: M97403-M97423, M98053-M98093, M98403-M99313, M99453-M99463, M99503-M99683, M-99753-M96703).⁵⁴

Age at diagnosis was determined according to the cancer incidence date and categorized in three age groups (0-49; 50-69, ≥70 years). The 50-69-year age group coincided with the target population for population-based colorectal and breast cancer screening programs in Catalonia. The study period was divided into two intervals: (i) a pre-pandemic validation set (1 January-31 December 2019) and (ii) the pandemic as analysis set (14 March 2020-31 January 2022). The pandemic period was then divided into seven cycles according to the six Catalan pandemic waves⁵⁰: (i) first: 14 March-20 June 2020; (ii) summer 2020, 21 June-30 September 2020; (iii) second: 1 October-23 December 2020; (iv) third: 24 December 2020-25 March 2021; (v) fourth: 26 March-1 July 2021; (vi) fifth: 2 July-31 October 2021; and (vii) sixth: 1 November 2021-31 January 2022.

The pre-pandemic period (2019) was likewise segmented into seven analogous cycles.

Data for primary care caseload (14 March 2020-31 January 2022) and occupancy in conventional hospital wards (1 January 2020-31 January 2022) and intensive care units (ICUs: 1 April 2020-31 January 2022) due to COVID-19 were supplied by the Catalan Health Department's Agency for Healthcare Quality and Evaluation.⁵⁰ COVID-19 cases were confirmed by PCR/rapid antigen test; in patients with more than one positive test, we included the first one. In the first wave, COVID-19 diagnosis was mainly based on PCR. ICD-10 codes used to identify COVID-19 cases in the Catalan hospital census register were: B97.29, B34.2 (before 1 July 2020), B97.21, J12.81 and U07.1 (from 1 July 2020).⁵⁰

To analyze data, CPR cancer diagnoses were aggregated weekly to avoid the effect of weekends and holidays. Likewise, mean weekly COVID-19 occupancy in ambulatory and inpatient settings during the pandemic was calculated. The temporal association between cancer diagnoses and health facility workload was investigated by means of a dynamic correlation analysis, assuming a window size of 13 weeks.⁵⁶ The linear correlation between weekly CPR incident cancers and health care workload due to COVID-19 during each pandemic wave was calculated using Pearson's correlation coefficient and its 95% confidence intervals (95% CI).⁵⁷ To estimate CPR cancer underdiagnosis, excess deaths that occurred in the pandemic were taken into account.^{2,58,59} Expected incident cancers (E) in the CPR during the pandemic were estimated by applying 2019 cancer incidence specific rates by sex and 5-year age groups to the updated 2020 and 2021 Catalan population pyramids for each tumor site.⁶⁰ CPR incident cancers during the pandemic were considered observed cancers (O). Standardized incidence ratios (SIR) with their 95% CIs were calculated using the ratio O/E ,⁶¹ with values of 1 indicating that observed and expected cancers were equal before and during the pandemic, and therefore there were no differences in cancer diagnosis between pre-pandemic and pandemic periods. SIRs below and above 1 indicate, respectively, underdiagnosis and overdiagnosis of cancer. The value obtained by subtracting the SIR value from the unit was interpreted as the percentage variation of underdiagnosis or overdiagnosis of cancer. If the 95% CI did not include the value 1, it was considered statistically significant. Negative differences between O and E cancers were considered an estimate of the undetected cancers in the pandemic.

Specific statistical analyses were carried out for pediatric tumors (0-14 years) according to the International Classification of Childhood Cancer.⁶² Statistical analysis and representation of the results using a color-blind friendly palette⁶³ was carried out using R statistical software.⁶⁴

The study was approved by the Research Ethics Committee of the Bellvitge University Hospital (PR264/21). Due to its retrospective design and the use of pseudonymized data, it did not require consent to participate.

RESULTS

At two years from the start of the COVID-19 pandemic, cancer diagnosis had decreased by 12% (7700 incident cancers) in the CPR (SIR 0.88; 95% CI 0.87-0.89) compared with those expected based on the pre-pandemic period. If nonmelanoma skin cancer is included, the decrease is estimated at 14% (SIR 0.86, 95% CI 0.85-0.86); 13 000 undetected cancers (Table 1). From now on, to ease reading, we will omit information on nonmelanoma skin cancer as it can be found in the figures and tables of this paper and in the Supplementary Material, available at <https://doi.org/10.1016/j.esmoop.2022.100486>. Altogether, ~72.2% of the cancer underdiagnosis was generated in 2020 (Supplementary Tables S1 and S2, available at <https://doi.org/10.1016/j.esmoop.2022.100486>). This pattern was similar in both sexes, but the decline was more evident in men (whole pandemic, 2020, 2021 men: -14%, -21%, -8%; women: -9%, -19%, -3%, respectively; Figure 1, Supplementary Tables S3-S5, available at <https://doi.org/10.1016/j.esmoop.2022.100486>).

Overall, cancer diagnoses dropped significantly in all but the fifth pandemic wave (Figure 1), with a gradual return to pre-pandemic levels after spring 2020 (first wave -37%, summer 2020 -6%, second wave -16%, third wave -9%, fourth wave -6%, fifth wave -2%, and sixth wave -6%). In men, observed diagnoses were significantly lower than expected cases in all waves and in summer 2020 (first -36%, summer 2020 -9%, second -18%, third -11%, fourth -8%, fifth -4%, sixth -11%). In contrast, data for women indicated underdiagnosis only in the first four waves (first -39%; second -13%, third -6%, fourth -4%) and a stabilization approaching pre-pandemic diagnostic levels in summer 2020 and in the fifth and sixth waves (summer 2020 -1%, fifth 0%, sixth -1%; Supplementary Tables S3-S5, available at <https://doi.org/10.1016/j.esmoop.2022.100486>). Figure 2 shows specific cancer diagnosis for each tumor site during the entire pandemic.

In the first wave, cancer diagnosis was inversely and significantly correlated with high COVID-19 caseload in primary care (R: -0.91, 95% CI -0.97 to -0.75), conventional hospital wards (R: -0.91, 95% CI -0.99 to -0.48), and ICUs (R: -0.91, 95% CI -0.98 to -0.70). In the summer of 2020, this pattern persisted only for conventional wards and ICUs (R: -0.56, 95% CI -0.83 to -0.09; R: -0.68, 95% CI -0.88 to -0.28, respectively). In the rest of the pandemic, no association was detected between cancer diagnosis and health care workload due to COVID-19. In the fifth wave, a positive association was found only in primary care (R: 0.48, 95% CI 0.02-0.77) (Figure 3).

Cancer diagnoses dropped similarly and significantly among the 0-49, 50-69, and >70 years age groups during the pandemic (pandemic: -13%, -12%, -11%; 2020: -19%, -20%, -21%; 2021: -10%, -7%, -4%, respectively) (Figure 1, Table 1; Supplementary Tables S1 and S2, available at <https://doi.org/10.1016/j.esmoop.2022.100486>). A significant level of underdiagnosis was maintained throughout the first four waves in all three age

Table 1. Estimated undetected cancers during the COVID-19 pandemic in Catalonia. Comparison of cancer incidence in the Catalan Pathology Registry (CPR) between pre-pandemic (2019) and pandemic (March 2020-January 2022) periods by age and tumor site (both sexes)

Tumor site	0-49				50-69				>= 70				All ages			
	O	E	Dif	SIR (95% CI)	O	E	Dif	SIR (95% CI)	O	E	Dif	SIR (95% CI)	O	E	Dif	SIR (95% CI)
Lip, oral cavity, pharynx (COO-C14)	182	223	-41	0.82 (0.70-0.94)	843	1069	-226	0.79 (0.74-0.84)	868	1032	-164	0.84 (0.79-0.90)	1893	2324	-431	0.81 (0.78-0.85)
Esophagus (C15)	58	41	17	1.42 (1.08-1.83)	330	356	-26	0.93 (0.83-1.03)	294	341	-47	0.86 (0.77-0.97)	682	738	-56	0.92 (0.86-1.00)
Stomach (C16)	110	159	-49	0.69 (0.57-0.84)	583	720	-137	0.81 (0.75-0.88)	859	1101	-242	0.78 (0.73-0.83)	1552	1980	-428	0.78 (0.75-0.82)
Colon, rectum, anus (C17-C21)	427	504	-77	0.85 (0.77-0.93)	2993	3710	-717	0.81 (0.78-0.84)	4299	4827	-528	0.89 (0.86-0.92)	7719	9041	-1322	0.85 (0.83-0.87)
Liver, gallbladder, ext. bile ducts (C22-C24)	246	251	-5	0.98 (0.86-1.11)	1393	1447	-54	0.96 (0.91-1.01)	1356	1551	-195	0.87 (0.83-0.92)	2995	3249	-254	0.92 (0.89-0.96)
Pancreas (C25)	65	59	6	1.10 (0.85-1.40)	412	398	14	1.03 (0.94-1.14)	449	452	-3	0.99 (0.90-1.09)	926	910	16	1.02 (0.95-1.09)
Larynx (C32)	24	49	-25	0.49 (0.31-0.73)	420	486	-66	0.86 (0.78-0.95)	273	340	-67	0.80 (0.71-0.90)	717	875	-158	0.82 (0.76-0.88)
Lung (C34)	264	317	-53	0.83 (0.74-0.94)	2627	2975	-348	0.88 (0.85-0.92)	2470	2789	-319	0.89 (0.85-0.92)	5361	6080	-719	0.88 (0.86-0.91)
Thymus, heart, mediast., pleura (C37-C39)	12	20	-8	0.59 (0.30-1.03)	48	46	2	1.04 (0.76-1.37)	80	115	-35	0.69 (0.55-0.86)	140	182	-42	0.77 (0.65-0.91)
Bones (C40-C41)	37	62	-25	0.60 (0.42-0.83)	33	41	-8	0.80 (0.55-1.13)	23	10	13	2.37 (1.50-3.56)	93	113	-20	0.83 (0.67-1.01)
Soft tissues (C47-C49)	166	163	3	1.02 (0.87-1.19)	251	308	-57	0.81 (0.72-0.92)	177	218	-41	0.81 (0.70-0.94)	594	690	-96	0.86 (0.79-0.93)
Skin, melanoma (C44)	315	344	-29	0.91 (0.82-1.02)	493	566	-73	0.87 (0.80-0.95)	562	653	-91	0.86 (0.79-0.93)	1370	1564	-194	0.88 (0.83-0.92)
Skin, nonmelanoma (C44)	1677	1857	-180	0.90 (0.86-0.95)	5749	7124	-1375	0.81 (0.79-0.83)	14 058	17 917	-3859	0.78 (0.77-0.80)	21 484	26 898	-5414	0.80 (0.79-0.81)
Breast (C50)	1808	1993	-185	0.91 (0.87-0.95)	3869	4278	-409	0.90 (0.88-0.93)	2676	2841	-165	0.94 (0.91-0.98)	8353	9112	-759	0.92 (0.90-0.94)
Vulva, vagina (C51-C52)	45	31	14	1.46 (1.07-1.96)	102	146	-44	0.70 (0.57-0.85)	239	251	-12	0.95 (0.84-1.08)	386	427	-41	0.90 (0.82-1.00)
Cervix (C53)	208	247	-39	0.84 (0.73-0.97)	187	243	-56	0.77 (0.66-0.89)	151	127	24	1.19 (1.00-1.39)	546	617	-71	0.89 (0.81-0.96)
Endometrium (C54)	182	163	19	1.12 (0.96-1.29)	807	874	-67	0.92 (0.86-0.99)	632	605	27	1.04 (0.96-1.13)	1621	1642	-21	0.99 (0.94-1.04)
Ovary (C56)	153	162	-9	0.95 (0.80-1.11)	306	259	47	1.18 (1.05-1.32)	150	137	13	1.10 (0.93-1.29)	609	558	51	1.09 (1.01-1.18)
Prostate (C61.9)	53	61	-8	0.87 (0.65-1.14)	2533	2908	-375	0.87 (0.84-0.91)	3280	3849	-569	0.85 (0.82-0.88)	5866	6818	-952	0.86 (0.84-0.88)
Testis (C62)	208	259	-51	0.80 (0.70-0.92)	45	52	-7	0.87 (0.64-1.17)	19	12	7	1.64 (0.99-2.57)	272	322	-50	0.85 (0.75-0.95)
Kidney (C64)	182	178	4	1.02 (0.88-1.18)	711	820	-109	0.87 (0.80-0.93)	612	661	-49	0.93 (0.85-1.00)	1505	1658	-153	0.91 (0.86-0.95)
Urinary tract (C66.9-C68)	98	132	-34	0.75 (0.60-0.91)	1528	1588	-60	0.96 (0.91-1.01)	2642	2768	-126	0.95 (0.92-0.99)	4268	4488	-220	0.95 (0.92-0.98)
Meninges, brain, spinal cord (C70-C72)	290	435	-145	0.67 (0.59-0.75)	526	610	-84	0.86 (0.79-0.94)	253	354	-101	0.71 (0.63-0.81)	1069	1399	-330	0.76 (0.72-0.81)
Thyroid (C73.9)	350	443	-93	0.79 (0.71-0.88)	392	496	-104	0.79 (0.71-0.87)	174	226	-52	0.77 (0.66-0.89)	916	1165	-249	0.79 (0.74-0.84)
Lymphoid	419	537	-118	0.78 (0.71-0.86)	834	1069	-235	0.78 (0.73-0.84)	1004	1149	-145	0.87 (0.82-0.93)	2257	2755	-498	0.82 (0.79-0.85)
Myeloid	116	155	-39	0.75 (0.62-0.90)	289	360	-71	0.80 (0.71-0.90)	430	540	-110	0.80 (0.72-0.88)	835	1055	-220	0.79 (0.74-0.85)
Other tumor sites ^a	121	143	-22	0.84 (0.70-1.01)	332	378	-46	0.88 (0.79-0.98)	372	445	-73	0.84 (0.75-0.93)	825	966	-141	0.85 (0.80-0.91)
Unknown primary site ^b	491	529	-38	0.93 (0.85-1.01)	1614	1709	-95	0.94 (0.90-0.99)	1632	1838	-206	0.89 (0.85-0.93)	3737	4076	-339	0.92 (0.89-0.95)
All sites	8307	9516	-1209	0.87 (0.85-0.89)	30 250	35 036	-4786	0.86 (0.85-0.87)	40 034	47 149	-7115	0.85 (0.84-0.86)	78 591	91 700	-13 109	0.86 (0.85-0.86)
All but nonmelanoma of skin	6630	7659	-1029	0.87 (0.84-0.89)	24 501	27 911	-3410	0.88 (0.87-0.89)	25 976	29 232	-3256	0.89 (0.88-0.90)	57 107	64 802	-7695	0.88 (0.87-0.89)

O: observed incident cancers in the CPR, E: expected incident cancers in the CPR, Dif: estimated number of undetected cancers, difference between O and E. The sum of the estimated undetected cancers from all tumor sites may not be equal to the total in the table. SIR (95% CI): standardized incidence ratio (95% confidence interval). 95% CIs including 1 are not statistically significant (colorless), SIRs >1 indicate significant overdiagnosis (yellow) and <1, significant underdiagnosis (red).

^aOther tumor sites include small intestine, placenta, penis, eye and adnexa, endocrine glands without thyroid.

^bUnknown primary site includes all unspecific tumour sites in specimens from the CPR.

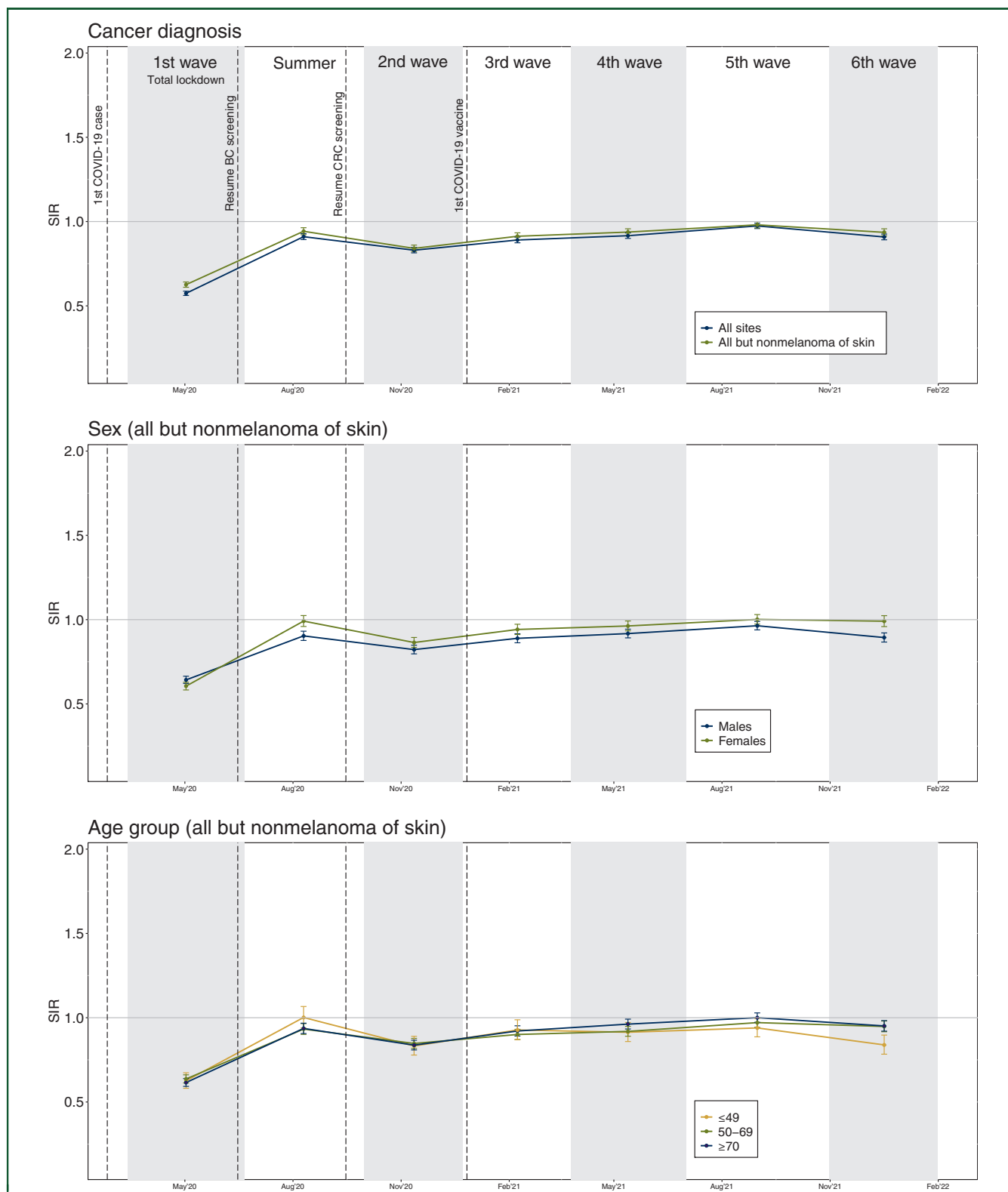


Figure 1. Global comparison of cancer incidence in the Catalan Pathology Registry between pre-pandemic (2019) and pandemic (March 2020 to January 2022) periods by sex, age groups, and pandemic wave.

SIR (figure dots). Whiskers represent 95% confidence intervals (95% CI) for estimated SIR. 95% CIs including value 1 (horizontal line) are not statistically significant. SIR significant values over or below 1 indicate over- and underdiagnosis of cancer, respectively.

BC, breast cancer; CRC, colorectal cancer; SIR, standardized incidence ratio.

groups (first –37%, –36%, –38%; second –17%, –15%, –16%; third –7%, –10%, –8%; fourth –9%, –8%, –4%, respectively). In the fifth wave, cancer detection stabilized

at pre-pandemic levels in all age groups except 0-49 years. (5th –6%, –3%, 0%), whereas it dropped significantly again in the sixth one (sixth –16%, –5%, –5%) (Supplementary

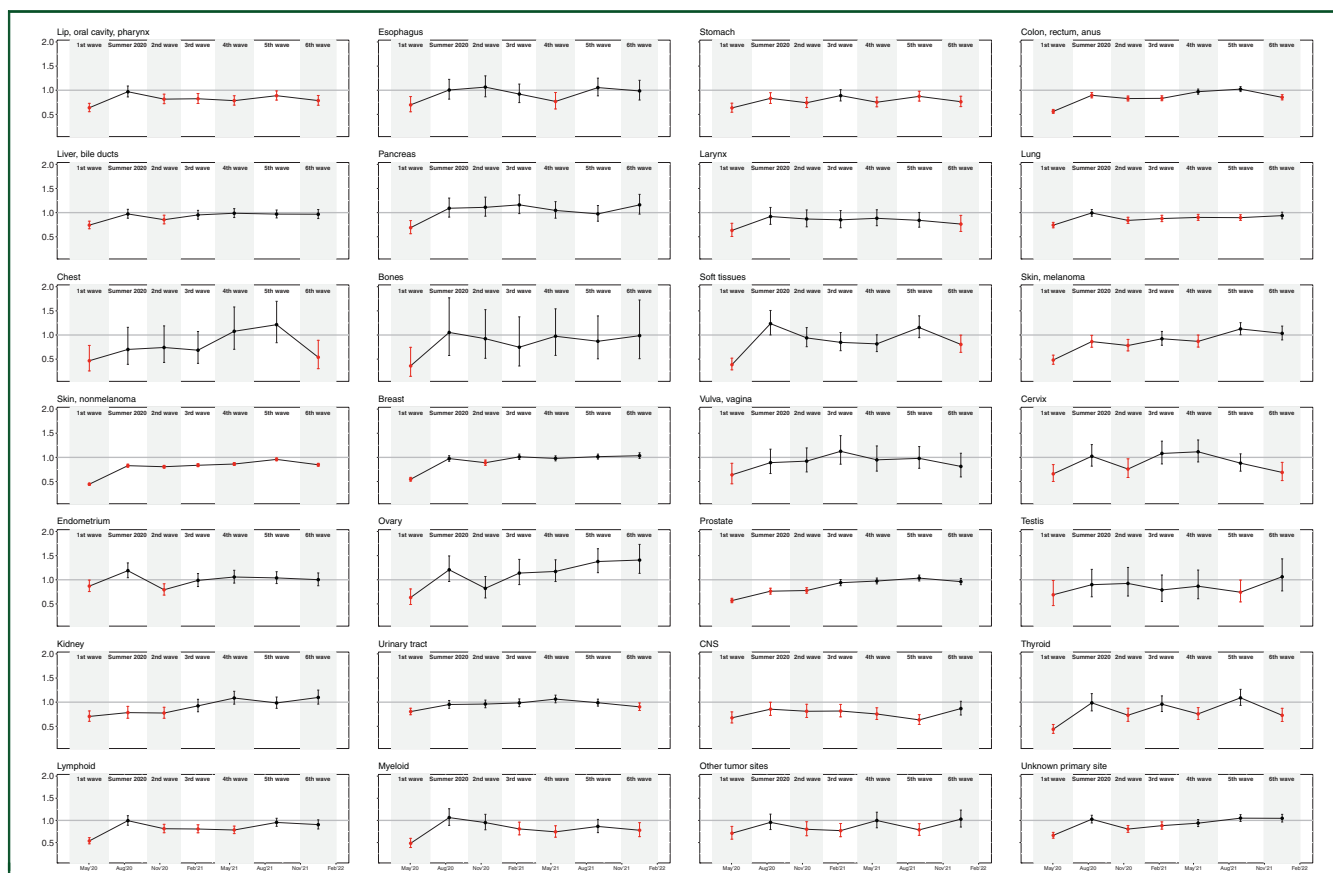


Figure 2. Comparison of cancer incidence in the Catalan Pathology Registry between pre-pandemic (2019) and pandemic (March 2020 to January 2022) periods by tumor site and pandemic wave. Liver, bile duct: liver, gallbladder, extrahepatic bile ducts; chest: thymus, heart, mediastinum, pleura; soft tissues: soft tissues, peritoneum, retroperitoneum; urinary tract: urethra, bladder, ureter, renal pelvis; CNS: meninges, brain, spinal cord. SIR (figure dots). Whiskers represent 95% confidence intervals (95% CI) for estimated SIR. 95% CIs including value 1 (horizontal line) are not statistically significant. SIR significant values over or below 1 (red color) indicate over- and underdiagnosis of cancer, respectively. SIR, standardized incidence ratio.

Tables S6-S12, available at <https://doi.org/10.1016/j.esmoop.2022.100486>). Pediatric cancers (0-14 years) presented significant overall cancer underdiagnosis throughout the pandemic (−35%), attributable specifically to hematological malignancies, retinoblastoma, and hepatic and bone tumors (Supplementary Table S13, available at <https://doi.org/10.1016/j.esmoop.2022.100486>).

As of February 2022, after two pandemic years, the relative decrease and estimated number of undetected cancers in the CPR was, according to tumor site, colorectal cancer (−15%, −1300), followed by cancers of the prostate (−14%, −950), breast (−8%, −750), lung (−12%, −700), lymphoid malignancies (−18%, −500), head and neck (−19%, −430), stomach (−22%, −430), nervous system (−24%, −330), liver (−8%, −250), thyroid (−21%, −250), myeloid malignancies (−21%, −220), urinary tract (−5%, −220), melanoma (−12%, −190), larynx (−18%, −160), and kidney (−9%, −150). Unknown primary site, other tumor sites, and chest tumors (different from lung) have likewise not returned to pre-pandemic diagnostic levels (missing cancers: −500). In contrast, cancers of the pancreas, esophagus, bone, vulva, vagina, and endometrium have recovered (SIRs 95% CI crosses the value 1). Only

ovarian cancer has shown a significant increase in diagnosis during the pandemic (+9%, 50) (Table 1). Undetected cases according to sex, age, and tumor site are shown in Figure 4.

The only cancer consistently underdiagnosed throughout the entire pandemic was nonmelanoma skin cancer (Figure 1; Supplementary Table S3, available at <https://doi.org/10.1016/j.esmoop.2022.100486>). Diagnosis of breast and colorectal cancers fell sharply during the first wave (breast −45%, −650; colorectal −44%, −600), especially in the 50-69-year age group (breast −52%, −350; colorectal −51%, −280) (Figure 2; Supplementary Table S6, available at <https://doi.org/10.1016/j.esmoop.2022.100486>). Overall, breast cancer diagnoses returned to pre-pandemic levels in the summer of 2020 and then from the third wave onwards (summer 2020 −2%, −30; third +1%, 15; fourth −2%, −30; fifth +2%, 25; sixth +4%, 40). In contrast, colorectal cancer reached pre-pandemic diagnostic levels from the fourth wave (summer 2020 −10%, −120; second −17%, −200; third −17%, −215; fourth −3%, −40; fifth +2%, 40) but declined significantly again in the sixth wave (sixth −15%, −170). Lung cancer was also significantly underdiagnosed throughout the whole pandemic except in

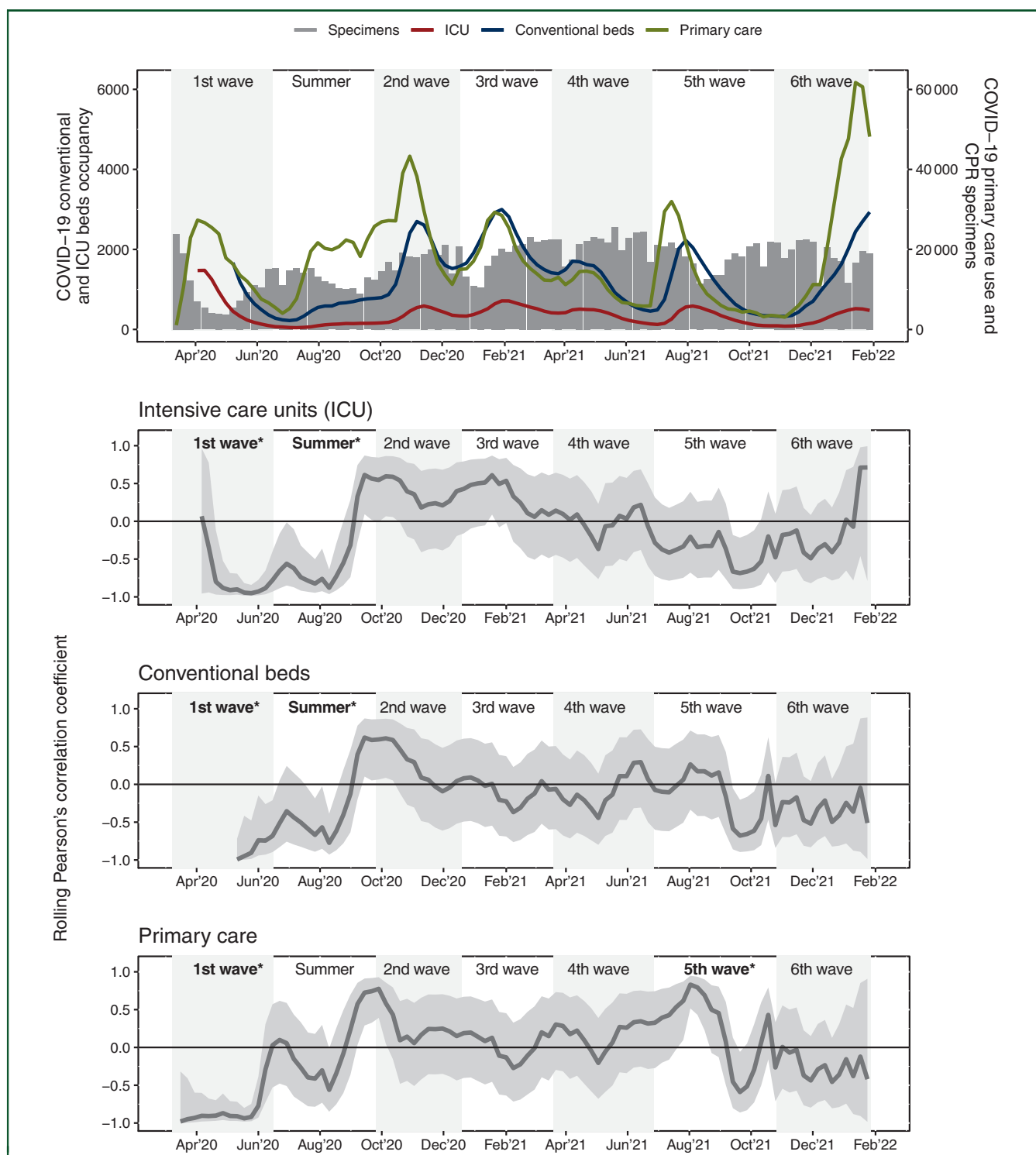


Figure 3. Catalan COVID-19 health care caseload due to COVID-19 and its rolling correlation with incident cancers from the Catalan Pathology Registry (CPR) during the pandemic. Conventional and ICU beds occupancy and primary care caseload due to COVID-19 are shown as a weekly average. CPR specimens are per week. Shaded bands represent the rolling correlation and 95% confidence interval. Shaded bands containing 0 (horizontal line) are statistically not significant. *Significant Pearson's correlation coefficients (R): R_{ICU} 1st wave -0.91 (-0.98 to -0.70), $R_{Conventional\ beds}$ 1st wave -0.91 (-0.99 to -0.48), $R_{Primary\ care}$ 1st wave -0.91 (-0.97 to -0.75), R_{ICU} Summer 2020 -0.68 (-0.88 to -0.28), $R_{Conventional\ beds}$ Summer 2020: -0.56 (-0.83 to -0.09), $R_{Primary\ care}$ 5th wave: 0.48 (0.02 - 0.77). COVID-19 pandemic waves: (i) 1st wave, 14 March-20 June 2020; (ii) summer 2020, 21 June-30 September 2020; (iii) 2nd wave, 1 October-23 December 2020; (iv) 3rd wave, 24 December 2020-25 March 2021; (v) 4th wave, 26 March-1 July 2021, (vi) 5th wave, 2 July-31 October 2021, and (vii) 6th wave, 1 November 2021-31 January 2022. ICU, intensive care unit.

the summer of 2020 (-1% , -5) and in the sixth wave (-6% , -50). Prostate cancer, however, after a very significant decline in the first wave (-43% , -460), gradually

recovered to baseline levels from the third wave on (summer 2020 -24% , -200 ; second -22% , -220 ; third -6% , -50 ; fourth -3% , -30 ; fifth $+3\%$, 40 ;

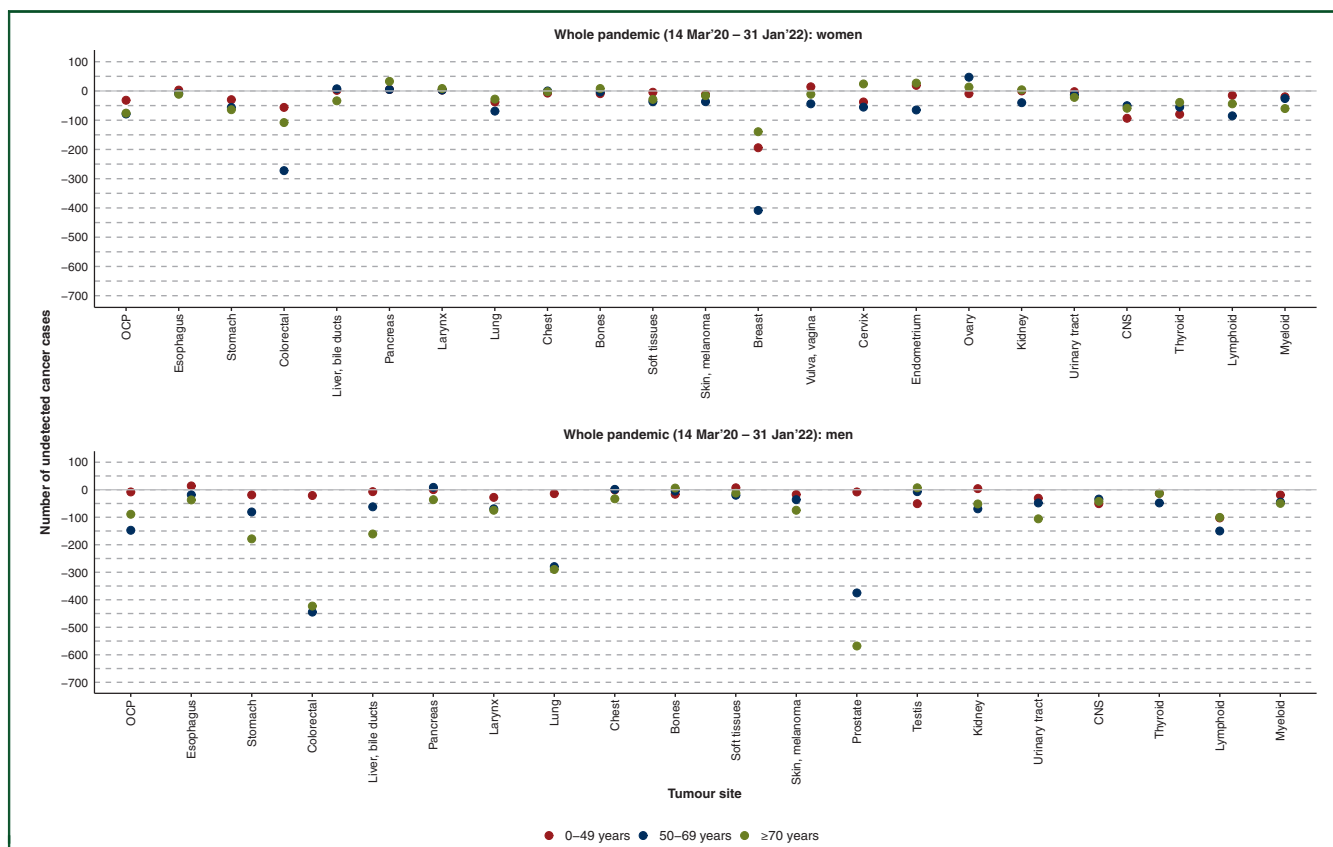


Figure 4. Estimated undetected cancer cases in the Catalan Pathology Registry during the COVID-19 pandemic by sex, age, and tumour site. OCP: lip, oral cavity, pharynx; colorectal: colon, rectum, anus; liver, bile duct: liver, gallbladder, extrahepatic bile ducts; chest: thymus, heart, mediastinum, pleura; soft tissues: soft tissues, peritoneum, retroperitoneum; urinary tract: urethra, bladder, ureter, renal pelvis; CNS: meninges, brain, spinal cord. CNS, central nervous system.

sixth –4%, –40) (Figure 2; Supplementary Tables S6-S12, available at <https://doi.org/10.1016/j.esmoop.2022.100486>).

Certain tumors with a worse prognosis, such as those of the head and neck (–19%), stomach (–22%), larynx (–18%), nervous system (–24%), and hematological malignancies (lymphoid: –18%, myeloid: –21%) also presented a significant drop in diagnosis in both sexes throughout the pandemic (Table 1, Figures 2 and 4).

DISCUSSION

According to the CPR, Catalonia saw a substantial reduction in incident cancers over two pandemic years compared with the preceding year. Our data show an estimated 7700 undetected cancers, or 13 000 if nonmelanoma skin cancer is included. Excluding nonmelanoma skin cancer, an estimated 12% of expected cancer cases were left undetected during the pandemic.⁶⁵ Although the decline in cancer diagnosis was concentrated in 2020 with a trend towards normality in 2021, diagnostic levels of incident cancers have not yet fully recovered. Data up to 31 January 2022 show that cancers with a generally good prognosis (skin, testis) have not yet returned to pre-pandemic diagnostic levels, nor have cancers with a relatively good prognosis if diagnosed early (colorectal, prostate, breast, larynx, thyroid, cervix, urinary

system) or those with a poor prognosis (head and neck, stomach, liver, nervous system, lung, and hematological). The only cancers that did not present suboptimal diagnosis levels in the pandemic were those of the esophagus, pancreas, bone, vulva, vagina, endometrium, and ovary; the last showed even higher rates of diagnosis. In fact, the pandemic had less impact on women than on men, mainly due to the early recovery of diagnoses of breast and gynecological tumors and the lower incidence of colorectal and tobacco-related cancers.⁶⁵ Although published studies over this large timeframe are limited, our results show an impact of the pandemic on cancer diagnosis similar to that of other European countries during the first wave,^{4-8,11,12} but perhaps with signs of a slower recovery afterward.⁷

The decrease in detected incidence in the CPR has been uneven during the pandemic. The most important drop was observed in the first wave, in line with previous reports from Catalan primary care³⁸⁻³⁹ and elsewhere in Europe, North America, and Hong Kong.⁴⁻³² The strong inverse correlation between COVID-19 workload in health care settings and cancer diagnosis reflects the sudden, overwhelming pressure on the Catalan health care system as COVID-19 cases began to skyrocket in the spring of 2020. The decline in detected cases during this wave is probably largely attributable to the temporary suspension of organized cancer screening programs and non-essential surgery,

the substitution of face-to-face visits with telemedicine, and patients' fear of going to health care facilities. After the first wave lay bare the fragility of the health system, Catalan policymakers reinforced community identification of COVID-19 cases and contact tracing, redefined priority circuits for high suspicion of cancer in primary care, expanded ICU capacity, and reactivated delayed cancer surgeries and cancer screening.⁶⁶ It was reassuring to note that by the summer of 2020, cancer diagnosis in Catalonia had almost recovered to baseline levels for most malignancies.

In the second wave (October to December 2020), incident cancers fell again, but to a lesser magnitude. This smoother decline suggests that health interventions implemented in the summer of 2020 were successful in mitigating the new pandemic shock. Even milder was the drop in cancer diagnoses in the third wave (January to March 2021), which is partly attributable to the launch of the vaccination campaign against COVID-19 in the high-risk population on 27 December 2020.⁵⁰ In early 2021, diagnosis of breast and prostate cancers reached pre-pandemic levels in all age groups. The resumption of population-based breast cancer screening in June 2020 (before the pandemic, 30% of invasive breast cancers were detected by screening; unpublished data), together with the lower impact on referrals and first active treatments in both cancers, could partly explain the rebound that has continued to date.^{11,12,30,43,44,67}

In the fourth wave (March to July 2021), cancer underdiagnosis continued to abate. For the first time in the pandemic, colorectal cancer diagnosis normalized to pre-pandemic levels, and these levels persisted until the sixth wave, when data once again indicated suboptimal detection. Invitations to the fecal immunochemical test (FIT) based colorectal cancer screening program resumed in September 2020, but ~43% of the target population had not yet received their invitation by December 2020. Given that before the pandemic ~11% of invasive colorectal cancers in Catalonia were detected by screening (unpublished data), the lower rates of participation, adherence to colonoscopy, and cancer detection due to the increased FIT positivity threshold during the pandemic⁶⁸ could explain why colorectal cancer diagnoses did not return to baseline levels until 6 months after reopening the screening program. The progressive increase in endoscopies and elective surgeries as the pandemic progressed probably helped the rebound in diagnosis of this cancer in all age groups, not only in the target age group of the colorectal cancer screening.^{9,31,43,44}

During the fifth wave (July to October 2021), overall cancer diagnoses reached the 2019 baseline levels for the first time since the start of the pandemic. This wave was characterized by community transmission of the COVID-19 delta variant, which primarily affected adolescents and young adults, in whom COVID-19 vaccination coverage was still relatively low.^{50,69} The good vaccination rates in adults—among the highest in Europe³—and the concentration of cases of the delta variant among young people,⁵⁰ who are at lower risk of developing both cancer and severe

COVID-19 disease, helped to preserve the health system's capacity to detect cancers. The sixth wave (November 2021 to January 2022) was marked by the fast-spreading omicron variant,⁴⁸ a new but discreet drop in overall cancer diagnoses, and, for the first time in the pandemic, a return to pre-pandemic levels of lung cancer diagnosis. The lower impact of this wave can be largely attributed to previously administered booster doses among the high-risk population and the elderly,^{50,70} the concentration of transmission in low-risk children and young adults,⁵⁰ and the presumed lower severity of this variant.⁷¹

Cancer incidence in children under the age of 15 years is low, reaching at most about 200 incident cases yearly in Catalonia before the pandemic.^{72,73} Since the pandemic began, we have estimated a loss of ~90 pediatric cancers (52% corresponding to leukemia's, lymphomas, and tumors of the nervous system). Worldwide, substantial disruptions in pediatric cancer diagnosis and management were described in the first pandemic wave, particularly in low- and middle-income countries.⁷⁴ Whereas a study conducted in the UK reported a significant reduction in cancer diagnoses during the first wave,⁷⁵ however, two studies from Canada and Germany^{76,77} did not find a decrease in the first pandemic year. These heterogeneous published data, combined with the insufficient statistical power of our pediatric series which did not allow us to analyze incident cases according to pandemic waves for all tumor types, mean that our estimates must be interpreted with great caution.

Clinically diagnosed cancers and those that may not require histological verification, especially hematological cancers and tumors of the prostate and nervous system, could have generated a possible underestimation of the impact of the COVID-19 pandemic in Catalonia. In addition to pediatric, bone, and testicular cancers, there was insufficient statistical power for some age groups, which may not have been adequately evaluated. Due to the lack of clinical data, it was not possible for us to assess stage at diagnosis. Due to the long study period and the fact that two-thirds of undetected cancers during the pandemic occurred in the last 9 months of 2020, staging would have contributed to a better interpretation of the cancer diagnosis rebound in 2021. In particular, for cancers with a relatively good prognosis, staging might have helped characterize cancers with delayed diagnosis versus cancers that debuted in 2021. Short- and long-term clinical consequences, such as stage at diagnosis and changes in survival rates, will need to be carefully evaluated later through population-based cancer registries. Other possible limitations of our study include its focus on patients diagnosed in the public health system, without taking into account the increased use of private insurance in low educational groups under 50 years of age, although its impact would be quite limited due to the low cancer risk in this age group. Moreover, we could not account for the loss of population that occurred during the pandemic due to the fall in internal and external immigration. The impact of this attrition on our results would be limited, however, since the calculation of the expected cancers was based on

the Catalan population pyramids updated in January 2022, which took into account both excess mortality and the migratory balance.⁶⁰

To our knowledge, this is the first Spanish study to evaluate the impact of the whole pandemic on cancer diagnosis on a large scale and with minimal selection bias. Pending cancer incidence data from Spanish population-based cancer registries,⁷⁸ the early data collection in the CPR could inform the development of national cancer control plans. In summary, at 2 years since the start of the COVID-19 pandemic, there may still be 7700 individuals with undetected cancers in Catalonia. Colorectal ($n = 1300$), prostate ($n = 950$), and breast ($n = 750$) cancers alone could account for 40% of these cases. Public health interventions to address decreases in cancer diagnoses will be critical to minimize the potentially increased incidence of advanced cancers because of delayed detection.

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DISCLOSURE

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