

ARTICLE



Epidemiology

Impact of the SARS-CoV-2 pandemic on female breast, colorectal and non-small cell lung cancer incidence, stage and healthcare pathway to diagnosis during 2020 in Wales, UK, using a national cancer clinical record system

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BACKGROUND: COVID-19 pandemic responses impacted behaviour and health services. We estimated the impact on incidence, stage and healthcare pathway to diagnosis for female breast, colorectal and non-small cell lung cancers at population level in Wales.

METHODS: Cancer e-record and hospital admission data linkage identified adult cases, stage and healthcare pathway to diagnosis (population ~2.5 million). Using multivariate Poisson regressions, we compared 2019 and 2020 counts and estimated incidence rate ratios (IRR).

RESULTS: Cases decreased 15.2% ($n = -1011$) overall. Female breast annual IRR was 0.81 (95% CI: 0.76–0.86, $p < 0.001$), colorectal 0.80 (95% CI: 0.79–0.81, $p < 0.001$) and non-small cell lung 0.91 (95% CI: 0.90–0.92, $p < 0.001$). Decreases were largest in 50–69 year olds for female breast and 80+ year olds for all cancers. Stage I female breast cancer declined 41.6%, but unknown stage increased 55.8%. Colorectal stages I–IV declined (range 26.6–29.9%), while unknown stage increased 803.6%. Colorectal Q2-2020 GP-urgent suspected cancer diagnoses decreased 50.0%, and 53.9% for non-small cell lung cancer. Annual screen-detected female breast and colorectal cancers fell 47.8% and 13.3%, respectively. Non-small cell lung cancer emergency presentation diagnoses increased 9.5% (Q2-2020) and 16.3% (Q3-2020).

CONCLUSION: Significantly fewer cases of three common cancers were diagnosed in 2020. Detrimental impacts on outcomes varied between cancers. Ongoing surveillance with health service optimisation will be needed to mitigate impacts.

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BACKGROUND

Responses to the COVID-19 pandemic, including mandated societal lockdowns [1], citizen behavioural change [2] and health system reconfiguration [3, 4] during 2020, led to paused cancer screening programmes, altered presentation to primary care, and impacted suspected cancer referrals, diagnostic procedures [5] and treatment modalities [6]. Several studies modelled pandemic effects on excess cancer mortality [7–9], but despite concern about the impact on cancer services and outcomes [10], most studies reported limited data on observed cancer mortality, incidence, stage and healthcare pathways to diagnosis. These parameters have not been assessed at the population level in the UK. We undertook an analysis of clinically ascertained: (I) female

breast (good prognosis and screening programme in place), (II) colorectal (moderate prognosis and screening programme in place) and (III) non-small cell lung cancers (poor prognosis and no current screening programme in Wales) at a whole-population level in Wales during the pandemic's first full-year of 2020 compared to 2019, to determine the impact on cancer incidence, stage at diagnosis and healthcare pathways to diagnosis, to inform cancer service adaptation to the pandemic and subsequent recovery from it.

METHODS

We conducted a retrospective observational study of the resident population of Wales aged 18+ years ($n = 2,539,714$) [11] in the Con-COV

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- February 2020: Preparations to free hospital beds for Covid-19 patients
- 28 February 2020: First identified Covid-19 case in Wales, followed by pandemic 'first wave' to summer 2020 with April 2020 peak.
- Early March 2020: non-urgent outpatient appointments and surgery suspended; measures to expedite the discharge of vulnerable patients from acute hospitals to care homes were announced
- March 2020: Cancer screening services paused.
- 23 March 2020: Strict national societal 'lockdown', preceded by a week of advisory restrictions, with easing over the summer months.
- April 2020: Virtual GP appointments formally commenced, although GP practices had altered the way they consulted with patients, minimising face-to-face appointments since early March 2020.
- June – August 2020: Cancer screening phased restart
- August/September 2020: 'Second wave' started, with a peak in October 2020, and larger second peak in December 2020.
- September 2020: A series of local 'lockdowns' started, with a brief strict national 'lockdown' 23 October – 9 November 2020, followed by another strict national 'lockdown' during 16 December 2020 – 19 February 2021.

Fig. 1 Chronology of the SARS-Cov-2 pandemic in Wales in 2020. Mitigations to health and cancer services during the pandemic (GP=general practitioner).

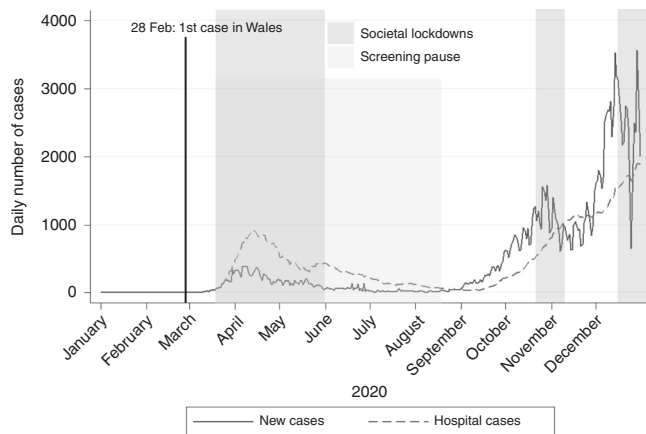


Fig. 2 Trends in numbers of confirmed incident SARS-CoV-2 infection cases and hospitalised Covid-19 cases in Wales, 2020. Overlay of the periods of societal lockdowns and the period in which cancer screening programmes were paused.

cohort [12] within the Secure Anonymised Information Linkage (SAIL) Databank [13].

Cases of new primary female breast (ICD-10: C50), colorectal (C18, C19, C20) and non-small cell lung cancers (C33, C34 with morphology M8041) between January 1, 2019, and December 31, 2020, inclusive, were identified from the Cancer Network Information System Cymru (CaNISC) —the national electronic clinical cancer patient record system, largely covering the population of Wales.

The exposure evaluated was the effect of the COVID-19 pandemic and pandemic mitigations [14] (Figs. 1 and 2). Diagnosis from January 1, 2020, to December 31, 2020, constituted exposure. Non-exposure (as the comparator) was diagnosed from January 1, 2019, to December 31, 2019.

Outcome measures

Outcome measures included annual and monthly incident case counts, stage at diagnosis and annual and quarterly healthcare pathway to diagnosis. The pathway to diagnosis was derived from CaNISC with person-level linkage to Patient Episode Database Wales hospital admission data (Fig. S2) and categorised into: (I) screening, (II) general practitioner urgent suspected cancer referral, (III) emergency presentation/admission, (IV) in-patient referral, (V) out-patient referral, (VI) other or (VII) not known. The summary stage at diagnosis I–IV, including the unknown stage, was

available from CaNISC for female breast and colorectal cancers. CaNISC is awaiting replacement, and until then, it is impossible to correctly record the stage at diagnosis in CaNISC for non-small cell lung cancer.

Co-variables

Co-variables included sex, age (18–49, 50–59, 60–79 and 80+) and quintile of the income domain of the Welsh Index of Multiple Deprivation data [15]. All the index domains were not used together, as its health domain already includes registry-based cancer incidence, so its inclusion would introduce a reverse cause bias.

Analysis

We presented descriptively incident counts by cancer type for 2019 and 2020 and calculated absolute and relative differences in annual counts between years for each cancer. Monthly counts and absolute and relative differences between corresponding months in 2019 and 2020 were also determined.

We used mid-year population estimates to test the null hypotheses that there were no differences in incident cases of the female breast, colorectal and non-small-cell lung cancers in 2020 compared with 2019. Multivariate Poisson regression analyses estimated unadjusted incidence rate ratios (IRR) and IRRs adjusted for age differences, sex (for colorectal and non-small cell cancers) and income deprivation quintile from the Welsh Index of Multiple Deprivation. Similarly, we also calculated the post-Poisson estimated marginal means to undertake a series of pairwise comparisons between 2020 and 2019. In addition, pairwise comparisons in the rates between 2019 and 2020 for the stage at presentation, healthcare pathway to diagnosis, sex, age category and deprivation quintile were carried out. Due to a large number of comparisons, all 95% confidence intervals around the IRR and their subsequent p-values were adjusted using the Bonferroni correction (adjusted alpha = 0.05/number of comparisons). All models were tested for overdispersion, and none was found.

The stage at diagnosis for female breast and colorectal cancers only was estimated as counts/percentage of the total incidence for each stage for each year. The absolute and relative difference in counts between years was calculated for each cancer and each stage. Counts of incident cases in each healthcare pathway to diagnosis category and absolute and relative differences for each pathway between years were determined.

RESULTS

Annual and monthly incidence

A total of –1011 (–15.2%) fewer cases of the three cancers was diagnosed during 2020 ($n = 5640$) compared to 2019 ($n = 6651$). Decreases occurred for female breast (–19.1%, $n = -474$), colorectal (–17.2%, $n = -383$) and less so for non-small cell lung cancers (–7.9%, $n = -154$) (Table 1 and Fig. 3a).

Table 1. Absolute and relative changes in annual and monthly incidence count, stage at diagnosis and healthcare pathway to diagnosis from 2019 to 2020, by sex, age group and income area-deprivation quintile for female breast cancer, colorectal cancer and non-small cell lung cancer, Wales, UK.

	Female breast cancer N (%)			Colorectal cancer N (%)			Non-small cell lung cancer N (%)		
	2019	2020	Difference	2019	2020	Difference	2019	2020	Difference
Annual incidence	2482 (100)	2008 (100)	-474 (-19.10)	2221 (100)	1838 (100)	-383 (-17.24)	1948 (100)	1794 (100)	-154 (-7.91)
Monthly incidence									
January	211 (8.50)	233 (11.60)	22 (10.43)	210 (9.46)	183 (9.96)	-27 (-12.86)	187 (9.60)	204 (11.37)	17 (9.09)
February	182 (7.33)	182 (9.06)	0	178 (8.01)	175 (9.52)	-3 (-1.69)	168 (8.62)	179 (9.98)	11 (6.55)
March	186 (7.49)	204 (10.16)	18 (9.86)	175 (7.88)	184 (10.01)	9 (5.14)	161 (8.26)	152 (8.47)	-9 (-5.59)
April	190 (7.66)	104 (5.18)	-86 (-45.26)	182 (8.19)	73 (3.97)	-109 (-59.89)	148 (7.60)	107 (5.96)	-41 (-27.70)
May	232 (9.35)	119 (5.93)	-113 (-41.85)	168 (7.56)	93 (5.06)	-75 (-44.64)	166 (8.52)	124 (6.91)	-42 (-15.56)
June	190 (7.66)	135 (6.72)	-55 (-28.37)	181 (8.15)	162 (8.81)	-19 (-10.50)	151 (7.75)	138 (7.96)	-13 (-4.81)
July	260 (10.48)	148 (7.37)	-112 (-43.48)	190 (8.55)	167 (9.09)	-23 (-12.11)	173 (8.88)	176 (9.81)	3 (1.11)
August	196 (7.90)	104 (5.18)	-92 (-46.07)	185 (8.33)	146 (7.94)	-39 (-21.08)	172 (8.83)	145 (8.08)	-27 (-10.00)
September	207 (8.34)	201 (10.01)	-6 (-2.90)	195 (8.78)	155 (8.43)	-40 (-20.51)	140 (7.19)	174 (9.70)	34 (12.59)
October	243 (9.79)	178 (8.86)	-65 (-26.07)	200 (9.00)	164 (8.92)	-36 (-18.00)	188 (9.65)	144 (8.03)	-44 (-16.30)
November	197 (7.94)	225 (11.21)	28 (14.37)	186 (8.37)	182 (9.90)	-4 (-2.15)	150 (7.70)	130 (7.25)	-20 (-7.41)
December	188 (7.57)	175 (8.72)	-13 (-6.81)	171 (7.70)	154 (8.38)	-17 (-9.94)	144 (7.39)	121 (6.74)	-23 (-8.52)
Stage at diagnosis									
Stage I	899 (35.95)	525 (25.99)	-374 (-41.60)	308 (13.87)	216 (11.75)	-92 (-29.87)	-	-	-
Stage II	984 (39.34)	782 (38.71)	-202 (-20.53)	405 (18.24)	296 (16.10)	-109 (-26.91)	-	-	-
Stage III	259 (10.36)	212 (10.50)	-47 (-18.15)	946 (42.59)	681 (37.05)	-265 (-28.01)	-	-	-
Stage IV	46 (1.84)	31 (1.53)	-15 (-32.61)	534 (24.04)	392 (21.33)	-142 (-26.59)	-	-	-
Unknown	294 (11.76)	458 (22.67)	164 (55.78)	28 (1.26)	253 (13.76)	225 (803.57)	-	-	-
Healthcare pathway to diagnosis									
Screening	943 (37.99)	492 (24.50)	-451 (-47.83)	279 (12.56)	242 (13.17)	-37 (-13.26)	-	-	-
GP urgent	1198 (48.27)	1224 (60.96)	26 (2.17)	1072 (48.27)	859 (46.74)	-213 (-19.87)	737 (37.85)	602 (33.56)	-135 (-18.32)
Emergency	46 (1.85)	41 (2.04)	-5 (-10.87)	488 (21.97)	450 (24.48)	-38 (-7.79)	615 (31.59)	602 (33.56)	-13 (-2.11)
From in-patient	105 (4.23)	126 (6.27)	21 (20.00)	201 (9.05)	132 (7.18)	-69 (-34.33)	265 (13.61)	261 (14.55)	-4 (-1.51)
From out-patient	117 (4.71)	99 (4.93)	-18 (-15.38)	71 (3.20)	65 (3.54)	-6 (-8.45)	160 (8.22)	161 (8.97)	1 (0.63)
Other	67 (2.70)	26 (1.29)	-41 (-61.19)	59 (2.66)	36 (1.96)	-23 (-38.98)	61 (3.13)	61 (3.40)	0 (0.00)
Not known	6 (0.24)	0 (0)	-6 (-100.00)	52 (2.34)	54 (2.94)	2 (3.85)	110 (5.65)	107 (5.96)	-3 (-2.73)
Sex									
Male	-	-	-	1239 (55.79)	1089 (59.25)	-150 (-12.11)	1018 (52.29)	899 (50.11)	-119 (-11.69)
Female	2482 (100)	2008 (100)	-474 (-19.10)	982 (44.21)	749 (40.75)	-233 (-23.73)	930 (47.77)	895 (49.89)	-35 (-3.76)
Age									
Under 50	341 (13.74)	326 (16.24)	-15 (-4.40)	132 (5.94)	114 (6.20)	-18 (-13.64)	38 (1.95)	42 (2.34)	4 (10.53)
50-69	1208 (48.67)	916 (45.62)	-292 (-24.17)	767 (34.53)	658 (35.80)	-109 (-14.21)	565 (29.02)	561 (31.27)	-4 (-0.71)
70-79	540 (21.76)	459 (22.86)	-81 (-15.00)	744 (33.50)	605 (32.92)	-139 (-18.68)	806 (41.40)	762 (42.47)	-44 (-5.46)
80+	393 (15.83)	307 (15.29)	-86 (-21.88)	578 (26.02)	461 (25.08)	-117 (-20.24)	539 (27.68)	429 (23.91)	-110 (-20.41)

Table 1. continued

	Female breast cancer N (%)			Colorectal cancer N (%)			Non-small cell lung cancer N (%)		
	2019	2020	Difference	2019	2020	Difference	2019	2020	Difference
WIMD income									
1—least deprived	557 (22.44)	420 (20.92)	-137 (-24.60)	488 (21.97)	378 (20.57)	-110 (-22.54)	270 (13.86)	240 (13.38)	-30 (-11.11)
2	528 (21.27)	389 (19.37)	-139 (-26.33)	484 (21.79)	402 (21.87)	-82 (-16.94)	341 (17.51)	300 (16.72)	-41 (-15.19)
3	551 (22.20)	424 (21.12)	-127 (-23.05)	438 (19.72)	358 (19.48)	-80 (-18.26)	403 (20.69)	379 (21.13)	-24 (-8.89)
4	446 (17.97)	431 (21.46)	-15 (-3.36)	452 (20.35)	383 (20.84)	-69 (-15.27)	437 (22.43)	400 (22.30)	-37 (-13.70)
5—most deprived	400 (16.12)	344 (17.13)	-56 (-20.74)	359 (16.16)	317 (17.25)	-42 (-11.70)	497 (25.51)	475 (26.48)	-22 (-8.15)

Changes in monthly incidence differed for each cancer (Fig. 3b, Table 1). For all three cancers, steep decreases in monthly incidence did not occur until April 2020. April incidence for female breast cancer was -45.3% lower in 2020 than in 2019, recovering to 2019 levels by September 2020. Colorectal cancer had an even greater decrease of -59.9% in April 2020, partially recovering by June 2020 (-10.5%), but remained below 2019 monthly incidence until December 2020. The April 2020 decrease was less steep for non-small cell lung cancer (-27.7%, $n = -41$), recovering by June 2020, but decreasing to below 2019 levels at the end of 2020 (2019 vs 2020: -16.3% October, -7.4% November and -15.3% December).

Colorectal cancer cases decreased by -23.7% ($n = -233$) in females and -12.1% ($n = -150$) in males between 2019 and 2020 (Table 1), although for non-small cell lung cancer the relative decline was larger for males (-11.7%, $n = -119$) compared to females (-3.8%, $n = -35$).

The largest age-group decreases were amongst 50–69-year-old female breast cancer patients (-24.2%, $n = -292$) (Table 1). Among 80+ year olds, relative incidence declines were similar for all three cancers: female breast -21.9% ($n = -86$); colorectal -20.2% ($n = -117$) and non-small cell lung cancers -20.4% ($n = -110$). Declines occurred in all quintiles of income area-deprivation and were highest in the three least deprived quintiles for female breast cancer, ranging from -23.1 to -26.3%. There was a gradient of increasing relative decline from 2019 to 2020 in the most to the least deprived quintiles for colorectal cancer. For non-small lung cancer, there was no clear gradient.

The results of the Poisson regression and unadjusted and adjusted annual and pairwise monthly IRRs for 2020 compared to 2019 are shown in Table 2. The unadjusted annual IRRs for female breast (0.81 [95% CI 0.76, 0.86; $p < 0.001$]), colorectal (0.80 [95% CI 0.79, 0.81; $p < 0.001$]) and non-small cell lung (0.91 [95% CI: 0.90, 0.92; $p < 0.001$]) cancers were all largely unchanged by adjustment for age, sex (for colorectal and non-small cell cancers) and income area-deprivation quintile (Table 2). The unadjusted IRRs were highly statistically significant for the pairwise comparisons of months between 2020 and 2019, showing large to moderate declines in the descriptive analysis for all three cancer types. However, adjustment removed the IRR statistical significance for all 12 months in non-small cell lung cancer and for all except April and May 2020 for colorectal cancer. For female breast cancer, the large declines in incident cases observed from March to November 2020, except for September, remained highly significant ($p < 0.001$) during May, July and August 2020 when IRRs were adjusted for age and area-level income deprivation.

Stage at diagnosis

There was a large decrease in stage I female breast cancer -41.6% ($n = -374$) in 2020 compared to 2019 (Table 1). Relative declines in stages II and III were similar at -20.5% ($n = -202$) and -18.2% ($n = -47$), respectively. Stage IV decline was based on smaller case numbers ($n = -15$). Female breast cancers recorded with stage unknown increased by 55.8% ($n = +164$) between 2019 and 2020. The relative decrease in colorectal cancer cases was similar across the stages I–IV (ranging between 26.6 and 29.9%). There was a substantial increase of 803.6% ($n = +225$) in colorectal cancers with stage unknown recorded in 2020, compared to 2019. Cumulative monthly case counts of female breast and colorectal cancers for 2019 and 2020 by stage at diagnosis are shown in Fig. 4a and b.

Healthcare pathway to diagnosis

The annual decrease in screen-detected female breast cancer diagnoses was -47.8% ($n = -451$) (Table 1), with a large decline between Q2 (April, May and June), 2019 and Q2, 2020 (-86.7%, $n = -214$), followed by partial recovery to around half the 2019

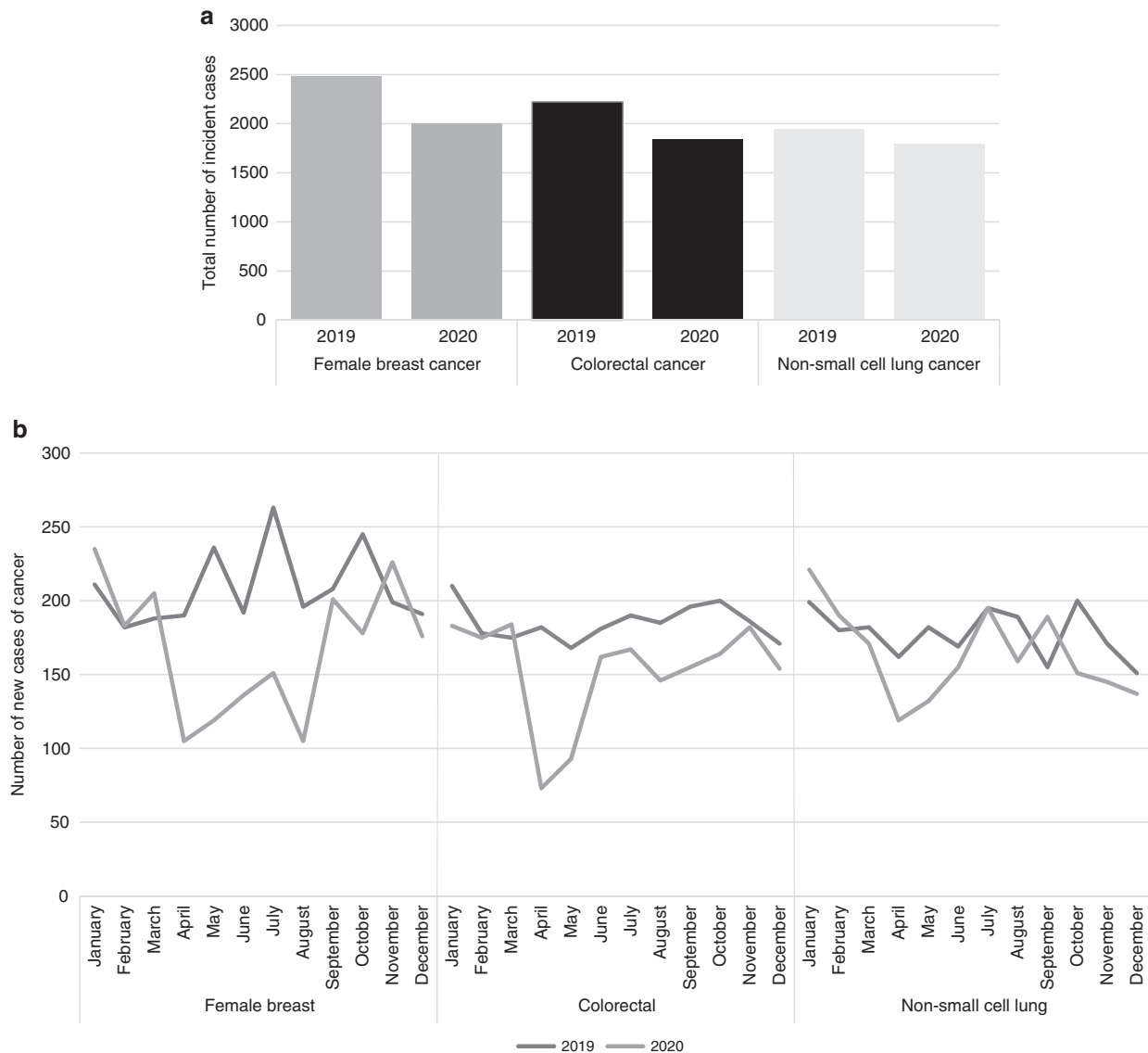


Fig. 3 Incident case counts for female breast, colorectal and non-small cell lung cancers for 2019 and 2020. **a** Annual counts **b** Monthly counts.

diagnoses in Q4 (Fig. 5). Female breast cancer diagnosis via GP urgent suspected cancer referral increased slightly (+2.2%, $n = +26$) over the whole of 2020 compared to 2019. After a slight drop during Q2-2020, GP urgent suspected cancer referral diagnoses rebounded above 2019 levels in Q3 (+1.0%) and Q4 (+11.1%), 2020.

GP urgent suspected cancer referral colorectal cancer diagnoses declined by -19.9% ($n = -213$) in 2020 compared to 2019 but remained the most frequent pathway to diagnosis (Table 1). Diagnoses via this pathway declined by -50.0% ($n = -135$) in Q2-2020 compared to Q2 2019, partially recovered in Q3-2020, surpassing 2019 by Q4 (Fig. 5). Emergency presentation/admission diagnoses were maintained and had only a small annual change (-7.8%, $n = -38$), but were slightly lower in Q1 and Q4 2020 than in corresponding 2019 quarters and slightly higher in Q2 and Q3 (Fig. 5). The screening was the third most frequent pathway to diagnosis; it showed a -13.3% ($n = -37$) annual reduction in 2020, with an increase in Q1, 2020 compared to Q1 2019, a large decline in Q2-2020 (-56.7%, $n = 34$), and recovery by Q3 to just below the Q3 2019 level. However, the Q4 diagnoses were below Q4, 2019. An annual decline of -34.3% ($n = -69$) occurred in the in-patient referral route, occurring during Q2-Q4.

A decline of -18.3% ($n = -135$) in non-small cell lung cancer GP urgent suspected cancer diagnoses occurred over the whole of 2020, compared to 2019 (Table 1), with a considerable decline of -53.9% ($n = -83$) in Q2-2020, followed by a partial recovery in Q3 that did not recover further in Q4 (Fig. 5). In Q1 2020, diagnoses via this pathway were slightly higher (+7.0%, $n = +14$) than cases observed during the same period in 2019. In contrast, there was little annual change in emergency presentation diagnoses (-2.1%, $n = -13$), although diagnoses were higher in Q2 and Q3-2020, compared with 2019, then declined rapidly in Q4. Diagnosis via referral as an existing in-patient increased slightly above 2019 levels in Q1 and Q3-2020 but decreased in Q2 and Q4.

The trends in incidence, stage at diagnosis and healthcare pathway to diagnosis coincided with the timing of the pandemic and mitigation responses introduced in 2020 (Fig. 1).

DISCUSSION

To our knowledge, this is the first national population-level study using electronic cancer clinical data to quantify COVID-19 pandemic effects on cancer diagnosis, stage and healthcare

Table 2. Unadjusted and adjusted annual and monthly pairwise Incidence Rate Ratios (IRRs) (Bonferroni corrected 95% confidence intervals) comparisons of 2020 and 2019 for female breast, colorectal and non-small cell lung cancer.

	Female breast cancer						Colorectal cancer						Non-small-cell lung cancer					
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted			
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI		
Year	0.81	0.76, 0.86***	0.79	0.74, 0.84***	0.80	0.79, 0.81***	0.80	0.75, 0.85***	0.91	0.90, 0.92***	0.89	0.83, 0.95***						
Month																		
January	1.10	1.03, 1.18***	1.12	0.77, 1.61	0.87	0.81, 0.93***	0.75	0.40, 1.63	1.10	1.03, 1.17***	1.02	0.69, 1.48						
February	1.00	0.93, 1.10	1.03	0.69, 1.53	0.98	0.92, 1.06	0.97	0.44, 2.12	1.05	0.98, 1.13	1.03	0.70, 1.54						
March	1.10	1.02, 1.17***	1.12	0.75, 1.65	1.05	0.98, 1.12	1.08	0.60, 1.94	0.94	0.87, 1.01	0.95	0.63, 1.42						
April	0.58	0.50, 0.59***	0.62	0.38, 0.98*	0.40	0.37, 0.44***	0.43	0.21, 0.87**	0.73	0.68, 0.80***	0.75	0.48, 1.19						
May	0.51	0.48, 0.55***	0.49	0.32, 0.76***	0.55	0.51, 0.60***	0.57	0.28, 0.98*	0.73	0.67, 0.78***	0.71	0.46, 1.11						
June	0.71	0.66, 0.77***	0.71	0.46, 1.01	0.90	0.83, 0.96***	1.02	0.42, 2.48	0.92	0.85, 0.99**	0.90	0.59, 1.37						
July	0.60	0.53, 0.61***	0.56	0.38, 0.83***	0.88	0.82, 0.94***	0.91	0.45, 1.84	0.99	0.92, 1.06	0.99	0.67, 1.46						
August	0.53	0.49, 0.58***	0.51	0.32, 0.82***	0.79	0.73, 0.85***	0.77	0.41, 1.45	0.84	0.78, 0.90***	0.80	0.52, 1.22						
September	0.87	0.91, 1.04	0.95	0.65, 1.39	0.79	0.74, 0.85***	0.92	0.51, 1.62	1.21	1.13, 1.31***	1.14	0.75, 1.73						
October	0.73	0.69, 0.78***	0.73	0.50, 1.07	0.82	0.76, 0.88***	0.86	0.42, 1.76	0.75	0.70, 0.81***	0.75	0.49, 1.14						
November	1.14	1.07, 1.22***	1.16	0.80, 1.69	0.98	0.91, 1.05	0.94	0.52, 1.73	0.86	0.77, 0.93***	0.82	0.53, 1.27						
December	0.93	0.87, 0.99*	0.96	0.64, 1.43	0.90	0.84, 0.97***	0.92	0.46, 1.82	0.91	0.84, 0.98**	0.88	0.56, 1.40						
Stage at diagnosis																		
Stage I	0.58	0.49, 0.70***	0.57	0.48, 0.70***	0.77	0.58, 1.03	0.72	0.53, 0.97*	-	-	-	-						
Stage II	0.79	0.68, 0.93***	0.78	0.67, 0.93***	0.80	0.63, 1.03	0.76	0.59, 0.98*	-	-	-	-						
Stage III	0.82	0.61, 1.11	0.85	0.62, 1.16	0.73	0.62, 0.87***	0.71	0.60, 0.84***	-	-	-	-						
Stage IV	0.71	0.33, 1.52	0.62	0.28, 1.37	0.77	0.62, 0.95**	0.72	0.58, 0.90***	-	-	-	-						
Unknown	1.56	1.22, 1.98***	1.56	1.21, 2.00***	4.68	2.47, 8.87***	5.06	2.61, 9.80***	-	-	-	-						
Healthcare pathway to diagnosis																		
Screening	0.52	0.43, 0.63***	0.56	0.46, 0.69***	0.90	0.67, 1.22	0.82	0.60, 1.12										
GP urgent	1.02	0.89, 1.18	1.01	0.88, 1.17	0.84	0.73, 0.98**	0.81	0.69, 0.95***	0.81	0.67, 0.97**	0.78	0.65, 0.94***						
Emergency	0.89	0.42, 1.87	1.00	0.47, 2.16	0.92	0.74, 1.56	0.92	0.73, 1.16	0.88	0.73, 1.06	0.96	0.79, 1.16						
From in-patient	1.20	0.76, 1.89	1.33	0.82, 2.15	0.72	0.49, 1.07	0.66	0.45, 0.98*	0.94	0.70, 1.25	0.97	0.72, 1.30						
From out-patient	0.84	0.57, 1.36	0.78	0.48, 1.27	0.95	0.52, 1.71	0.96	0.53, 1.75	1.08	0.78, 1.50	0.93	0.67, 1.30						
Other	0.39	0.17, 0.86***	0.47	0.21, 1.11	0.98	0.47, 2.03	0.87	0.41, 1.82	1.16	0.65, 2.08	1.08	0.60, 1.96						
Not known	N/A	N/A	N/A	N/A	0.86	0.44, 1.68	0.93	0.46, 1.86	0.89	0.61, 1.30	0.91	0.62, 1.33						
Sex																		
Male	-	-	-	-	0.84	0.75, 0.94***	0.85	0.76, 0.95***	0.83	0.81, 0.85***	0.88	0.86, 0.89***						
Female	0.82	0.77, 0.87***	0.83	0.74, 0.92**	0.73	0.65, 0.84***	0.73	0.64, 0.84***	0.94	0.92, 0.96***	0.96	0.94, 0.98***						
Age																		
Under 50	0.99	0.78, 1.26	0.94	0.73, 1.20	0.92	0.62, 1.37	0.95	0.63, 1.44	1.00	0.90, 1.13	1.05	0.94, 1.18						
50-69	0.76	0.66, 0.87***	0.77	0.67, 0.88***	0.79	0.67, 0.93***	0.81	0.68, 0.96**	0.99	0.96, 1.02	1.00	0.96, 1.03						
70-79	0.82	0.67, 1.01	0.83	0.67, 1.01	0.74	0.63, 0.88***	0.78	0.65, 0.93***	0.90	0.88, 0.92***	0.93	0.91, 0.96***						

Table 2. continued

	Female breast cancer				Colorectal cancer				Non-small-cell lung cancer			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
80+	0.81	0.64, 1.03	0.79	0.62, 1.01	0.77	0.63, 0.93**	0.77	0.63, 0.94	0.76	0.73, 0.78***	0.79	0.76, 0.81***
WIMD income												
1—least deprived	0.78	0.63, 0.97**	0.74	0.60, 0.92***	0.75	0.60, 0.94**	0.76	0.61, 0.96**	0.86	0.82, 0.90***	0.87	0.82, 0.91***
2	0.71	0.57, 0.89***	0.75	0.60, 0.94**	0.74	0.59, 0.93**	0.77	0.62, 0.97**	0.89	0.85, 0.93***	0.86	0.83, 0.90
3	0.76	0.61, 0.95**	0.76	0.61, 0.94**	0.77	0.61, 0.98*	0.80	0.63, 1.01	0.87	0.84, 0.91***	0.96	0.92, 1.00
4	0.93	0.74, 1.16	0.97	0.77, 1.22	0.80	0.63, 1.00	0.80	0.64, 1.01	0.92	0.89, 0.96***	0.92	0.88, 0.95***
5—most deprived	0.90	0.70, 1.51	0.86	0.67, 1.10	0.83	0.64, 1.07	0.87	0.67, 1.12	0.95	0.91, 0.98***	0.95	0.92, 0.99**

Adjusted for age group (under 50, 50–69, 70–79, 80+), sex (for colorectal and NSCL cancers) and area-level income deprivation quintiles (WIMD).

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

pathway to diagnosis in detail for the whole of 2020. Our analyses used linked population data to compare the effects on three common cancers of contrasting prognosis and screening programme availability, facilitating consideration of differential outcomes between demographic groups over time and against dynamic changes of the pandemic and mitigation responses.

We observed detrimental changes in incidence, with over a thousand fewer cases in 2020 compared with 2019 across the three cancers, in stage at diagnosis, and in healthcare pathway to diagnosis, coinciding with the timing of pandemic COVID-19 incidence and dynamic responses such as societal restrictions and health service reconfiguration. There was considerable variation between cancer types and demographic groups, particularly affecting older age groups. The pausing of screening had a major impact on early female breast cancer diagnosis, however, decreased diagnoses through GP urgent suspected cancer referral had a greater impact on colorectal cancer and non-small cell lung cancers.

Our data demonstrate that impacts varied considerably between cancers and demographic groups, coinciding with dynamic changes in community COVID-19 cases and pandemic mitigation responses and according to their pre-pandemic pattern of healthcare pathway routes to diagnosis. Other studies that examined cancer incidence during the pandemic used prediction modelling or proxy measures such as diagnostic or treatment activity [5, 6, 8, 16–18]. Of the few studies that used clinical data, one study examined colorectal cancer cases from a single tertiary hospital serving a regional Spanish catchment area [19]. Ascertainment fell by 47.7% in spring 2020 compared to spring 2019, whereas we found decreases of almost a fifth in colorectal cancer incidence during 2020 overall, and 59.9% in April 2020 compared to April 2019, greater than the Spanish study, yet of a broadly similar order of magnitude. Our results were also consistent with their finding of no change in colorectal cancer stage distribution and a greater decline amongst women than men. A south-east London clinical-data study [20] examined a smaller urban population, including a tertiary hospital. It compared 6-month periods before and after the March 2020 UK lockdowns rather than corresponding months in 2019 and 2020. Nevertheless, our results demonstrated broadly consistent month-on-month incidence trends with the London study for female breast cancer, colorectal cancer and non-small cell lung cancers, as reported until September 2020.

The main strength of our study was the deployment of clinical data from a single national system with near whole-population coverage. Rapid and confidential data linkage was possible within the SAIL Databank [13] Trusted Research Environment, enabling detailed analysis by demographic factors, area deprivation and granular healthcare pathway to diagnosis. We studied the whole of 2019 and 2020 rather than simply before and after the first national lockdown, allowing a more precise longitudinal analysis of the impact of lockdowns, health service measures, citizen behaviour change and accounted for seasonal variations.

Given health service reconfiguration to maintain essential emergency procedures and surgery during pandemic waves, a clinical diagnosis could still be possible. Limitations included the low completeness of stage data for non-small cell lung cancer, although the missing stage for female breast and colorectal cancers was higher during 2020 (Table 3 and Fig. 4a, b). Information such as from pathology samples, for example, that would allow full and final staging at diagnosis might have been less available during 2020 [5, 6, 19]. Such healthcare restrictions are likely to have affected colorectal cancer patients more than many breast cancer cases, with surgery being required for staging, and this is reflected in the considerable increase in unknown stages for colorectal cancer during 2020. Non-small cell lung cancer staging would have also relied more on staging at surgery than breast cancer, although we could not obtain data on this

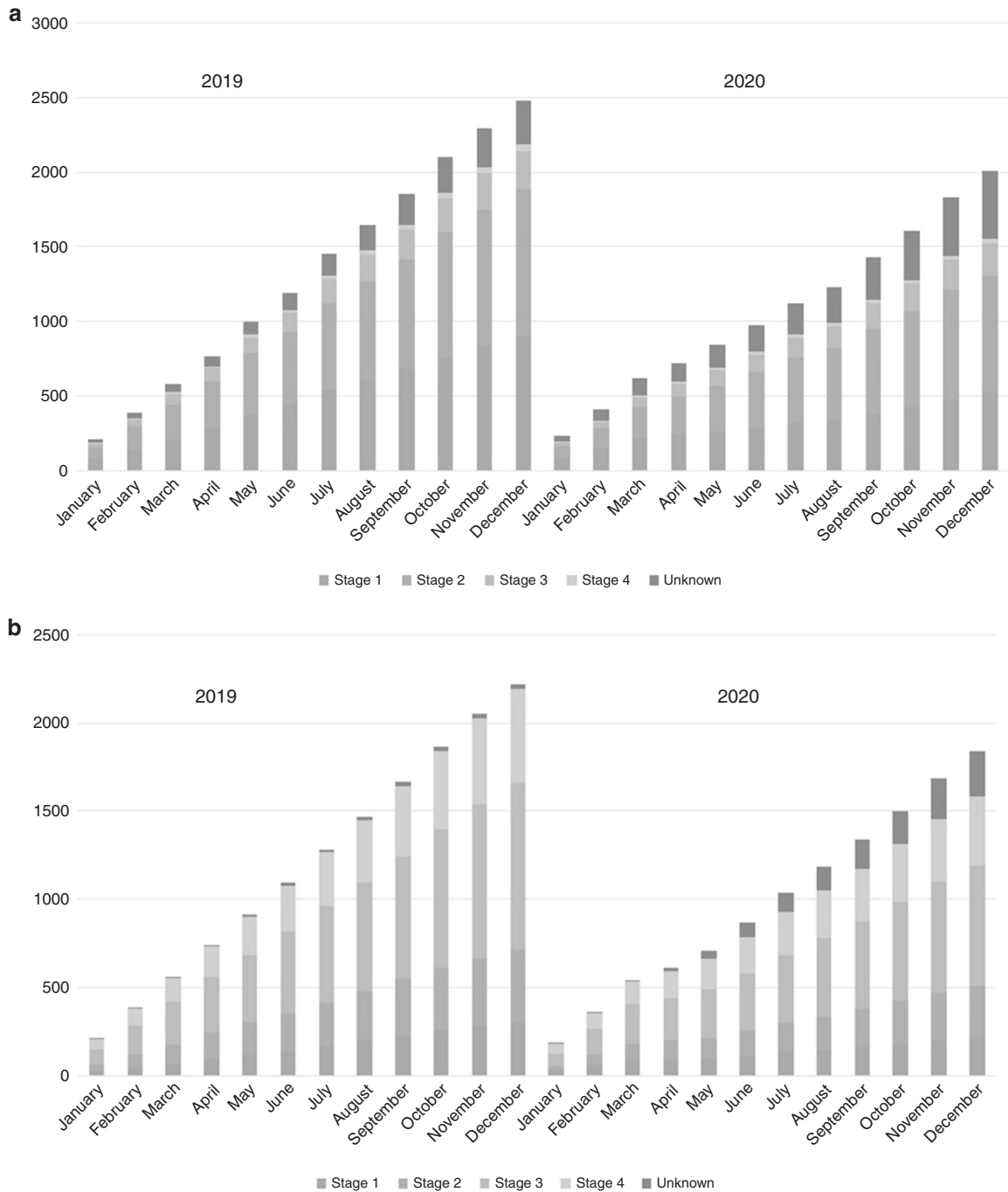


Fig. 4 Cumulative monthly case counts for 2019 and 2020 by stage at diagnosis. a Female breast cancer b Colorectal cancer.

occasion. Some breast surgery can be performed in a less intensive hospital setting than for advanced colorectal and non-small cell lung cancer. Furthermore, some observed more minor changes in stage distribution may have occurred through misclassification of the stage due to staging occurring without the usual full information sources to clinicians.

Despite preceding COVID-19 cases, specific health system changes and a brief period of societal advisory restrictions (Fig. 1) in Wales during early 2020, our results did not show major impacts on cancer incidence until April 2020, following a strict lockdown implemented on March 23, 2020, and significant health system reconfiguration to prioritise COVID-19 infection control. Using sub-regional primary care data, a study in Catalonia, Spain [21], demonstrated that cancer incidence decreased from March 2020,

corresponding to earlier community infections and lockdown. Our findings of changing diagnosis patterns during the summer of 2020 coincided with a partial lifting of restrictions and early readjustment of health services toward managing non-COVID-19 patients. According to our analysis, starting October 2020 (Fig. 1), another brief lockdown coincided with increased monthly declines in diagnoses. Strict restrictions were re-imposed in early December 2020, when diagnoses decreased further. GP urgent suspected cancer referral diagnoses decreased during Q2, 2020, after the first lockdown when primary care access was altered.

Citizen behaviour changed in response to restrictions and instructions to stay at home or 'shield' [22], which had the unintended consequence of causing a reluctance by some to seek health care services due to concerns about SARS-Cov-2 infection,

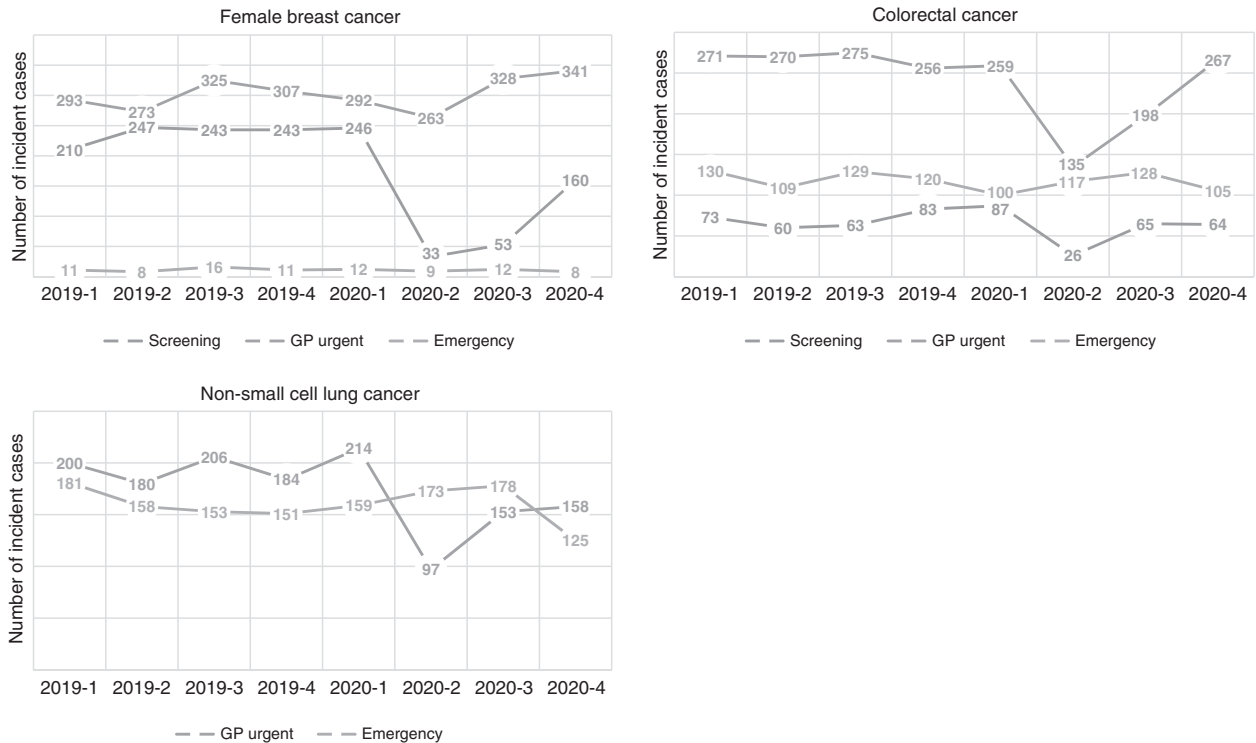


Fig. 5 Quarterly counts of incident cases by healthcare pathway to diagnosis, 2019 and 2020. Female breast cancer, Colorectal cancer, Non-small cell lung cancer.

and others not wanting to burden a health system busy with COVID-19 [2, 23]. This behaviour change was particularly impactful for those with potential lung cancer. A persistent cough is an early sign of disease and the main symptom of COVID-19 infection. The potential risk from SARS-Cov-2 infection became a reason to stay at home and not consult a GP. Health service data in England, Northern Ireland and Wales indicated measurable decreased cancer-related referrals [5, 6, 8, 24, 25] of similar trends to actual diagnoses via this pathway in our study. We demonstrated that screen-detected female breast cancer diagnoses fell by almost half, consistent with the temporary cessation of screening services from March 2020 (see Fig. 2), although in the interim, during Q2–Q3, breast screening services diverted to support symptomatic patient diagnosis via GP urgent suspected cancer [26]. Increases in screen-detected colorectal cancer diagnoses from Q3, 2019 to Q1, 2020, likely followed the known introduction of faecal immunochemical testing in Wales. During the pausing of colorectal cancer screening, faecal immunochemical testing was diverted to prioritise symptomatic patients awaiting colonoscopy. Cancer screening programmes restarted in a phased approach from the end of June–August 2020, increasing female breast cancer diagnoses. The overall impact on screen-detected colorectal cancer was less, possibly because it was easier to send a faecal immunochemical testing kit to homes, with the uptake in colorectal screen-detected diagnoses improving soon after the service restarted. Existing colorectal cancer screening patients awaiting colonoscopy were reviewed for symptoms during the paused programme and referred to the symptomatic pathway if required.

Despite attendance at emergency departments decreasing [27], colorectal cancer and non-small cell-lung cancers diagnoses through emergency presentations increased in Q2–Q3, 2020. It is unclear if this was due to a shift from other less accessible pathways or increased emergency complications of cancer or non-cancer conditions. Multi-morbidities are common amongst colorectal cancer and non-small cell lung cancers patients [28],

making them more likely to be instructed to ‘shield’ at home. Shielding could partly explain their lower recovery in GP urgent suspected cancer diagnoses than female breast cancer and increased emergency presentations with an incidental cancer diagnosis. Patients 80+ years old were more likely to be shielding, which might explain their similar declines of around a fifth in incidence for all three cancers. We observed an increase in non-small cell lung cancer diagnoses as an existing in-patient in Q1 2020 when COVID-19 community infections had started in Wales, which suggested they might have been incidental diagnoses.

We cannot conclude from our current study that a shift to a later stage at diagnosis occurred in the true population cancer incidence during 2020, as many cases remained undiagnosed. Instead, we observed decreases of various extents in all stages for female breast and colorectal cancers. The pausing of screening disproportionately affected stage I female breast cancer detection in 50–69 year-old women. Those cancer patients at a late stage may have died without being diagnosed, as predicted by modelling studies [7, 8].

With over a thousand fewer cases diagnosed across three common cancers during 2020, our study suggests large numbers of undiagnosed cancer patients more widely due to the ongoing pandemic, societal mitigations and health service reconfiguration in response. Although the pandemic has abated somewhat, along with societal and healthcare responses to it, our study still suggests that extensive alterations to healthcare pathways to diagnosis, increases in later-stage diagnoses and an increase in the number of undiagnosed patients with new cancers will occur. With continued research and surveillance, the accumulation of incidence, stage and healthcare pathway data will allow more accurate forecasting through the stage of diagnosis and mortality prediction modelling to inform effective cancer services’ responses. Ongoing optimisation of cancer screening programmes and the transformation of cancer services and primary care referral are urgently required.

DATA AVAILABILITY

The data used in this study are available in the SAIL Databank at Swansea University, Swansea, UK, but they are not publicly available as restrictions apply. All proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). Before any data can be accessed, approval must be given by the IGRP. The IGRP carefully considers each project to ensure the proper and appropriate use of SAIL data. When access has been granted, it is gained through a privacy-protecting Safe Haven and remote access system referred to as the SAIL Gateway. SAIL has established an application process to be followed by anyone who would like to access data via SAIL at <https://www.saildatabank.com/application-process>

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AUTHOR CONTRIBUTIONS

GG—methodology, project administration, resources, software, supervision, validation, data curation, formal analysis, investigation, writing—original draft, RG—data curation, validation, methodology, investigation, directly accessed and verified the underlying data, writing—review and editing, AA—project administration, resources, data curation, writing—review and editing, JH—data curation, investigation, validation, writing—review and editing, MJ—investigation, supervision, methodology, writing—review and editing, JL—visualisation, investigation, writing—review and editing, ML—funding acquisition, investigation, methodology, resources, writing—review and editing, RL—funding acquisition, investigation, methodology, resources, writing—review and editing, supervision, EM—investigation, methodology, supervision, writing—review and editing, MR—methodology, resources, writing—review and editing, supervision, FT—investigation, writing—review and editing, JW—investigation, methodology, supervision, writing—review and editing, DWH—conceptualisation, writing—original draft, methodology, supervision, resources, investigation, writing—review and editing.

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COMPETING INTERESTS

ML has received an unrestricted educational grant from Pfizer for research unrelated to this work. ML has received honoraria from Pfizer, EMF Serono, Roche, Bayer, Novartis and Carnall Farrar unrelated to this work. DWH has received research consultancy fees from Pfizer for research unrelated to this work, and his department

(Welsh Cancer Intelligence and Surveillance Unit, Public Health Wales) has received analysis partnership funding from Macmillan Cancer Support for unrelated work. The remaining authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All research conducted has been completed under the permission and approval of the SAIL independent Information Governance Review Panel (IGRP) project number 0911. The support of DATA-CAN, the UK's Health data Research Hub for Cancer, is acknowledged. The advice of the Screening Division, Public Health Wales, is also acknowledged.

CONSENT FOR PUBLICATION

This study uses anonymised data held in the Secure Anonymised Information Linkage (SAIL) Databank. This work uses data provided by patients and collected by the NHS as part of their care and support. We would also like to acknowledge all data providers who make anonymised data available for research.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41416-022-01830-6>.

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