We Can Do Better

Re-establishing care equity for cancer

October 5, 2025

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Background

Ontario's COVID-19 Response

In March 2020, the World Health Organization (WHO) declared a Public Health Emergency of International Concern due to reports of a novel coronavirus, initially causing a respiratory pneumonia in China, which was later named acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ The first official report by the WHO-China Joint Commission on the coronavirus disease 2019 (COVID-19) highlighted a high case severity (13.8% requiring hospitalization, 6.1% critical care) and an initial crude case-fatality rate (CFR) of 3.8%, which was as low as 0.7% in some regions.¹¹² In Canada, these elevated case severity and fatality rates prompted the invocation of the Quarantine Act (2005)³ at the federal level and similar pieces of legislation at the provincial level,⁴¹⁵ which would position public health officials as the primary decision-makers for Canada's COVID-19 response.⁶

Early in 2020, China had implemented aggressive community-wide containment measures, or "lockdowns," under its zero-COVID policy, which successfully limited viral spread.^{27,8} Given this, the WHO recommended a similar global approach as a primary means of slowing the virus's spread and gaining time to test therapeutics and vaccines.^{1,2,9,10} This represented a shift away from their historical position of avoiding these types of measures due to their increased risk of societal, health and economic harm (Table 1).¹¹ Aligned with WHO guidance, governments around the globe fulfilled their legal obligation under International Health Regulations to take preventative steps to stop the spread of COVID-19.^{12,13} These recommendations were adopted by Public Health Officials around the world and lockdowns were implemented globally to protect the vulnerable and preserve health care capacity,¹⁴ including physical distancing, school closures, workplace restrictions, and limits on public gatherings.¹⁵ WHO risk communication plans were also adopted to encourage compliance with public health policy.^{16,17} These policies would be in place for two years.¹⁸

On March 17, 2020, under advisement of Public Health Officials, Ontario declared a State of Emergency under the Emergency Management and Civil Protection Act, ^{19,20} allowing them to enforce the necessary emergency orders to protect "the health and safety of individuals, families and communities from the threat of the COVID-19 virus." Following the declaration the Chief Medical Officer of Health (CMOH) of Ontario began issuing directives under the Health Protection and Promotion Act (HPPA).^{5,22} Health care providers were directed to cease or reduce to minimal levels all non-essential health care services, to ensure infection prevention and control (IPAC), to prioritize essential services, and to preserve health system capacity during the COVID-19 pandemic.^{23,24} Hospitals were directed to implement pandemic plans by ramping down elective surgeries and non-emergent clinical activities.²⁵⁻²⁷ Deferred services were permitted to resume gradually beginning on May 26, 2020, ²⁸ however, they were

once again suspended from April 20, 2021 to May 19, 2021²⁹ and January 4, 2022 to February 10, 2022^{30,31} before all directives were revoked in June 2022.³²

In March of 2022, China implemented a second multi-province lockdown to eradicate COVID-19 under their zero-COVID policy. These lockdowns persisted until December 2022, when the policy was abandoned due to significant social and economic strain.³³ In early 2023, both the US Department of Energy and the Federal Bureau of Investigation suggested a possible lab leak origin of SARS-CoV-2.^{34,35} On May 8, 2023, the US House Oversight Committee, investigating the origins of COVID-19, concluded that there was mounting evidence indicating the virus originated from a lab in Wuhan China.³⁶ This was the same lab where gain-of-function experiments, designed to exacerbate the virulence of SARS-like viruses, had been conducted.³⁷ Finally, On January 25, 2025 the US Central Intelligence Agency determined that a lab leak was more likely the cause of the COVID-19 outbreak than animal transmission.³⁸

Another unique feature of the COVID-19 response was the expedited development and mass deployment of COVID-19 vaccines, which began in December 2020.³⁹⁻⁴¹ When first deployed, governments were reminded of their legal obligation to take steps to stop the spread of COVID-19¹³ and to act without discrimination.¹² Those at greatest risk of complications (elderly) or exposure (healthcare workers) were prioritized⁴¹ before the vaccines were offered to adults in the wider population on May 18, 2021.^{41,42} By August 2021, the CMOH began mandating COVID-19 vaccination policies for staff at long-term care homes,⁴³ retirement homes, and finally, hospitals with the goal of achieving full vaccination coverage by September 7, 2021.⁴¹ By the end of 2021, 87% of Canadians 16 years and older had received two doses of a COVID-19 vaccine with Pfizer and Moderna vaccines being the commonly delivered.⁴⁴

This white paper details the impact that Ontario's public health response had on the cancer care system and female cancer outcomes, considers whether our response accomplished its purpose, and proposes ways to improve decision-making moving forward.

Table 1: Timeline of key events over the COVID-19 period in Ontario

Date	Action
201911	WHO guidance on non-pharmaceutical interventions (NPIs) for flu pandemics - The WHO emphasizes the need for minimizing disruption to society, prioritizing voluntary measures and less invasive interventions over mandatory closures. Outlines low levels of evidence supporting mandatory closures and significant societal, health and economic risks associated with such an approach.

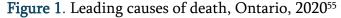
November 17, 2019 ⁴⁵	The first case of COVID-19 in China was reported in Wuhan, Hubei Province.
January 23, 2020 ⁴⁶	China implemented its first major COVID-19 lockdown in Wuhan, Hubei Province under a zero-COVID policy
January 30, 2020 ⁹	WHO declared COVID-19 a Public Health Emergency of International Concern (PHEIC) and recommended containment strategies like testing, contact tracing, and isolating cases.
February 2020 ¹	Strictest phase of lockdowns peaked in China and select measures persisted in some form through March and April 2020.
February 28, 2020 ^{1,2}	WHO-China Joint Mission report praised China's lockdown in Wuhan, as "bold" and effective, reducing cases significantly and recommended a tailored approach, such as travel advisories, case isolation, and community engagement.
March 7, 2020 ¹⁰	WHO released guidance on "community-wide" containment public health measures, or "lockdowns", including physical distancing, school closures, workplace restrictions, and limits on public gatherings to reduce peak case numbers.
March 11, 2020 ⁴⁷	WHO declared pandemic as global cases surge.
March 15, 2020 ^{24,26}	Ontario government asked health care providers to ramp down elective surgeries and nonemergent clinical activities and to cease or reduce to minimal levels all nonessential health care services.
March 17, 2020 ²⁰	Ontario declared a state of emergency and implemented two weeks of lockdowns to flatten the curve.
April 8, 2020 ³³	China lifted Wuhan's final lockdown restrictions having halted SARS-CoV-2 spread.
December 15, 2020 ⁴⁰	COVID-19 vaccination began.
December 2021 ⁴⁴	>85% of eligible adults have been fully vaccinated.
December 2021-February 2022 ⁴⁸⁻⁵¹	The Omicron variant sweeps through Canada, resulting in the largest COVID-19 wave despite high levels of vaccination and reimposition of public health measures.
March 2022 ⁵²	China entered second multi-province lockdown under a zero-COVID policy.
March 9, 2022 ⁵³	Ontario government announced a plan to bring an end to all COVID-19 restrictions by April 27, 2022.

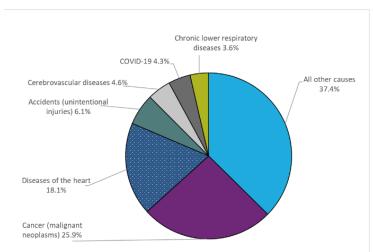
December	China abandoned its zero-COVID policy due to civil unrest, economic
202254	strain and lack of effectiveness.
Early 2023 ³⁴⁻³⁶ -	United States federal agencies and Oversight Committee determined that
January	SARS-CoV-2 was more likely to have originated from a laboratory than
202538	an animal.

In March 2020, the WHO declared a Public Health Emergency and recommended community-wide measures and closures (lockdowns) to curb SARS-CoV-2 viral spread reversing their long-held stance against such measures. The implementation of lockdowns and deployment of COVID-19 vaccines by governments across Canada satisfied their legal obligation to take steps to slow the spread of COVID-19. These measures continued for 2 years and governments used risk-communication plans to encourage compliance. Elective surgeries and non-emergent clinical activities were repeatedly suspended until all pandemic directives were revoked on June 2022. This white paper details the impact that Ontario's public health response had on the cancer care system and female cancer outcomes, considers whether our response accomplished its purpose, and proposes ways to improve decision-making moving forward.

Cancer Care in Ontario

Cancer is the leading cause of death in Ontario.^{55,56} In 2020, the worst year of the pandemic, there were six times more deaths from cancer than COVID-19 deaths in Ontario (25.9% vs 4.3%, Figure 1). A total of 30,054 people died from cancer that year while there were only 4,758 confirmed COVID-19 deaths.⁵⁵





The wellbeing of women is foundational to the healthy functioning of our families, communities, and society at large. The prevention and effective management of female cancers, those cancers that are unique to women, is therefore of particular importance. Breast cancer is the most common female cancer and has the best outcomes of all female cancers (89.4% 5-year survival, Table 2).⁵⁵ Uterine cancer is also fairly common while ovarian and cervical cancers are considerably more rare. Survival outcomes for uterine and cervical cancer are generally favorable (~70-80%, 5-year survival) while those for ovarian cancer are poor (~46%, 5-year survival). Although cancer is predominantly a disease of the elderly, cervical cancer is common among younger women.

Table 2: Ontario cancer statistics on female cancers (2024)55

	Breast	Uterine	Ovarian	Cervical
New Cases (2024, projected)	13,039	3,629	1,368	669
Median Age at Diagnosis (2018- 2020)	64 years	64 years	64 years	48 years
5-year survival (2016-2020)	89.4%	79.6%	45.9%	68.8%
Lifetime probability of dying of cancer (2016-2020)	3.1%	0.8%	1.0%	0.2%

The COVID-19 pandemic introduced unprecedented challenges for women in Ontario. Community-wide measures significantly disrupted daily life, compounding existing concerns about illness with societal, relational, and economic stressors. Many women were also serving on the frontline of Ontario's fight against COVID-19 and were subject to prolonged periods of hardship and stress.^{57,58} Over the course of the pandemic, women began reporting unusual symptoms like swollen lymph nodes⁵⁹ and abnormal menstrual bleeding,⁶⁰ which are known indicators of female cancers.⁶¹ For women already battling cancer, anxieties were heightened due to the perceived increased risk of SARS-CoV-2 exposure and severe complications from COVID-19, particularly given potential immune suppression from their disease or treatment, and a general elevated risk of secondary infections.⁶²⁻⁶⁴

Cancer Care Ontario, now part of Ontario Health, is the Ontario government's principal cancer advisor, responsible for coordinating and improving the province's cancer care system.⁶⁵ Its mission is to connect and coordinate Ontario's health care system to ensure Ontarians receive the best possible care, driving improvements in cancer prevention, screening, diagnosis, treatment, and support services.⁶⁶ At the outset of the pandemic Ontario Health anticipated that there would be multiple waves of COVID-19⁶⁷ that would strain cancer care capacity and create staffing shortages.⁶⁷ It was also anticipated that patients and their families would worry about how the pandemic would affect their care and treatment. To guide allocation of limited resources the ethical principle of justice was used to prioritize care for patients with need and efficacy of treatment and deprioritize prevention, screening and routine follow-ups.⁶⁷

As expected, the prolonged lockdowns introduced unique challenges to cancer care delivery in Ontario.^{24,67} To avoid the negative impacts of delaying health care, Ontario implemented strategies to help minimize COVID-19 exposure in hospitals and align with public health guidelines.²⁴ These strategies included instructing people to stay at home, increasing the use of virtual care, prioritizing care for certain populations (*e.g.*, people fit enough to undergo treatment), and using radiation hypofractionation (*i.e.*, larger doses of radiation over fewer appointments), modifying systemic treatment regimens and same-day discharge after surgery.⁶⁷⁻⁶⁹

Data Sources & Analysis

Data for Ontario's COVID-19 response and cancer outcomes were gathered from diverse sources. Provincial public health resources and published literature provided information on Ontario's public health response, while female cancer outcome data was sourced from both the Ontario claims database⁷⁰ and the Ontario Cancer Registry (OCR).⁷¹ The OCR serves as the provincial database for all Ontario residents diagnosed with cancer. It continuously collects, manages, and analyzes cancer data to provide timely, high-quality information on the

province's cancer burden.⁷¹ This includes data on cancer incidence (new cases), cancer stage (advancement), mortality (deaths), and survival (longevity).⁷² Registry data is the preferred source for understanding cancer patterns due to its detail and reliability. However, a significant limitation of this data is its lengthy collection time, spanning multiple years.

Claims data offers a timely source of real-world insights into cancer care.^{72,73} These administrative databases, which are used to reimburse doctors for their services, collect diagnostic information, detailing a patient's medical conditions.⁷³ After a patient visit, doctors record key medical details when submitting reimbursement requests to the government. This information can then be analyzed to understand cancer patterns in a real-world context.^{72,73} Ontario Health Insurances Plan (OHIP) is the largest claims database in Canada and one of the largest in North America, reflecting the healthcare needs of over 16 million residents.⁷⁴ As data is entered by qualified health professionals, it is generally considered accurate although at times it may be considered incomplete as recording diagnostic data is not mandatory.⁷³ In addition, claims data captures diagnostic information at a patient's initial visit and because not all suspected cancers are confirmed it may overestimate cancer rates. Our analysis considered both claims and Ontario cancer registry data to gain the most comprehensive insight into cancer outcomes during the COVID period.⁷⁵

To account for changing cancer rates and population shifts, we analyzed cancer outcomes during the COVID-19 period relative to a five-year pre-pandemic period (2015–2019) whenever possible. For claims data, we employed linear regression to project billing incidence rates (BIRs) for the COVID-19 period relative to the pre-pandemic period. Excess billing rates were derived by comparing reported values to projected values. For registry data, a age-adjusted incidence rates were plotted from 2015 to 2022. Stage, mortality and survival data were also considered when available.

Cancer is the leading cause of death in Ontario. There were six times more deaths from cancer than COVID-19 in 2020. Female cancers are prevalent in Ontario with 5-year survival rates ranging from 46% to 90%. Many women served on the frontline of Ontario's fight against COVID-19 and were subject to prolonged periods of hardship and stress. Women battling cancer had heightened anxiety due to their perceived greater risk for COVID-19 complications. Ontario implemented strategies to help minimize COVID-19 exposure in hospitals and align with public health guidelines. We used public health guidance, announcements, and the published literature to detail the impacts of lockdowns on the cancer delivery system and real-world data to assess female cancer outcomes.

Early Cancer Detection

Screening

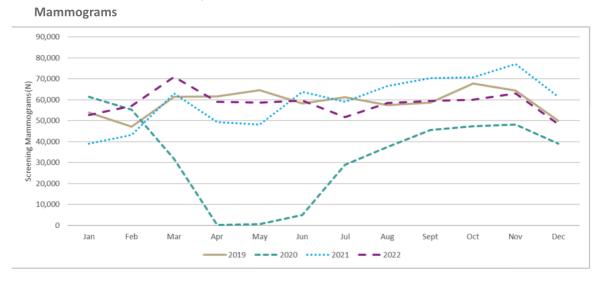
Both screening programs and primary care physicians play an important role in the early detection of cancer, enabling timely intervention to completely remove the tumor, reduce mortality, and enhance quality of life. Ontario Health oversees screening programs for the early detection of breast and cervical cancer. The Ontario Breast Screening Program (OBSP) offers women between the ages of 50 to 74 years at an average-risk of breast cancer a mammogram every two years, and offers women aged 30 to 69 years at a high-risk of breast cancer both annual mammograms and magnetic resonance imaging (MRI).⁷⁶ In Canada 36% of breast cancers are screen-detected.⁷⁷ The Ontario Cervical Screening Program (OCSP) offers women between the ages of 21 to 70 years who are or have ever been sexually active a cervical cytology test every three years followed by colposcopy for those with a high-grade cytology result.⁷⁸ Participation in the OCSP has been consistently below the target of >80% and has been decreasing over time - only 54.5% of eligible women during 2019-2021 had a cytological test in the last 42 months.⁷⁸

In March 2020, Ontario Health advised the suspension of all routine breast and lung screening services to permit the deployment of staff elsewhere if needed.⁷⁹ Family doctors and other primary care providers were advised to consider cancelling cervical screening services.^{67,80} Screening services were permitted to resume on May 26, 2020, in accordance with operational public health requirements, and screening correspondence restarted in January 2021.⁸¹ Given ongoing capacity constraints due to the gradual resumption of services, a prioritization framework, favouring abnormal results and high-risk screens, was distributed to OBSP sites in June 2020 and to primary care providers in July 2020.⁶⁷ Efforts were also made to increase screening volumes to beyond pre-pandemic levels in order to clear remaining backlogs.^{82,83}

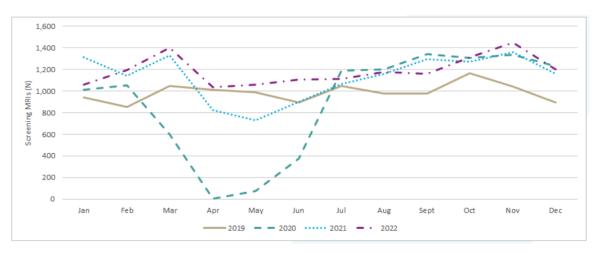
As of March 2020, the number of mammograms declined rapidly with a >99% reduction seen in April and May 2020 relative to 2019 (Figure 2).^{78,80,84} A total of 294,852 fewer mammograms (-42.6%) were performed the first year of the pandemic.⁸⁴ By March 2021, prioritization strategies had only marginally decreased backlogs for average-risk annual screenings (13.5%), had not changed backlogs for initial screens, and had increased backlogs for bi-annual screens by 7.6%.⁷⁹ Mammography volumes above pre-pandemic levels were achieved by mid-2021 and continued until April 2022, a likely indication of backlog clearance.⁷⁸ Peak drops in breast assessments following abnormal mammograms occurred in April and May 2020 and volumes exceeded pre-pandemic levels by mid-2021 and remained elevated until July 2022 potentially indicating backlog clearance.⁷⁸ Peak drops in high-risk MRIs were also seen in April 2020,⁸⁴ however, effectively cleared MRI backlogs within the first year.⁷⁹

Despite these disruptions, there was only a modest 4.2% drop in the percentage of screen-eligible women in 2020/2021 that completed one mammogram within a 30-month period relative to 2018/2019.⁷⁸ And only a slight 1% and 1.7% increase in the proportion of abnormal mammographs in 2020 and 2021 relative to 2019, which coincided with prioritization strategies.⁷⁸ The number of women with screen-detected DCIS and invasive cancer remained steady in 2020 relative to 2019.⁷⁸ The number of women receiving a breast MRI dipped by 29.0% in the first six months of the pandemic and had recovered by March 2021 with an yearly volume slightly above that of previous year (+1.3%).⁸⁴ The number of high-risk women with a diagnosis of DCIS or invasive breast cancer after screen detection increased by 1.2% in 2020 relative to 2019 with DCIS rates remaining steady and a slight increase in invasive cancers of 1.8 per 1,000 screened, which coincided with implementation of prioritization strategies.⁷⁸

Figure 2: Number of screening mammograms and high-risk breast magnetic resonance imaging (MRI) performed in Ontario by month 2019 to 2022.⁷⁸



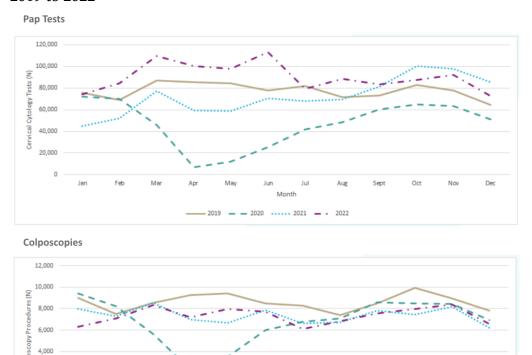
Breast MRIs



Regular screening and timely follow-up and treatment of abnormal results are crucial for preventing most invasive cervical cancers.⁸⁵ In Ontario, the Cervical Screening Program (OCSP)⁷⁶ offers women aged 25 to 69 years a cervical cytology test every five years. If abnormal cytology tests are detected, colposcopies are performed, allowing clinicians to identify cervical lesions, confirm a diagnosis via biopsy, and recommend treatment.^{78,85} Despite these measures, a significant portion of women diagnosed with invasive cervical cancer in Ontario between 2017 and 2019 were not adequately screened; nearly 35.5% have never been screened, and only 13.5% have had a cytology test in the past 2 to 3 years.⁷⁸

As of March 2020, routine cervical screening services were paused, leading to substantial reductions in the number of cytological cervical exams with peak reductions seen in April 2020 (92.3%, Figure 3).85 A total of 341, 394 fewer tests (-38.3%) were performed in the first year of the pandemic relative to 201984 and test volumes exceeded normal levels by October 2021 and remained elevated until July 2022 when they returned to normal potentially indicating backlog clearance.78 In June 2020, high-grade cytology tests were prioritized for colposcopy to manage backlogs.85 Reductions in cytology test volumes in 2020-2021 relative to 2019 coincided with changes in the age of screening eligibility from 21 to 25 years as well as shifts to virtual care.78,82 However, by March 2024, the number of cytological tests performed remained 21.5% below pre-pandemic levels.82 The number of colposcopies, the procedure required to diagnose cervical cancer, also dropped significantly in April 2020 (-75.1%)85 with 21,013 fewer colposcopies (-20.6%) performed the first year of the pandemic along with 1,716 fewer surgeries for pre-cancerous lesions (-20.0).84 The number of colposcopies performed returned to normal levels as of September 2020 and annual volumes increased by 8.5% from 2020 to 2021 supporting a potential backlog clearance by the end of 2021.78

Figure 3: Number of cervical cytology tests and colposcopies performed in Ontario by month 2019 to 2022⁷⁸



In 2020, the proportion of abnormal cytology tests with high-grade results were steady and then climbed by 1.3% in 2021 relative to 2019.⁷⁸ This increase coincided with prioritization of high-risk patients. Median wait times to colposcopy for women with a high grade cytology decreased by 4-5 days in 2020 and 2021 relative to 2019.⁷⁸ The number of screen-detected precancers remained steady in 2020 relative to 2019 while the number of invasive cancers doubled (0.22 vs 0.14 per 100,000 screened), coinciding with prioritization strategies.⁷⁸ More than half of women diagnosed with invasive cancers in Ontario (58.1% in 2017-2019) had not had a cytological screening test in the last 5 years.⁷⁸

— — 2020 ······ 2021 **— · ·** 2022

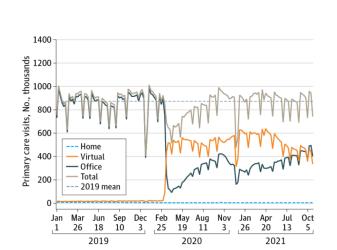
Primary Care

In Ontario, primary care physicians play an important role in diagnosing both screen-detected and symptom-detected female cancers. Primary care physicians and emergency departments

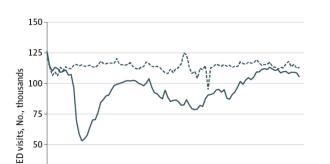
are often the first point of contact for individuals concerned about cancer.⁸⁶ Their role encompasses discussing screening risks and benefits, interpreting results, and performing physical assessments. They also order follow-up tests, such as imaging or biopsies, and refer patients to specialists. Physical assessments are vital in detecting cancer signs like lumps, skin changes, or organ irregularities in both asymptomatic and symptomatic patients. For those without a primary care physician, patients may present to emergency departments with complaints.⁸⁷ The majority of female cancers, are symptomatically detected through physical examination.⁸⁸ Uterine cancer is often diagnosed at an earlier stage due to abnormal bleeding being an obvious clinical symptom, whereas ovarian cancer is detected at later stages due to a less distinct symptomology.⁸⁹

There was a significant decrease in visits to primary care providers and emergency departments (Figure 4) coinciding with directives to suspend care in March 2020, 26,80 While emergency department visits rebounded to pre-pandemic levels by August 2020, primary care visits did not recover until October 2020. As volumes did not exceed pre-pandemic levels it is likely that backlogs persisted beyond October 2021. According to the Ontario Medical Association as of February 2024, 2.3 million of 16 million Ontarians (14.3%) do not have a family doctor. Additionally, there was a shift from in-person care to virtual care. This rapid shift to virtual care occurred in the absence of the requisite guidance and frameworks that would have accomplished such a significant shift prior to the pandemic. As of April 2020, 82% of primary care visits were virtual with high levels of virtual care (49%) persisting up to October 2021. Ontario is committed to expanding appropriate virtual care and as of March 2024, 16.2% of visits were occurring virtually indicating a potential persistent backlog in in-person care. It is unclear how this ongoing shift to virtual care will impact early detection of cervical cancer.

Figure 4: Primary care visits, emergency department (ED) visits, and percentage of total primary care visits delivered virtually.⁹²



Weekly primary care visits



Weekly emergency department visits

OHIP Billing Incidence Rates

Billing incidence rates (BIRs) for ovarian cancer, were lower than expected in 2020, and then higher than expected in 2021, returning to closer to normal levels by 2022 (Figure 5).⁷⁵ These changes coincided with the suspension and resumption of in-person care. A cumulative excess BIR of 12.2% relative to 2019 values for ovarian cancer was seen through the COVID-19 period,⁹³ which is difficult to explain based on recovery of in-person care alone.

25

Jan

--- Pre-COVID-19 ED visits
— COVID-19 ED visits

Sep

Dec

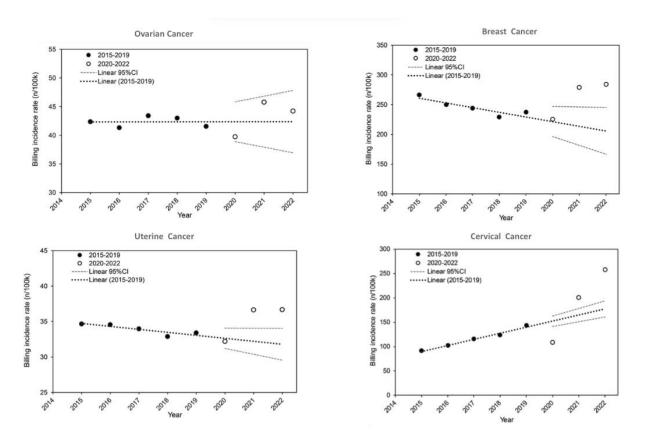
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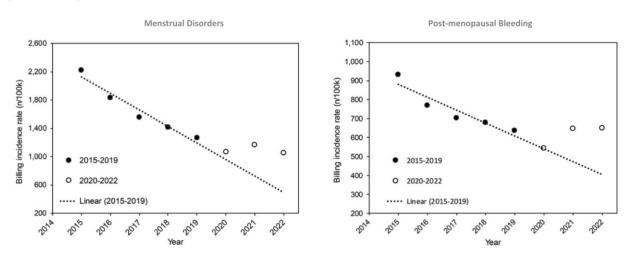
BIRs for breast cancer aligned with expectations in 2020, consistent with prioritization strategies for high-risk breast cancer and abnormal mammography results which may have compensated for the large decrease in screening volumes (Figure 5).⁷⁵ However, BIRs were higher than expected in 2021 and 2022, coinciding with the clearance of screening backlogs for lower-risk breast cancer, which extended to mid-2022. A 32.2% excess BIR relative to 2019 was observed for breast cancer over the COVID-19 period,⁹³ a phenomenon not easily explained by screening recovery. Increased reports of post-vaccination lymphadenopathy in up to 16% of women following a second COVID-19 vaccine dose in 2021,^{76,94} may at least partially account for these excess BIRs.

BIRs for uterine cancer were as expected in 2020, potentially reflecting accessible care for symptomatic cancer (Figure 5).⁷⁵ However, higher than expected BIRs in 2021 and 2022 contributed to an excess BIR of 15.8% over the COVID-19 period relative to 2019.⁹³ Conversely, BIRs for cervical cancer were below expected in 2020, coinciding with suspension of screening and reduced access to in-person care (Figure 5). They subsequently increased in 2021 and 2022, aligning with prioritization strategies and screening recovery.⁷⁸ Over the

COVID-19 period, there was a 96% excess BIR relative to 2019 for cervical cancer,⁹³ which is difficult to attribute to screening recovery alone.

In 2021, there were reports of menstrual irregularities (including excessive bleeding) following COVID-19 vaccination.⁹⁵ Surveys confirmed initial anecdotal reports,^{95,96} while some cohort studies showed either a weak or lack of association,^{41,97-100} several other cohort and case-control studies found an association between the COVID-19 vaccine and abnormal bleeding in both younger^{60,101-104} and older women.^{60,105-107} Our review of OHIP billing data over the COVID period confirmed an increase in billing event rates for menstrual disorders (OHIP 626) and post-menopausal bleeding (OHIP 827, Figure 6) in 2021 and 2022 coinciding with the rollout of the COVID-19 vaccines in Ontario.⁹³ These findings may partially explain the excess BIRs in women with both uterine and cervical cancer.

Figure 6: Billing events for menstrual disorders (OHIP 626) and post-menopausal bleeding (OHIP 627)⁹³



The suspension of non-emergent care in 2020 resulted in a near-complete halt of breast and cervical screenings, creating backlogs that persisted until mid-2022. Significant disruptions to in-person care limited access to physical exams crucial for cancer detection. While most primary care visits occurred virtually in early 2020, there has been a shift back to in-person care, with virtual visits comprising 16.2% as of March 2024. The initial suspension of screening and in-person care resulted in lower-than-expected BIRs in 2020, followed by higher-than-expected BIRs in 2021 and 2022. coinciding with the recovery of screening services and a return to in-person care. Excess BIRs over the COVID-19 period are challenging to explain solely by cancer service recovery and align with the emergence of post-vaccination symptoms.

Rapid Diagnosis

Imaging

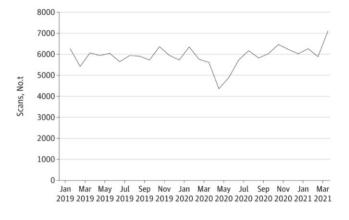
Improving access to a more rapid and accurate diagnosis is a priority for cancer care in Ontario. The Diagnostic Assessment Programs (DAPs), implemented in 2008, aim to decrease waiting times for diagnosis and treatment while improving the coordination and communication of care. Imaging and pathology are crucial diagnostic components aiding in arriving at a definitive diagnosis and in developing an appropriate treatment plan. The Cancer Imaging Program promotes timely access to high-quality imaging in Ontario, and the Pathology and Laboratory Medicine Program strives to enhance the quality of pathology and laboratory medicine services across the province. Magnetic resonance imaging (MRI) and computed tomography (CT) scans are essential for the diagnosis and staging of female cancers.

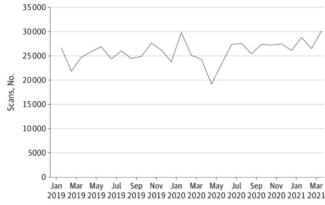
In March 2020, the Ontario government suspended non-emergent care. 26,80 By April 2020, the number of CT (-25.9%) and MRI (-26.7%) scans dropped relative to 2019 (Figure 7). 84 By March 2021, backlogs had been cleared with more CT (2.3%) and MRI (0.03%) scans being completed relative to 2019 levels. 84

Figure 7: Cancer imaging volumes, Ontario, January 1, 2019, to March 31, 202184



Computed Tomography (CT)





Pathology

Dramatic drops in pathology volumes were also seen in March 2020 (Figure 8).⁸⁴ Peak reductions in biopsy reports were seen in July 2020 (-41.2) and resection reports in May 2020 (-37%). The number of biopsy reports remained low until late July 2020 (week 31), and exceeded 2019 levels by early 2021 clearing backlogs by the end of 2021.⁸⁴ Resection report volumes remained below pre-pandemic levels through to February 2021,⁸⁰ despite the absence of backlogs for P2 and P3 surgeries.

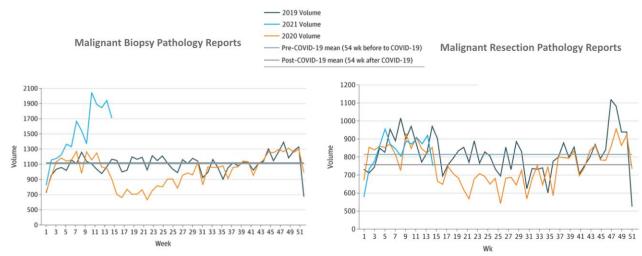


Figure 8: Pathology report volumes, Ontario, December 31, 2018, to April 4, 2021⁸⁴

Stage Migration

The size and degree to which a cancer spreads is described in terms of stages (Table 3). Stage 1 tumours are localized and small and are often associated with good outcomes, while stage 4 cancers have spread to another part of the body and are associated with poor outcomes. For example, stage 1 breast cancer has a 99.7% 5-year survival rate, but the 5-year survival rate for stage 4, advanced cancer, is only 28.7%. In 2020, Ontario cancer statistics, reported 2.5% fewer screen-detected stage 1 breast and 7.3% fewer stage 1 cervical cancers relative to 2019 (Table 3). Conversely, there was a concerning increase in stage 2 and 3 cervical cancers (6.8% and 2.0%, respectively). A Canadian modeling study estimated that missed or delayed diagnoses and other cancer care disruptions seen through 2020 and 2021 could lead to a 2% increase in cancer mortality in the next 10 years. Multiple modeling studies have estimated substantial and statistically significant increases in mortality due to missed diagnosis during

the pandemic period and subsequent later-stage presentations of cancers with established screening programs, including breast and cervix. 112-116

Table 3: Cancer stages and percent differences in staging of new cancers in 2020 relative to 2019 for breast and cervical cancer.⁵⁵

	Stage 1	Stage 2	Stage 3	Stage 4
	Cancer is small and contained within the organ	Cancer is larger than but has not started to spread into surrounding tissues	Cancer is larger and may have started to spread into surrounding tissues and there are cancer cells in the lymph nodes nearby	started to another
Breast, %	-2.5%	+1.4	+0.4	+0.7
Cervical, %	-7.3%	+6.8	+2.0	-1.4

Imaging and pathology are integral to an accurate diagnosis and development of a stage appropriate treatment plan. Reductions in imaging and pathology services through 2020 created backlogs in diagnostic services that persisted into early 2021 for imaging (March 2021) and late 2021 for pathology reports (December 2021). There was a shift from stage 1 breast (-2.5%) and cervical cancer (-7.3%) cancer relative to 2019 and a concerning increase in stage 2 breast (1.4%) and stage 2/3 cervical (8.8%) cancer.

Timely Treatment

Surgery

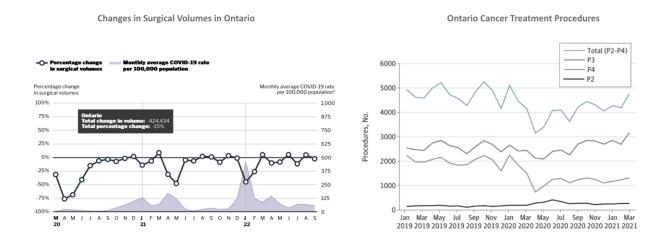
Optimal cancer management is crucial to the survival and quality of life of individuals living with cancer. For early-stage tumors, timely surgery is critical for optimal cancer management, as it can completely remove the tumor and potentially lead to a cure.¹¹⁷ It also plays an important role in reducing complications, preserving organ function, improving quality of life,

and extending survival. Ontario Health's Surgical Oncology Program ensures timely access to safe, high-quality cancer surgery across the province. The program focuses on improving access and quality of cancer surgery through continuous improvement initiatives and by actively engaging surgeons in planning and quality improvement.

To this end, Ontario Health standardized surgical treatments by categorizing and prioritizing them by wait times.⁸⁴ P1 procedures are considered "life or limb" emergencies requiring immediate attention and P2 surgeries urgent treatments such as highly aggressive cancers (14-day maximum wait time). P3 surgeries are for known or suspected invasive cancer (28-day maximum wait time) and P4 surgeries for indolent malignancies (84-day maximum wait time).^{119,120} Over the course of the pandemic, Ontario Health issued three directives to pause elective surgical procedures in order to preserve hospital capacity.^{80,121} During this time, health care providers were advised to prioritize P1 & P2 surgeries,⁶⁷ expand use of same-day discharge after surgery,⁶⁷⁻⁶⁹ and not to treat patients who exhibited infectious symptoms unless there was a life-threatening situation.⁶⁷

In March 2020, there was a decline in P2 to P4 surgeries, with the most significant reductions observed in April 2020 (-37%, Figure 9).⁸⁴ This resulted in 8,020 fewer P2-P4 cancer surgeries (-14.1%).⁸⁴ Surgical volumes remained 5% to 16% below pre-pandemic levels from June 2020 through to February 2021.¹²² As of March 2021, P2 surgeries saw a 65.6% increase, P3 surgeries showed no change, and P4 surgeries decreased by 40%.⁸⁴ A 2020 survey of gynecologic oncologists in France reported that surgery was disrupted in 23% of women with cancer¹²³ while only 4.4% of women had or were suspected of contracting COVID-19.¹²³ As of March 2021, non-emergent care would be suspended two additional times resulting in a total of 424,434 fewer surgeries as of September 2022¹²⁴ and 398,000 fewer surgeries as of the end of 2022, relative to 2019.¹²¹

Figure 9: Overall¹²⁴ and cancer⁸⁴ surgical volumes in Ontario over the COVID-19 period



While the number of surgeries largely normalized for the remainder of the COVID-19 period, the likelihood of clearing backlogs remained low until March 2022 when the number of surgeries performed began to exceed (105%) pre-pandemic levels. ¹²⁴⁻¹²⁶ Prioritization strategies (priority to P1 and P2 surgeries) ^{127,128} along with \$858 million in investment ¹²¹ were deployed to mitigate the impact of surgical backlogs, ^{126,128} however, backlogs persisted. According to the Financial Accountability Office of Ontario, as of September 2022, 250,000 patients were on waitlists for surgical procedures up 50,000 compared to pre-pandemic levels. ¹²¹ Of the those on surgical waitlists, 107,000 (43%) were waiting longer than the maximum clinical guidelines for their surgery, up from an average of 38,000 (20%) before the COVID-19 pandemic. ¹²¹ And according to Ontario Health's 2023–2024 Annual Report, as of March 2024, about half of patients with aggressive cancer (48%, P2) and a third of patients with suspected or invasive cancer (28%, P3) were waiting beyond the recommended wait time for their surgery (14-and 28-day periods, respectively). ⁸²

Modeling studies have sought to gauge the impact of surgical delays on survival. Authors estimated that these delays could translate into 843 life-years lost among patients with cancer in Ontario. A modeling study published in 2020 reported that as little as a 3-month delay in breast cancer surgery could negatively impact overall survival (HR 1.46, 95%CI 1.28–1.65) particularly for stage I (HR 1.27, 95%CI 1.16–1.40) and II cancers (HR 1.13, 95%CI 1.02–1.24). Similarly, a UK cancer registry study indicated that a 3-month delay could substantially impact overall survival for stage II and III patients with multiple cancers, including ovarian cancer, resulting in a >17% and >30% reduction in 5-year survival with 3-and 6-month delays in surgery, respectively. The long-term implications on survival of these slowdowns for patients with cancer is unknown.

Timely cancer surgery is critical for optimal survival. Ontario Health issued three directives over the pandemic period to pause elective surgical procedures and prioritize P1 & P2 surgeries. This resulted in reductions in considerable surgical backlogs. By September 2022, 424,434 fewer surgeries had been performed relative to 2019. Despite prioritization strategies and investment, surgery backlogs have been persistent. As of March 2024, 48% of surgeries for aggressive cancer and 28% of surgeries for suspected or invasive cancer were exceeding target wait times. Modeling studies estimated that surgical delays of even 3-months can negatively impact overall survival for stage I and II breast and ovarian cancer.

Systemic Therapy

Optimal cancer treatment, encompassing both systemic and radiation therapy, is vital for improving patient survival and quality of life.¹³¹ These therapies are crucial for addressing microscopic or metastatic disease that surgery alone cannot eliminate.¹³² When integrated with surgery, personalized treatment plans prevent stage migration and effectively manage advanced cancers, leading to better outcomes and reducing long-term healthcare burdens.^{133,134} For advanced cancers, systemic therapy prevents progression, while both systemic and radiation therapy are integral to patient well-being. Ontario Health's Systemic Therapy Program offers a range of treatment options, including chemotherapy, hormone therapy, targeted therapy, and immunotherapy, to address various cancer types and stages.^{67,132} Ontario Health's Radiation Treatment Program provides comprehensive radiation treatment services across the province, ensuring access to safe, evidence-based, and high-quality radiation therapy.¹³⁵

In March 2020, health care providers were advised to prioritize patients with aggressive tumours and those in life-threatening situations and to give lower priority to those receiving chemotherapy or those on oral hormonal therapy, follow-up care, and palliative care.⁶⁷ As patients undergoing immunosuppressive therapies¹³⁶ and potentially immunotherapies,^{137,138} were deemed at higher risk of severe COVID-19 outcomes^{63,64} providers were encouraged to modify regimens in order to reduce visits or provide alternate treatment options when surgery or radiation therapy was not available and to reduce the risk of toxicities that may require medical care.¹³⁹ Health care providers were also advised to defer treatment for patients who exhibited infectious symptoms unless there was a life-threatening situation.⁶⁷ As deferred services were permitted to resume following each lockdown, patients on waiting lists were prioritized for care with priority care given to those at high-risk or with effective available treatments.⁶⁷ This rapid shift in treatment occurred in the absence of evidence-based guidance that would have ensured optimal outcomes prior to the pandemic.¹⁴⁰

According to a Cancer System Quality Index report of November 2021 treatment protocols were adapted to offset the risk of surgical delay.²⁷ For instance some patients on surgical waitlists received neo-adjuvant rather than adjuvant systemic treatments and some patients were diverted from surgery to radiation alone or chemo-radiation alternative treatments.²⁷ Protocols were also adapted to reduce the risk of COVID-19 exposure in patients who were immunocompromised by eliminating some hospital visits.²⁷ Changes included switching from parenteral to oral systemic therapy, offering flexible start dates or extending treatment breaks, extending dosing interval between systemic therapy cycles, and increasing the use of hypofractionation for patients undergoing radiation treatments.^{27,28,67}

As of March 2020, systemic and radiation treatment visits decreased relative to 2019, though total consultation volumes recovered relative to 2019 by March 2021 (Figure 10).⁸⁴ In the first 6 months of the pandemic new consultations for systemic therapy decreased by 5,500 visits (-15.1%) and delivery of supportive or adjunctive treatment visits by 23,051 visits (-31.1%). Less dramatic changes were seen for suite visits (-4.5%) and oral antineoplastic visits (-0.1%) and increases were seen in parenteral (1.8%) and follow-up visits (7.1%). Treatment consultations and treatment visits began to rise in the fall of 2020 with the number of monthly visits returning to pre-pandemic levels by March 2021.⁸⁴ However, visits for supportive or adjunctive care remained low even a full year into the pandemic (-27.4%). Drops in new treatment consultation visits coincided with drops in cancer diagnoses and drops in supportive and adjunctive visits coincided with Ontario Health directives to prioritize life-saving care.⁶⁸ The maintenance of follow-up and oral therapy visits coincided with the shift to virtual care. It is unclear how long these backlogs will take to clear, especially in the absence of increased treatment volumes.^{27,84}

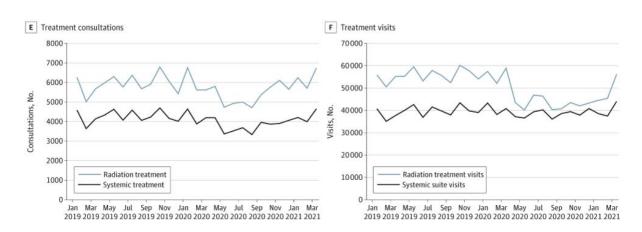


Figure 10: Treatment consultation volumes, Ontario, January 1, 2019, to March 31, 202184

A 2021 survey of cancer patients and their care providers by the Canadian Cancer Survivor Network, reported that half of all patients (50%) said their care appointments had been cancelled, postponed or rescheduled — a figure that climbed to 69% for patients with metastatic cancer.¹⁴¹ A Dutch survey reported similar findings.⁶³ As patients undergoing immunosuppressive therapies and potentially immunotherapies,^{137,138} were deemed at higher risk of severe COVID-19 outcomes^{63,136} adjustments including delays, cancellations, or switches to alternative administration methods were made to reduce hospital visits and minimize COVID-19 exposure. Such changes included alternative dosing schedules or routes of administration, as well as delayed or discontinued chemotherapy sessions, especially for

palliative care, to further limit hospital visits.^{67,68} Disruptions in care were linked to an overall loss of wellbeing in patients.¹⁴² One patient wrote "Not knowing is worse than knowing. Knowing gets action put into place. Fear breeds anxiety, and that is NOT GOOD for cancer patients. I feared being bumped out of the system. I FEEL DISPLACED. I now feel lost. I feel that NO ONE cares about me/my health."¹⁴²

Radiation Therapy

Similar disruptions in radiation treatment were apparent. In the first six months of the pandemic there were 4,783 fewer new consultations (-14.8%) and 141,629 fewer radiation treatment visits (-22.8%).84 Radiation treatment visits began to recover in the fall of 2020 but both new treatment consultations (-9.3%) and visits for radiation (-21.0%) remained below pre-pandemic levels by March 2021. Shifts in treatment coincided with COVID-19 policy, reductions in screening and diagnostic services, and directives on increased utilization of hypofractionation.68 As considerable backlogs remained early in 2021, it is likely that these backlogs persisted well into 2021 in the absence of increased volumes.27,84

Cancer Mortality

Delays in cancer detection, diagnosis and treatment can negatively impact survival. Registry data for deaths among cancer patients in Ontario was available for 2020 alone. All-cause mortality among cancer patients increased by 4.5% (n=1,976) in 2020 relative to 2019 (45,931 in 2020 versus 43,955 in 2019).⁵⁵ The majority of deaths were in the elderly (>75 years) and only a fraction of the deaths in cancer patients were attributable to COVID-19 (333, 0.7%).⁵⁵ This is in line with Canadian statistics showing that 80.4% of all COVID-19 attributable deaths were in the elderly (65 years and older)¹⁴³ and the majority of them were residents of long-term care facilities.^{144,145} It is notable the proportion of COVID-19 deaths in long-term care residents was higher that the average among countries from the Organization for Economic Cooperation and Development.¹⁴⁶

Changes in short-term (one-year and two-year) survival are a way of estimating the impact of the COVID-19 pandemic on cancer survival.⁵⁵ During the first year of the pandemic short-term survival decreased slightly. In 2020, the 1-year relative survival ratio (RSR, -1.9%) and 2-year RSR (-2.5%) decreased for all cancers relative to 2019 while cervical cancer had a slight increase in 1 and 2-year RSR (2.7% and 1.4%, respectively) relative to 2019.⁵⁵ However, negative impacts on mortality and survival due to delayed and suboptimal treatment will only be fully realized in another 5 to 10 years.^{55,147}

Optimal cancer treatment, integrating both systemic and radiation therapy, is crucial for patient survival and quality of life. In March 2020, Ontario Health halted non-emergency surgical procedures and prioritized delivery of systemic therapy and radiotherapy. Treatment protocols were subsequently adjusted to mitigate risks associated with COVID-19 exposure and surgical delays. There were dramatically fewer new systemic therapy and radiation therapy consultations in the first year as well as a dramatic drop in supportive or adjunctive care visits. These reductions in care created backlogs that left patients feeling anxious and displaced. The COVID-19 period marked an unprecedented shift in treatment in the absence of a standard evidence-based framework to ensure optimal care.

Disruptions in cancer care can negatively impact survival. There was a 4.5% increase in all-cause mortality among all cancer patients in 2020 relative to 2019 that was primarily limited to the elderly and only minimally attributable to COVID-19 (16%). In 2020, there were slight reductions in the 1- and 2-year relative survival ratios for cancer with an increase in RSR seen in women with cervical cancer. Impacts on mortality and survival will require 5 to 10 years to fully realize.

Cancer Prevention

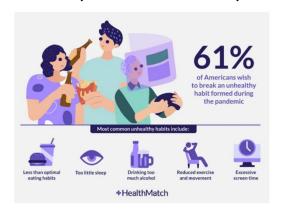
Healthy Lifestyle

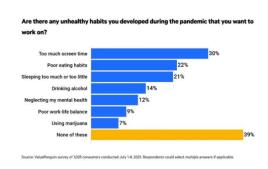
Well-being in cancer patients is significantly influenced by physical exercise, healthy eating habits, and good mental health.^{17,148} Physical activity, in particular, is known to reduce the risk of cancer recurrence and mortality. It also mitigates the severity of treatment side effects, lessens fatigue, enhances quality of life, positively impacts mental health, and improves aerobic fitness in cancer patients.¹⁴⁹ Diet and nutrition are crucial modifiable factors that can influence cancer risk. Various dietary components, such as alcohol consumption, fruit and vegetable intake, and dietary fiber, have been shown to significantly impact cancer risk.¹⁵⁰

Psychological stress is a recognized risk factor in both the initiation and progression of cancer. 151,152 Chronic stress can worsen inflammation and lead to metabolic disorders, disrupting the body's ability to maintain homeostasis and increasing its susceptibility to cancer. Furthermore, stress can indirectly encourage unhealthy behaviors like smoking or poor diet, which in turn elevate cancer risk. 153 Ontario Health actively supports cancer prevention by promoting healthy lifestyle changes through its programs and initiatives, including encouraging smoking cessation, increased physical activity (*e.g.*, 30 minutes daily to lower cancer risk), and improved diet.

From 2020 to 2022, the COVID-19 pandemic dramatically disrupted the lives of Ontarians, leading to widespread separation, stress, and illness. These changes were linked to an increase in unhealthy habits and a decline in mental health. Unhealthy habits observed included decreased physical activity, increased screen time, and poor eating and drinking behaviors. Excessive screen time was particularly problematic for adolescents. Additionally, increased distress, anxiety, insomnia, and depression were commonly reported. A 2021 survey by revealed that 61% of Americans developed an unhealthy habit during the pandemic that they wished to change (Figure 11). These habits included poor work-life balance, unhealthy eating, excessive alcohol and marijuana consumption, excessive screen time, and insufficient sleep.

Figure 11: Survey outcomes of unhealthy habits developed during the COVID-19 pandemic. 162





A 2022 survey conducted by the Canadian Cancer Survivor Network reported that stress and anxiety about cancer care are overwhelmingly common. The anxiousness never goes away, it's one thing after another, one let down after another. More than half of all respondents (58 per cent) were concerned about being able to receive cancer treatment in a timely fashion. Many patients were afraid of getting COVID-19 and others were afraid to get in-person medical care for cancer-related symptoms because they felt their COVID-19 risk was too great. In the first year of the pandemic, psychosocial oncological care services rose by 5.2% resulting in an increase of 7,260 care events relative to 2019.

Safe Vaccines

Safe and effective vaccines can play an important role in preserving the health and well-being of cancer patients. ¹⁶³ Ontario's COVID-19 vaccine program aims to ensure that Ontarians are protected against COVID-19 disease, including severe outcomes such as hospitalization and death. ⁴¹ The mRNA vaccines were the most widely administered vaccines in Ontario. ¹⁶⁴ Based

on their mode of action, mRNA vaccines meet the designation of a gene therapy product by both the FDA165-167 and EMA.168,169 However, their designation as vaccines, 169,170 allowed for their preclinical development according to the outdated WHO 2005 guidelines for vaccines during the pandemic, which excluded them from the extensive regulatory controls in place for gene therapy products such as determining the structure, concentration, and biodistribution of their protein products in vivo. 166,171 They also underwent expedited development requiring less than a year to develop¹⁷² compared to the standard 10 years.^{173,174} As a result, the extensive multi-phase safety testing that is usually measured in years¹⁷³ was measured in months.¹⁷² Additionally, these products received emergency use listing by the WHO^{175,176} and emergency approvals in Canada¹⁷⁷ and other countries^{176,178} with limited or absent pharmacokinetic and toxicological assessments, genotoxicity and oncogenicity studies, and prolonged safety assessments usually required prior to product approval. 169 This is particularly concerning given the wide systemic biodistribution¹⁷⁹⁻¹⁸¹ and known biological activities¹⁸²⁻²⁰⁷ of both vaccine components and their products. Finally, two distinct mRNA production methods were employed: one for clinical testing and another for large-scale production which is more prone to issues with DNA impurities.²⁰⁸ While unpublished reports had previously suggested the presence of residual DNA in marketed mRNA vaccines, 209,210 a recent published study has now confirmed these suspicions. This study showed that the total DNA levels in marketed vaccine vials exceeded regulatory limits for residual DNA established by both the US Food & Drug Administration (FDA) and WHO.²⁰⁸ Specifically, Pfizer's vaccines showed levels were 36-153fold higher and Moderna's vaccines were 112-627-fold higher, even after accounting for nonspecific binding to mRNA. The deployment of COVID-19 vaccines beginning in December 2020 marked the first time this novel technology, with a largely uncharacterized clinical safety profile, 177,211-216 was administered to humans at a global scale within a limited time period. 217-219

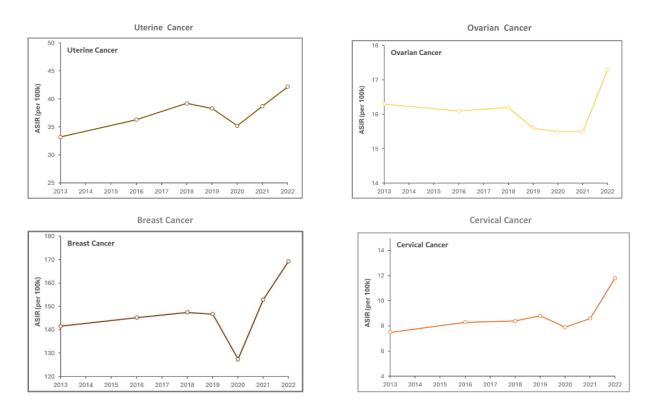
Complications related to COVID-19 and associated inflammation are linked to the spike protein. ²²⁰⁻²²⁴ The spike protein is also the immuno-active substance (i.e., antigen) produced by COVID-19 vaccines. ²²⁵ Both infection and vaccination can lead to systemic circulation and extrapulmonary localization of the spike protein ^{179,226,227} and multiple studies have identified lingering systemic spike several weeks, months and up to nearly two years after infection ²²⁸⁻²³² or vaccination. ^{179,211,212,233-236} This protein also binds to and modulates estrogen receptors, leading to cytoplasmic accumulation and ER-dependent biological effects. ²³⁷ High estrogen levels can fuel estrogen-dependent breast cancer growth, ²³⁸ and may also contribute to endometrial and ovarian cancer growth. ²³⁹ *In vitro* studies have demonstrated that estrogen metabolite production can also fuel HPV growth, ²⁴⁰ while preclinical and epidemiological studies indicate a role in promoting cervical cancer in combination with HPV oncogenes. ²⁴¹ Therefore, increased spike exposure from COVID-19 infection or vaccination over the COVID-19 period may have contributed to an estrogen-dominant, pro-inflammatory environment, conducive to female cancer growth.

Two epidemiological studies have recently shown a link between COVID-19 vaccination and cancer incidence.²⁴²⁻²⁴⁴ A recently published, population-based retrospective study, showed a significantly increased risk of specific cancers including breast (HR 1.12; 95% CI: 1.07-1.34), thyroid, gastric, colorectal, lung and prostate 1-year after COVID-19 vaccination in a cohort of 8,407,849 residents from the Korean National Health Insurance Database.²⁴⁴ The increased risk of breast cancer was observed following both mRNA and heterologous vaccination, particularly in a relatively younger population (<65 years). Another population-wide cohort analysis using official National Health System data found that individuals receiving ≥1 doses had a slightly higher likelihood of hospitalization for cancer (HR 1.23; 95% CI: 1.10-2.16) compared to unvaccinated individuals. This study followed 296,015 residents of the Pescara province, Italy from June 2021 (six months after the first vaccination) to December 2023. The rate of hospitalization for cancer of any site was 0.85% in the unvaccinated group, and 1.15% in the group vaccinated with ≥ 1 dose (p<0.001). More than one dose of the COVID-19 vaccine was associated with an increased risk of hospitalization for breast cancer (HR 1.54; 95% CI: 1.10-2.16, p=0.012) as well as other cancers. Increased hospitalization risks for ovarian (HR 1.71; 95% CI: 0.60-4.82, p=0.3) and uterine (HR 1.77; 95% CI: 0.76-4.13, p=0.19) cancers were not significant. After ≥3 doses, similar results were observed for breast cancer (HR 1.36; 95% CI: 1.08-1.72) and for any type of vaccine. No association between vaccines and cancer were observed among the individuals with a recorded previous infection.

Age-adjusted Incidence Rates

Age-adjusted incidence rates (ASIR)s for uterine and ovarian cancer decreased in 2020, aligning with reduced in access to diagnostic services and in-person care (Figure 12).⁵⁵ However, ASIRs for uterine cancer rose in 2021 and ovarian cancer in 2022, coinciding with a return to in-person care. Over the COVID-19 period, there was a net 3.1% ASIR increases for uterine cancer and a 9.6% ASIR increase for ovarian cancer relative to 2019. The increase in ovarian cancer followed reductions in prophylactic surgeries to reduce cancer risk (P4) in 2020 resulting in lesions that would have otherwise been removed to progress to invasive cancer.²⁴⁵

Figure 12: Plots of Age-adjusted Incidence Rates (ASIRs) of Female Cancers reported by Ontario Cancer Statistics (2015 to 2022)⁵⁵



In 2020, ASIRs for both breast and cervical cancer declined, with breast cancer experiencing the most significant drop (Figure 12).⁵⁵ These decreases coincided with disruptions in screening, diagnostic services, and in-person care. ASIRs for both cancers increased in 2021 and 2022, aligning with recovery of screening programs and a return to in-person medical attention. Over the COVID-19 period, there was a net ASIR increase of 6.5% for breast and 21.6% for cervical cancer. These increases followed the suspension of surgeries for in-situ cervical (-20%)⁸⁴ or ductal carcinoma lesions in 2020. It is possible that lesions that would have been removed in 2020 progressed to invasive cancer by 2022, at least partially explaining the net ASIR increases. Overall, a concerning 6.7% increase in ASIRs for female cancers, despite a 7.1% decrease for cancers overall.⁵⁵ This significant increase coincides with COVID-19 vaccine delivery and warrants further investigation.

Physical exercise, healthy eating habits, and good mental health significantly influence well-being in cancer patients. Lockdowns and associated risk communications increased cancer risk by promoting unhealthy habits and elevating stress levels. The expedited

development and emergency use authorization of COVID-19 vaccines led to the broad administration of a product with a poorly characterized safety profile. Furthermore, increased exposure to the spike protein, through infection or vaccination over the COVID-19 period may have contributed to an estrogen-dominant pro-inflammatory environment conducive to the growth of female cancers. Reductions in age-adjusted incidence rates in 2020 aligned with suspension of cancer services, while increases in 2021 and 2022 coincided with a recovery of cancer services and a reduction in surgical procedures for in-situ cervical and breast lesions. A net increase of 13.8% in age-adjusted incidence rates for female cancer relative to cancers overall during the COVID-19 period. This significant increase coincides with COVID-19 vaccine delivery and warrants further investigation.

Overall Impact on Cancer Care

Cancer is the leading cause of death in Ontario. In 2020, during the height of the pandemic, there were at least six-times more deaths due to cancer than linked to COVID-19. Non-emergent care was repeatedly suspended over the pandemic period in order to protect vulnerable populations and preserve hospital capacity. The impact of these disruptions rippled across the cancer care continuum delaying detection, diagnosis and treatment. During the first year of the pandemic alone, there was a 20.7% reduction in cancer services offered in Ontario, producing a backlog of 1,167,412 cancer services.⁸⁴ Although efforts were made to clear backlogs, repeated lockdowns extended waitlists, and delayed care. This resulted in stage in migration for breast and cervical cancers, a 4.5% increase all-cause mortality in 2020 relative to 2019, and a net increase in age-adjusted incidence rates for female cancers of 13.8% relative to cancers overall.

Lockdowns resulted in considerable disruption to cancer care with devastating outcomes for female cancers. With the pandemic behind us, it is now time to consider whether public health measures achieved their purpose, and to propose ways to improve decision-making moving forward.

Were Cancer Patients Protected from COVID-19?

COVID-19 Risk

The aggressive, community-wide public health measures were implemented to slow the spread of SARS-CoV-2,¹³ to protect vulnerable populations and preserve healthcare capacity.¹⁴⁵ To determine whether cancer patients were protected from COVID-19, we must first characterize their risk of infection and severe complication.

PHAC acted as Canada's contact for WHO-coordinated surveillance^{13,246} and worked with provinces and territories to create a national COVID-19 surveillance system to track viral infection rates and spread in Canada. The Canadian system aligned with WHO-specified case definitions, tests and testing protocols. The PCR test was the preferred test for COVID-19 due to its high technical accuracy when administered by a qualified professional and high levels of diagnostic sensitivity and specificity (90% to 95%). Surveillance consisted of tracking and reporting confirmed cases, defined simply as a positive approved COVID-19 test result.

Testing protocols changed over time beginning with PCR use as a diagnostic tool in those with COVID-19 symptoms and then shifting to use as screening tool in those without symptoms and at risk of COVID-19.251 In the early months of the pandemic, PCR tests were primarily used as a diagnostic tools^{249,252} but their use as a screening tool broadened considerably as the definition of those at risk for COVID-19 expanded (Table 4).^{251,253} With this increased use as a screening tool, sampling and handling moved from the hands of qualified professionals to less qualified professionals. By the summer of 2020, provincial public health officials documented concern regarding PCR testing accuracy noting a 20% (range 10-30%) false negative rate, likely due improper sampling and handling, and a high clinical false-positivity rate, reflected in patients testing positive for up to 82 days post symptom resolution.²⁵⁴ A study assessing duration of infectivity using viral culture found low infectivity levels in PCR-detected COVID-19 cases run at CT>24 cycles or with symptom duration >8 days.²⁴⁷ In immunocompromised patients, the window of infectivity may extend to more than 14 days.²⁵⁵ National guidance on the PCR test initially stated that interpretation of results was complicated by detection of non-infectious material (October 7, 2020)²⁵⁶ and later that PCR tests cannot distinguish between infectious or recovered, non-infectious individuals (June 11, 2021).²⁵⁷ However, rather than reverting back to use as a diagnostic tool to improve accuracy,²⁵⁸ their use as a screening tool expanded but now with a 90-day screening exemptions were offered to confirmed cases who had recovered from COVID-19.247,254 It is unclear how effective this exemption was as seroprevalence studies in 2020, showed that the number of COVID-19

infections was up to 9.3x greater than the monthly reported cases.²⁵⁹ It is notable that the surge in cases in the fall of 2020 coincided with the expanded use of PCR tests as screening tools (3,000 cases vs 20,941 cases, Table 4).^{251,260}

In early 2021, point-of-care testing became common place. The PanBio™ rapid antigen test (RAT) package insert states that the test is for diagnostic purposes and "is not intended to be used as a donor screening test for SARS-CoV-2".²6¹ However, some experts felt that RATs "have shown adequate sensitivity in identifying cases of infection with higher viral loads and can be used to good effect in screening programs", although no supporting data was provided.²6² Therefore use of RATs as a screening tool expanded greatly especially in high-risk settings in early 2021²6³ and then for the general public toward the end of 2021.²6⁴ The definition of a confirmed case was expanded to include a positive RAT tests performed through an Occupational Health and Safety program or by trained professionals on January 2021²6³ and subsequently further expanded to positive tests performed "at home" and other settings on February 2022.²6⁵ Use of PCR and RAT tests as screening tools in the absence of robust clinical evidence supporting their clinical accuracy raises significant questions as to the reliability of case-based COVID-19 data.

Table 4: Overview of Alberta testing policy and hospital capacity Wave 1 through 3 of the COVID-19 pandemic.

	Collection	Test	Population	Cases	Case Fatality Rate
China-based projections February, 2020 ^{1,2,260}	NR	Lab-based PCR	Symptomatic and asymptomatic travelers	15,000	3.8% overall ^{1,}
Wave 1, AB March ²⁶⁶ to April 2020 ²⁵³	Health care professional	Lab-based PCR	Symptomatic and asymptomatic travelers	3,000	
Interim, AB May ²⁶⁷ to August	Health care professional	Lab-based PCR	Symptomatic and asymptomatic in high-risk settings	NA	
2020 ²⁵⁴	Aug 2020 ²⁵⁴ , Clinical sensitivity issues detected • 20% false negative rate in symptomatic patients				

	High rates of clinical false positives with patients testing positive up to 82 days post symptom resolution					
Wave 2, AB Early October 2020 ²⁵⁴ to January 2021 ²⁵¹	Non- professional	asymptomatic in 20 941				
Wave 3, AB November 2021 ²⁶⁴ to February 2022 ²⁶⁵	Non- professional	RAT	Wide-scale asymptomatic screening	25,159		

COVID-19 Severity & Mortality

A COVID-19 hospitalization or death was defined by WHO as a hospitalized or dead person who has tested positive for COVID-19 including probable deaths from COVID-19 as well as deaths from clinically compatible illnesses. ^{266,269} Early case severity rates for COVID-19 were high (13.8% of cases would require hospitalization and 6.1% critical care) as were initial CFR rates (3.8%). CFR rates varied across regions between 5.8% for the epidemic epicenter in Wuhan and 0.7% for other cities. A CFR of 21.9% was assigned to those over 80 years and a CFR of 7.6% to cancer patients. By the spring of 2020, studies from China and the US indicated that 20% to 40% of cancer patients would require hospitalization. ²⁷⁰⁻²⁷³

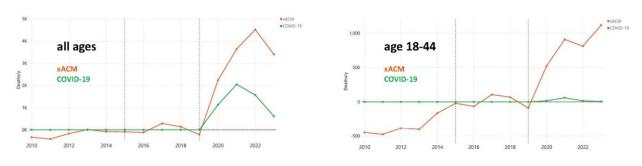
By the fall of 2020, a review of seroprevalence trials, most of which were conducted in pandemic epicentres, estimated a much lower COVID-19 infection fatality rate (median of 0.27%).²⁶⁸ Ontario registry data also reported that age-standardized COVID-19 hospitalization rates among cancer patients in 2020 to 2021 were only twice that of the general population and indicated that hospitalizations may not necessarily have been due to COVID-19.⁵⁵ It is notable that cancer patients are generally hospitalized 2–5 times more often than the general population, raising questions regarding true COVID-19 risk.^{274,275} Determining infection risk levels for cancer patients with COVID-19 is challenging due to primarily case-based severity estimates, though these risks are likely lower than initially projected.²⁷⁰⁻²⁷³

Excess All-cause Death

In the absence of reliable epidemiological data on COVID-19 complications, excess all-cause mortality can be a helpful measure of health impact. Excess mortality is calculated by calculating the difference between actual deaths and the deaths that would have been expected

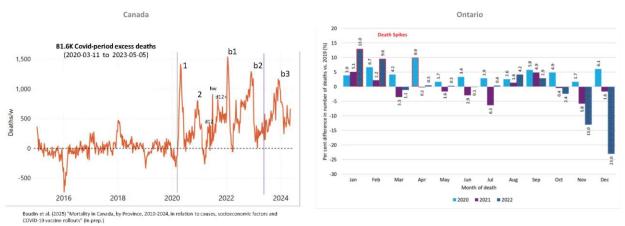
based on trends from previous. An analysis of annual excess all-cause mortality in Alberta from 2015 to 2024 (Figure 13) showed that excess all-cause mortality for all ages greatly exceeded COVID-19 deaths. The difference between excess deaths and COVID-19-associated deaths was particularly pronounced among those aged 18 to 44 years. This raises questions regarding the proportionality of public health measures overall but especially among younger individuals.

Figure 13: Excess all-cause mortality by year in Alberta from 2010 to 2024²⁷⁶



A second Canadian analysis of excess all-cause mortality of the general population from 2015 to 2024 found peaks in excess death coinciding with the first and second lockdowns and excess death peaks with the rollout of the boosters (Figure 14).²⁷⁶ Similar peaks in all-cause mortality were reported among cancer patients from 2020 to 2022.⁵⁵ The first peak was seen in April 2020 (9.9%) coinciding with the start of lockdowns and the second in the first two months of 2022 (13.0% and 9.6%) coinciding with the arrival of the Omicron variant²⁷⁷ and the rollout of COVID-19 boosters in elderly populations.²⁷⁸

Figure 14: Excess all-cause mortality by week from 2015 to 2024 in Canada²⁷⁶ and excess all-cause mortality by month among cancer patients from 2020 to 2022 in Ontario⁵⁵



While the clinical safety testing of COVID-19 boosters in the elderly was limited prior to rollout (<20 participants each trial) $^{279-281}$ and real-world safety estimates that rely on passive surveillance may underrepresent harm, 282,283 questions remain regarding the safety of boosters in this population. Two population-based studies have recently investigated the link between all-cause mortality and COVID-19 vaccine rollout. 243 The first, utilizing data from United Kingdom Office for National Statistics, found an increase in all-cause death standardized mortality ratios over time in vaccinated individuals compared to unvaccinated individuals. 243 The second study, followed 296,015 residents of the Pescara province, Italy from June 2021 (six months after the first vaccination) to December 2023. 242 This study found that unvaccinated individuals were markedly younger than vaccinated individuals. It also found that among those who had not previously been infected, all-cause death was much lower among those who had received at least ≥ 1 dose (adjusted HR 0.42; 95% CI: 0.39-0.44, p<0.001) or at ≥ 3 doses (adjusted HR 0.65; 95% CI: 0.62-0.67, p<0.001) compared to the unvaccinated. Emerging evidence suggests a potential association between all-cause mortality and COVID-19 vaccination, warranting further investigation.

As a WHO member-state, Canada contributed to COVID-19 surveillance following WHO guidance on tests, definitions of cases and testing protocols. By the summer of 2020, public health officials recognized that the PCR test lacked clinical accuracy. Given the use of COVID-19 tests as screening tools, the reliability of case-based COVID-19 data is questionable. It is therefore difficult to gauge the level of COVID-19 risk among cancer patients. Rates of excess all-cause mortality far exceeded rates of COVID-19 deaths in the province of Alberta and spikes in all-cause mortality among cancer patients coincided with implementation of the first lockdown and booster deployment in early 2022. Emerging evidence suggests a potential association between all-cause mortality and COVID-19 vaccination, warranting further investigation.

Was Hospital Capacity Preserved?

Cancer Care Capacity

Lockdowns were implemented to preserve hospital capacity.²⁸⁴ However, our review of cancer care in Ontario showed that lockdowns undermined every aspect of cancer care resulting in delays in cancer detection, diagnosis and treatment relative to 2019.²⁷ Cancer was left growing and spreading in the bodies of women for longer. This resulted in increases in new cancers, stage migration, and higher rates of all-cause mortality relative to 2019. Overall lockdowns had a devastating effect on cancer care and female cancer outcomes.

Acute Care Capacity

Details on the benefits of lockdowns as it relates to preserving acute care capacity are limited for Ontario but available through the Alberta COVID-19 Task Force Report²⁵¹ and the affidavit of Deborah Gordon, Vice-President of Clinical Operations at Alberta Health Services (AHS).²⁶⁰ It is likely that the measures taken by Ontario's to ensure acute care capacity were similar to those undertaken by Alberta, as public health responses in Canada were coordinated through the Council of Chief Medical Officers of Health to Federal, Provincial, and Territorial Ministers of Health²⁸⁵ and followed public health policy guidance provided by the Council of Chief Medical Officers of Health to Federal, Provincial, and Territorial Ministers of Health.²⁸⁶

According to the vice-president of clinical operations in Alberta,²⁶⁰ healthcare capacity needs were projected by the AHS Data and Analytics teams using statistical models and public health factors. Initial statistical models were informed by case-based data from China, Italy and France drawing on real-world case-based data from the Alberta COVID-19 Surveillance Dashboard. The AHS Emergency Coordination Centre (ECC), composed of AHS leadership, who were responsible for creating an Acute Care Capacity Plan. For each wave, the ECC forecasted COVID-19 cases and estimated inpatient hospital capacity needs in anticipation of the approaching wave of COVID-19 patients.

Figure 15 summarizes the number of COVID-19 beds allocated based on AHS projections for the first three COVID-19 waves. Wave 1 forecasts used data from China and predicted 15,000 COVID-19 cases, with an estimated 15% hospitalization rate and a 5% ICU admission rate. To ensure surge capacity, surgical capacity was reduced by 60% and 2,225 hospital beds and 325 ICU beds were reserved for potential COVID-19 patients. However, in Wave 1 hospital bed utilization peaked at only 75 beds and ICU admissions at 22 beds, leaving >95% of beds reserved for potential COVID-19 patients empty. Similar estimates were made for Waves 2 and 3 this time using case-based surveillance data from Alberta. Although projections proved slightly more accurate, less than half of the surge hospital beds (≤41%) and ICU beds (≤44%) were used in waves 2 and 3.

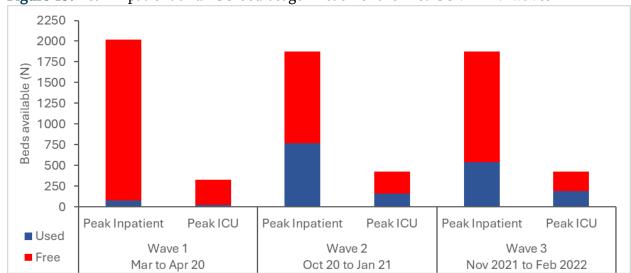


Figure 15: Peak inpatient and ICU bed usage in each of the first COVID-19 waves²⁶⁰

Accurate forecasting presents a significant challenge, as both underlying data and assumptions must be precise to yield reliable estimates. Alberta's projections, which relied on case-based data, failed to accurately estimate surge capacity needs. During wave 1 alone, 40,000 surgeries in Alberta were postponed or rescheduled, resulting in an increase in both the number of patients awaiting surgery and extended wait times.²⁶⁰ Although wave 1 surgeries were successfully rebooked by AHS as of the spring of 2021, wave 2 and 3 waitlists were more difficult to reschedule leaving patients waiting life-saving care longer. Lockdowns and the associated suspension in non-emergent services devastated cancer care and squandered life-saving hospital capacity.

This review of Alberta hospital capacity showed that case-based data was unreliable in predicting surge capacity and that life-saving hospital capacity was squandered on largely empty acute care wards. Lockdowns and the associated suspensions of non-emergent services diverted resources away from cancer care system leaving cancer growing and spreading in the bodies of cancer patients for longer.

We Can Do Better

An Ethical Imperative

The ethical principles that govern public health in Ontario include the principles of justice and minimizing harm. Justice entails treating all persons and groups fairly and equitably, with equal concern and respect, and involves minimizing or eliminating inequities in opportunities to preserve health and well-being. Minimizing harm involves an obligation to avoid causing undue harm and, given that some harm is likely unavoidable, to minimize risk of harm and to reduce suffering. COVID-19 policies, were implemented to protect the vulnerable and preserve health care capacity.¹⁴⁵

Guidance on allocation of limited resources over the course of the pandemic was guided by these ethical principles and care for patients with need and efficacy of treatment were to be prioritised.⁶⁷ Cancer is six times more deadly than COVID-19 and effective well-established treatment protocols exist for all stages of cancer.⁵⁵ And yet, over the COVID-19 period, lockdowns were implemented to slow the spread of the virus and prevent potential COVID-19 complications before the threat of the virus was well-characterized.¹ Beds that were necessary for providing life-saving care for cancer patients were diverted to acute care wards.²⁶⁰ This co-option of resources away from real cancer patients toward potential COVID-19 patients was unjust, avoidable, and exposed them to undue harm.¹⁴⁵ An affront that is particularly egregious, given that the infection fatality rate of COVID-19 had been established at <1% with little to no risk among those younger than 75 years in the fall of 2020.^{1,268} Trust is integral to the proper functioning of public health and relies on officials acting in an ethical and transparent manner.²⁸⁷ There is therefore an urgent need to remedy the disparities in care that arose during COVID-19 and ensure that systems are put in place to avoid these types of disparities moving forward.

Pandemic Decision-Making Revisited

Clinical guidelines evolve incrementally, with major changes driven by systematic review of randomized controlled trials (RCTs) and other high-quality evidence, followed by consensus among international experts. The rapid pace of the COVID-19 pandemic precluded traditional approaches to evaluating clinical research and guidelines. Often times clinicians and policy makers had limited evidence to guide decision making requiring adaption of previous evidence-based guidance. According to the WHO, lockdowns were adopted

globally based on low quality evidence consisting primarily of anecdotal reports of success in China.¹ Public Health guidance documents in Alberta confirm this stating that lockdowns were "based on current available scientific evidence and expert opinion and were subject to change as new information on transmissibility and epidemiology becomes available."266 In time, COVID-19 dashboards, that tracked cases by jurisdiction became an integral tool for guiding decision-making.²⁵¹ Reductions in case counts following lockdown implementation were often interpreted as a sign of effectiveness which fueled continued use.²⁵¹ Reliable infection-based data and data reflecting the collateral damage of lockdowns did not factor into regular decision-making.⁷⁵ For future pandemics, reliable-methods of collecting and monitoring infection-based data and formal mechanisms of collecting and reviewing data on harm related to public health measures will be integral to good decision-making. The complexity of this task underscores the need for shared-decision making to ensure that the well-being of all patients are considered. There is an urgent need to right the harm done to women by investigating the rise of female cancers as well as ensure that future pandemic planning moves out of silos toward shared decision-making that empowers teams of clinical experts to weigh reliable evidence and shape policy that balances the needs of all patients.

The ethical principles that govern public health in Ontario include the principles of justice and minimizing harm. Resource allocation over the pandemic period was to prioritize care for patients with need and efficacy of treatment. Cancer is at least six times more deadly than COVID-19. And yet over the course of the pandemic, precious cancer care resources were diverted away from patients and allocated to acute care wards where previous beds lay largely empty. The prioritization of potential COVID-19 patients over real cancer patients robbed cancer patients of the opportunity to preserve their well-being, exposed them to avoidable harm, as well as undue suffering and even death. There is an urgent need to avoid this type of discrimination moving forward.

We can do better. For future pandemics we need to improve-decision making by monitoring infection-based data as well as the harm arising from public health measures. The complexity of this task underscores the need for shared-decision making to ensure that the well-being of all patients are considered. There is an urgent need to right the harm done to women by investigating the rise of female cancers as well as ensure that future pandemic planning moves out of silos toward shared decision-making that empowers teams of clinical experts to weigh reliable evidence and shape policy that balances the needs of all patients.

References

- 1. WHO-China Joint Mission. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). 2020. (Accessed May 5, 2025, at https://www.who.int/publications/i/item/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)).
- 2. WHO-China Joint Mission. Press Conference of WHO-China Joint Mission on COVID-19. World Health Organization,, 2020. (Accessed May 5, 2025, at https://www.who.int/docs/default-source/coronaviruse/transcripts/joint-mission-press-conference-script-english-final.pdf?sfvrsn=51c90b9e 10).
- 3. Government of Canada. Quarantine Act. 2005. (Accessed September 17, 2025, at https://laws-lois.justice.gc.ca/eng/acts/q-1.1/page-1.html).
- 4. Government of Alberta. Public Health Act. 2000. (Accessed May 5, 2025, at https://kings-printer.alberta.ca/1266.cfm?page=P37.cfm&leg_type=Acts&isbncln=9780779855506).
- 5. Ontario Ministry of Health. COVID-19 Fully Vaccinated and Previously Positive Individuals: Case, Contact and Outbreak Management Interim Guidance. 2021.
- 6. Public Health Agency of Canada. Public Health Agency of Canada's COVID-19 Response: Lessons Learned. 2023. (Accessed September 10, 2025, at https://www.canada.ca/en/public-health/corporate/transparency/corporate-management-reporting/evaluation/covid-19-response-lessons-learned-summary.html#a3.4).
- 7. Pan Amarican Health Organization (PAHO). Timeline of WHO's Response to COVID-19. July 2, 2020. (Accessed June 1, 2025, at https://www.paho.org/en/news/2-7-2020-timeline-whos-response-covid-19).
- 8. Keng S, Zhong L, Xie F. Why Did China's Zero-COVID Policy Persist? Decision Urgency, Regime Type, and Political Opportunity Structures. Journal of Contemporary China 2024;33:206-22.
- 9. World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). 2020. (Accessed May 5, 2025, at https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)).
- 10. World Health Organization. Responding to community spread of COVID-19: interim guidance, 7 March 2020. World Health Organization. 2020. (Accessed October 1, 2025, at https://www.who.int/publications/i/item/responding-to-community-spread-of-covid-19).
- 11. World Health Organization. Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza. 2019. (Accessed May 5, 2025, at https://iris.who.int/bitstream/handle/10665/329438/9789241516839-eng.pdf).
- 12. Ontario Health. Ethical framework for COVID-19 vaccine distribution. (Accessed May 5, 2025, at https://www.ontario.ca/page/ethical-framework-covid-19-vaccine-distribution).

- 13. Government of Canada. Canada and the International Health Regulations (IHR): Overview. 2024. (Accessed May 5, 2025, at https://www.canada.ca/en/public-health/services/emergency-preparedness-response/international-health-regulations.html).
- 14. Filip R, Gheorghita Puscaselu R, Anchidin-Norocel L, Dimian M, Savage WK. Global Challenges to Public Health Care Systems during the COVID-19 Pandemic: A Review of Pandemic Measures and Problems. J Pers Med 2022;12.
- 15. Ontario Government n. Enhanced Measures to Protect Ontarians from COVID-19. May 16, 2020. (Accessed May 10, 2025, at https://news.ontario.ca/en/statement/56348/enhanced-measures-to-protect-ontarians-from-covid-19).
- 16. Porat T, Nyrup R, Calvo RA, Paudyal P, Ford E. Public Health and Risk Communication During COVID-19-Enhancing Psychological Needs to Promote Sustainable Behavior Change. Front Public Health 2020;8:573397.
- 17. Trevena L. Assessing, communicating, and managing risk in general practice. Br J Gen Pract 2014;64:166-7.
- 18. Oh KB, Doherty TM, Vetter V, Bonanni P. Lifting non-pharmaceutical interventions following the COVID-19 pandemic the quiet before the storm? Expert Rev Vaccines 2022;21:1541-53.
- 19. Government of Ontario. Emergency Management and Civil Protection Act, R.S.O. 1990, c. E.9. 2019. (Accessed May 5, 2025, at https://www.ontario.ca/laws/statute/90e09/v9).
- 20. Government of Ontario. Report on Ontario's Provincial Emergency from March 17, 2020 to July 24, 2020. 2020. (Accessed May 5, 2025, at https://www.ontario.ca/document/report-ontarios-provincial-emergency-march-17-2020-july-24-2020).
- 21. Ontario Health Newsroom. Ontario Enacts Declaration of Emergency to Protect the Public. March 17, 2020. (Accessed September 10, 2025, at https://news.ontario.ca/en/release/56356/ontario-enacts-declaration-of-emergency-to-protect-the-public).
- 22. Government of Ontario. Ontario Takes Further Action to Stop the Spread of COVID-19. 2020. (Accessed October 1, 2025, at https://news.ontario.ca/en/release/56642/ontario-takes-further-action-to-stop-the-spread-of-covid-19).
- 23. Ontario Chief Medical Officer of Health. Directive #1 for Health Care providers and Health Care Facilities; PPE & Social Distancing. March 12, 2020. (Accessed September 10, 2025, at https://www.corhealthontario.ca/CMOH-Directive1-Health-Care-Proviers-HPPA-03-30-2020-Shared.pdf).
- 24. Government of Ontario Minister of Health. COVID-19 Operational Requirements: Health Sector Restart 2020 (Accessed May 5, 2025, at https://www.cmto.com/wp-content/uploads/2021/11/operational_requirements_health_sector.pdf).
- 25. Ontario Chief Medical Officer of Health. Directive #2 for Health Care Providers (Regulated Health Professionals or Persons who operate a Group Practice of Regulated Health Professionals) March 19, 2020. (Accessed September 10, 2025, at

- https://www.ctcmpao.on.ca/resources/CMOH_Directive_2-RHPA_professionals_2020-03-19.pdf).
- 26. Government of Ontario. Ontario Hospitals Asked to Take a Planned Approach to Ramping Down Elective Surgeries. 2020. (Accessed May 5, 2025, at https://news.ontario.ca/en/statement/56328/ontario-hospitals-asked-to-take-a-planned-approach-to-ramping-down-elective-surgeries).
- 27. Ontario Health Cancer Quality Council of Ontario. Onset of the COVID-19 Pandemic and its Impact on the Ontario Cancer System. 2021. (Accessed September 7, 2025, at https://www.ontariohealth.ca/news/covid-19-impact-cancer-system).
- 28. Ontario Chief Medical Officer of Health. Directive #2 for Health Care Providers (Regulated Health Professionals or Persons who operate a Group Practice of Regulated Health Professionals) May 26, 2020 Update. 2020. (Accessed September 10, 2025, at https://cono.wpengine.com/wp-content/uploads/2020/11/Directive-2-May-26-2020.pdf).
- 29. Ontario Health Office of Chief Medical Officer of Health. RE: Revocation of Chief Medical Officer of Health Directive #2 and the Resumption of non-urgent and non-emergent surgeries and procedures. 2021. (Accessed September 17, 2025, at https://collegept.org/wp-content/uploads/2021/05/moh_revocation_directive2.pdf).
- 30. Ontario Chief Medical Officer of Health. Directive #2 for Health Care Providers (Regulated Health Professionals or Persons who operate a Group Practice of Regulated Health Professionals) January 5, 2022 Update. 2022. at http://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/directives/directive-2.pdf).
- 31. Ontario Chief Medical Officer of Health. Directive #2.1 for hospitals within the meaning of the Public Hospitals Act, private hospitals within the meaning of the Private Hospitals Act, psychiatric facilities within the meaning of the Mental Health Act and regulated health professionals who practice within them (Health System Coordination re: Transfers). 2022. Hospital Patient (Accessed September 10. 2025, at https://www.afhto.ca/sites/default/files/documents/2022-02/cmoh_directive_2.1health care providers-system coordination-v3 feb 9 2022 final aoda en.pdf).
- 32. Ontario Chief Medical Officer of Health. Revocation of CMOH Directives #1, #2.1, #3, #4, and #5 June 10, 2022. (Accessed September 10, 2025, at https://www.cmrito.org/pdfs/covid/cmoh-memo-06-10-22.pdf).
- 33. CNN. China lifts 76-day lockdown on Wuhan as city reemerges from coronavirus crisis. 2020. (Accessed October 1, 2025, at https://www.cnn.com/2020/04/07/asia/coronavirus-wuhan-lockdown-lifted-intl-hnk).
- 34. Max Matza NY. FBI chief Christopher Wray says China lab leak most likely. 1 March 2023. (Accessed May 5, 2025, at https://www.bbc.com/news/world-us-canada-64806903).
- 35. Barnes J. Lab leak most likely caused pandemic, Energy Department Says. The New York Times February 26, 2023.
- 36. US Oversight Comittee. COVID Origins Hearing Wrap Up: Facts, Science, Evidence Point to a Wuhan Lab Leak. 2023. (Accessed May 5, 2025, at https://oversight.house.gov/release/covid-origins-hearing-wrap-up-facts-science-evidence-point-to-a-wuhan-lab-leak%EF%BF%BC/).
- 37. Berche P. Gain-of-function and origin of Covid19. Presse Med 2023;52:104167.

- 38. Honderich H. CIA says lab leak most likely source of Covid outbreak. 2025. (Accessed October 5, 2025, at https://www.bbc.com/news/articles/cd9qjjj4zy50).
- 39. Slaoui M, Hepburn M. Developing Safe and Effective Covid Vaccines Operation Warp Speed's Strategy and Approach. N Engl J Med 2020;383:1701-3.
- 40. Government of Ontario. Ontario Begins Rollout of COVID-19 Vaccine. 2020. (Accessed May 5, 2025, at https://news.ontario.ca/en/release/59607/ontario-begins-rollout-of-covid-19-vaccine).
- 41. AlShurman BA, Tetui M, Nanyonjo A, et al. Understanding the COVID-19 Vaccine Policy Terrain in Ontario Canada: A Policy Analysis of the Actors, Content, Processes, and Context. Vaccines (Basel) 2023;11.
- 42. Canadian Institute for Health Information. Canadian COVID-19 Intervention Timeline. 2022. (Accessed May 17, 2024, at https://www.cihi.ca/en/canadian-covid-19-intervention-timeline).
- 43. Ontario Chief Medical Officer of Health. Directive #3 for Long-Term Care Homes under the LongTerm Care Homes Act, 2007 2021. (Accessed September 10, 2025, at https://pub-northumberland.escribemeetings.com/filestream.ashx?DocumentId=52).
- 44. Government of Canada. COVID-19 vaccination in Canada. 2022. (Accessed Spetember 17, 2025, at https://health-infobase.canada.ca/covid-19/vaccination-coverage/).
- 45. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: An overview. J Chin Med Assoc 2020;83:217-20.
- 46. Xu W, Wu J, Cao L. COVID-19 pandemic in China: Context, experience and lessons. Health Policy Technol 2020;9:639-48.
- 47. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 11 March 2020. 2020. (Accessed September 17, 2025, at https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020).
- 48. Detsky AS, Bogoch II. COVID-19 in Canada—The Fourth Through Seventh Waves. JAMA Health Forum 2022;3:e224160-e.
- 49. Statistics Canada. Canada at a Glance, 2022 Impacts of COVID-19. 2022. (Accessed October 4, 2025, at https://www150.statcan.gc.ca/n1/pub/12-581-x/2022001/sec14-eng.htm).
- 50. Brown PE, Fu SH, Bansal A, et al. Omicron BA.1/1.1 SARS-CoV-2 Infection among Vaccinated Canadian Adults. New England Journal of Medicine 2022;386:2337-9.
- 51. COVID-19 Immunity Task Force. The Omicron tsunami: Analysis of data from blood testing suggests over 17 million Canadians were infected with Omicron in only 5 months. 2022. (Accessed October 4, 2025, at https://www.covid19immunitytaskforce.ca/the-omicron-tsunami-analysis-of-data-from-blood-testing-suggests-over-17-million-canadians-were-infected-with-omicron-in-only-5-months/).
- 52. BBC News. China Covid: The politics driving the hellish lockdowns. 2022. (Accessed October 1, 2025, at https://www.bbc.com/news/world-asia-china-63310524).
- 53. Comartin M, Ilunga G. Ontario Provides Timeline to Lift All COVID-19–Related Restrictions. natlawreview.com, 2022. (Accessed October 1, 2025, at

- https://natlawreview.com/article/ontario-provides-timeline-to-lift-all-covid-19-related-restrictions).
- 54. Gan N. Zero-Covid was supposed to prove China's supremacy. How did it all go so wrong for Xi Jinping? CNN.com, 2022. (Accessed October 4, 2025, at https://edition.cnn.com/2022/12/27/china/china-2022-zero-covid-intl-hnk-mic).
- 55. Ontario Health Cancer Care Ontario. Ontario Cancer Statistics 2024. 2024. (Accessed July 2025, 2024, at https://www.cancercareontario.ca/sites/ccocancercare/files/assets/OCS2024.pdf).
- 56. Ontario Health Cancer Care Ontario. Ontario Cancer Statistics 2022 Ch 7: Cancer Prevalence. 2022. (Accessed December 17, 2024, at https://www.cancercareontario.ca/en/data-research/view-data/statistical-reports/ontario-cancer-statistics-2022/ch-7-cancer-prevalence-2022).
- 57. Murphy L, Markey K, C OD, Moloney M, Doody O. The impact of the COVID-19 pandemic and its related restrictions on people with pre-existent mental health conditions: A scoping review. Arch Psychiatr Nurs 2021;35:375-94.
- 58. Legislative Assembly of Canada Legislative Branch. Women on the Frontlines inOntario's Fight Against COVID-19. October 2021. (Accessed 2025, May 10, at https://www.ola.org/sites/default/files/node-files/llrs/document/pdf/2022/2022-07/Women%20on%20the%20Frontlines%20in%20Ontarios%20Fight%20Against%20COVID-19%20RP%2021-01.pdf).
- 59. Ontario Health. Guidance for Ontario Breast Screening Program (OBSP) Sites Adenopathy Related to Vaccination (Updated 2022-01-28). 2022. (Accessed September 17, 2025, at https://www.cancercareontario.ca/sites/ccocancercare/files/assets/AdenopathyAndScreeningGuidanceForOBSPSites.pdf).
- 60. Blix K, Laake I, Juvet L, *et al.* Unexpected vaginal bleeding and COVID-19 vaccination in nonmenstruating women. Sci Adv 2023;9:eadg1391.
- 61. Hippisley-Cox J, Coupland C. Symptoms and risk factors to identify women with suspected cancer in primary care: derivation and validation of an algorithm. Br J Gen Pract 2013;63:e11-21.
- 62. Wang S, Quan L, Chavarro JE, *et al.* Associations of Depression, Anxiety, Worry, Perceived Stress, and Loneliness Prior to Infection With Risk of Post–COVID-19 Conditions. JAMA Psychiatry 2022;79:1081-91.
- 63. de Joode K, Dumoulin DW, Engelen V, et al. Impact of the coronavirus disease 2019 pandemic on cancer treatment: the patients' perspective. Eur J Cancer 2020;136:132-9.
- 64. Gulati S, Muddasani R, Gustavo Bergerot P, Pal SK. Systemic therapy and COVID19: Immunotherapy and chemotherapy. Urol Oncol 2021;39:213-20.
- 65. Ontario Health Cancer Care Ontario. About us. 2025. (Accessed September 17, 2025, at https://www.cancercareontario.ca/en/cancer-care-ontario/about-us).
- 66. Ontario Health Cancer Care Ontario. Ontario Cancer Plan 6 (2024 to 2028). 2024. (Accessed September 17, 2025, at https://www.cancercareontario.ca/en/cancerplan#:~:text=The%20Ontario%20Cancer%20Plan%206,for%20the%20people%20of%20Ontario).

- 67. Ontario Health Cancer Care Ontario. Pandemic Planning Clinical Guideline for Patients with Cancer. 2020. (Accessed September 10, 2025, at https://www.accc-cancer.org/docs/documents/cancer-program-fundamentals/oh-cco-pandemic-planning-clinical-guideline final 2020-03-10.pdf).
- 68. Ontario Health Cancer Care Ontario. COVID-19 Supplemental Clinical Guidance for Patients with Cancer. 2021. (Accessed September 17, 2025, at https://www.cancercareontario.ca/sites/ccocancercare/files/derivative/PandemicPlanningSupplementalGuidanceCancer.pdf).
- 69. Canadian Institute for Health Information Wait Times for Priority Procedures in Canada. 2022. (Accessed May 8, 2025, at https://www.cihi.ca/en/wait-times-for-priority-procedures-in-canada-2022).
- 70. Ontario Ministry of Health. Diagnostic Codes Ontario Health Insurance Plan. 2023. (Accessed Januaray 28, 2025, at https://files.ontario.ca/moh-diagnostic-codes-en-2023-09-01.pdf).
- 71. Ontario Health Cancer Care Ontario. Ontario Cancer Registry. 2025. (Accessed September 17, 2025, at https://www.cancercareontario.ca/en/cancer-care-ontario/programs/data-research/ontario-cancer-registry).
- 72. Richard E G, M.D, Michelle B. Leavy, Nancy A. Dreyer. Chapter 13 Analysis, Interpretation, and Reporting of Registry Data To Evaluate Outcomes. Agency for Healthcare Research and Quality (US) 2020.
- 73. Penberthy LT, Rivera DR, Lund JL, Bruno MA, Meyer AM. An overview of real-world data sources for oncology and considerations for research. CA Cancer J Clin 2022;72:287-300.
- 74. Savage RD, Rosella LC, Crowcroft NS, Horn M, Khan K, Varia M. Accuracy of health administrative data to identify cases of reportable travel or migration-related infectious diseases in Ontario, Canada. PLoS One 2018;13:e0207030.
- 75. McLeod D, Martins I, Tinker AV, et al. Changes in female cancer diagnostic billing rates over the COVID-19 period in the Ontario Health Insurance Plan. Ther Adv Med Oncol 2025;17:17588359251339919.
- 76. Ontario Health Cancer Care Ontario. Screening Programs. 2024. (Accessed July 25, 2024, at https://www.cancercareontario.ca/en/cancer-care-ontario/programs/screening-programs).
- 77. Government of Canada. Original quantitative research Breast cancer detection method, diagnostic interval and use of specialized diagnostic assessment units across Ontario, Canada. 2011. (Accessed June 5, 2025, at https://www.canada.ca/en/public-health/services/reports-publications/health-promotion-chronic-disease-prevention-canada-research-policy-practice/vol-38-no-10-2018/breast-cancer-detection-method-diagnostic-interval-specialized-diagnostic-assessment-units.html).
- 78. Ontario Health. Ontario Cancer Screening Performance Report 2023. 2024. (Accessed July 25, 2024, at https://www.cancercareontario.ca/sites/ccocancercare/files/assets/OCSPRfullReport.pd f).

- 79. Chiarelli AM, Walker MJ, Espino-Hernandez G, et al. Adherence to guidance for prioritizing higher risk groups for breast cancer screening during the COVID-19 pandemic in the Ontario Breast Screening Program: a descriptive study. CMAJ Open 2021;9:E1205-e12.
- 80. Walker MJ, Meggetto O, Gao J, et al. Measuring the impact of the COVID-19 pandemic on organized cancer screening and diagnostic follow-up care in Ontario, Canada: A provincial, population-based study. Prev Med 2021;151:106586.
- 81. Government of Ontario Ontario Health. Ontario Releases Three-Step Roadmap to Safely Reopen the Province. 2021. (Accessed September 10, 2025, at https://news.ontario.ca/en/release/1000161/ontario-releases-three-step-roadmap-to-safely-reopen-the-province).
- 82. Ontario Health. Ontario Health Annual Report; 2023/2024. 2024. (Accessed May 5, 2025, at https://www.ontariohealth.ca/content/dam/ontariohealth/documents/annual-report-2023-24.pdf).
- 83. Thériault G. Screening backlogs: How to move forward. Can Fam Physician 2022;68:880-1.
- 84. Walker MJ, Wang J, Mazuryk J, et al. Delivery of Cancer Care in Ontario, Canada, During the First Year of the COVID-19 Pandemic. JAMA Netw Open 2022;5:e228855.
- 85. Meggetto O, Jembere N, Gao J, et al. The impact of the COVID-19 pandemic on the Ontario Cervical Screening Program, colposcopy and treatment services in Ontario, Canada: a population-based study. BJOG 2021;128:1503-10.
- 86. Schrager S, Burnside E. Breast Cancer Screening in Primary Care: A Call for Development and Validation of Patient-Oriented Shared Decision-Making Tools. J Womens Health (Larchmt) 2019;28:114-6.
- 87. Hargarten SW, Richards MJ, Anderson AJ. Cancer presentation in the emergency department: a failure of primary care. Am J Emerg Med 1992;10:290-3.
- 88. Starikov A, Askin G, Blackburn A, *et al.* Mode of detection matters: Differences in screen-detected versus symptomatic breast cancers. Clin Imaging 2021;80:11-5.
- 89. Dilley J, Burnell M, Gentry-Maharaj A, et al. Ovarian cancer symptoms, routes to diagnosis and survival Population cohort study in the 'no screen' arm of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Gynecol Oncol 2020;158:316-22.
- 90. Ontario Medical Association. Fact Sheet: Ontario's Doctor Shortage. 2024. (Accessed May 5, 2024, at https://www.oma.org/siteassets/oma/media/public/hcp-factsheet-doctor-shortage.pdf).
- 91. Science Table Covid Advisory for Ontario. Brief on Primary Care Part 1: The Roles of Primary Care Clinicians and Practices in the First Two Years of the COVID-19 Pandemic in Ontario. 2022. (Accessed May 5, 2025, at https://covid19-sciencebrief/brief-on-primary-care-part-1-the-roles-of-primary-care-clinicians-and-practices-in-the-first-two-years-of-the-covid-19-pandemic-in-ontario/).
- 92. Kiran T, Green ME, Strauss R, et al. Virtual Care and Emergency Department Use During the COVID-19 Pandemic Among Patients of Family Physicians in Ontario, Canada. JAMA Netw Open 2023;6:e239602.

- 93. McLeod D, Martins I. OHIP billing rates for menstrual disorders and post-menopausal bleeding; cumulative excess billing rates for female cancers during 2020-2022 relative to 2019. Data on record 2024.
- 94. Ontario Health Cancer Care Ontario. Guidance for Ontario Breast Screening Program (OBSP) Sites Adenopathy Related to Vaccination (Updated 2022-01-28). January 28, 2022. (Accessed May 10, 2025, at https://www.cancercareontario.ca/sites/ccocancercare/files/assets/AdenopathyAndScreeningGuidanceForOBSPSites.pdf).
- 95. Couzin-Frankel J. Thousands report unusual menstruation patterns after COVID-19 vaccination. 2022. (Accessed May 5, 2025, at https://www.science.org/content/article/thousands-report-unusual-menstruation-patterns-after-covid-19-vaccination).
- 96. Lee KMN, Junkins EJ, Luo C, Fatima UA, Cox ML, Clancy KBH. Investigating trends in those who experience menstrual bleeding changes after SARS-CoV-2 vaccination. Sci Adv 2022;8:eabm7201.
- 97. Brooks N, Irving SA, Kauffman TL, et al. Abnormal uterine bleeding diagnoses and care following COVID-19 vaccination. Am J Obstet Gynecol 2024;230:540.e1-.e13.
- 98. Kauffman TL, Irving SA, Brooks N, et al. Postmenopausal bleeding after COVID-19 vaccination. Am J Obstet Gynecol 2024;230:71.e1-.e14.
- 99. Ljung R, Xu Y, Sundström A, et al. Association between SARS-CoV-2 vaccination and healthcare contacts for menstrual disturbance and bleeding in women before and after menopause: nationwide, register based cohort study. BMJ 2023;381:e074778.
- 100. Alvergne A, Kountourides G, Argentieri MA, et al. A retrospective case-control study on menstrual cycle changes following COVID-19 vaccination and disease. iScience 2023;26:106401.
- 101. Botton J, Bertrand M, Jabagi MJ, et al. Risk of heavy menstrual bleeding following COVID-19 vaccination: A nationwide case-control study. Vaccine 2024;42:126252.
- 102. Trogstad L, Laake I, Robertson AH, et al. Heavy bleeding and other menstrual disturbances in young women after COVID-19 vaccination. Vaccine 2023;41:5271-82.
- 103. Fallatah NI, Alrehaili BO, Alsulami SS, Al-Zalabani AH. Menstrual Changes Following COVID-19 Vaccination: A Cross-Sectional Study. Medicina (Kaunas) 2024;60.
- 104. Caspersen IH, Juvet LK, Feiring B, et al. Menstrual disturbances in 12- to 15-year-old girls after one dose of COVID-19 Comirnaty vaccine: Population-based cohort study in Norway. Vaccine 2023;41:614-20.
- 105. Pastor-Goutherot L, Miralpeix E, Fabregó B, et al. COVID-19 vaccination and postmenopausal bleeding: a retrospective cohort study. Climacteric 2024;27:489-93.
- 106. Nazir M, Asghar S, Rathore MA, et al. Menstrual abnormalities after COVID-19 vaccines: A systematic review. Vacunas (English Edition) 2024;162:S77-S87.
- 107. Maybin JA, Watters M, Rowley B, Walker CA, Sharp GC, Alvergne A. COVID-19 and abnormal uterine bleeding: potential associations and mechanisms. Clin Sci (Lond) 2024;138:153-71.
- 108. Canadian Partnership Against Cancer. Diagnostic pathways and rapid referral services Models of Care Toolkit. 2025. (Accessed May 5, 2025, at

- https://www.partnershipagainstcancer.ca/topics/models-of-care/coordination-primary-care/diagnostic-pathways-rapid-referral-services/).
- 109. Ontario Health Cancer Care Ontario. Cancer Imaging Program. 2025. (Accessed May 5, 2025, at https://www.cancercareontario.ca/en/cancer-care-ontario/programs/clinical-services/cancer-imaging).
- 110. Ontario Health Cancer Care Ontario. Pathology & Laboratory Medicine Program. 2025. (Accessed May 5, 2025, at https://www.cancercareontario.ca/en/cancer-careontario/programs/clinical-services/pathology-laboratory-medicine).
- 111. Weir HK, Bryant H, Turner D, et al. Population-Based Cancer Survival in Canada and the United States by Socioeconomic Status: Findings from the CONCORD-2 Study. J Registry Manag 2022;49:23-33.
- 112. Malagón T, Yong JHE, Tope P, Miller WH, Jr., Franco EL. Predicted long-term impact of COVID-19 pandemic-related care delays on cancer mortality in Canada. Int J Cancer 2022;150:1244-54.
- 113. Ward ZJ, Walbaum M, Walbaum B, et al. Estimating the impact of the COVID-19 pandemic on diagnosis and survival of five cancers in Chile from 2020 to 2030: a simulation-based analysis. Lancet Oncol 2021;22:1427-37.
- 114. Guven DC, Sahin TK, Yildirim HC, et al. Newly diagnosed cancer and the COVID-19 pandemic: tumour stage migration and higher early mortality. BMJ Supportive & Palliative Care 2024;14:e456-e61.
- 115. Maringe C, Spicer J, Morris M, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. Lancet Oncol 2020;21:1023-34.
- 116. Sud A, Jones ME, Broggio J, et al. Collateral damage: the impact on outcomes from cancer surgery of the COVID-19 pandemic. Ann Oncol 2020;31:1065-74.
- 117. Ontario Health Cancer Care Ontario. Surgery. 2025. (Accessed May 5, 2025, at https://www.cancercareontario.ca/en/cancer-treatments/surgery).
- 118. Ontario Health Cancer Care Ontario. Surgical Oncology Program. 2025. (Accessed May 5, 2025, at https://www.cancercareontario.ca/en/cancer-care-ontario/programs/clinical-services/surgical-oncology-program).
- 119. Health Quality Ontario. Measuring wait times for other surgeries and procedures 2025. (Accessed May 5, 2025, at https://www.hqontario.ca/System-Performance/Measuring-Wait-Times-for-Other-Surgeries-and-Procedures).
- 120. Health Quality Ontario. MEASURING WAIT TIMES FOR CANCER SURGERIES. 2025. (Accessed Sept 9, 2025, at https://www.hqontario.ca/System-Performance/Measuring-Wait-Times-for-Cancer-Surgeries).
- 121. Financial Accountability Office of Ontario. Ontario Health Sector: Spending Plan Review. 2023. (Accessed May 5, 2025, at https://fao-on.org/wp-content/uploads/2024/08/Ontario-Health-Sector-Spending-Plan-Review-EN.pdf).
- 122. Fu R, Kamalraj P, Li Q, et al. The Changing Face of Cancer Surgery During Multiple Waves of COVID-19. JNCI Cancer Spectr 2022;6.
- 123. Jouen T, Gauthier T, Azais H, et al. The impact of the COVID-19 coronavirus pandemic on the surgical management of gynecological cancers: Analysis of the multicenter database

- of the French SCGP and the FRANCOGYN group. J Gynecol Obstet Hum Reprod 2021;50:102133.
- 124. Canadian Institute for Health Information. Surgeries impacted by COVID-19: An update on volumes and wait times. 2023. (Accessed September 11, 2024, at https://www.cihi.ca/en/surgeries-impacted-by-covid-19-an-update-on-volumes-and-wait-times).
- 125. Callan I, D'Mello C. Ontario sees 100K-plus waiting longer than recommended for surgery during pandemic. January 24, 2023. (Accessed May 5, 2025, at https://globalnews.ca/news/9329715/ontario-long-waiters-pandemic-surgery/).
- 126. Ontario Health. Ontario Health Highlights 2021/22. 2023. (Accessed May 5, 2025, at https://www.ontariohealth.ca/news/highlights-2021-22).
- 127. Donckier V, Estache A, Liberale G, Goldman M. Prioritization of Surgery in Cancer Patients During the COVID-19 Pandemic: Lessons From a Failed Balancing Act. Ann Surg Open 2021;2:e108.
- 128. Finley C, Prashad A, Camuso N, et al. Guidance for management of cancer surgery during the COVID-19 pandemic. Can J Surg 2020;63:S2-s4.
- 129. Parmar A, Eskander A, Sander B, Naimark D, Irish JC, Chan KKW. Impact of cancer surgery slowdowns on patient survival during the COVID-19 pandemic: a microsimulation modelling study. CMAJ 2022;194:E408-e14.
- 130. Johnson BA, Waddimba AC, Ogola GO, Fleshman JW, Jr., Preskitt JT. A systematic review and meta-analysis of surgery delays and survival in breast, lung and colon cancers: Implication for surgical triage during the COVID-19 pandemic. Am J Surg 2021;222:311-8.
- 131. Canadian Cancer Society. Making treatment decisions. 2025. (Accessed May 5, 2025, at https://cancer.ca/en/living-with-cancer/coping-with-changes/working-with-your-healthcare-team/making-treatment-decisions).
- 132. Ontario Health Cancer Care Ontario. Systemic Treatment Program. 2025. (Accessed May 5, 2025, at https://www.cancercareontario.ca/en/cancer-careontario/programs/clinical-services/systemic-treatment).
- 133. National Cancer Institute. Types of Cancer Treatment. 2025. (Accessed May 5, 2025, at https://www.cancer.gov/about-cancer/treatment/types).
- 134. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019;380:617-28.
- 135. Ontario Health Cancer Care Ontario. Radiation Treatment Program. 2025. (Accessed September 10, 2025, at https://www.cancercareontario.ca/en/cancer-careontario/programs/clinical-services/radiation-treatment).
- 136. Ayhan M, Laçin Ş, Özyükseler DT, et al. Does systemic anti-tumor therapy increase COVID-19 risk in patients with cancer? J Oncol Pharm Pract 2021;27:1461-7.
- 137. Hatic H, Hearld KR, Das D, Deshane J. Clinical Outcomes in COVID-19 Patients Treated with Immunotherapy. Cancers (Basel) 2022;14.
- 138. Bersanelli M, Zielli T, Perrone F, et al. Clinical impact of COVID-19 in a single-center cohort of a prospective study in cancer patients receiving immunotherapy. Immunotherapy 2020;12:1139-48.

- 139. Ontario Health Cancer Care Ontario. COVID-19 and Cancer Resources and Information for Healthcare Providers. 2025. (Accessed September 10, 2025, at https://www.cancercareontario.ca/en/guidelines-advice/covid19-resources).
- 140. Lee CK, Merriam LT, Pearson JC, Lipnick MS, McKleroy W, Kim EY. Treating COVID-19: Evolving approaches to evidence in a pandemic. Cell Rep Med 2022;3:100533.
- 141. Canadian Cancer Survivor Network. Cancer patients face double jeopardy with COVID-19. July 14, 2020. (Accessed May 4, 2025, at https://survivornet.ca/learn/news/cancer-patients-face-double-jeopardy-with-covid-19/).
- 142. Canadian Cancer Survivor Network. Thrown under the bus!! June 2022. (Accessed May 5, 2025, 2025, at https://survivornet.ca/wp-content/uploads/2022/06/Cancer-Cant-Wait-Final-Report-2022-06-
- 14.pdf?utm_source=newswire&utm_medium=mediarelease&utm_campaign=4thsurvey).
- 143. Government of Canada. COVID-19 and deaths in older Canadians: Excess mortality and the impacts of age and comorbidity. 2020. (Accessed May 5,, 2025, at https://www.canada.ca/content/dam/phac-aspc/documents/services/diseases-maladies/coronavirus-disease-covid-19/epidemiological-economic-research-data/excess-mortality-impacts-age-comorbidity/covid-19-deaths-older-canadians-en.pdf).
- 144. Akhtar-Danesh N, Baumann A, Crea-Arsenio M, Antonipillai V. COVID-19 excess mortality among long-term care residents in Ontario, Canada. PLoS One 2022;17:e0262807. 145. Auditor General of Ontario. COVID-19 Preparedness and Management, Special Report on Pandemic Readiness and Response in Long-Term Care. 2021. (Accessed May 5, 2025, at https://www.auditor.on.ca/en/content/specialreports/specialreports/COVID-19_ch5readinessresponseLTC_en202104.pdf).
- 146. Canadian Institute for Health Information. CIHI Snapshot, Pandemic Experience in the Long-Term Care Sector. 2020. (Accessed October 2, 2025, at https://www.cihi.ca/sites/default/files/document/covid-19-rapid-response-long-term-care-snapshot-en.pdf).
- 147. Sun Y, Zhang P, Zhang D. Impact of treatment delays on future survival outcomes in non-surgical patients with esophageal cancer in Shandong Province, China. Front Oncol 2024;14:1445267.
- 148. Sharman R, Harris Z, Ernst B, Mussallem D, Larsen A, Gowin K. Lifestyle Factors and Cancer: A Narrative Review. Mayo Clin Proc Innov Qual Outcomes 2024;8:166-83.
- 149. Misiąg W, Piszczyk A, Szymańska-Chabowska A, Chabowski M. Physical Activity and Cancer Care-A Review. Cancers (Basel) 2022;14.
- 150. Di Sebastiano KM, Murthy G, Campbell KL, Desroches S, Murphy RA. Nutrition and Cancer Prevention: Why is the Evidence Lost in Translation? Adv Nutr 2019;10:410-8.
- 151. Zhang L, Pan J, Chen W, Jiang J, Huang J. Chronic stress-induced immune dysregulation in cancer: implications for initiation, progression, metastasis, and treatment. Am J Cancer Res 2020;10:1294-307.
- 152. National Cancer Institute. Stress and Cancer. (Accessed May 5, 2025, at https://www.cancer.gov/about-cancer/coping/feelings/stress-fact-sheet).

- 153. Rodriquez EJ, Gregorich SE, Livaudais-Toman J, Pérez-Stable EJ. Coping With Chronic Stress by Unhealthy Behaviors: A Re-Evaluation Among Older Adults by Race/Ethnicity. J Aging Health 2017;29:805-25.
- 154. Cummings JR, Ackerman JM, Wolfson JA, Gearhardt AN. COVID-19 stress and eating and drinking behaviors in the United States during the early stages of the pandemic. Appetite 2021;162:105163.
- 155. Simone M, Emery RL, Hazzard VM, Eisenberg ME, Larson N, Neumark-Sztainer D. Disordered eating in a population-based sample of young adults during the COVID-19 outbreak. Int J Eat Disord 2021;54:1189-201.
- 156. Marashi MY, Nicholson E, Ogrodnik M, Fenesi B, Heisz JJ. A mental health paradox: Mental health was both a motivator and barrier to physical activity during the COVID-19 pandemic. PLoS One 2021;16:e0239244.
- 157. Wagner BE, Folk AL, Hahn SL, Barr-Anderson DJ, Larson N, Neumark-Sztainer D. Recreational Screen Time Behaviors during the COVID-19 Pandemic in the U.S.: A Mixed-Methods Study among a Diverse Population-Based Sample of Emerging Adults. Int J Environ Res Public Health 2021;18.
- 158. Killgore WDS, Cloonan SA, Taylor EC, Lucas DA, Dailey NS. Alcohol dependence during COVID-19 lockdowns. Psychiatry Res 2021;296:113676.
- 159. Park AH, Zhong S, Yang H, Jeong J, Lee C. Impact of COVID-19 on physical activity: A rapid review. J Glob Health 2022;12:05003.
- 160. Nagata JM, Cortez CA, Cattle CJ, et al. Screen Time Use Among US Adolescents During the COVID-19 Pandemic: Findings From the Adolescent Brain Cognitive Development (ABCD) Study. JAMA Pediatrics 2022;176:94-6.
- 161. Morin CM, Bjorvatn B, Chung F, et al. Insomnia, anxiety, and depression during the COVID-19 pandemic: an international collaborative study. Sleep Med 2021;87:38-45.
- 162. PR Newswire. Over 60% of Americans Trying to Break Unhealthy Pandemic Habits According to a ValuePenguin.com Survey. 2021. (Accessed October 4, 2025, at https://www.prnewswire.com/news-releases/over-60-of-americans-trying-to-break-unhealthy-pandemic-habits-according-to-a-valuepenguincom-survey-301342083.html).
- 163. Ariza-Heredia EJ, Chemaly RF. Practical review of immunizations in adult patients with cancer. Hum Vaccin Immunother 2015;11:2606-14.
- 164. Public Health Ontario. COVID-19 Vaccine Uptake in Ontario: December 14, 2020 to June 30, 2024. 2024. (Accessed May 5, 2025, at https://www.publichealthontario.ca/-/media/Documents/nCoV/epi/covid-19-vaccine-uptake-ontario-epi-summary.pdf?rev=fa58f191e0e04d8d8ae6ef380e3110d7&sc_lang=en).
- 165. U.S. Food and Drug Admnistration. Guidance for Human Somatic Cell Therapy and Gene Therapy. 1998. (Accessed May 5, 2025, at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-human-somatic-cell-therapy-and-gene-therapy).
- 166. U.S. Department of Health Human Services Food and Drug Administration Center for Biologics Evaluation Research. Preclinical Assessment of Investigational Cellular and Gene Therapy Products 2013. (Accessed September 17, 2025, at https://www.fda.gov/media/87564/download).

- 167. U.S. Food and Drug Admnistration. Long Term Follow-Up After Administration of Human Gene Therapy Products Guidance for Industry. 2020. (Accessed April 7, 2024, at https://www.fda.gov/media/113768/download).
- 168. DIRECTIVE C. Amending Directive 2001/83/EC of the European Parliament and of the Council on the Community Code Relating to Medicinal Products for Human Use as Regards Advanced Therapy Medicinal Products. 14 September 2009. (Accessed May 5, 2025, at https://europepmc.org/article/MED/37445690#B12-ijms-24-10514).
- 169. Banoun H. mRNA: Vaccine or Gene Therapy? The Safety Regulatory Issues. Int J Mol Sci 2023;24.
- 170. World Health Organization. WHO Guidelines on Non-Clinical Evaluation of Vaccines, Annex 1, TRS No 927. 2005. (Accessed May 5, 2025, at https://europepmc.org/article/MED/37445690#B14-ijms-24-10514).
- 171. Oldfield PR, Gutschi LM, McCullough PA, Speicher DJ. Pfizer/BioNTech's COVID-19 modRNA Vaccines: Dangerous Genetic Mechanism of Action Released before Sufficient Preclinical Testing. Journal of American Physicians and Surgeons 2020:2024.29.118-126.
- 172. Saag M. Wonder of wonders, miracle of miracles: the unprecedented speed of COVID-19 science. Physiol Rev 2022;102:1569-77.
- 173. History of Vaccines. Vaccine Development, Testing, and Regulation. (Accessed May 5, 2025, 2025, at https://historyofvaccines.org/vaccines-101/how-are-vaccines-made/vaccine-development-testing-and-regulation).
- 174. Saville M, Cramer JP, Downham M, et al. Delivering Pandemic Vaccines in 100 Days What Will It Take? N Engl J Med 2022;387:e3.
- 175. World Health Organization. Prequalification of Medical Products COMIRNATY. 2020. (Accessed October 3, 2025, at https://extranet.who.int/prequal/vaccines/comirnaty).
- 176. World Health Organization. COVID-19 Vaccine Tracker 12 Vaccines Granted Emergency Use Listing (EUL) by WHO. 2025. (Accessed October 3, 2025, at https://covid19.trackvaccines.org/agency/who/).
- 177. Edmonds S, MacGregor A, Doll A, *et al*. Transparency too little, too late? Why and how Health Canada should make clinical data and regulatory decision-making open to scrutiny in the face of COVID-19. J Law Biosci 2020;7:lsaa083.
- 178. Kalinke U, Barouch DH, Rizzi R, et al. Clinical development and approval of COVID-19 vaccines. Expert Rev Vaccines 2022;21:609-19.
- 179. Pateev I, Seregina K, Ivanov R, Reshetnikov V. Biodistribution of RNA Vaccines and of Their Products: Evidence from Human and Animal Studies. Biomedicines 2024;12:59.
- 180. Pfizer. SARS-CoV-2 mRNA Vaccine (BNT162, PF-0 7302048): 2.6.5.5B. Pharmacokinetics: organ distribution, report number: 185350. 2020. (Accessed October 2, 2025, at https://ia802305.us.archive.org/28/items/pfizer-confidential-translated/pfizer-confidential-translated.pdf).
- 181. Kent SJ, Li S, Amarasena TH, et al. Blood Distribution of SARS-CoV-2 Lipid Nanoparticle mRNA Vaccine in Humans. ACS Nano 2024;18:27077-89.
- 182. Hong L, Wang Z, Wei X, Shi J, Li C. Antibodies against polyethylene glycol in human blood: A literature review. J Pharmacol Toxicol Methods 2020;102:106678.

- 183. Klimek L, Novak N, Cabanillas B, Jutel M, Bousquet J, Akdis CA. Allergenic components of the mRNA-1273 vaccine for COVID-19: Possible involvement of polyethylene glycol and IgG-mediated complement activation. Allergy 2021;76:3307-13.
- 184. Nittner-Marszalska M, Rosiek-Biegus M, Kopeć A, et al. Pfizer-BioNTech COVID-19 Vaccine Tolerance in Allergic versus Non-Allergic Individuals. Vaccines (Basel) 2021;9.
- 185. Kedmi R, Ben-Arie N, Peer D. The systemic toxicity of positively charged lipid nanoparticles and the role of Toll-like receptor 4 in immune activation. Biomaterials 2010;31:6867-75.
- 186. Dokka S, Toledo D, Shi X, Castranova V, Rojanasakul Y. Oxygen radical-mediated pulmonary toxicity induced by some cationic liposomes. Pharm Res 2000;17:521-5.
- 187. Sedic M, Senn JJ, Lynn A, et al. Safety Evaluation of Lipid Nanoparticle-Formulated Modified mRNA in the Sprague-Dawley Rat and Cynomolgus Monkey. Vet Pathol 2018;55:341-54.
- 188. Lv H, Zhang S, Wang B, Cui S, Yan J. Toxicity of cationic lipids and cationic polymers in gene delivery. J Control Release 2006;114:100-9.
- 189. Lonez C, Vandenbranden M, Ruysschaert JM. Cationic lipids activate intracellular signaling pathways. Adv Drug Deliv Rev 2012;64:1749-58.
- 190. Nuovo GJ, Magro C, Shaffer T, et al. Endothelial cell damage is the central part of COVID-19 and a mouse model induced by injection of the S1 subunit of the spike protein. Ann Diagn Pathol 2021;51:151682.
- 191. Rhea EM, Logsdon AF, Hansen KM, et al. The S1 protein of SARS-CoV-2 crosses the blood-brain barrier in mice. Nat Neurosci 2021;24:368-78.
- 192. Idrees D, Kumar V. SARS-CoV-2 spike protein interactions with amyloidogenic proteins: Potential clues to neurodegeneration. Biochem Biophys Res Commun 2021;554:94-8.
- 193. Yapici-Eser H, Koroglu YE, Oztop-Cakmak O, Keskin O, Gursoy A, Gursoy-Ozdemir Y. Neuropsychiatric Symptoms of COVID-19 Explained by SARS-CoV-2 Proteins' Mimicry of Human Protein Interactions. Front Hum Neurosci 2021; Volume 15 2021.
- 194. Trougakos IP, Terpos E, Alexopoulos H, et al. Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis. Trends Mol Med 2022;28:542-54.
- 195. Freitas RS, Crum TF, Parvatiyar K. SARS-CoV-2 Spike Antagonizes Innate Antiviral Immunity by Targeting Interferon Regulatory Factor 3. Front Cell Infect Microbiol 2021;11:789462.
- 196. Aldén M, Olofsson Falla F, Yang D, et al. Intracellular Reverse Transcription of Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 In Vitro in Human Liver Cell Line. Curr Issues Mol Biol 2022;44:1115-26.
- 197. Montezano AC, Camargo LL, Mary S, et al. SARS-CoV-2 spike protein induces endothelial inflammation via ACE2 independently of viral replication. Sci Rep 2023;13:14086.
- 198. Gultom M, Lin L, Brandt CB, et al. Sustained Vascular Inflammatory Effects of SARS-CoV-2 Spike Protein on Human Endothelial Cells. Inflammation 2024.
- 199. Li F, Li J, Wang P-H, *et al.* SARS-CoV-2 spike promotes inflammation and apoptosis through autophagy by ROS-suppressed PI3K/AKT/mTOR signaling. Biochimica et Biophysica Acta (BBA) Molecular Basis of Disease 2021;1867:166260.

- 200. Perico L, Benigni A, Remuzzi G. SARS-CoV-2 and the spike protein in endotheliopathy. Trends Microbiol 2024;32:53-67.
- 201. Bocquet-Garçon A. Impact of the SARS-CoV-2 Spike Protein on the Innate Immune System: A Review. Cureus 2024;16:e57008.
- 202. Zheng Y, Zhao J, Li J, et al. SARS-CoV-2 Spike Protein Causes Blood Coagulation and Thrombosis by Competitive Binding to Heparan Sulfate. Int J Biol Macromol 2021;193:1124-9.
- 203. Li K, Yao L, Wang J, et al. SARS-CoV-2 Spike protein promotes vWF secretion and thrombosis via endothelial cytoskeleton-associated protein 4 (CKAP4). Signal Transduction and Targeted Therapy 2022;7:332.
- 204. Ryu JK, Sozmen EG, Dixit K, et al. SARS-CoV-2 spike protein induces abnormal inflammatory blood clots neutralized by fibrin immunotherapy. bioRxiv 2021.
- 205. Zhang S, El-Deiry WS. Transfected SARS-CoV-2 spike DNA for mammalian cell expression inhibits p53 activation of p21(WAF1), TRAIL Death Receptor DR5 and MDM2 proteins in cancer cells and increases cancer cell viability after chemotherapy exposure. Oncotarget 2024;15:275-84.
- 206. Gómez-Carballa A, Martinón-Torres F, Salas A. Is SARS-CoV-2 an oncogenic virus? J Infect 2022;85:573-607.
- 207. Suzuki YJ, Nikolaienko SI, Dibrova VA, et al. SARS-CoV-2 spike protein-mediated cell signaling in lung vascular cells. Vascul Pharmacol 2021;137:106823.
- 208. Speicher DJ, Rose J, McKernan K. Quantification of residual plasmid DNA and SV40 promoter-enhancer sequences in Pfizer/BioNTech and Moderna modRNA COVID-19 vaccines from Ontario, Canada. Autoimmunity 2025;58:2551517.
- 209. McKernan K, Helbert Y, Kane LT, McLaughlin S. Sequencing of Bivalent Moderna and Pfizer mRNA Vaccines Reveals Nanogram to Microgram Quantities of Expression Vector dsDNA per Dose. OSF Preprints 2023; April 10, doi:10.31219/osf.io/b9t7m.
- 210. Buckhaults P. South Carolina Senate Medical Affairs, Pandemic Preparedness Listening Session Phillip-Buckhaults. 2023. (Accessed October 5, 2025, at https://www.scstatehouse.gov/CommitteeInfo/SenateMedicalAffairsCommittee/PandemicPreparedness/Phillip-Buckhaults-SC-Senate-09122023-final.pdf).
- 211. Brogna C, Cristoni S, Marino G, et al. Detection of recombinant Spike protein in the blood of individuals vaccinated against SARS-CoV-2: Possible molecular mechanisms. Proteomics Clin Appl 2023;17:e2300048.
- 212. Bansal S, Perincheri S, Fleming T, et al. Cutting Edge: Circulating Exosomes with COVID Spike Protein Are Induced by BNT162b2 (Pfizer-BioNTech) Vaccination prior to Development of Antibodies: A Novel Mechanism for Immune Activation by mRNA Vaccines. J Immunol 2021;207:2405-10.
- 213. Hanna N, De Mejia CM, Heffes-Doon A, et al. Biodistribution of mRNA COVID-19 vaccines in human breast milk. eBioMedicine 2023;96.
- 214. Brook B, Goetz M, Duval V, Micol R, Dowling DJ. mRNA vaccines: miRNA-based controlled biodistribution and directed adjuvantation. Trends Immunol 2025;46:357-60.
- 215. Krauson AJ, Casimero FVC, Siddiquee Z, Stone JR. Duration of SARS-CoV-2 mRNA vaccine persistence and factors associated with cardiac involvement in recently vaccinated patients. npj Vaccines 2023;8:141.

- 216. Sass E. mRNA "vaccine" biodistribution, persistence, and adjuvant toxicity library (Version 1). Zenodo, 2024. (Accessed May 28, 2025, at https://zenodo.org/records/14559625).
- 217. Glassman A, Kenny C, Yang G. COVID-19 Vaccine Development and Rollout in Historical Perspective. Center for Global Development, 2022. (Accessed September 17, 2025, at https://www.cgdev.org/publication/covid-19-vaccine-development-and-rollout-historical-perspective).
- 218. Gergen J, Petsch B. mRNA-Based Vaccines and Mode of Action. Curr Top Microbiol Immunol 2022;440:1-30.
- 219. Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. Nature Human Behaviour 2021;5:947-53.
- 220. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
- 221. Forsyth CB, Zhang L, Bhushan A, et al. The SARS-CoV-2 S1 Spike Protein Promotes MAPK and NF-kB Activation in Human Lung Cells and Inflammatory Cytokine Production in Human Lung and Intestinal Epithelial Cells. Microorganisms 2022;10.
- 222. Khan S, Shafiei MS, Longoria C, Schoggins JW, Savani RC, Zaki H. SARS-CoV-2 spike protein induces inflammation via TLR2-dependent activation of the NF-κB pathway. eLife 2021;10:e68563.
- 223. Saadi F, Pal D, Sarma JD. Spike Glycoprotein Is Central to Coronavirus Pathogenesis-Parallel Between m-CoV and SARS-CoV-2. Ann Neurosci 2021;28:201-18.
- 224. Almehdi AM, Khoder G, Alchakee AS, Alsayyid AT, Sarg NH, Soliman SSM. SARS-CoV-2 spike protein: pathogenesis, vaccines, and potential therapies. Infection 2021;49:855-76.
- 225. Bettini E, Locci M. SARS-CoV-2 mRNA Vaccines: Immunological Mechanism and Beyond. Vaccines (Basel) 2021;9.
- 226. Duloquin G, Pommier T, Georges M, et al. Is COVID-19 Infection a Multiorganic Disease? Focus on Extrapulmonary Involvement of SARS-CoV-2. J Clin Med 2024;13.
- 227. Louis TJ, Qasem A, Abdelli LS, Naser SA. Extra-Pulmonary Complications in SARS-CoV-2 Infection: A Comprehensive Multi Organ-System Review. Microorganisms 2022;10:153.
- 228. Fehrer A, Sotzny F, Hoheisel F, et al. Long-term serum spike protein persistence but no correlation with post-COVID syndrome. medRxiv 2024:2024.11.11.24317084.
- 229. Theoharides TC. Could SARS-CoV-2 Spike Protein Be Responsible for Long-COVID Syndrome? Mol Neurobiol 2022;59:1850-61.
- 230. Rong Z, Mai H, Ebert G, et al. Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19. Cell Host & Microbe 2024;32:2112-30.e10.
- 231. Fehrer A, Sotzny F, Kim L, *et al.* Serum Spike Protein Persistence Post COVID Is Not Associated with ME/CFS. Journal of Clinical Medicine 2025;14:1086.
- 232. Menezes F, Palmeira JdF, Oliveira JdS, et al. Unraveling the SARS-CoV-2 spike protein long-term effect on neuro-PASC. Front Cell Neurosci 2024;Volume 18 2024.
- 233. Bhattacharjee B, Lu P, Monteiro VS, *et al.* Immunological and Antigenic Signatures Associated with Chronic Illnesses after COVID-19 Vaccination. medRxiv 2025:2025.02.18.25322379.

- 234. Ota N, Itani M, Aoki T, et al. Expression of SARS-CoV-2 spike protein in cerebral Arteries: Implications for hemorrhagic stroke Post-mRNA vaccination. J Clin Neurosci 2025;136:111223.
- 235. Yonker LM, Swank Z, Bartsch YC, et al. Circulating Spike Protein Detected in Post-COVID-19 mRNA Vaccine Myocarditis. Circulation 2023;147:867-76.
- 236. Patterson BK, Yogendra R, Francisco EB, *et al.* Detection of S1 spike protein in CD16+ monocytes up to 245 days in SARS-CoV-2-negative post-COVID-19 vaccine syndrome (PCVS) individuals. Hum Vaccin Immunother 2025;21:2494934.
- 237. Solis O, Beccari AR, Iaconis D, et al. The SARS-CoV-2 spike protein binds and modulates estrogen receptors. Sci Adv 2022;8:eadd4150.
- 238. Al-Shami K, Awadi S, Khamees A, et al. Estrogens and the risk of breast cancer: A narrative review of literature. Heliyon 2023;9:e20224.
- 239. Persson I. Estrogens in the causation of breast, endometrial and ovarian cancers evidence and hypotheses from epidemiological findings. J Steroid Biochem Mol Biol 2000;74:357-64.
- 240. Auborn KJ, Woodworth C, DiPaolo JA, Bradlow HL. The interaction between HPV infection and estrogen metabolism in cervical carcinogenesis. Int J Cancer 1991;49:867-9.
- 241. Chung SH, Franceschi S, Lambert PF. Estrogen and ERalpha: culprits in cervical cancer? Trends Endocrinol Metab 2010;21:504-11.
- 242. Martellucci CA, Capodici A, Soldato G, et al. COVID-19 vaccination, all-cause mortality, and hospitalization for cancer: 30-month cohort study in an Italian province. Excli j 2025;24:690-707.
- 243. Alessandria M, Malatesta G, Di Palmo G, Cosentino M, Donzelli A. All-cause mortality according to COVID-19 vaccination status: An analysis of the UK office for National statistics public data. F1000Res 2024;13:886.
- 244. Kim HJ, Kim MH, Choi MG, Chun EM. 1-year risks of cancers associated with COVID-19 vaccination: a large population-based cohort study in South Korea. Biomark Res 2025;13:114.
- 245. Wang Y, Chang L, He H, et al. The impact of the COVID-19 pandemic on the diagnosis, treatment, and prognosis of ovarian cancer in the United States: a retrospective cohort study based on the SEER database. Discov Oncol 2025;16:545.
- 246. World Health Organization. Global surveillance for COVID-19 caused by human infection with COVID-19 virus. 2020. (Accessed September 17, 2025, at https://www.who.int/docs/default-source/coronaviruse/2020-03-20-surveillance.pdf).
- 247. Bullard J, Dust K, Funk D, et al. Predicting Infectious Severe Acute Respiratory Syndrome Coronavirus 2 From Diagnostic Samples. Clin Infect Dis 2020;71:2663-6.
- 248. Shyu D, Dorroh J, Holtmeyer C, et al. Laboratory Tests for COVID-19: A Review of Peer-Reviewed Publications and Implications for Clinical Use. Mo Med 2020;117:184-95.
- 249. Alberta Health. Public Health Disease Management Guidelines | Coronavirus, COVID-19 February 2020. 2020. (Accessed May 5, 2025, at https://open.alberta.ca/dataset/a86d7a85-ce89-4e1c-9ec6-
- <u>d1179674988f/resource/57a3621c-1e4a-4f21-a688-25e2ba687746/download/healthguidelines-coronavirus-novel-2020-02-11.pdf</u>).

- 250. Government of Canada. National case definition: Coronavirus disease (COVID-19). 2023. (Accessed May 5, 2025, at https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals/national-case-definition.html#conf).
- 251. Alberta Health. Alberta's COVID-19 pandemic response: Alberta COVID-19 Pandemic Data Review Task Force: final report. 2025. (Accessed September 5, 2025, at https://open.alberta.ca/publications/albertas-covid-19-pandemic-response).
- 252. Public Health Ontario. An Overview of Cycle Threshold Values and their Role in SARS-CoV-2 Real-Time PCR Test Interpretation. 2020. (Accessed May 5, 2025, at https://www.publichealthontario.ca/-/media/documents/ncov/main/2020/09/cycle-threshold-values-sars-cov2-pcr.pdf?la=en).
- 253. Alberta Health. Public Health Disease Management Guidelines | Coronavirus, COVID-19 April 28, 2020. 2020. (Accessed May 5, 2025, at https://open.alberta.ca/publications/coronavirus-covid-19).
- 254. Alberta Health. Public Health Disease Management Guidelines | Coronavirus, COVID-19 August 28 2020. 2020. (Accessed May 5, 2025, at https://open.alberta.ca/dataset/a86d7a85-ce89-4e1c-9ec6-
- <u>d1179674988f/resource/fbf3906c-0ebe-462d-bb23-0f2bbaa7598c/download/covid-19-guidelines-2020-08-28.pdf</u>).
- 255. Berengua C, López M, Esteban M, *et al.* Viral culture and immunofluorescence for the detection of SARS-CoV-2 infectivity in RT-PCR positive respiratory samples. J Clin Virol 2022;152:105167.
- 256. Government of Canada. National polymerase chain reaction (PCR) testing indication guidance for COVID-19. 2020. (Accessed October 5, 2025, at https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/national-laboratory-testing-indication.html).
- 257. Government of Canada. Web.archive.org Polymerase chain reaction (PCR) and cycle threshold (Ct) values in COVID-19 testing (June 11, 2021). 2021. (Accessed October 5, 2025,

https://web.archive.org/web/20210611161522/https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/polymerase-chain-reaction-cycle-threshold-values-testing.html).

- 258. Government of Canada. Polymerase chain reaction (PCR) and cycle threshold (Ct) values in COVID-19 testing. (Accessed June 3, 2025, at https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/polymerase-chain-reaction-cycle-threshold-values-testing.html).
- 259. Taylor KM, Ricks KM, Kuehnert PA, et al. Seroprevalence as an Indicator of Undercounting of COVID-19 Cases in a Large Well-Described Cohort. AJPM Focus 2023;2:100141.
- 260. Gordon D. Affidavit of Deborah Gordon Affirmed on July 12 2021. 2021. (Accessed September 16, 2025, at https://www.dropbox.com/scl/fi/f4cgrlt2qg3m68b8472dg/Affidavit-of-Deborah-Gordon-Filed-July-13-2021-copy.pdf?rlkey=if0ehbbsm3ei7gztvf321ilot&dl=0).

- 261. Abbott. Panbio | COVID-19 Ag Rapid Test Device. 2021. (Accessed May 5, 2025, at https://dam.abbott.com/en-gb/panbio/120007883-v1-Panbio-COVID-19-Ag-Nasal-AsymptomaticSe.pdf).
- 262. Schwartz KL, McGeer AJ, Bogoch, II. Rapid antigen screening of asymptomatic people as a public health tool to combat COVID-19. CMAJ 2021;193:E449-e52.
- 263. Alberta Health. Public Health Disease Management Guidelines | Coronavirus, COVID-19 January 2021. 2021. (Accessed May 5, 2025, at https://open.alberta.ca/dataset/a86d7a85-ce89-4e1c-9ec6-
- d1179674988f/resource/b652b873-2a55-496b-ba10-42d138db3016/download/health-disease-management-guidelines-covid-19-2021-01-14.pdf).
- 264. Alberta Health. Public Health Disease Management Guidelines | Coronavirus, COVID-19 November 9, 2021. (Accessed September 5, 2025, at https://open.alberta.ca/dataset/a86d7a85-ce89-4e1c-9ec6-
- d1179674988f/resource/10ac51a3-45a0-438a-b0de-ba5dc6e486de/download/health-disease-management-guidelines-covid-19-2021-11.pdf).
- 265. Alberta Health. Public Health Disease Management Guidelines | Coronavirus, COVID-19 February 23, 2022. 2022. (Accessed May 5, 2025, at https://open.alberta.ca/dataset/a86d7a85-ce89-4e1c-9ec6-
- <u>d1179674988f/resource/3f711f03-f4f2-4508-a9cf-ecdc7481ec31/download/health-disease-management-guidelines-covid-19-2022-02.pdf</u>).
- 266. Alberta Health. Public Health Disease Management Guidelines | Coronavirus, COVID-19 March 10, 2020. 2020. (Accessed May 5, 2025, at https://open.alberta.ca/dataset/a86d7a85-ce89-4e1c-9ec6-
- <u>d1179674988f/resource/9cfe3c52-b349-499c-832b-092ae1002b29/download/healthguidelines-coronavirus-covid-19-2020-03-17.pdf</u>).
- 267. Alberta Health. Public Health Disease Management Guidelines | Coronavirus, COVID-19 May 2020. 2020. (Accessed May 5, 2025, at https://open.alberta.ca/dataset/a86d7a85-ce89-4e1c-9ec6-
- <u>d1179674988f/resource/ba1e9346-ac17-4dba-b957-47d1230dd2b3/download/covid-19-guideline-2020-05-21.pdf</u>).
- 268. Ioannidis JPA. Infection fatality rate of COVID-19 inferred from seroprevalence data. Bull World Health Organ 2021;99:19-33f.
- 269. World Health Organization. International guidelines for certification and classification (coding) of covid-19 as cause of death. (Accessed May 5, 2025, at https://www.who.int/docs/default-source/classification/icd/covid-19/guidelines-cause-of-death-covid-19-20200420-en.pdf).
- 270. Yang K, Sheng Y, Huang C, et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. Lancet Oncol 2020;21:904-13.
- 271. Mehta V, Goel S, Kabarriti R, *et al.* Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System. Cancer Discov 2020;10:935-41.
- 272. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020;395:1054-62.

- 273. Solimando AG, Bittrich M, Shahini E, Albanese F, Fritz G, Krebs M. Determinants of COVID-19 Disease Severity-Lessons from Primary and Secondary Immune Disorders including Cancer. Int J Mol Sci 2023;24.
- 274. Febbraro M, Conlon M, Caswell J, Laferriere N. Access to cancer care in northwestern Ontario-a population-based study using administrative data. Curr Oncol 2020;27:e271-e5.
- 275. Rico JF, Caterino JM, Stephens JA, *et al.* Variables associated with admission rates among cancer patients presenting to emergency departments: a CONCERN group study. Emergency Cancer Care 2023;2:7.
- 276. Dennis G. Rancourt. 2025-03-03 ::: Towards understanding the government assault and persistent excess mortality (presentation in Calgary). 2025. (Accessed Jun 23, 2025, at https://denisrancourt.ca/videos.php?id=135&name=2025_03_03_towards_understanding_the_government_assault_and_persistent_excess_mortality_presentation_in_calgary).
- 277. Ontario Government n. Ontario Taking Action to Protect Against Omicron Variant. December 10, 2021. (Accessed May 5, 2025, at https://news.ontario.ca/en/release/1001327/ontario-taking-action-to-protect-against-omicron-variant).
- 278. Ontario Health Newsroom. Ontario Expanding Booster Eligibility to More Ontarians. 2021. (Accessed May 5, 2025, at https://news.ontario.ca/en/release/1001100/ontario-expanding-booster-eligibility-to-more-ontarians).
- 279. Moreira ED, Jr., Kitchin N, Xu X, et al. Safety and Efficacy of a Third Dose of BNT162b2 Covid-19 Vaccine. N Engl J Med 2022;386:1910-21.
- 280. Hall VG, Ferreira VH, Ku T, et al. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. N Engl J Med 2021;385:1244-6.
- 281. Pfizer. VRBPAC Briefing Document Evaluation of a Booster Dose (Third Dose), BNT162b2 [COMIRNATY (COVID-19 Vaccine, mRNA)]. 2021. (Accessed September 25, 2025, at https://www.fda.gov/media/152161/download).
- 282. Miller ER, McNeil MM, Moro PL, Duffy J, Su JR. The reporting sensitivity of the Vaccine Adverse Event Reporting System (VAERS) for anaphylaxis and for Guillain-Barré syndrome. Vaccine 2020;38:7458-63.
- 283. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf 2006;29:385-96.
- 284. Auditor General of Ontario. Auditor General's 2017 Annual Report. Ministry of Health and Long-Term Care, Cancer Treatment Services. 2017. (Accessed June 5, 2025, at https://www.auditor.on.ca/en/content/annualreports/arreports/en17/v1 302en17.pdf).
- 285. Govenment of Canada. Federal/Provincial/Territorial Public Health Response Plan for Biological Events. 2017. (Accessed May 5, 2025, at https://www.canada.ca/en/public-health-response-plan-biological-events.html).
- 286. Pan-Canadian Public Health Network. About the Pan-Canadian Public Health Network. (Accessed May 5, 2025, at https://www.phn-rsp.ca/en/about/index.html#a1).
- 287. Public Health Ontario. A Framework for the Ethical Conduct of Public Health Initiatives. (Accessed May, 2025, at https://jcb.utoronto.ca/wp-content/uploads/2021/03/framework-ethical-conduct.pdf).