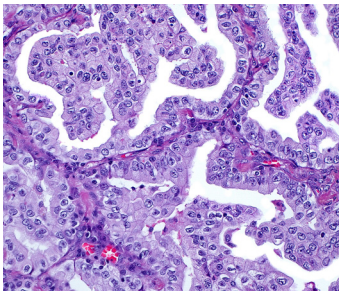
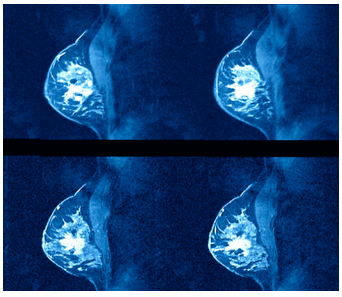
research

Covid-19 associated disease burden p 21



Novel treatments for non-small cell lung cancer p 24



Risk of invasive breast cancer without surgery p 26

Addressing the indirect health burden of covid-19

ORIGINAL RESEARCH Time series modelling analysis of GBD 2021 study

Global, regional, and national characteristics of the main causes of increased disease burden due to the covid-19 pandemic

Chen C, Zhou W, Cui Y, et al

Cite this as: *BMJ* 2025;390:e083868
Find this at doi: 10.1136/bmj-2024-083868

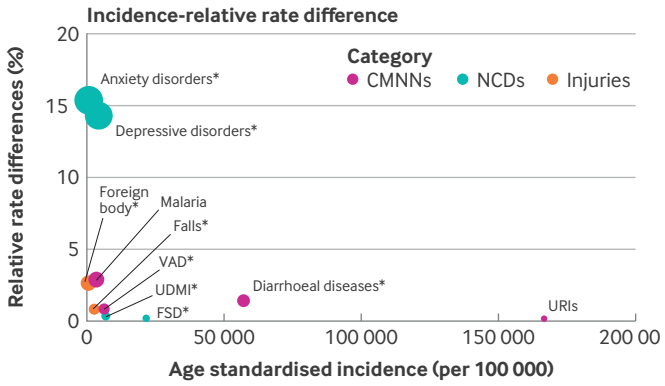
Study question Which health conditions increased in disease burden due to the covid-19 pandemic?

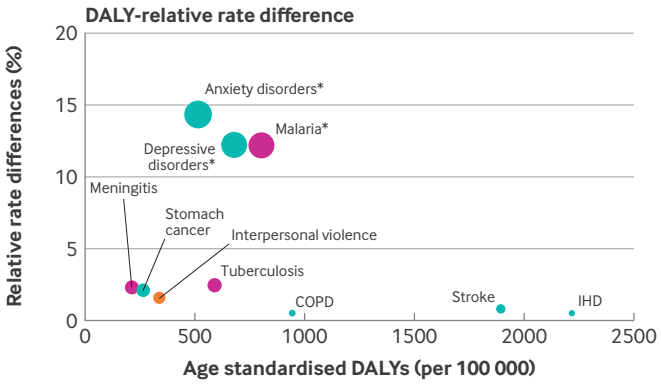
Methods A secondary analysis of Global Burden of Disease 2021 study data of 174 level 3 health conditions with forecasting models was performed. Absolute and relative rate differences and corresponding 95% confidence intervals (CIs) were calculated between the observed and expected rates for these causes in incidence, prevalence, disability adjusted life years (DALYs), and deaths in 2020-21. A statistically significant increase was indicated if the 95% CIs of the rate differences were above 0.

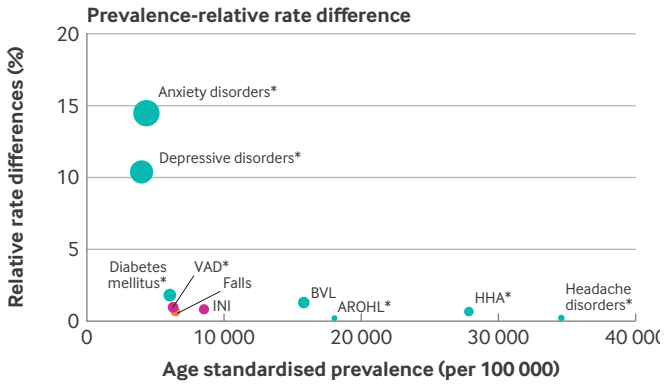
Study answer and limitations The covid-19 pandemic has significantly increased the burden of several conditions, particularly mental health disorders (absolute difference of age standardised DALYs per 100 000 people was 83.0 (95% CI 79.2 to 86.8) for depressive disorders and 73.8 (72.2 to 75.4) for anxiety disorders), malaria in young children (97.9 (46.9 to 148.9)), and stroke (169.0 (100.8 to 237.1)) and ischaemic heart disease (27.0 (14.4 to 39.6)) in older adults, with notable inequalities across age and sex. Although we included 174 health conditions, not all health conditions were encompassed, potentially underestimating the pandemic's indirect health impacts and limiting the generalisability of our findings.

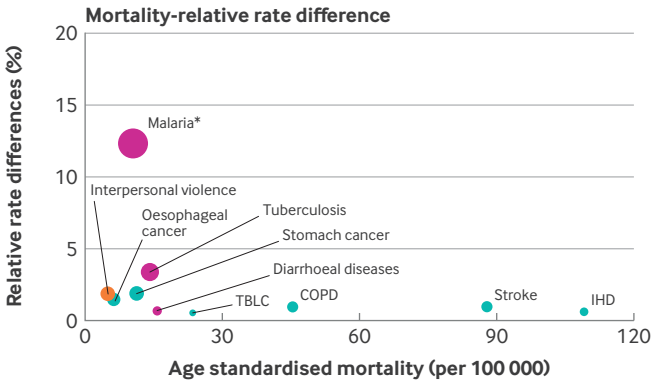
What this study adds Depressive and anxiety disorders, along with malaria, were the most significantly affected conditions among the 174 studied. The findings highlight the need to bolster health services to prevent indirect increases in disease burden during future infectious disease pandemics and other public health emergencies of international concern.

Funding, competing interests, and data sharing This study was supported by grants from the National Natural Science Foundation of China, the Zhejiang Province Vanguard Goose-Leading Initiative, the National Key R&D Program of China, and the Mega-Project of National Science and Technology for the 13th Five-Year Plan of China. No competing interests declared. Publicly available datasets were analysed in this study, which can be found at http://ghdx.healthdata.org/gbd-results-tool.









COMMENTARY Consider collateral impacts when planning for future crises

The covid-19 pandemic's impact extends far beyond the direct effects of infection and death, resulting in sharp increases in other causes of illness and death that demand attention. A new time series analysis of the Global Burden of Disease data by Chen and colleagues quantifies these shifts and identifies which conditions had excess burden during 2020-21.[1] Their key finding is that many countries had greater than expected morbidity and mortality from non-covid causes—a signal that health systems were strained in multiple ways. As such, policy makers must look past the virus itself and address collateral impacts. Health experts have noted that assessing health-system resilience now is "vital in helping policymakers plan for sustainable recovery" and to strengthen systems for future crises.[2]

The indirect health burdens have been profound. For example, a modelling study suggested that even modest service disruptions related to covid-19 in Africa could nearly double annual malaria deaths if routine programmes were interrupted.[3] In practice, the findings suggest that malaria

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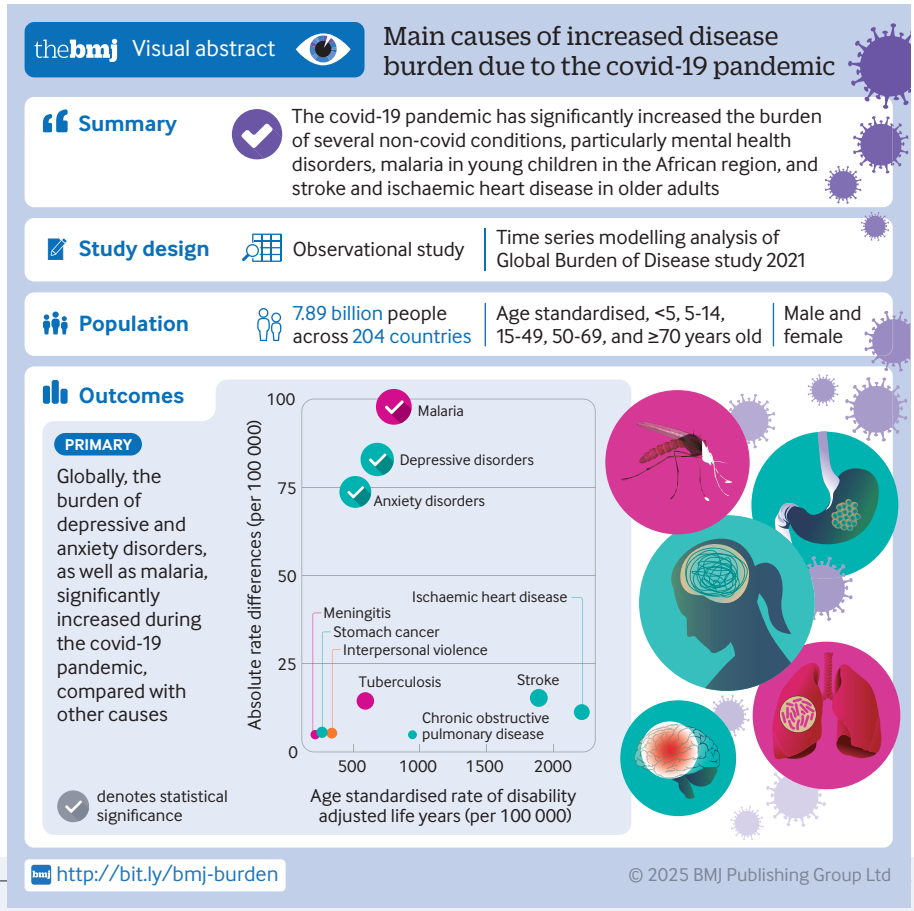
The cost of inaction is documented excess burden

control campaigns could not simply be paused without consequences. Likewise, the pandemic has provoked a mental health crisis. The World Health Organization (WHO) reported a 25% global rise in anxiety and depression in 2020, reflecting the effects of lockdowns, fear, and isolation.[4] Even well before the pandemic, mental illness was among the leading causes of disability worldwide; the new findings support the claims that covid-19 has worsened this burden. Other conditions, from diabetes to tuberculosis to maternal-child health, also experienced disrupted care. Taken together, the evidence signals that post-pandemic health planning must explicitly "build in" catch-up programmes for diseases such as malaria and for mental health services. The quantitative evidence from Chen and colleagues' study provides a roadmap for this by identifying which diseases and regions were most affected.[1]

Enhancing preparedness

A crucial lesson is that surveillance systems must be preserved and expanded. WHO's guidance stresses that even as



The global main causes of increased incidence, prevalence, DALYs, and mortality burden during the covid-19 pandemic, by absolute differences, standardised by age. *Statistical significance. AROHL=age related and other hearing loss; BVL=blindness and vision loss; CMNNs=communicable, maternal, neonatal, and nutritional diseases; COPD=chronic obstructive pulmonary disease; DALYs=disability adjusted life years; FSD=fungal skin diseases; HHA=haemoglobinopathies and haemolytic anaemias; IHD=ischaemic heart disease; INI=intestinal nematode; NCDs=non-communicable diseases; TBLC=tracheal, bronchus, and lung cancer; UDMI=urinary diseases and male infertility; URIs=upper respiratory infections; VAD=vitamin A deficiency

the acute crisis fades, countries should "maintain and strengthen surveillance" to give early warning of changing patterns and monitor health system burdens.[5] In other words, health authorities need integrated data for both infectious and non-communicable conditions to rising trends of illness. As Clark and Gruending comment, without robust surveillance and preparedness "outbreaks place an enormous burden on health services."[6] This preparation calls for investments in unified health information systems, regular community surveys, and genomic tracking. In practice, health authorities should not shut down monitoring of malaria, HIV, or non-communicable disease while grappling with a pandemic, nor should data for mental health and substance use be neglected. Effective surveillance will allow timely interventions; for example, triggering extra mosquito net distributions or tele-mental health outreach, to blunt the indirect effects of future emergencies.

Building resilience and equity into health systems is equally vital. A multicountry review emphasised that recovery plans must "preserve functions and resources within and beyond the health system to maintain routine and acute care" even during shocks.[2] WHO leadership likewise calls on governments to invest in core public health functions, to strengthen primary care and to involve communities in planning.[7] Critically, they highlight the need to "address pre-existing inequities and the disproportionate impact of covid-19 on marginalized and vulnerable populations."[7] The pandemic has shown that weak health systems and social divides amplify harm: as Tedros Ghebreyesus, WHO's Director-General observed, the brunt of the crisis has been borne by the most vulnerable, "when health is at risk, all other sectors are at risk."[7] Thus, policy measures should include expanded access to affordable care and social support for low income groups, migrants, and elderly people; measures that not only improve equity but strengthen society's pandemic defences. Resilient countries also "activated whole-of-government approaches" and repurposed community health workers to sustain essential services for chronic diseases and mental wellness.[2] These examples illustrate that policies that are not strictly medical, such as paid sick leave, food assistance, and continuity of education, are critical parts of a health protecting strategy.

Policy implications

The study by Chen and colleagues highlights how data can guide smarter recovery.[1] The findings show policy makers where to target resources during the "rebuild" phase: immunisation and infectious disease programmes delayed by covid-19, mental health outreach to youth and frontline workers, and screening and treatment for chronic conditions deferred in lockdown. In each case, the cost of inaction is documented excess burden. By integrating these insights into postpandemic plans, countries can improve resilience. Concrete steps include: allocating budgets for essential services in emergencies, reinforcing primary health care, expanding disease surveillance networks, and prioritising universal health coverage with a focus on those left behind. Such actions are aligned with WHO's recommendations and the broader call to "build back better," which aims that future health crises disrupt lives less and afflict populations more evenly.[6 7] Ultimately, recognising and planning for the pandemic's indirect toll will save lives and leave health systems stronger and fairer for future public health emergencies.

Cite this as: *BMJ* 2025;390:r1268

Find the full version with references at http://dx.doi.org/10.1136/bmj.r1268

EGFR-mutated non-small cell lung cancer

ORIGINAL RESEARCH Multicentre, open label, randomised controlled trial

Sacituzumab tirumotecan versus docetaxel for previously treated *EGFR*-mutated advanced non-small cell lung cancer

Fang W, Li X, Wang Q, et al

Cite this as: *BMJ* 2025;389:e085680
Find this at doi: 10.1136/bmj-2025-085680

Study question Does sacituzumab tirumotecan improve objective response rates compared with docetaxel in patients with epidermal growth factor receptor (*EGFR*)-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) after previous treatment failure with EGFR-tyrosine kinase inhibitors and platinum based chemotherapy?

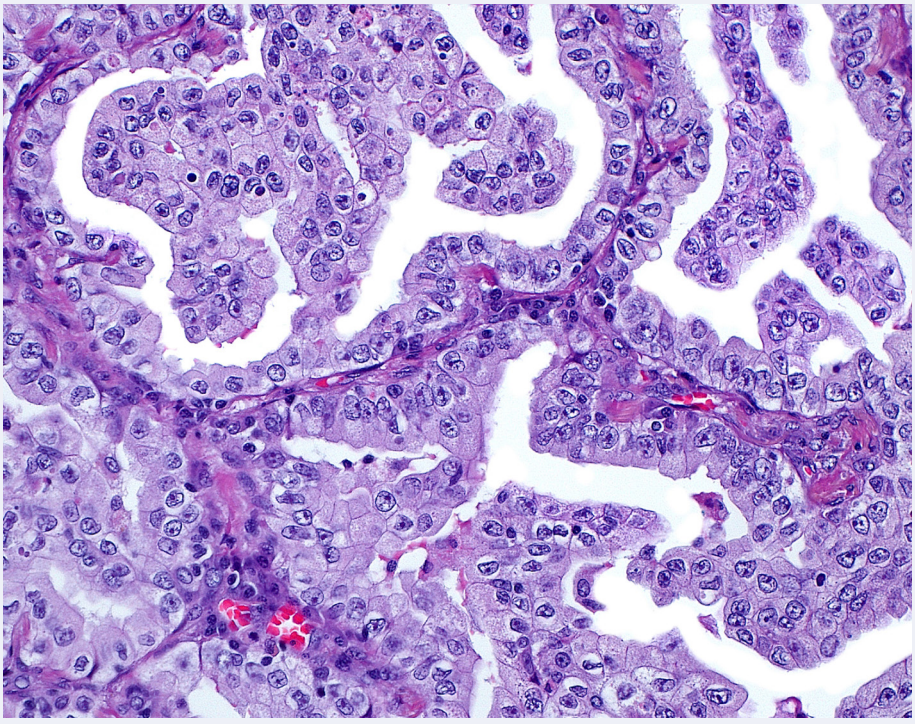
Methods This multicentre, open label, randomised controlled trial enrolled 137 adults (aged 18-75 years) with *EGFR*-mutated advanced or metastatic NSCLC with disease progression after treatment with EGFR-tyrosine kinase inhibitors and platinum based chemotherapy. Patients were randomly assigned (2:1) to receive sacituzumab tirumotecan (5 mg/kg every two weeks) or docetaxel (75 mg/m^2 every three weeks). The primary endpoint was objective response rate assessed by blinded independent review committee. Secondary endpoints included progression-free and overall survival.

Study answer and limitations 91 patients were randomised to receive sacituzumab tirumotecan and 46 to receive docetaxel. Median follow-up was 12.2 months at the data cut-off for efficacy (31 December 2024). The objective response rate was significantly higher in the sacituzumab tirumotecan group (45% (41/91)) versus docetaxel group (16% (7/45)): difference 29% (95% confidence interval (CI) 15% to 43%). Median progression-free survival was significantly longer with sacituzumab tirumotecan than with docetaxel (6.9 *v* 2.8 months; hazard ratio 0.30 (95% CI 0.20 to 0.46)). The 12 month overall survival rate was 73% with sacituzumab tirumotecan and 54% with docetaxel (hazard ratio 0.49 (0.27

COMMENTARY Sacituzumab tirumotecan shows promise

Activating mutations in the epidermal growth factor receptor (EGFR) gene drive about 15% of the cases of non-small cell lung cancer (NSCLC) in non-Asian populations and up to 50% in Asian populations.[1] Although tyrosine kinase inhibitors targeting these mutations are initially highly effective, most patients with advanced disease eventually experience cancer progression owing to the development of drug resistance.[2] The current treatment options for resistance to tyrosine kinase inhibitors are limited. Most patients receive standard chemotherapy, with limited efficacy and substantial toxicity.[3] In their study, Fang and colleagues addressed this critical clinical challenge by showing that sacituzumab tirumotecan, a novel antibody-drug conjugate targeting trophoblast cell surface antigen 2, showed remarkable efficacy in Chinese patients with *EGFR*-mutated NSCLC with disease progression after treatment with both tyrosine kinase inhibitors and platinum based chemotherapy.

Trophoblast cell surface antigen 2 is a protein overexpressed in many NSCLC tumours, particularly those with *EGFR*-activating mutations, making it an attractive target for the development of antibody-drug conjugates, which combine targeted antibodies with potent chemotherapy drugs.[4 5] Previous trophoblast cell surface antigen 2 directed antibody-drug conjugates showed early promise but failed to demonstrate clinically meaningful survival benefits in unselected populations with NSCLC in phase 3 trials.[5 6] Sacituzumab tirumotecan is a novel trophoblast cell surface antigen 2 directed antibody-drug conjugate, engineered with an enhanced drug delivery system to improve stability and bioactivity.[7] Post hoc analyses from earlier trials showed that patients with *EGFR*-mutated tumours responded favourably to this drug, likely due to increased expression of trophoblast cell surface antigen 2 and enhanced cellular uptake.[8] These findings were further strengthened by the positive results from a non-randomised trial in 64 previously treated patients with *EGFR*-mutated NSCLC



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Blinded independent review committee assessed efficacy endpoints in patients with *EGFR*-mutated non-small cell lung cancer, according to treatment. Values are numbers (percentages) unless stated otherwise

Efficacy endpoints	Sacituzumab tirumotecan (n=91)	Docetaxel (n=45)
Tumour response:		
Partial response	41 (45)	7 (16)
Stable disease	34 (37)	20 (44)
Progressive disease	11 (12)	17 (38)
Not evaluable	5 (5)	1 (2)
Objective response rate:		
No (%, 95% CI)	41 (45, 35 to 56)	7 (16, 7 to 30)
Difference (% (95% CI))	29 (15 to 43)	—
P value (one sided)	0.0004	—
Disease control rate (No (%, 95% CI))	75 (82, 73 to 90)	27 (60, 44 to 74)
Difference (% (95% CI))	22 (6 to 39)	—

Data cut-off date for efficacy analysis was 31 December 2024. The blinded independent review committee assessed responses according to RECIST version 1.1. Members of the committee were masked to treatment group assignments. All responses were confirmed by blinded independent review committee.
CI=confidence interval; EGFR=epidermal growth factor receptor; RECIST=response evaluation criteria in solid tumour.

to 0.88)). Grade ≥3 treatment related adverse events were less frequent with sacituzumab tirumotecan than with docetaxel (56% *v* 72%), with no new safety signals identified. Limitations include the modest sample size and absence of quality of life assessment.

What this study adds Sacituzumab tirumotecan showed statistically significant and clinically meaningful improvements in objective response rate, progression-free survival, and overall survival compared with docetaxel in patients with *EGFR*-mutated locally advanced or metastatic NSCLC, and with a manageable safety profile.

Funding, competing interests, and data sharing
The study was funded by Sichuan Kelun-Biotech Biopharmaceutical and partly supported by the National Natural Science Foundation of China and Noncommunicable Chronic Diseases-National Science and Technology Major Project. Authors JY, YD, XJ, and JG are employed by Sichuan Kelun-Biotech Biopharmaceutical and authors YD, XJ, and JG hold company stock. Data supporting the findings of this study are available on the Research Data Deposit public platform (www.researchdata.org.cn; RDDA2025220748). Data are available from the corresponding author (LZ) upon reasonable scientific request.

Study registration ClinicalTrials.gov NCT05631262.

that provided compelling rationale for testing sacituzumab tirumotecan in a randomised trial specifically designed for this patient population.[8]

What do the results mean?

In their study, Fang and colleagues reported the results of such a trial conducted in China. In this multicentre, open label, randomised controlled, the investigators enrolled 137 patients with *EGFR*-mutated NSCLC with disease progression after treatment with tyrosine kinase inhibitors and subsequent platinum based chemotherapy. Patients were randomised 2:1 to receive either sacituzumab tirumotecan or docetaxel as standard of care. The results were striking: 45% of patients responded to sacituzumab tirumotecan compared with only 16% with docetaxel; median progression-free survival was more than doubled (6.9 *v* 2.8 months), and the 12 month overall survival rate was also higher (73% *v* 54%). Importantly, the safety profile appears manageable, with fewer grade 3 or higher adverse effects compared with docetaxel (56% *v* 72%) and no patient discontinued treatment due to adverse effects.

This study is the first randomised trial demonstrating that a trophoblast cell surface antigen 2 directed antibody-drug conjugate can deliver statistically significant and clinically meaningful improvements in patients with *EGFR*-mutated NSCLC, leading to approval in China.[9] However, several limitations affect broader application. The study used tumour shrinkage rather than patient survival as the primary endpoint, which limited interpretation of long term benefit.[10 11] The trial was conducted exclusively in Chinese patients, so findings may not apply to other populations with different genetic backgrounds.[12] Additionally, data on patient quality of life—an increasingly important measure of treatment benefit—were limited.[13] Given these constraints and the lack of established clinical guidelines, clinicians outside China should await results from ongoing international phase 3 trials[14-16] before incorporating sacituzumab tirumotecan into routine practice.

The promise of sacituzumab tirumotecan exemplifies the power of precision medicine

What's next?

The promise of sacituzumab tirumotecan exemplifies the power of precision medicine, showing how targeting a disease molecular subtype can yield substantial clinical benefits. However, several important questions remain that will shape future clinical guidelines and practice. For immediate clinical implementation, guidelines for patient selection criteria, optimal treatment sequences, and management strategies for patients when sacituzumab tirumotecan stops working need to be developed. This includes identifying biomarkers beyond expression levels of trophoblast cell surface antigen 2 that could predict treatment responsiveness, given that not all patients respond. From a research perspective, investigators should explore the underlying mechanisms of primary and acquired resistance, which could lead to more effective treatment strategies. Future clinical trials should evaluate combination strategies, including integration with EGFR tyrosine kinase inhibitors as first line treatment or with immune checkpoint inhibitors to enhance efficacy. Parallel studies are needed to optimise dosing regimens and formulations to improve potency while reducing adverse effects.

These promising results offer renewed hope for patients with advanced *EGFR*-mutated NSCLC and provide a foundation for future innovation in the treatment of this challenging disease. As we anticipate this important milestone—the potential for sacituzumab tirumotecan to transform treatment for patients with *EGFR*-mutated NSCLC—we must continue to harness the power of precision medicine to deliver better treatments to patients worldwide.

Cite this as: *BMJ* 2025;389:r1154

Find the full version with references at http://dx.doi.org/10.1136/bmj.r1154

Cancer outcomes in women without upfront surgery for ductal carcinoma in situ

Ryser MD, Thomas SM, Li Y, et al

Cite this as: *BMJ* 2025;390:e083542
Find this at doi: 10.1136/bmj-2024-083542

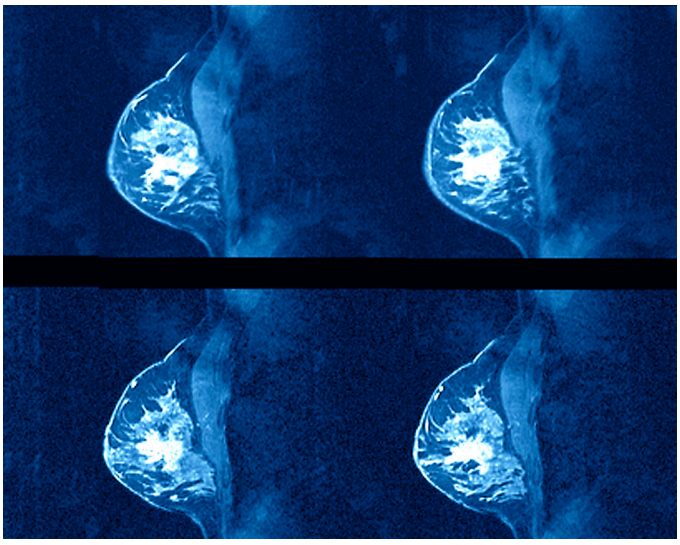
Study question In women who do not receive upfront surgery on diagnosis of ductal carcinoma in situ (DCIS), what is the subsequent risk of invasive cancer in the same breast?

Methods This observational cohort study used data from women who received a diagnosis of primary DCIS between 2008 and 2015 at 1330 American College of Surgeons Commission on Cancer accredited facilities in the US. The final cohort included 1780 women who did not undergo upfront surgery within six months of diagnosis and who were alive and free of invasive breast cancer at that time. The primary outcome was ipsilateral invasive breast cancer, assessed using Kaplan-Meier estimators over eight years. Subgroup analyses classified women as being at low risk (age ≥40, imaging detected, nuclear grade I/II, hormone receptor positive DCIS) or high risk (not meeting all low risk criteria).

Study answer and limitations The overall eight year cumulative incidence of ipsilateral invasive breast cancer was 10.7% (95% confidence interval 8.4% to 12.8%), ranging from 8.5% (4.7% to 12.1%) among women at low risk (n=650) to 13.9% (10.5% to 17.2%) among those at high risk (n=833). Limitations include incomplete generalisability owing to the higher prevalence of comorbid conditions and death from other causes compared with women who receive upfront surgery for DCIS.

What this study adds This is the largest US based cohort to evaluate outcomes in women with DCIS who did not undergo upfront surgery. Among these women, the risk of invasive progression at eight years ranged from 8% to 14%, depending on tumour and patient related characteristics. These findings underscore the need for effective risk stratification and shared decision making for this patient population.

Funding, competing interests, and data sharing This study was funded by a Patient-Centered Outcomes Research Institute Award. Three authors report industry relationships (see bmj.com). Data are available through the National Cancer Database with appropriate agreements.



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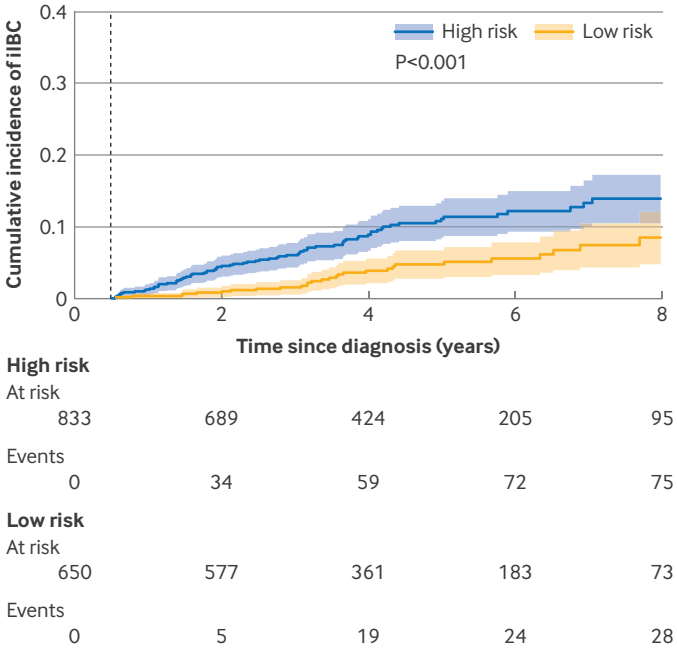

High risk					
At risk	833	689	424	205	95
Events	0	34	59	72	75
Low risk					
At risk	650	577	361	183	73
Events	0	5	19	24	28

Kaplan-Meier estimates of cumulative incidence of ipsilateral invasive breast cancer (iIBC), stratified by risk group

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