Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians

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STUDY QUESTION Does ionising radiation from computed tomography (CT) scans lead to an increased risk of cancer?
SUMMARY ANSWER For people exposed to at least one CT scan before age 20 years, cancer incidence was increased by 24% on average; the proportional increase in cancer risk was greater after scans at younger ages.
WHAT IS KNOWN AND WHAT THIS PAPER ADDS
The carcinogenic effect of ionising radiation has been well documented at larger doses, but not at the doses typically delivered by CT scans (5-50 mGy per organ imaged). This study reports increases for most types of cancer following CT scan exposure, and confirms an earlier report of increases in leukaemia and brain cancer.

Participants and setting
The cohort included all people with an Australian Medicare record, aged 0-19 years on 1 January 1985 or born during 1985-2005. All Medicare funded CT scans of cohort members aged 0-19 years during 1985-2005 were identified. Cohort members were followed to 31 December 2007 by record linkage to national cancer and death registers.

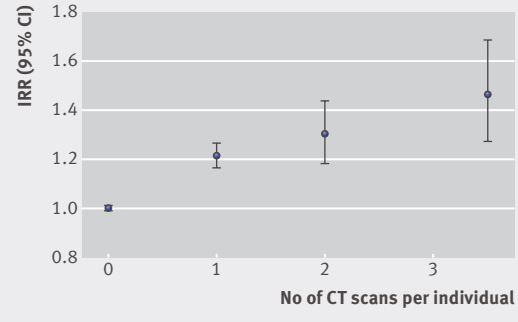
Design, size, and duration
For the 680 211 people with a Medicare record of a CT scan, we compared cancer incidence from one year after the first scan with rates for 10 259 469 unexposed people, by means of Poisson regression with stratification for sex, age, and year of birth. Mean length of follow-up in exposed individuals was 9.5 years.

Main results and the role of chance
The study cohort had 60 674 cancers, including 3150 in the exposed group. Overall cancer incidence was 24% greater for exposed people than for unexposed people (incidence rate ratio (IRR) 1.24 (95% confidence interval 1.20 to 1.29); P<0.001). We saw a dose-response association, with an IRR increase of 0.16 (0.13 to 0.19) for each additional CT scan. IRRs were greater following exposures at younger ages (P<0.001 for trend). At 1-4, 5-9, 10-14, and 15 or more years after first exposure, IRRs were 1.35 (1.25 to 1.45), 1.25 (1.17 to 1.34), 1.14 (1.06 to 1.22), and 1.24 (1.14 to 1.34), respectively. IRRs increased significantly for many types of solid cancer (digestive organs, melanoma, soft tissue, female genital, urinary tract, brain, and thyroid), and for leukaemias, myelodysplasias, and other lymphoid cancers. For all cancers, the absolute excess incidence rate was 9.38 per 100 000 person years at risk. An excess of 608 cancers was associated with exposure (147 brain, 356 other solid, 34 leukaemia, 14 myelodysplasia, and 57 other lymphoid or haematopoietic).

Bias, confounding, and other reasons for caution
Some people would have been wrongly classified as unexposed because we had no information about CT exposures not billed to Medicare (including exposures outside Australia) and exposures after the age of 19 years. Such misclassification would have weakened slightly the observed association between exposure and subsequent cancer risk. Although symptoms of some brain cancers could have led to brain scans several years before they were correctly diagnosed, such reverse causation is unlikely to explain the increased risks at longer periods after exposure.

Generalisability to other populations
In this cohort, most of the increased cancer incidence following CT scan exposure was likely to be due to irradiation. Similar risks after scans would be expected in other populations. Future risks could be reduced in all populations by restricting scans to cases with a definite clinical indication, and by improving procedures to provide a diagnostic image at the lowest possible radiation dose.

Incidence of all cancers in exposed versus unexposed cohorts, based on one year lag period



Study funding/potential competing interests
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Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis

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- Research: Validation of two age dependent D-dimer cut-off values for exclusion of deep vein thrombosis in suspected elderly patients in primary care: retrospective, cross sectional diagnostic analysis (*BMJ* 2012;344:e2985)
- Research: Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis (*BMJ* 2009;339:b2990)
- Research: Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study (*BMJ* 2012;345:e6564)

STUDY QUESTION What is the diagnostic value of D-dimer testing in older patients with suspected venous thromboembolism when the conventional cut-off value is applied, and is the use of an age adjusted cut-off value (age×10 µg/L in patients aged 50 or more) a safe and more efficient strategy?

SUMMARY ANSWER D-dimer testing is of limited utility in older patients when the conventional cut-off value is applied. Application of age adjusted cut-off values increases the specificity without modifying the sensitivity, thereby largely increasing the proportion of older patients with a non-high clinical probability in whom imaging can be safely avoided.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Since D-dimer levels increase with age, D-dimer testing is less useful to exclude venous thromboembolism in older patients if the conventional cut-off value (500 µg/L) is used. The specificity of D-dimer testing increased substantially when the age adjusted cut-off value was applied and was more than doubled in the eldest patients (>80 years). This would result in imaging examinations being correctly avoided in 30% to 55% of elderly patients with a non-high probability of venous thromboembolism.

Selection criteria for studies

We searched Medline and Embase for studies published before 21 June 2012 and contacted the authors of primary studies. We selected studies that enrolled older patients with suspected venous thromboembolism in whom D-dimer testing (using both conventional (500 µg/L) and age adjusted (age×10 µg/L in patients aged >50 years) cut-off values) and reference testing were performed. 2×2 tables were reconstructed and stratified by age category and D-dimer cut-off value.

Primary outcomes

Sensitivity and specificity of D-dimer testing in patients aged over 50 years.

Main results and role of chance

13 cohorts including 12 497 patients with a non-high clinical probability were included in the meta-analysis. The specificity of the conventional cut-off value decreased with increasing age, from 58% (95% confidence interval 51% to 64%) in patients aged 51-60 years to 39% (34% to 46%) in those aged 61-70 years, 25% (20% to 30%) in those aged 71-80 years, and 15% (11% to 19%) in those aged >80 years. Age adjusted cut-off values revealed higher specificities over all age categories: 62% (56% to 68%), 50% (43% to 56%), 44% (38% to 51%), and 35% (30% to 42%), respectively. Sensitivities of the age adjusted cut-off remained above 97% in all age categories.

Bias, confounding, and other reasons for caution

The results of this meta-analysis are not applicable to patients with a high clinical probability of venous thromboembolism, as additional imaging is warranted in these patients to confirm or refute the diagnosis, irrespective of the D-dimer test results. Additional analyses showed that the relative merit of application of the age adjusted instead of the conventional cut-off value is higher in the case of a low prevalence of venous thromboembolism compared with a higher prevalence. We found some heterogeneity in sensitivity and specificity of D-dimer among studies, partly explained by the application of different D-dimer assays. In 12 of the 13 included cohorts, venous thromboembolism was excluded without imaging examination in patients who were not at high risk, with a negative D-dimer (<500 µg/L) test result and no recurrence of symptoms during follow-up. This could have introduced small overestimations of the diagnostic accuracy of the D-dimer test, as small thrombi might have been missed in these patients.

Study funding/potential competing interests

This study was supported by the Netherlands Organization for Scientific Research. The authors were independent of the funders for all aspects of the study.

Pooled estimates of diagnostic accuracy of D-dimer testing in older patients suspected of having venous thromboembolism with a non-high clinical probability, per age category and cut-off value (13 study cohorts)

		Pooled sensitivity (95% CI)		Pooled specificity (95% CI)	
Age (years)	No of patients	Conventional cut-off (%)	Age adjusted cut-off (%)	Conventional cut-off (%)	Age adjusted cut-off (%)
≤50	5528	97.6 (95.0 to 98.9)	NA	66.8 (61.3 to 72.0)	NA
51-60	2043	100.0 (NA)	99.4 (97.3 to 99.9)	57.6 (51.4 to 63.6)	62.3 (56.2 to 68.0)
61-70	1815	99.0 (96.7 to 99.7)	97.3 (93.8 to 98.8)	39.4 (33.5 to 45.6)	49.5 (43.2 to 55.8)
71-80	1842	98.7 (96.5 to 99.5)	97.3 (94.3 to 98.8)	24.5 (20.0 to 29.7)	44.2 (38.0 to 50.5)
>80	1269	99.6 (96.9 to 99.9)	97.0 (92.9 to 98.8)	14.7 (11.3 to 18.6)	35.2 (29.4 to 41.5)

Age adjusted cut-off value (age×50 µg/L) does not apply (NA) to patients aged ≤50 years.

Day of week of procedure and 30 day mortality for elective surgery: retrospective analysis of hospital episode statistics

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STUDY QUESTION Is there any association between postoperative mortality and the day of the week on which the procedure is carried out?

SUMMARY ANSWER The risk of death is higher for patients who undergo elective surgical procedures later in the working week and at the weekend compared with those who have their operations carried out on Mondays. This does not seem to be explained by variations in case mix.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Previous research has suggested a significantly higher risk of death if patients are admitted as an emergency at the weekend compared with weekdays, but no large nationally representative studies have examined the day of elective procedure while also accounting for deaths after discharge. Our study suggests a potentially much stronger "weekday" and "weekend" effect for elective procedures than is seen in emergency admissions.

Participants and setting

Patients undergoing elective operating room procedures in English public hospitals over three financial years from 2008-09 to 2010-11.

Design

A retrospective analysis of national hospital administrative data.

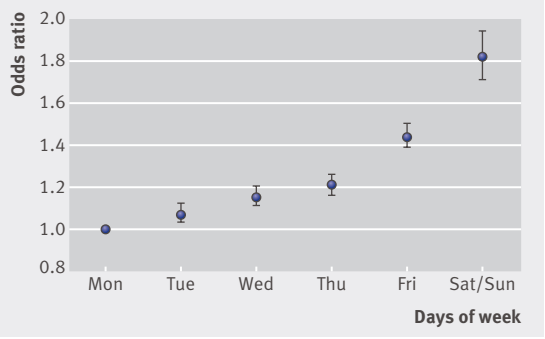
Primary outcome

Death in or out of hospital within 30 days of the procedure.

Main results and the role of chance

There were 27 582 deaths by 30 days after 4 133 346 inpatient admissions for elective operating room procedures (overall crude mortality rate 6.7 per 1000). The number of weekday and weekend procedures decreased over the three years (by 4.5% and 26.8%, respectively). The adjusted odds of death were 44% and 82% higher, respectively, if the procedures were carried out on Friday (odds ratio 1.44, 95% confidence interval 1.39 to 1.50) or at the weekend (1.82, 1.71 to 1.94) compared with Monday.

Adjusted odds of death by day of procedure in English hospitals for 2008-09 to 2010-11



Bias, confounding, and other reasons for caution

One of the weaknesses of using administrative data is that we were unable to completely adjust for the selection bias that probably exists for elective procedures that are scheduled at weekends. Our findings around weekend mortality should therefore be interpreted with caution. Weekday procedures are less prone to such extreme selection bias, and our findings of higher adjusted 30 day mortality for patients who have procedures carried out closer to the end of the week are more robust. Daily variation in those risk factors that we were able to account for seemed to suggest that patients operated on towards the end of the week and at the weekend actually had a lower risk profile than Monday patients. Without more detailed information related to surgical care processes, it remains unclear if the estimated risks can be entirely attributed to differences in quality of care.

Generalisability to other populations

Our analysis was based on national administrative data from English hospitals and is therefore likely to be generalisable to the rest of the United Kingdom. We did find some heterogeneity by procedure, and there is also likely to be some heterogeneity by hospital. As a result of this work, other countries with healthcare systems operating reduced services/staffing at weekends could benefit from looking at their own outcomes by weekday.

Study funding

The Dr Foster Unit at Imperial College London is funded by a research grant from Dr Foster Intelligence (an independent health service research organisation) and joint venture with the Department of Health. The Dr Foster Unit at Imperial is affiliated with the Imperial Centre for Patient Safety and Service Quality at Imperial College Healthcare NHS Trust, which is funded by the National Institute of Health Research.

Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study

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STUDY QUESTION How well does a new risk algorithm (QStroke) estimate risk of stroke or transient ischaemic attack in patients without prior stroke events, including patients with atrial fibrillation?

SUMMARY ANSWER QStroke provides a valid measure of absolute stroke risk in the general population of patients and in the subset with atrial fibrillation, as shown by its performance in a validation cohort.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Methods to classify patients at high or low risk of stroke are needed to identify those for whom interventions may be required, especially those with atrial fibrillation, who might need anticoagulation. QStroke shows some improvement on current risk scoring methods for the subset of patients with atrial fibrillation.

Participants and setting

In the derivation cohort for QStroke, we studied 3.5 million patients aged 25-84 years with 24.8 million person years who experienced 77 578 first stroke events. For the validation cohort, we identified 1.9 million patients aged 25-84 years with 12.7 million person years who experienced 38 404 first stroke events. We excluded patients with a prior diagnosis of stroke or transient ischaemic attack and those prescribed oral anticoagulants at study entry.

Design, size, and duration

This prospective open cohort study used routinely collected data from QResearch general practices in England and Wales. We used 451 practices to develop the scores (derivation cohort) and a separate set of 225 practices to validate the scores (validation cohort). We used Cox proportional hazards models in the derivation cohort to derive risk equations. Risk factors considered included self assigned ethnicity, age, sex, smoking status, systolic blood pressure, ratio of total serum cholesterol to high density lipoprotein cholesterol, body mass index, history of coronary heart disease in a first degree relative aged <60 years, Townsend deprivation score, treated hypertension, type 1 and type 2 diabetes, renal disease, rheumatoid arthritis, coronary heart disease, congestive cardiac failure, valvular heart disease, and atrial fibrillation. We tested the performance of the QStroke algorithm in the validation dataset and made comparisons with other risk scores for stroke.

Main results and the role of chance

The QStroke algorithm explained 57% of the variation in women and 55% in men without a prior stroke. The D statistic (a measure of discrimination) for QStroke was 2.4 in women and 2.3 in men. QStroke had improved performance on all measures of discrimination and calibration compared with the Framingham risk score for stroke in patients without a prior stroke. In patients with atrial fibrillation, levels of discrimination were lower, but QStroke had some improved performance on all measures of discrimination compared with current risk scoring methods $CHADS_2$ and CHA_2DS_2VASc.

Bias, confounding, and other reasons for caution

Limitations include lack of formally adjudicated outcomes, information bias, potential for bias due to missing data, and residual confounding.

Generalisability to other populations

A strength of our study is that we have developed the algorithms in one cohort and validated in a separate cohort representative of the patients likely to be considered for preventive measures.

The algorithm is based on simple clinical variables that patients will know or that are routinely recorded in UK general practices. The algorithm could be integrated into GP clinical computer systems and used to assess risk of stroke in patients.

Study funding/potential competing interests

JHC is co-director of QResearch, a partnership of University of Nottingham and EMIS (commercial supplier of IT for UK general practices), and is director of ClinRisk, which produces software for clinical risk algorithms. CC works for University of Nottingham and is a consultant statistician for ClinRisk.

Validation statistics for the QStroke prediction algorithm in the validation cohort

Prediction algorithm and validation statistic		Mean (95% CI) Women	Men
All patients		**(n=962 083)**	**(n=935 085)**
QStroke (25-84 years)	R^2 (%)*	57.3 (56.8 to 57.8)	55.1 (54.6 to 55.7)
	D statistic*	2.37 (2.35 to 2.40)	2.27 (2.24 to 2.30)
	ROC statistic*	0.877 (0.875 to 0.879)	0.866 (0.864 to 0.868)
QStroke (35-74 years)	R^2 (%)*	43.7 (42.9 to 44.5)	41.9 (41.1 to 42.7)
	D statistic*	1.80 (1.77 to 1.83)	1.74 (1.71 to 1.77)
	ROC statistic*	0.814 (0.810 to 0.818)	0.806 (0.802 to 0.809)
Framingham stroke equation (35-74 years)	R^2 (%)*	38.5 (37.7 to 39.4)	35.7 (34.8 to 36.5)
	D statistic*	1.62 (1.59 to 1.65)	1.52 (1.50 to 1.55)
	ROC statistic*	0.798 (0.794 to 0.802)	0.788 (0.784 to 0.791)
Patients with atrial fibrillation at baseline		**(n=3180)**	**(n=4509)**
QStroke	R^2 (%)*	14.0 (9.2 to 18.7)	24.1 (19.3 to 28.9)
	D statistic*	0.82 (0.66 to 0.99)	1.15 (1.00 to 1.30)
	Harrell's C statistic*	0.65 (0.62 to 0.67)	0.71 (0.69 to 0.73)
CHA_2DS_2VASc	R^2 (%)*	9.6 (5.5 to 13.8)	18.3 (13.7 to 22.8)
	D statistic*	0.67 (0.51 to 0.83)	0.97 (0.82 to 1.12)
	Harrell's C statistic*	0.62 (0.59 to 0.65)	0.67 (0.65 to 0.69)
$CHADS_2$	R^2 (%)*	9.1 (4.9 to 13.2)	13.5 (9.1 to 17.9)
	D statistic*	0.64 (0.49 to 0.81)	0.81 (0.66 to 0.96)
	Harrell's C statistic*	0.61 (0.59 to 0.64)	0.63 (0.61 to 0.66)

*Measures of discrimination, higher values indicate better discrimination.