RESEARCH

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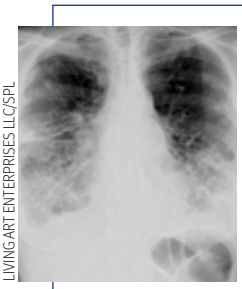


LIVING ART ENTERPRISES LLC/SPL

THIS WEEK'S RESEARCH QUESTIONS

1348 What risk of mortality is associated with tiotropium delivered by mist inhaler in patients with chronic obstructive pulmonary disease?

1349 Is cryotherapy with liquid nitrogen more clinically effective than 50% salicylic acid for treatment of plantar warts?

1350 Are maternal snoring and supine sleep position associated with increased risk of late stillbirth?

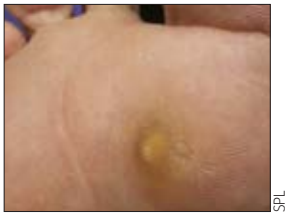
1351 What are the outcomes of pregnancy in women admitted to hospital with H1N1 influenza in pregnancy?

1352 Could deficiencies in the cancer registration system explain the lower survival after cancer in the UK?

Mortality associated with use of tiotropium mist inhaler

The tiotropium mist inhaler is aimed at patients with chronic obstructive pulmonary disease who find it hard to take this anticholinergic drug via a standard inhaler. It is available in more than 50 countries but not yet in the United States, perhaps because there has been conflicting evidence on the cardiovascular safety of inhaled anticholinergics and because this inhaler leads to relatively high plasma concentrations of the drug. Sonal Singh and colleagues' meta-analysis of five randomised controlled trials with a total of 6522 patients found that, when compared with placebo, the mist inhaler was associated with a significantly increased risk of mortality (p 1348). The authors estimated that the number needed to treat for a year with the 5 µg dose to see one additional death was 124 (95% confidence interval 52 to 5682). In the long version of the paper on bmj.com the authors urge clinicians to tell patients about the possibility of this increased risk and to be cautious when prescribing tiotropium mist inhaler, particularly for those with possible underlying cardiac disease (doi:10.1136/bmj.d3215).

Freezing warts is no more effective than keratolysis with salicylic acid



SPL

For such a common problem, we know surprisingly little about the best treatment for cutaneous warts. Now Sarah Cockayne and colleagues have compared, in a randomised controlled trial, two of the most common treatments (and the only ones with a good evidence base), cryotherapy with liquid nitrogen and salicylic acid (at 50% strength), on plantar warts (p 1349). They found no difference in effectiveness at 12 weeks but suggest that, since cryotherapy is more costly, salicylic acid is the more attractive treatment.

However, with cure rates of only 14% for both treatments, one might also conclude that they are probably no more effective than a wait and see policy—as Jan Nico Bouwes Bavinck and colleagues do in their accompanying editorial (p 1320). They also point out that little is known about the epidemiology of the various types of human papillomavirus that cause warts and their sensitivity to different treatments, so it may be unsurprising that treatments often fail. Despite most warts clearing spontaneously quite quickly, many cause problems from discomfort or disfigurement for a definitive treatment to be desirable.

Late stillbirth and maternal sleeping position

The Auckland Stillbirth Study was set up to identify potentially modifiable risk factors for late stillbirth (≥28 weeks' gestation), for which there is usually no medical explanation. Maternal obesity is one of the known risk factors, but the underlying mechanisms for its association with stillbirth are not understood. Since obesity is also associated with sleep disordered breathing, this could be a possible explanation.

In this week's *BMJ* Tomasina Stacey and colleagues report on the association between maternal sleep practices and late stillbirth risk, using self reported snoring and daytime sleepiness as markers for sleep disordered breathing (p 1350). They found no relation between either marker and risk of late stillbirth, but women who slept on their back or on their right side on the last night of pregnancy (the night before when the woman thought that her baby had died or, for the controls, the night before interview) were twice as likely to have a late stillbirth as women who slept on their left side. The absolute risk of late stillbirth remained low, however: for those who went to sleep on their left it was 1.96 stillbirths per 1000 and for those who slept in any other position it was 3.93 per 1000. The study also found a high correlation between a woman's position on going to sleep and her position on waking up, so it looks as though pregnant women tend to stay in the same sleeping position overnight.

The authors warn that this novel finding needs to be replicated in other studies before public health recommendations can be made. In a linked editorial, Lucy Chappell from King's College London, says "any simple intervention that reduces the risk of stillbirth would be extremely welcome," but warns that these findings need to be interpreted with extreme caution (p 1321). She concludes that "a forceful campaign urging pregnant women to sleep on their left side is not yet warranted" and that this study is only hypothesis generating.

LATEST RESEARCH: For these and other new research articles see www.bmj.com/research

Effectiveness of a multifaceted podiatry intervention to prevent falls in community dwelling older people with disabling foot pain Martin Spink and colleagues concluded that this intervention—comprising foot orthoses, advice on footwear, subsidy for footwear, home based exercises, education about preventing falls, and routine podiatry care for 12 months—was effective and potentially simple to implement (doi:10.1136/bmj.d3411).

Management of severe sepsis in patients admitted to Asian intensive care units In a prospective cohort study, Jason Phua and colleagues assessed how well Asian intensive care units and hospitals complied with recommendations of the Surviving Sepsis Campaign's resuscitation and management bundles (doi:10.1136/bmj.d3245).

Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials

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EDITORIAL by Cates

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bmj.com
Tiotropium and chronic obstructive pulmonary disease (*BMJ* 2010;340:c833)

STUDY QUESTION

What is the risk of all cause mortality associated with tiotropium solution delivered by mist inhaler (Respimat Soft Mist Inhaler; Boehringer Ingelheim) in patients with chronic obstructive pulmonary disease in randomised controlled trials?

SUMMARY ANSWER

Tiotropium mist inhaler was associated with a significantly increased risk of all cause mortality in patients with chronic obstructive pulmonary disease.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A meta-analysis of 17 trials found a significantly increased risk of major cardiovascular events with inhaled anticholinergics, but the risk of all cause mortality with tiotropium (an anticholinergic) by mist inhaler is not known. This systematic review and meta-analysis of the available randomised placebo controlled trials involving 6522 patients suggests the possibility of an increased risk of mortality associated with the mist inhaler.

Selection criteria for studies

We identified randomised controlled trials in Medline, Embase, and trial registries (from inception to July 2010) that compared tiotropium solution delivered using the Respimat Soft Mist Inhaler (Boehringer Ingelheim) with placebo among participants with chronic obstructive pulmonary disease and that reported on mortality.

Primary outcome(s)

We focused on patient oriented outcomes of all cause mortality (primary outcome) and cardiovascular death (secondary outcome).

Main results and role of chance

We included five placebo controlled randomised trials involving 6522 patients with chronic obstructive pulmonary disease. When compared with placebo the mist inhaler was associated with a significantly increased risk of mortality (90/3686 *v* 47/2836; relative risk 1.52, 95% confidence interval, 1.06 to 2.16; P=0.02). The number needed to treat for a year with the 5 µg dose to see one additional death was estimated to be 124 (95% confidence interval 52 to 5682).

Bias, confounding, and other reasons for caution

The populations, doses of tiotropium, and length of follow-up differed between the trials. The estimates are imprecise owing to the fairly low event rate in the trials, and time to event data were unavailable.

Study funding/potential competing interests

SS is supported by a grant from the National Center for Research Resources, a component of the National Institutes of Health (No 1KL2RR025006-03). PE has received about $30 000 (£18 000; €21 000) from Pfizer to review the quality of spirometry tests done for an international study of varenicline for smoking cessation in patients with chronic obstructive pulmonary disease.

RISK OF MORTALITY AND CARDIOVASCULAR DISEASE ACCORDING TO DOSE OF TIOTROPIUM MIST INHALER IN 6522 PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Outcome and dose	No of studies	Relative risk (95% CI)	Annualised number needed to treat to harm (95% CI)
Mortality:			
5 µg and 10 µg	5	1.52 (1.06 to 2.16)	110 (49 to 947)
5 µg	5	1.46 (1.01 to 2.10)	124 (52 to 5862)
10 µg	4	2.15 (1.03 to 4.51)	50 (17 to 1894)
Cardiovascular death:			
5 µg and 10 µg	5	2.05 (1.06 to 3.99)	208 (73 to 3624)

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CME

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Cryotherapy versus salicylic acid for the treatment of plantar warts (verrucae): a randomised controlled trial

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EDITORIAL by Bavnik et al

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bmj.com
Common skin infections in children

STUDY QUESTION

Is cryotherapy with liquid nitrogen more clinically effective than 50% salicylic acid for treatment of plantar warts?

SUMMARY ANSWER

No, there was no evidence of a difference in the clearance rates of plantar warts treated with salicylic acid or cryotherapy.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

There are many different treatments for cutaneous warts but the evidence base on which to inform clinical decision making is poor. This study found no evidence of a difference in cure rates between plantar warts treated by cryotherapy or salicylic acid.

Design

In this parallel group, randomised controlled trial participants were randomised to receive either cryotherapy with nitrogen (maximum of four treatments, two to three weeks apart) or 50% salicylic acid (self treatment applied daily for a maximum of eight weeks). Randomisation was performed by a member of the research team either telephoning an independent, secure, remote, telephone randomisation service or accessing a secure online randomisation programme to receive a concealed treatment allocation. The randomisation schedule used a simple computer generated list with no stratification or blocking.

Participants and setting

We recruited 240 participants aged 12 years and over with a plantar wart that was suitable for treatment with both cryotherapy or salicylic acid from UK and Irish university podiatry school clinics, NHS podiatry clinics, and primary care.

Primary outcome

Complete clearance of all plantar warts at 12 weeks.

Main results and the role of chance

We found no significant difference in the cure rate between the two groups. The cure rates were 17/119 (14%) in the salicylic acid group and 15/110 (14%) in the cryotherapy group (difference 0.65% (95% CI −8.33 to 9.63), P=0.89).

Harms

A total of 28 adverse events were reported in 19 participants. One event was serious and unrelated to the trial treatment. The remainder were not serious, with two events related to the cryotherapy treatment (a blister that was larger than expected in routine practice).

Bias, confounding, and other reasons for caution

The overall cure rate is lower than we anticipated based on previously published studies. However, we are unable to determine the spontaneous clearance rate in this population as a "no treatment group" was not included.

Generalisability to other populations

We evaluated patient self treatment with salicylic acid, and so these results cannot be extrapolated to the effectiveness of treatment delivered by a healthcare professional. Recruitment from a wide range of centres means the results are broadly generalisable across the UK and Ireland and potentially to other similar populations.

Study funding/potential competing interests

This project was funded by the National Institute for Health Research, Health Technology Assessment Programme and will be published in full in *Health Technology Assessment*. William Ransom and Son supplied the salicylic acid at no cost, and BOC provided one site with liquid nitrogen equipment at reduced cost. These manufacturers had no role in the design of the trial or in the collection, analysis, and interpretation of the data.

Trial registration number

ISRCTN18994246.

SECONDARY OUTCOMES FOR CLEARANCE OF PLANTAR WARTS WITH SALICYLIC ACID OR CRYOTHERAPY

Outcome	Salicylic acid *v* cryotherapy
Clearance at 12 weeks controlling for age, previous treatment, and type of wart	Odds ratio 0.96 (95% CI 0.44 to 2.11)
Clearance at 6 months controlling for age, previous treatment, and type of wart	29/95 (31%) *v* 33/98 (34%) Odds ratio 1.17 (95% CI 0.62 to 2.21)
Time to clearance (days)	Median 163 (95% CI 145 to 181) *v* 177 (159 to 195) Hazard ratio 0.80 (95% CI 0.51 to 1.25)

CME

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Association between maternal sleep practices and risk of late stillbirth: a case-control study

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EDITORIAL by Chappell and Smith

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- Research: Babies sleeping with parents (*BMJ* 1999;319:1457)
- Research: Environment of infants during sleep and risk of the sudden infant death syndrome (*BMJ* 1996;313:191)

STUDY QUESTION

Are maternal snoring and supine sleep position associated with increased risk of late stillbirth?

SUMMARY ANSWER

Maternal non-left sided sleep position was associated with a roughly doubled risk of late stillbirth (absolute risk 3.93/1000), but maternal snoring was not associated with increased risk.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Maternal body position in late pregnancy can influence maternal cardiac output and fetal oxygen saturation. This study found that women who did not go to sleep on their left side on the last night before late stillbirth had a doubled risk compared with women who went to sleep on their left. These findings must be treated with caution unless confirmed.

Participants and setting

Women with a singleton late stillbirth (≥28 weeks' gestation) without congenital abnormality in Auckland, New Zealand, were eligible to participate. For each case, we recruited two controls with singleton ongoing pregnancies and gestation matched to that at which the stillbirth occurred.

Design, size, and duration

During the period of this case-control study (from July 2006 to June 2009), 215 eligible women had a late stillbirth. Of these, 155 (72%) consented to participate, as did 310/429 (72%) of the eligible controls. Multivariable logistic regression adjusted for known confounding factors.

Primary outcome(s), risks, exposures

As well as late stillbirth, we assessed maternal snoring, daytime sleepiness (measured with the Epworth sleepiness scale), and sleep position at the time of going to sleep and on waking (left side, right side, back, and other).

Main results and the role of chance

No relation was found between snoring and risk of late stillbirth. However, women who slept on their back or on their right side on the last night (before stillbirth or, for the controls, before the interview) were more likely to experience a late stillbirth compared with women who slept on their left side (table). Women who got up to the toilet once or less during the last night were more likely to experience a late stillbirth than women who got up more frequently. Women who regularly slept during the day in the last month of the pregnancy, were also more likely to experience a late stillbirth than those who did not.

Bias, confounding, and other reasons for caution

Case-control studies are potentially subject to recall bias. Recall bias was reduced as far as possible in this study by using a structured interview and ensuring that participants were unaware of the study hypotheses. Sleep position and getting up in the night have not previously been related to stillbirth, so it is unlikely that recall bias had a significant impact on our findings. This is the first time that an association has been reported between maternal sleep practices and late stillbirth risk. These findings need to be treated with caution, and further studies are needed to confirm or refute these findings before public health recommendations can be made.

Generalisability to other populations

These findings did not alter after adjustment for maternal characteristics such as age, body mass index, or ethnicity. If our findings are confirmed, promoting optimal sleep position in late pregnancy may have the potential to reduce the incidence of late stillbirth. The absolute risk of late stillbirth in the population we studied was 3.09/1000 (95% confidence interval 2.70 to 3.53/1000); extrapolating our results to this population would give a risk of late stillbirth for women who went to sleep on the left of 1.96/1000 (1.50 to 2.51/1000) and a risk of 3.93/1000 (3.35 to 4.59/1000) for women who did not go to sleep on their left.

Study funding/potential competing interests

The study was funded by Cure Kids, the Nurture Foundation, and the Auckland District Health Board Trust fund. EAM, JMDT, and TS are supported in part by Cure Kids.

MATERNAL SLEEPING PRACTICES AND RISK OF LATE STILLBIRTH: MULTIVARIABLE ANALYSIS

Practice	No (%) of women: Cases (n=155)	Controls (n=310)	Adjusted odds ratio (95% CI)*	P value of difference
Sleeping position on last night of pregnancy:				
Left side	42 (27)	132 (43)	1.00	x^2=7.77, P=0.005
Right side	49 (32)	84 (27)	1.74 (0.98 to 3.01)	
Back	15 (10)	15 (5)	2.54 (1.04 to 6.18)	
Other	49 (32)	79 (25)	2.32 (1.28 to 4.19)	
Regular sleep in daytime in last month of pregnancy:				
No	77 (50)	194 (63)	1.00	x^2=9.23, P=0.002
Yes	78 (50)	116 (37)	2.04 (1.26 to 3.30)	
Hours of night time sleep in last month of pregnancy:				
<6	30 (19)	46 (15)	1.89 (0.98 to 3.65)	x^2=6.13, P=0.05
6–8	82 (53)	205 (66)	1.00	
>8	43 (28)	59 (19)	1.71 (0.99 to 2.95)	
No of times getting up to toilet during last night of pregnancy:				
>1	86 (55)	207 (67)	1.00	x^2=9.99, P=0.002
≤1	69 (45)	103 (33)	2.42 (1.46 to 4.00)	

*Adjusted for age, ethnicity, overweight or obesity, parity, social deprivation level, smoking, and the other variables in the table.

Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study

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EDITORIAL by Joseph and Liston

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bmj.com
Research: Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women (*BMJ* 2010;340:c1279)

STUDY QUESTION

What are the outcomes of pregnancy in women admitted to hospital with confirmed 2009/H1N1 influenza in pregnancy?

SUMMARY ANSWER

Women infected with 2009/H1N1 influenza have an increased risk of poor pregnancy outcomes, including perinatal mortality and preterm delivery, compared with uninfected women.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Pregnancy is known to be a risk factor for critical illness and death in pregnant women after 2009/H1N1 infection. Women infected with 2009/H1N1 influenza in pregnancy are also at risk of poor pregnancy outcomes, with an increased risk of preterm and very preterm delivery and perinatal mortality.

Participants and setting

Participants comprised all women admitted with confirmed 2009/H1N1 infection in pregnancy to hospitals with obstetrician led maternity units in the United Kingdom during the second wave of pandemic infection between September 2009 and January 2010 and comparison pregnant women from the same units. We did not include postpartum women.

Design, size, and duration

This was a national cohort study using the UK Obstetric Surveillance System to identify cohort and comparison women. We included 256 pregnant women with confirmed 2009/H1N1 influenza and 1220 uninfected pregnant women for comparison. We followed up women with 2009/H1N1 influenza who had not delivered at the time of their infection until completion of their pregnancy.

Primary outcomes

The main outcomes were rates of stillbirth, perinatal mortality, neonatal mortality, and preterm delivery and odds ratios adjusted for maternal socioeconomic status, ethnicity, parity, age, smoking status, multiple birth, and body mass index.

Main results and the role of chance

Perinatal mortality was higher in infants born to infected women (10 deaths among 256 infants; rate 39 (95% confidence interval 19 to 71) per 1000 total births) than in infants of uninfected women (nine deaths among 1233 infants; rate 7 (3 to 13) per 1000 total births) (P<0.001). This was principally explained by a higher rate of stillbirth (27 v 6 per 1000 total births; P=0.001). Infants of infected women were also more likely to be born prematurely (adjusted odds ratio 4.0, 95% confidence interval 2.7 to 5.9). Infected women who delivered preterm were more likely to be infected in their third trimester (P=0.046), to have been admitted to an intensive care unit (P<0.001), and to have a secondary pneumonia (P=0.001) than were those who delivered at term.

Bias, confounding, and other reasons for caution

As this was an observational study, persisting confounding that we were not able to account for may remain. Other possible known confounders, such as previous delivery by caesarean section, inter-pregnancy interval, or quality or type of obstetric care, may have contributed to the relation we found. In addition, the analysis had limited power to adjust fully even for known confounders when the number of outcomes was small, and the results should therefore be interpreted with caution.

Generalisability to other populations

This study is generalisable to other Western populations in countries with well developed health systems.

Study funding/potential competing interests

This research was funded by a grant from the National Institute for Health Research Health Technology Assessment Programme. MK was funded by a personal award from the NIHR National Coordinating Centre for Research Capacity Development.

OUTCOME OF PREGNANCY FOR WOMEN ADMITTED TO HOSPITAL WITH 2009/H1N1 INFECTION (INFECTED COHORT) AND UNINFECTED WOMEN (COMPARISON COHORT)

Outcome of pregnancy	No (%) in infected cohort (n=256)	No (%) in comparison cohort (n=1220)	Adjusted odds ratio (95% CI)
Stillbirth	7 (3)	7 (1)	4.2 (1.4 to 12.4)
Neonatal death	3 (1)	2 (0)	5.6 (0.5 to 64.2)
Perinatal death	10 (4)	8 (1)	5.7 (2.2 to 15.1)
Preterm (<37 weeks)	59 (23)	89 (7)	4.0 (2.7 to 5.9)
Very preterm (<32 weeks)	18 (7)	18 (1)	4.9 (2.4 to 10.0)

Evidence against the proposition that "UK cancer survival statistics are misleading": simulation study with National Cancer Registry data

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STUDY QUESTION

Could deficiencies in the cancer registration system explain the lower survival after cancer in the UK than in other countries in western Europe?

SUMMARY ANSWER

Even implausibly extreme levels of errors in the cancer registry data could not explain the international differences in survival seen between the UK and other European countries.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A recent *BMJ* editorial asserted that lower survival after cancer in the UK than in other equally developed nations is due to two errors in the cancer registration process. Comprehensive simulations using the entire National Cancer Registry show that neither of these errors can plausibly explain low survival in England and Wales.

Participants and setting

We included all patients diagnosed as having cancer of the breast (women), lung, or colorectum in 1995-2007 in England and Wales with follow-up to 31 December 2007.

Design, size, and duration

We estimated relative survival up to five years after diagnosis by sex and site. We then simulated each of two hypothesised errors in the cancer registration process (recording of the date of cancer recurrence, instead of the date of diagnosis, for cancer registrations that are initiated from a death certificate; and long term survivors who are never notified to the registry) and estimated the change in survival that would arise if the errors occurred to varying degrees, by using 100 repetitions.

Main results and the role of chance

To explain the differences in one year survival after breast cancer between England and Sweden, under the first hypothesis the date of diagnosis would have to have been incorrectly recorded by an average of more than a year for more than 70% of women known to be dead (figure). Under the second hypothesis, failure to register 5% of long term survivors was associated with an increase in one year survival of 0.2% and failure to register 20% with an increase in one year survival of less than 1%. Even if 40% of long term survivors had not been registered, this would explain less than half the difference in one year survival. This degree of under-registration would also imply that the incidence of breast cancer by age in England had a completely different, unique pattern. Results were similar for lung and colorectal cancers. Even if the two proposed errors were to work together, the errors would still need to be implausibly extensive to explain the full difference. In all simulations, the survival averaged on the 100 datasets flattened after about the 60th replication, indicating convergence.

Bias, confounding, and other reasons for caution

Artefactual differences in survival could arise if information on the death of patients with cancer was substantially incomplete in one population.

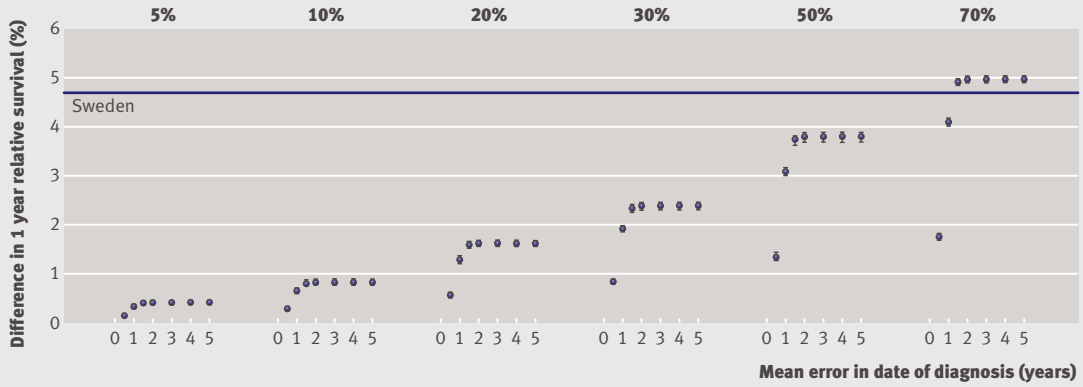
Generalisability to other populations

The proposed errors could occur in any population based cancer registry, but they are most unlikely to explain large differences in survival.

Study funding/potential competing interests

The study received no funding.

SIMULATED INCREASE IN 1 YEAR RELATIVE SURVIVAL IN ENGLAND AND WALES BY PERCENTAGE OF DECEASED PATIENTS WHOSE SURVIVAL TIME WAS EXTENDED, AND MEAN EXTENSION OF THEIR SURVIVAL



Baseline estimate is relative survival estimate in observed data before any simulated changes in survival time
Data points represent absolute percentage change in relative survival from baseline estimate