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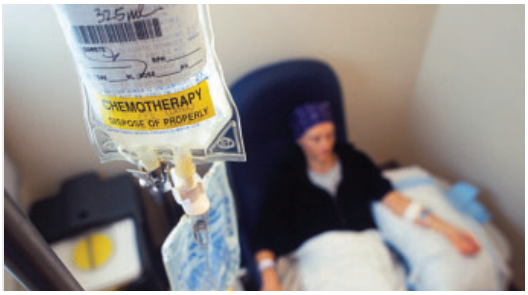

Cancer incidence and mortality in the UK
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Prevention of adverse perinatal outcomes
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Cancer trends in the UK

ORIGINAL RESEARCH Retrospective secondary analysis

25 year trends in cancer incidence and mortality among adults aged 35-69 years in the UK, 1993-2018

Shelton J, Zotow E, Smith L, et al

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Study question What are the trends in UK cancer incidence and mortality for men and women aged 35-69 years for all cancers combined and for the most common cancer sites?

Methods Secondary data of adults aged 35-69 years with a diagnosis of, or who died from, cancer between 1993 and 2018 in the UK were retrospectively analysed. 23 cancer sites were included in the analysis. Cancer registration, mortality, and population data were obtained from each of the countries in the UK. The primary outcome was change in cancer incidence and deaths, and age standardised rates over time by sex.

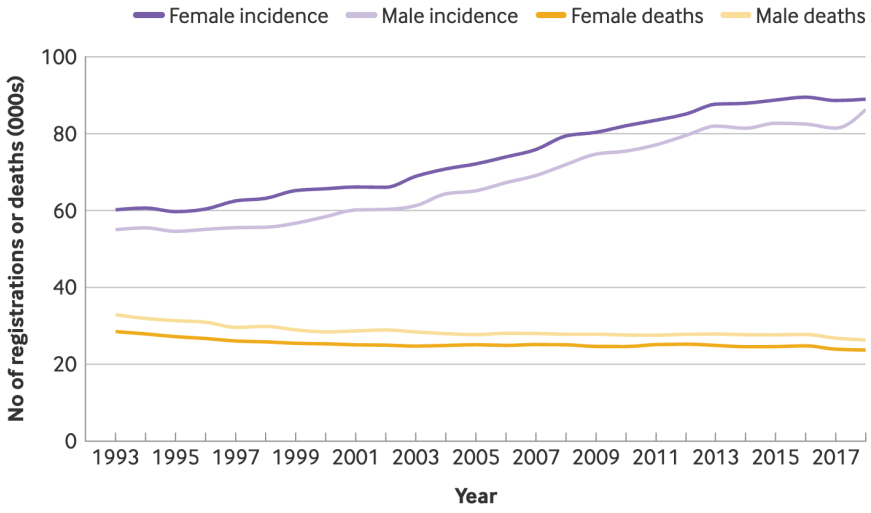
Study answer and limitations Between 1993 and 2018, the number of cancer registrations rose by 57% for men (55 014 to 86 297) and 48% for women (60 187 to 88 970), with an average 0.8% annual increase in incidence rates for both sexes. During 1993-2018, cancer mortality substantially declined in men (−37%) and women (−33%). The largest decreases in mortality were noted for stomach and bladder cancers and mesothelioma in men, and stomach and cervical cancers and non-Hodgkin's lymphoma in women. Lung and bowel cancers were the other two major sites of cancer in men and women (aside from prostate and breast cancer) that showed substantial reductions in mortality. These results are likely from primary prevention (historical reduction in smoking rates) for lung cancer, and earlier detection (eg, screening) and improved treatment for bowel cancer. Limitations include not breaking down cancer sites by histological type to further understand trends, and scarcity of recorded data for disease stage to understand diagnostic changes.

What this study adds This study found that cancer mortality substantially decreased in both men and women aged 35-69 years from 1993 to 2018. This decline is likely a reflection of successes in cancer

Largest decreases in mortality were noted for stomach and bladder cancers and mesothelioma in men, and stomach and cervical cancers and non-Hodgkin's lymphoma in women

prevention (eg, smoking prevention policies and cessation programmes), earlier detection (eg, screening programmes), improved diagnostic tests, and more effective treatment. In contrast, increased prevalence of non-smoking risk factors, such as overweight and obesity, are likely driving increases in other cancer sites.

Funding, competing interests, and data sharing
No funding or competing interests declared. Data sharing may be possible for additional analyses by contacting the corresponding author. All code is available from the corresponding author.



Number of newly diagnosed cancer registrations and deaths in the UK for all cancers, excluding non-melanoma skin cancer for incidence (international classification of diseases, 10th revision, codes C00-C97, excluding C44 for incidence), in men and women aged 35-69 years, 1993 to 2018

COMMENTARY Grounds for optimism but warning signs must not be ignored

Cancer is a major public health problem in the UK, and in most high income countries. The disease is the leading cause of death in both men and women, and one in four people die prematurely from it at ages 30-69 years.[1] A comprehensive assessment of the evolution of cancer incidence and mortality rates over time is not straightforward because of multiple disease types, each with its own underlying causes and effective means of control. Such an overarching assessment, nonetheless, serves as a report card on national progress in cancer control by enabling three lines of inquiry. How have cancer rates changed? What factors drive these trends? And what can be done to reduce the future burden?

In their paper, Shelton and colleagues undertook such an investigation in the UK, reviewing the trends in 23 cancer types in adults aged 35-69, over a quarter of a century from 1993 to 2018.[2] The results were generally encouraging, reaffirming previous investigations.[3 4] Despite an ageing population, the number of cancer deaths in the UK has continually declined, while age standardised mortality rates per 100 000 for all cancers combined fell by 2% for men and 1.6% for women, per annum. Mortality rates for 14 cancer types in men and 17 types in women reduced significantly by at least 0.5% per year, 12 of which types are linked to smoking.[5]

Lung, colorectal, breast, and prostate cancer—responsible for about half of all newly reported cancers and cancer deaths in the UK—had significant declines of around 2-3% per annum, hastened by tobacco control (lung cancer), alongside earlier detection through screening or testing, and improved curative treatment (for colorectal, breast, and prostate cancer). The overlooked exception of lung cancer in women showcases the importance of a joint assessment of incidence and mortality. While incidence trends among women are only beginning to plateau, the corresponding mortality trends are starting to decline, suggestive of marginal gains arising from improvements in early detection and more effective treatment.

Why is the incidence of some cancers rising?

The authors note rising incidence rates of several cancers with diverse causes. Perhaps the most alarming are those cancers with poor prognosis that result in concomitant rises in mortality. For example, the 3% per annum increases in liver cancer mortality rates since the early 1980s parallel increases in incidence for both men and women. Alcohol consumption and excess body weight are key preventable risk factors for this disease and account for 4.1% of all cancers diagnosed in the UK in men and 6.3% in women.[6 7] A recent longitudinal study of UK Biobank participants suggests

Findings are grounds for optimism in the UK, given steady declines in both cancer deaths and cancer mortality rates

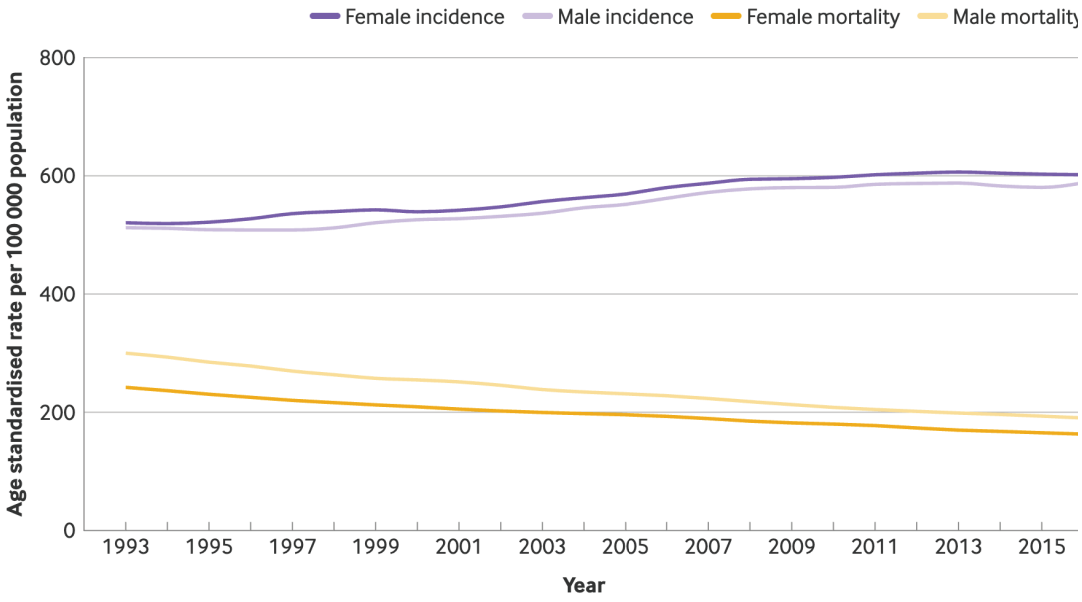
that excess body weight may amplify the effects of alcohol on cancer risk,[8] highlighting the importance of public health measures that help individuals limit alcohol intake and maintain a healthy weight.

Shelton and colleagues' focus on cancer trends among adults aged 35-69 years is understandable but may mask important changes in adult cancers in more specific age groups. For example, evidence is emerging of a rise in the incidence and mortality rates for colorectal cancer among adults younger than 50 years.[9-11] An upturn in risk among successive recent generations in some high income countries suggests that effects of risk factors during early life or young adulthood are critical. These may include a rising prevalence of obesity, physical inactivity, and the use of antibiotics affecting the gut microbiome.[12] Careful age and cohort specific analyses of trends across cancer types and populations are still needed to determine the extent of these early onset rises and their drivers.

Should we be optimistic about the future?

Deliberations on progress made against cancer and the effectiveness of different strategies to control it will undoubtedly continue in both scientific and political

Freddie Bray
brayf@iarc.who.int
See bmj.com for author details



European 2013 population age standardised incidence and mortality rates in the UK for all cancers, excluding non-melanoma skin cancer for incidence (international classification of diseases, 10th revision, codes C00-C97, excluding C44 for incidence), in men and women aged 35-69 years. Each year shown represents the first year of a three year period (eg, 1993-95)

BURGER/PHANIE/ALAMY

arenas. Shelton and colleagues' findings are grounds for optimism in the UK, given steady declines in both cancer deaths and cancer mortality rates in both sexes. Resulting from a combination of multiple small and large breakthroughs in prevention, early detection, screening, and treatment, mortality from common cancer types is also declining in countries such as France, Italy, the Netherlands, and Sweden today,[13] as it was 20 years ago.[3]

Will successes in cancer control continue for the next 20 years? Some early warning signs should raise alarm bells, including observational evidence of considerable heterogeneity in mortality trends in England at the district level,[14] and modelling evidence of excess cancer deaths in future years resulting from delays in diagnosis and treatment during the covid-19 pandemic.[15] The prospect of rising death rates from common cancers, including among younger (unscreened) age groups, are also of immediate concern. Effective interventions that increase awareness of modifiable risk factors for cancer—including, but not limited to, excess body weight and harmful alcohol consumption—must be urgently prioritised.

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Cervical pessary *v* vaginal progesterone in women with a singleton pregnancy, short cervix, and no history of spontaneous preterm birth at <34 weeks' gestation

Van Djik CE, van Gils AL, van Zijl MD, et al

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Study question What is the effectiveness of cervical pessary and vaginal progesterone in the prevention of adverse perinatal outcomes and preterm birth in women who are at low risk and have a short cervix and a singleton pregnancy?

Methods An open label, randomised, controlled trial was carried out in 20 hospitals and five obstetric ultrasound practices in the Netherlands. Women with singleton pregnancies were included if they did not have a spontaneous preterm birth at less than 34 weeks' gestation and had an asymptomatic short cervix of 35 mm or less between 18-22 weeks' gestation. Individuals were randomly assigned 1:1 to an Arabin cervical pessary or vaginal progesterone 200 mg daily. The primary outcome was a composite adverse perinatal outcome of periventricular leukomalacia of more than grade 1, chronic lung disease (severe respiratory distress syndrome or bronchopulmonary dysplasia), intraventricular haemorrhage grade III or IV, necrotising enterocolitis of more than stage 1, proved sepsis, stillbirth, and death of the baby (both perinatal and neonatal) before discharge from the hospital. Secondary outcomes included obstetric, neonatal, and maternal outcomes. A predefined subgroup analysis was planned for a cervical length of 25 mm or less.

Study answer and limitations From 1 July 2014 to 31 March 2022, 635 participants were randomly assigned to pessary (n=315) or to progesterone (n=320). No significant differences were found in the prevention of a composite adverse perinatal outcome; the composite adverse perinatal outcome occurred in 19 (6%) of 303 participants with a pessary versus 17 (6%) of 309 in the progesterone group (crude relative risk 1.1 (95% confidence interval 0.60 to 2.2)). In the subgroup analysis of a cervical length of 25 mm or less, adverse perinatal outcomes occurred more frequently in the pessary group (15/62 (24%) *v* 8/69 (12%), relative risk 2.1 (0.95 to 4.6)). Spontaneous preterm birth at less than 28 weeks occurred more often after pessary than after vaginal progesterone (10/62 (16%) *v* 3/69 (4%), relative risk 3.7 (1.1 to 12.9)). Additionally, adverse perinatal outcomes seemed more frequent in the pessary group (15/62 (24%) *v* 8/69 (12%), relative risk 2.1 (0.95 to 4.6)). This study was limited by self-reported adherence in the group assigned to progesterone treatment.

What this study adds Overall, for women with singleton pregnancies, a short cervix, and no previous spontaneous preterm birth less than 34 weeks' gestation, superiority of a cervical pessary compared with vaginal progesterone to prevent preterm birth and consecutive adverse outcomes could not be proved.

Funding, competing interests, and data sharing
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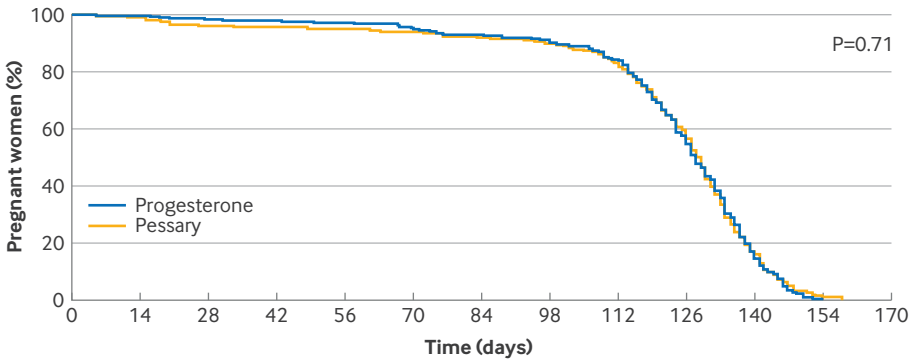
Study registration International Clinical Trial Registry Platform, EUCTR2013 002884-24-NL

Key outcomes by composite adverse perinatal outcome and by weeks of spontaneous preterm birth in the intention-to-treat population. Values are number of participants/total number in group (percentage) unless stated otherwise

Outcomes	Pessary (n=303)	Progesterone (n=309)	Relative risk (95% CI)	P value
Primary outcome				
Composite adverse neonatal outcome, crude	19/303 (6)	17/309 (6)	1.1 (0.60 to 2.2)	0.69
<34 weeks	23/303 (8)	23/309 (7)	1.0 (0.59 to 1.8)	0.95
<28 weeks	12/303 (4)	7/309 (2)	1.7 (0.70 to 4.4)	0.23
Subgroup analysis: cervical length <25 mm				
Composite adverse perinatal outcome, crude	15/62 (24)	8/69 (12)	2.1 (0.95 to 4.6)	—
<34 weeks	15/62 (24)	14/69 (20)	1.2 (0.63 to 2.3)	—
<28 weeks	10/62 (16)	3/69 (4)	3.7 (1.1 to 12.9)	—



Pregnant women per intervention

Progesterone	309	307	303	302	299	295	286	281	260	177	51	1
Pessary	303	300	291	290	287	284	278	272	252	181	51	3

Kaplan-Meier curve for time to delivery from randomisation