The two-week wait and other initiatives to improve cancer diagnosis: has it altered survival? The answer is unclear - the evidence is too weak.

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For many years, international comparisons have shown large differences in cancer survival between high-income countries, despite good access to health care, with the UK amongst the lowest ranked (Berrino et al, 2007; Coleman et al, 2008; Coleman et al, 2011; Angelis et al, 2014). It is known that later stage at diagnosis is a significant contributory factor to reduced survival (McPhail et al, 2015) and that for some cancers such as bladder, lung and ovarian there are lower survival rates at every stage, whereas for breast, prostate and melanoma reduced survival is only evident in advanced stage cancers (Public Health England, 2016). Since the introduction of the National Cancer Plan in 2000 (Department of Health, 2000) there have been concerted efforts to diagnose cancer earlier by reducing delays at all stages of the patient pathway.

The patient pathway comprises the following intervals: patient interval (between symptom onset and seeing a GP); primary care interval (also known as the diagnostic interval) between first GP appointment and referral to a specialist; and secondary care interval (between referral and definitive diagnosis) (Olesen, Hansen, Vedsted, 2009; Walter et al, 2012). This can help frame the problem, and it is now recommended that a model of diagnostic intervals is embedded within research focussing on early cancer diagnosis (Weller et al, 2012).

How important is the patient interval? Analysis of data from almost 11,000 patients diagnosed with cancer showed that the mean patient interval was longer than the primary care interval for many cancers, and for 10 cancers they were two- to five-times greater indicating that there is scope for improving patient presentations to primary care (Lyrtatzopoulos et al, 2015).

There have been various initiatives which aim to reduce the patient interval by increasing levels of cancer awareness. A systematic review of the literature concluded that individual-level interventions lead to a modest increase in cancer awareness, but there was insufficient evidence to draw conclusions about the impact on delays in presentation. There was limited evidence that community-level interventions may reduce stage at presentation for breast

cancer, malignant melanoma and retinoblastoma (Austoker et al, 2009). More recently, an on-going series of public health campaigns (the 'Be Clear on Cancer Campaigns') have been running in England since 2010 (Public Health England, 2017). The latest published evaluation of these campaigns has shown statistically significant increases in cancer awareness, GP attendance, urgent referrals, and diagnostic tests, but a lower proportion of referrals diagnosed with cancer (conversion rates). Cancer incidence rates, stage at diagnosis and survival rates have not yet been reported (Cancer Research UK, 2014).

The diagnostic interval in primary care has been addressed by setting referral guidelines and target times for specialist referrals, first introduced in the NHS Cancer Plan in 2000 (Department of Health, 2000), and most recently updated in 2015 (NICE, 2015). These targets (the two-week referral guidelines) state that patients with symptoms suggestive of suspected cancer should wait no longer than two weeks from urgent GP referral for suspected cancer to an appointment with a specialist.

So what has been the impact of the two-week referral guidelines? The numbers of urgent referrals have increased each year, from 903,000 in 2009/10 to over 1.5million in 2014/ (National Cancer Intelligence Network, 2016). This has been applauded by some as evidence of getting people to 'step up' and seek help, whilst others say it is overwhelming secondary care. In line with the increasing number of referrals, the cancer detection rate has increased from 42.3% to 48.4% and the conversion rate has decreased from 10.8% to 8.2% over the same time period (National Cancer Intelligence Network, 2016).

Has the time to diagnosis altered with the introduction of the two-week referrals? Analyses of routine data have compared the diagnostic interval for two cohorts of symptomatic cancer patients, before and after the introduction of the two-week referral guidelines. They showed that overall, the diagnostic interval was significantly reduced by 5.4 days (95% CI 2.4 – 8.5 days) between the two time periods, but there was large variation between the 15 cancers included, and for some cancers, presentations with symptoms not included in the referral guidelines led to an increase in time to diagnosis (Neal et al., 2014). Data from Denmark show a very similar picture, although interestingly the reductions observed after the introduction of a standardised cancer pathway were larger than those observed in the UK (Jensen et al, 2015).

So the diagnostic interval has shortened for several cancers, but does reducing this interval lead to survival differences? A Danish prospective study described the association between diagnostic interval and five-year mortality for five cancers and reported that longer diagnostic intervals were associated with increased mortality. They also reported that very short diagnostic intervals were also associated with reduced mortality. (Tørring et al, 2013).

A systematic review comparing improved outcomes and time to diagnosis could not produce any pooled estimates of effect due to heterogeneity in methods, reported outcomes and in the definitions of the exposure (time to diagnosis). The authors did, however, conclude that in more recent research that took the waiting time paradox into account, there was some evidence of longer diagnostic intervals being associated with worse outcomes (Neal et al, 2015).

However, an analysis of routinely collected primary care data did not highlight any consistent patterns between diagnostic interval and survival (Redaniel et al, 2015).

So far, the literature is reporting on only parts of the pathway between interventions to improve diagnosis and hard outcomes such as survival. So is there any direct evidence that the urgent referral pathway increases survival? The closest we get, is an analysis of GP practice-level data, which includes data from almost a quarter of a million cases of cancer diagnosed in the UK between 2009 and 2013. It showed that at a GP practice level, mortality was reduced in practices that were higher users of the two-week wait pathway than average or low referrers (Møller et al , 2015).

Can we learn anything from international comparisons? The International Cancer Benchmarking Partnership (ICBP), a research collaboration between six countries (Australia, Canada, Denmark, Norway, Sweden and the UK), are studying the variations between the countries, and investigating potential differences to develop our understanding of the reasons for the observed disparities (Butler et al, 2013).

Data from this collaboration has shown wide variations in stage-specific survival between the countries, suggesting that other factors are also important such as differences in treatment or access to treatment (Maringe et al, 2012; Maringe et al, 2013; Walters et al, 2013a; Walters et al 2013b).

Investigation of the patient interval showed that symptom awareness of all cancer types were similar across the countries involved in ICBP, with slightly lower awareness in Sweden than in the other 5 countries. However, respondents to the survey in the UK reported higher levels of barriers to health-seeking behaviours, even if symptomatic, and were particularly worried about wasting the doctor's time which may lead to longer patient intervals. (Forbes, BJC 2013).

A jurisdiction-level analysis showed a positive correlation between improved survival rates and willingness to act definitively (including referring to a specialist) when faced with 5 multi-staged vignettes of patients presenting with symptoms suggestive of cancer (Rose et al, 2015), but adherence to guidelines was not associated with 1-year survival (Nicholson et al, 2016).

In summary, initiatives to improve early diagnosis may raise cancer awareness in the population, and perhaps reduce the patient interval; can reduce the diagnostic interval between presentation and specialist appointment; and there may be survival benefits associated with increased willingness to refer, or actual referral. What is currently lacking is research that directly addresses whether the introduction of the 2-week wait referral process has led to improved survival amongst individuals. Surely, it must be time now to link information from sources such as the cancer waiting times database, with staging, time to treatment and survival data to analyse, at the individual-level, the impact of the 2 week wait on cancer survival?

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