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Invited Editorial

Detecting cancer in primary care: where does early diagnosis stop and overdiagnosis begin?

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Overdiagnosis is challenging to quantify and its consequences even harder to measure. Early diagnosis initiatives must prospectively evaluate where overdiagnosis may occur.

Cancer Overdiagnosis.

Overdiagnosis is the detection of cancer that would never cause symptoms or premature death (Welch and Black, 2010). Without intervention these cancers may never progress, may regress, or may progress so slowly that the patient dies of another cause. The (now) patient is exposed to the risks posed by the diagnosis, further investigation, and treatment, but without the benefits. Autopsy studies confirm a reservoir of asymptomatic cancer in populations who die of other causes (Bell et al., 2015).

Should we be concerned about overdiagnosis?

A pattern of stable mortality and increasing incidence is commonly used to denote overdiagnosis (Welch and Black, 2010) yet excess incidence will also include cancer that would progress without treatment (Etzioni and Gulati, 2016). Excess incidence may also reflect changing risk factors, and mortality can be modulated by improved treatment (Brawley and O'Regan, 2014). The Independent UK Panel on Breast Cancer Screening reported a 20% mortality reduction in screened women and three overdiagnosed cancers for every life saved, based on 11 RCTs (Marmot et al., 2013). The US Preventative Task Force reported a mortality reduction (although estimates were not significant for all ages) and overdiagnosis in 0-54% of women, based on data from RCTs, observational and modelling studies (Nelson et al., 2016a, Nelson et al., 2016b). RCTs reduce bias but limit external validity: they take a long time to conduct whilst technology and treatment move on (Carter et al., 2015). Well conducted ecological and cohort studies can lead to accurate estimates of overdiagnosis over time (Jørgensen et al., 2017). At present poor data quality, inadequate study length, and inconsistencies between programmes lead to wide variation in overdiagnosis estimates (Carter et al., 2015, Duffy and Parmar, 2013). Overdiagnosis, although difficult to quantify precisely, remains a plausible concern.

Differentiating overdiagnosis from early diagnosis.

Translating population level data into patient level advice is challenging (McCaffery et al., 2016). A barnyard analogy exists (Welch, 2015). The goal is to keep the animals in the pen—to keep cancer from spreading and becoming deadly. Turtles are slow-growing indolent cancers that will never

escape or cause harm, rabbits might escape but may also be caught by early treatment, and birds escape no matter what happens. Early detection would be most effective if it could select out the rabbits or find a way to catch the birds. Genomics, proteomics and metabolomics show potential for differentiating which cancer is which animal, but none are clinically validated (Vockley and Niederhuber, 2015, Mardis, 2012). Given the lack of certainty over the extent of overdiagnosis and the extreme variation in public acceptance it may be wise to avoid it at all costs (Van den Bruel et al., 2015). An alternative approach is to investigate only symptoms.

Does overdiagnosis occur outside of screening?

Only three in ten breast cancers and one in 20 colorectal cancers are detected through screening in the UK and Australia (Rubin et al., 2015). Most are diagnosed after symptomatic presentation to primary care (Elliss-Brookes et al., 2012). Experts acknowledge that overdiagnosis could exist as a consequence of early diagnosis initiatives but whilst the risks are considered minor in comparison to the benefits of early detection the scale and seriousness remains poorly understood (Hamilton et al., 2016, Neal et al., 2015, Rubin et al., 2015).

Overdiagnosis has been described in relation to an increasing number of conditions outwith cancer screening (Harris, 2015, Martin et al., 2014, Wiener et al., 2013, Tomas et al., 2015, Yudkin and Montori, 2014). Of the six recognised drivers, four are relevant to cancer in primary care: expanded disease definitions; health system incentives favouring more tests and treatments; technological changes detecting ever smaller “abnormalities”; and cultural beliefs that more is better (a faith in early detection unmodified by its risks) (Moynihan et al., 2012).

Could cancer overdiagnosis occur in primary care?

By following NICE guidance up to 32 of 33 patients referred for testing by their GP will not have cancer diagnosed (NICE, 2015). They will instead receive a cancer “screen” with a test chosen based on the clinical features present. Secondary analyses of case-control data used by NICE estimates that in 17-34% lung and 6-21% colorectal cancers the symptoms reported are not caused by the cancer (Ades et al., 2014, Biswas et al., 2015). These cancers are diagnosed “serendipitously” with longer lead-time, and at an earlier stage when compared to cancers diagnosed in patients with symptoms attributable to the cancer. A prolonged lead-time and the detection of asymptomatic cancer are both markers of overdiagnosis (Carter et al., 2015, Welch and Black, 2010).

NICE also gives GPs increased access to cancer diagnostics (NICE, 2015). RCT and observational study evidence shows that GPs select appropriate patients for direct access investigations but data are lacking on the downstream effects of increased primary care testing (MacKenzie et al., 2003, Simpson et al., 2010). A simple example is CA125, recommended since 2011 as a marker of ovarian cancer in females with vague abdominal symptoms, but for which there is no primary care evidence to support the threshold used to trigger further imaging (NICE, 2011). Multidisciplinary Diagnostic Centres (MDCs) are being developed for the rapid investigation of low-risk-but-not-no-risk symptoms that could be caused by multiple cancer sites. CT scanning often forms part of routine basic work-up (Ingeman et al., 2015, Cancer Research UK, 2017). Evidence from whole-body CT screening shows over one third of patients require further investigation for incidental findings (Furtado et al., 2005) .

Is it possible to stop early diagnosis becoming overdiagnosis?

Screening shows us there's no point closing the barnyard door once the rabbits have bolted! Drivers of cancer overdiagnosis exist outside of organised screening and evaluation is needed to assess their effect. When investigating novel diagnostic pathways and tests (or novel uses for existing tests) we should strive to quantify overdiagnosis in terms of patient outcomes (Moynihan et al., 2014). High quality datasets are needed to clarify rather than confuse the issue. Calls for a multinational group of unbiased researchers to set international standards for the assessment of overdiagnosis (Carter et al., 2015) and mechanisms developed to mitigate its harms (Esserman et al., 2014) should be extended beyond cancer screening.

Health professionals and researchers alike should commit to the early detection of overdiagnosis.

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