1 Division of Molecular Pathology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Netherlands

2 Leiden University Medical Center, Leiden, Netherlands

3 Patient author, Precision project, Netherlands

Correspondence to: M K Schmidt
mk.schmidt@nki.nl

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Invasive breast cancer and breast cancer death after non-screen detected ductal carcinoma in situ

Is it time for risk based screening and follow-up after a ductal carcinoma in situ diagnosis?

Marjanka K Schmidt, [1,2] Esther H Lips, [1] Renée SJM Schmitz, [1,2] Ellen Verschuur, [3] Jelle Wesseling[1,2]

Breast cancer screening began in the 1990s, with the aim of detecting invasive breast cancer early and reducing breast cancer deaths.[1] Rates of breast cancer deaths have declined over recent decades due to a combination of better systemic treatments, increased awareness, and screening.[2-4] However, since the introduction of screening, incidence of ductal carcinoma in situ (known as DCIS) has increased substantially, accompanied by growing concerns about overdiagnosis and overtreatment.[5-7] Moreover, a recent meta-analysis of randomised trials evaluating cancer screening programmes questioned the net benefit of screening in reducing cancer mortality.[8]

Although breast cancer screening attendance is high in the UK (70%),[9] a substantial number of women present with non-screen detected ductal carcinoma in situ: women too young or too old for official screening programmes, eligible women who do not attend screening, or eligible women who develop ductal carcinoma in situ between screens (interval carcinoma). In a linked paper,[10] Mannu and colleagues (doi:10.1136/bmj-2023-075498) report interesting data for 27 543 women with ductal carcinoma in situ detected outside the NHS breast screening programme between 1990 and 2018. In their cohort study, most women with non-screen detected ductal carcinoma in situ died of causes other than breast cancer (n=3950); 908 died of breast cancer. However, standardised rates of both invasive ipsilateral breast cancer and breast cancer death were four times higher among women with non-screen detected ductal carcinoma in situ than among women in the general population. Risk of these outcomes remained high for many years after a ductal carcinoma in situ diagnosis.

Who are these women with non-screen detected ductal carcinoma in situ, and is their mortality different from those who had their cancer detected at screening? Mannu and colleagues found that women with non-screen detected ductal carcinoma in situ were 1.37 times more likely to die from breast cancer (95% confidence interval 1.17 to 1.60) than women with screen detected carcinoma in the same age range (50-64 years).[10] Importantly, the absolute difference in 25 years cumulative risk of breast cancer death between the two groups within the 50-64 age range was small at 0.6% (6.5% for screened *v* 5.9% for non-screened women). The study supports earlier studies from the UK, US, and the Netherlands, reporting that the cumulative risk of dying from breast cancer for women with ductal carcinoma in situ is in the range of 2-3% over 10-20 years.[9 11 12]

About half of the 27 543 women with non-screen detected carcinoma were outside the screening age range, including 9903 who were younger than 50 years. The increase in mortality rate relative to the general population (of similar age) was greatest among women younger than 45 years. Equally important is the route of detection: some ductal carcinoma in situ may have been symptomatic, others may have been detected due to a family history of breast cancer, through opportunistic screening, or were incidental findings. Different routes of detection may be associated with varying risks of invasive ipsilateral (and contralateral) breast cancer and breast cancer death. Although Mannu and colleagues acknowledge the lack of this information in their study,[10] investigations into the detection mode are important in follow up studies.

Choice of treatment for ductal carcinoma in situ does not seem to affect mortality in non-screened women with ductal carcinoma in situ. Mastectomy was associated with a lower risk of ipsilateral invasive breast cancer over 25 years compared with breast conserving surgery, but this reduction did not translate into lower risk of breast cancer death.[10] A likely reason being that contralateral breast cancers also contribute to breast cancer death rates and treatments for invasive breast cancer are increasingly effective at preventing breast cancer deaths.[13-15]

Mannu and colleagues' study supports the assertion that some types of ductal carcinoma in situ (which are yet to be classified) should be considered a long term risk factor for any (ipsilateral and contralateral) invasive breast cancer, especially when diagnosed at a young age. Opportunities for more personalised risk based approach to breast cancer screening might be possible, especially for younger women. However, other factors need to be considered, including family history and hereditary genetic variants.[16 17] Some risk based screening strategies are already being evaluated.[18 19] Screening modalities, including mammograms, can also be used to develop and test AI based algorithms to help predict future risk of invasive breast cancer or death among women with a ductal carcinoma in situ diagnosis,[20] although the value for those predictors in younger women is not yet clear.

In conclusion, the study of Mannu and colleagues is highly relevant for three reasons. Firstly, to showcase the often overlooked risks of non-screen detected ductal carcinoma in situ in the context of the ongoing debate about ductal carcinoma in situ overdiagnosis and overtreatment. Secondly, because the results suggest that longer follow-up after ductal carcinoma in situ might be recommended because risks remain high for a long period after diagnosis. Finally, because the study provides essential information for

further development of personalised risk based screening strategies.

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