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Moles and melanoma

EDITORIAL

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How clear really are the boundaries between cancer, precursors to cancer and harmless pigment spots?

Cutaneous melanoma is the fastest growing cancer in Norway, as well as large areas of Europe and North America (1). The increase is often attributed to increased exposure to ultraviolet radiation due to changes in sun habits. However, in 2021, Welch et al. demonstrated that, even in a hypothetical extreme scenario, increased sun exposure can only explain a small proportion of the increased incidence of melanoma in the United States (2). There must be other contributory causes. The fact that mortality from melanoma has remained stable over the same period may point to significant overdiagnosis.

However, Norway stands out in the melanoma statistics. Not only is mortality from melanoma in Norway among the highest in the world, but it is also rising, unlike in most other countries. In Norway, patients have melanomas that are thicker and are discovered later than melanomas in patients in neighbouring countries (3). The size of the primary tumour is of prognostic significance for most forms of cancer, but whereas the prognostic yardstick is typically a few centimetres in other cancers, even microscopic differences in the thickness of a melanoma make a huge difference to the prognosis: Almost all patients who undergo surgery for melanomas thinner than one millimetre will be cured, whereas up to half of patients who undergo surgery for melanomas thicker than four millimetres will develop metastases within five years (4).

It is a peculiarity of melanoma that the primary tumour's growth can be inspected with the naked eye and removed in the early stages with no major risk or discomfort. However, thin melanomas and melanoma precursors are on

the same morphological spectrum as harmless moles with varying degrees of cellular changes. Since distinguishing between benign and malignant relies on subjective criteria and the pathologist's judgement, the assessment of pigmented skin lesions is a challenging task. International studies have demonstrated that there is wide interobserver variation, and that there has been a trend for lesions that were previously assessed as benign to be assessed as melanomas a few decades later (5, 6).

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Epidemiological differences mean that there is a good rationale for investigating whether this is also the case in Norway, which is what Gjersvik et al. have undertaken in a study currently being published in the Journal of the Norwegian Medical Association (7). In this study, 196 pigmented skin lesions from 2009 and 2018–2019 were systematically reassessed by three experienced pathologists. In line with previous international studies, they find unsatisfactory concordance between the pathologists in the study. Fortunately, concordance is best where it matters most, i.e. for invasive melanomas, but even here several examples of contradictory assessments are found. Unfortunately, destruction of the hospital's specimens from 1999 has limited the authors' ambition to study evolution in diagnostic evaluation over time. Nevertheless, the fact that almost one-third of the reassessments of specimens from 2009 result in a diagnosis more serious than the original make it reasonable to assume that diagnostic drift may also have contributed to the increasing incidence in Norway.

Although the millimetre precision of histopathological assessment means it is the undisputed gold standard for melanoma risk assessment, the study by Gjersvik et al. illustrates that the method has shortcomings, particularly in the grey area between clearly benign and clearly malignant. Several molecular pathological methods are already established as routine supportive methods to morphological appearance and immunohistochemical markers, but have far from demonstrated their full potential. For example, within a few years, analyses of the gene expression of primary melanomas could hopefully help detect those melanomas with a particularly high risk of metastasis (8).

Metastatic melanoma has historically been a disease with very limited treatment options. Fortunately, in the last decade, this has changed radically with the introduction of both targeted treatment and immunotherapy. These forms of treatment have also been demonstrated to be highly effective in preventing recurrence in patients who undergo surgery. Therefore, the role of the pathologist in establishing the correct prognosis is more important than ever. At the same time, there have also been considerable changes in surgical management. In a clinical review article also now being published in the Journal of the Norwegian Medical Association, Berentzen et al. provide up-to-date knowledge to ensure the correct investigation and primary treatment of primary melanomas, one of our most common cancers (9).

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