



Melanoma control: few answers, many questions

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Malignant melanoma exerts a high toll in New Zealand, and now looms large in the public consciousness, perhaps due to its relatively high incidence in younger people and its cruel association with the pleasures of the outdoors. Strategies are needed to control this disease.

In this issue of the *Journal*, Sneyd and Cox¹ calculate the likely effect of various cancer control activities on melanoma incidence and mortality in New Zealand. They conclude that prevention of excessive sun exposure and early diagnosis of melanoma are the options likely to have the greatest effect.

These conclusions are likely to find broad acceptance, but the detail in their analysis highlights how much more work is necessary if we are to seriously tackle melanoma.

Early detection of melanoma is a good start. Recent data from Australia suggest that earlier detection of melanoma² is beginning to impact on melanoma mortality.³ Anecdotal reports abound in New Zealand that primary melanomas are being excised “thinner” these days, but as yet there are no good studies to support this impression.

Monitoring the distribution of melanoma depths over time might help measure whether public education initiatives are successful in driving earlier detection. Breslow depth is available in the New Zealand Cancer Registry data, and has been analysed previously for the period 1995 to 1999.⁴ However more timely release of these data will be necessary if they are to be useful in monitoring cancer control strategies: as noted by Sneyd and Cox, the 2002 data has only just been published by the New Zealand Health Information Service (NZHIS).

Prevention of excessive sun exposure seems logical, although the science supporting this approach is surprisingly weak. Indeed, despite more than 20 years of primary prevention programmes in Australia, there is as yet little evidence of any effect on melanoma incidence.³ Such evidence is crucial because clinical trials testing the effect of modulating sun exposure are notoriously difficult to perform well, due to long timelines and low numbers of melanoma “events”.

It is not entirely unexpected that population-based reductions in sun exposure might take more than a decade to affect incidence rates, given the long time required for populations to change their behaviour, and for melanoma to become clinically apparent. But a lesson for New Zealand is immediately clear: it is highly unlikely that any influence of sun exposure education on melanoma incidence rates will be measurable for a considerable time.

In measuring incidence, it is important to note the limitations of the melanoma data available from the Cancer Registry prior to 1996. As highlighted by Sneyd and Cox¹ (and also observed for some other cancers) there is a “spike” in apparent incidence in 1994 and 1995 when registration became compulsory under the Cancer Registry Act 1993.

It seems likely that melanoma was significantly under-reported before 1994, and that reporting did not stabilise under the new regime until 1996 or 1997. Hence, by the end of this year, the Cancer Registry will probably have accumulated 10 years of reliable incidence data. As noted above, if the 4-year delay in data publication persists, this first 10-year dataset might not become available until 2010. Monitoring the effects of changes in sun exposure will require a long-term commitment to the provision of accurate, timely, and complete data for subsequent analysis.

Regrettably, there remains the possibility that preventing excessive sun exposure will not prevent melanoma. Sneyd and Cox estimate that a 10% reduction in the number of people who experience blistering sunburn could prevent 28 cases of melanoma per year in New Zealand.¹ One reason why this figure is so modest is that the relative risk used in their calculations is only 1.4: according to Sneyd's New Zealand-based case control study, this kind of sunburn only increases the risk of melanoma by a factor of 1.4.⁵ This surprisingly small relative risk is borne out by many other studies: one authoritative review of the reliable studies available estimated that excessive childhood sun exposure conferred, at most, a 1.95-fold increase in the risk of melanoma.⁶ The available studies also vary so much in their definition of excessive sun exposure, that the precise patterns of sun exposure conferring increased risk are uncertain, as are their interplay with different skin phenotypes.⁷

While it is certainly prudent to promote the reduction of sun exposure and sunburn in New Zealand, there remains a possibility that this strategy will have only a moderate impact on melanoma incidence. More work is urgently needed to better define the relationship between sun exposure and melanoma,⁷ and New Zealand is an environment very well suited to such studies.

Even if strategies for prevention or early detection are highly successful, the long lead-times mean other strategies need to be considered to deal with the melanoma burden. Better therapy is a realistic medium-term target.

Sneyd and Cox rightly highlight the lack of recent New Zealand guidelines for the management of melanoma.¹ Approaches to melanoma treatment vary dramatically, not just across the country but within regions and cities. However, a recent initiative has seen New Zealand clinicians (under the umbrella of the New Zealand Guidelines Group) collaborating with their Australian counterparts to produce high-quality evidence-based guidelines for the management of melanoma.

The release of these trans-Tasman guidelines in 2007 will help to unify and promote best practice. Several centres are also pursuing multidisciplinary management of local recurrences and metastases, and such approaches seem likely to improve quality of life, if not survival.

Surgery is still the mainstay of melanoma therapy, and it can be successful at arresting metastatic disease² while radiotherapy can be helpful for local control.⁸ Even current chemotherapeutic agents can occasionally induce remission, although the low response rates have meant that they have had little impact overall.² Although only a small minority of patients respond to these drugs, occasional complete responses suggest fundamental differences in the biology of the responding and non-responding tumours.

As with other types of cancer, melanoma is not a single disease in terms of its cell biology, and certainly not at the molecular level. One of the most fruitful areas of investigation in melanoma therapy may be the definition of molecular markers that correlate with responses to agents already available. Identifying even 10% of melanoma patients who are likely to have strong responses to such agents would substantially reduce the melanoma burden in New Zealand.

Recent advances in molecular medicine have also opened up new therapeutic possibilities for melanoma, including chemotherapy, biological therapy, and immunotherapy. The recent identification of the *BRAF* pathway, as a common source of molecular perturbation in melanoma,⁹ has offered hope that kinase inhibitors might be designed to specifically target the disease.

Numerous clinical trials are also underway testing novel agents that modulate aspects of melanoma biology or the immune response to melanoma (www.cancer.gov/clinicaltrials). While hopes have often been raised (and subsequently dashed) about these kinds of therapies, a body of evidence is building that suggests they will produce substantial clinical gains in at least a proportion of melanoma patients. Again, molecular typing may be required to determine which patients are likely to respond to which agents, but such patient stratification is rapidly becoming routine in modern cancer treatment.

In summary, what is needed to control and manage melanoma in New Zealand? In addition to the measures recommended by Sneyd and Cox, at least four other steps seem advisable: more detailed study of the relationship between sun exposure and melanoma incidence; timely release of accurate and complete data from the Health Information Service to allow changes in melanoma incidence and thickness to be tracked; development and adoption of agreed melanoma management guidelines across New Zealand; and intensive research into new therapeutic options and the molecular classification of melanomas.

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