N=736

Letter to the Editor

Re: High nevus counts confer a favorable prognosis in melanoma patients by S Ribero and co-workers, published in the *International Journal of Cancer*, 2015 (Online 21 March 2015).

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The study by S Ribero and co-workers is welcome because only few studies have examined the outcome of cutaneous melanoma patients according to host characteristics associated with greater risk to be diagnosed with this cancer [1]. Number and size of nevi is the strongest risk factor for melanoma occurrence, and despite a lack of evidence, it is generally assumed that higher risk of melanoma occurrence would also mean a higher risk of melanoma death. Because of this assumption, subjects with high nevus count are recommended to have regular skin examinations so that detection of melanoma at an early stage may prevent the occurrence of late stage, potentially lethal melanoma. However, contrary to assumptions, the study of Ribero et al rather suggests that a high nevus count could be associated with a lower risk to die from melanoma, and this lower risk was in a multivariate analysis independent of age, sex, anatomic location, tumour phenotype and sentinel lymph node status. Ribero et al concluded that in patients with an excessive number of nevi, melanoma would have a less aggressive biological behaviour.

This study raises several concerns. Multivariate models done by Ribero et al included Breslow thickness as a continuous variable. Use of a continuous variable assumes a linear relationship between increasing thickness and melanoma specific mortality. However, this relationship rather follows an inverse exponential curve, with steep rise in mortality from 0.1 to 2 mm thickness, and a progressively less steep rise until 4 mm. After 4 mm, the relationship slowly stabilizes [2]. In this regard, adjustment done with a continuous variable will fail to completely remove the greater melanoma survival of the high nevus group associated with a greater proportion of thin melanoma in this group. Multivariate models

including thickness categories as defined by the American Joint Committee on Cancer [3] would be more adequate.

Should a correct multivariate model confirm results obtained by Ribero et al, we believe that overdiagnosis of melanoma in subjects with high number of nevi could represent an alternative explanation to their results. Subjects with numerous nevi are recommended to have regular skin examinations. Unfortunately skin screening leads to more frequent removal of thin, non-metastasising indolent tumours that would never be life threatening during subject's lifetime (i.e., length time melanoma)[4]. Screen-detected indolent melanoma represents overdiagnosis that contributes to raising the incidence of melanoma in many light-skinned populations [5]. Overdiagnosis is also fuelled by the "diagnosis drift" whereby benign pigmented lesions are increasingly classified as stage 1 melanoma [6]. The consequence of more skin screening in subjects exhibiting large numbers of nevi is a higher rate of early stage melanoma, many of which are indolent. In Ribero et al study, melanomas in patients with high nevus count are significantly thinner, non-ulcerative, and of low mitotic index, all histological features that indicate the greater prevalence of indolent melanoma in this group of subjects.

It is well known that patients with screen-detected cancer have a survival advantage over patients with clinical cancer that is not explained by the clinical or histological characteristics of tumours or by patient's risk factors. The milder biological aggressiveness of screen-detected cancers is well documented for breast and for prostate cancers [7-9]. The survival advantage conferred by mild biological aggressiveness is substantial, in the order of 40 to 90% greater survival for cancer-specific and all-cause survival in the case of mammography-detected breast cancer, and probably even more for PSA-detected prostate cancer. We are not aware of a study that has estimated the survival advantage of screen-detected melanoma. But population level statistics show that the survival of melanoma patients increases with the incidence of melanoma, and not with decreases in melanoma mortality [10]. The dependence of survival on melanoma incidence rather than on melanoma mortality represents indirect evidence that the sluggish clinical behaviour of many screen-detected melanomas would be similar to that of many screen-detected breast and prostate cancers.

Hence, irrespective of risk factors known to be associated with the clinical course of melanoma, a greater proportion of screen-detected melanomas in the group of subjects with excessive nevus count could be partly responsible for the higher melanoma-specific survival.

In conclusion, the possibility of an association between a high nevus count and a more favourable melanoma-specific survival should be viewed with caution.

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Acknowledgements:

Authors have no conflict of interest to disclose.