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Benefits of a nationwide population-based skin cancer screening programme – still a controversial debate

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Since its introduction in 2008, the nationwide population-based skin cancer screening programme in Germany has faced a number of critical arguments, which in the end focused on the fact that no reduction in skin cancer-associated mortality has been observed.[1,2]

In this issue of the BJD, Datzmann and colleagues present data of a retrospective cohort study, based on health insurance data of 1 431 327 individuals from Saxony for the years 2010–2016.[3] The publication illustrates an association between favourable prognostic factors in patients with melanoma and participation in the nationwide population-based skin cancer screening programme in Germany. Thus, screened participants were diagnosed at earlier tumour stages and received less radical treatment upfront than patients diagnosed outside the screening programme. However, due to a relatively short observation period, the long-term effects of the programme could not be adequately analysed. The observed improvement in survival within the first few years after diagnosis may have been caused by selection bias and overdiagnosis or lead-time bias.

Even after the release of this data, we still cannot adequately answer the question of an improvement in melanoma-specific survival; we can only infer it indirectly, e.g. by improving prognostic factors. However, does a judgement of a screening programme have to be done solely by referring to the improvement in mortality? I think not.

Besides, melanoma target indications of skin cancer screening also include nonmelanoma skin cancer, mainly basal cell carcinoma and squamous cell carcinoma. These cancers can be treated surgically with curative intent and only in isolated cases – if left untreated for months or even years – end fatally. For these tumour types, a screening programme per se is not expected to improve mortality.

The general purpose of skin cancer screening programmes, in addition to reducing mortality, is early detection and thus a reduction in the number of extensive and difficult operations. In addition, the economic aspects should not be forgotten. Tumours diagnosed late often require inpatient treatment and multiple procedures, while smaller tumours can be treated on an outpatient basis, which in turn is cost-effective.

One aspect that is often forgotten is raising patients' awareness of their own skin tumour screening or, more importantly, raising their awareness of protection against ultraviolet radiation.[4] The screening programmes aim to achieve two long-term goals through prevention: firstly, to reduce skin cancer rates, which have been increasing for decades due to age and behaviour; and secondly, to reduce the rate of new cases as much as possible.

So, what is next? Currently, the 'EvaSCa' project is running to further evaluate skin cancer screening. For this purpose, a case–control study and several cohort studies are being conducted.[5] They aim to estimate the effect of skin cancer screening on melanoma mortality and to investigate the benefits of currently implemented skin cancer screening methods. Various medical and health economic factors will be compared between patients with skin cancer whose tumour was detected by skin cancer screening and patients with skin cancer whose skin cancer was not detected by skin cancer screening. The evaluation is intended to be the basis for proposals for the further development of skin cancer screening.

However, I do not expect the debate about the German skin cancer screening programme will die down after that.

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The expected missing heritability of hidradenitis suppurativa in perspective

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Hidradenitis suppurativa (HS) has long been recognized as a complex disease in which genetics and environmental factors contribute to the phenotypic presentation. In this issue of the *BJD*, the study by Kjærsgaard Andersen *et al.* cross-references Danish National Twin Registry data with International Classification of Diseases 8/10 codes for HS to provide a robust heritability estimate for HS of 80% [95% confidence interval (CI) 67–93].[1] This estimate is in line with a previous twin study, which identified a heritability for HS of 77% (95% CI 54–90), despite using different methodologies.[2]

In addition, Kjærsgaard Andersen *et al.* found an unusually high multilocus index, which is dependent on both the number of contributing genes and their degree of interaction (gene–gene interactions).[3] This indicates a predicted discrepancy between the study's heritability estimate and future genome-wide association study (GWAS) results, a concept that is well recognized in complex traits and commonly known as 'missing heritability'.[1,4] How large this predicted gap might be can be illustrated by looking at the heritability of Crohn disease (CD). The heritability of CD is estimated to be approximately 70–80%; however, only around 13·1% of this heritability has so far been explained through GWAS studies.[5] In addition to the gene–gene interactions suggested in this study, other causes may play a role in the expected missing heritability of HS. In a highly polygenic disease many single-nucleotide polymorphisms with small effect sizes are expected, but might not be identifiable until the sample size is large enough.[4] Moreover, copy number variants, epigenetic changes and rare variants, which have all been identified in HS, are not picked up in GWAS studies.[3,6,7]

In line with previous epidemiological evidence, the heritability estimate provided by Kjærsgaard Andersen *et al.* also allows for nongenetic (e.g. environmental) contributions to HS.[1,8] Distinct HS phenotypes each seem to be associated with different environmental factors such as smoking or obesity, suggesting an important role for gene–environment (G × E) interactions.[8] G × E interactions have statistical relevance in explaining some of the expected missing heritability but also have (in)direct clinical relevance. The clinical relevance of G × E interactions can be illustrated by findings from research in rheumatoid arthritis in which different combinations of *HLADR1* and *PTPN22* alleles were found to generate substantially different odds ratios for disease development when analysed in different combinations with smoking.[9] Such results could have very practical implications; by limiting the exposure of genetically susceptible children to (second-hand) smoke, we may mediate the development of rheumatoid arthritis or, in this context, HS.

As highlighted by the authors, the results from this twin study cannot readily be extrapolated to other populations. The prevalence of HS, reported family history, environmental factors and phenotypic presentation differ between populations.[10] These differences suggest that the heritability of HS, as well as associated risk loci, differ between Asian and Western populations, as was previously identified in relation to CD.[5] Therefore, it is essential to include non-Western populations in future twin and genetic studies.

In conclusion, this well-conducted study provides robust evidence for a primarily genetic basis of HS in the Western population. The high multilocus index indicates a high missing heritability for HS in future GWAS studies. A large, long-term, global collaboration will be required to fully elucidate the genetic basis of HS.[11]

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