Obituary

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The role of misclassification of exposure in the association between aspirin and nonsteroidal anti-inflammatory drug use and keratinocyte cancers: reply from the authors

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Dear Editor, Thank you for the opportunity to respond to the letter from Abtahi and colleagues[1] on our recent paper describing the association between aspirin and nonsteroidal anti-inflammatory drug (NSAID) use and keratinocyte cancer (KC).[2] It allows us to clarify several important points. Firstly, we reiterate that we assessed the cross-sectional exposure prevalence of aspirin and NSAID use at study baseline (within 1 year prior) and our results should be interpreted in that context. We appropriately acknowledged limitations of the data including lack of information on exposure recency and dose or duration of use (including during follow-up). However, we reject the premise that misclassification bias and immortal time bias have influenced our conclusions.

Given that these drugs are most commonly used 'over the counter', and the self-reported nature of the exposure, some level of misclassification is unavoidable; however, the high repeatability of these self-reported measures in our study (kappa = 0·79 for aspirin and 0·63 for NSAIDs)[3] suggests that the likelihood of misclassification is small, and we do not believe it was differential. Nondifferential misclassification biases towards the null. The fact that the estimates of effect we observed were similar to recent summary estimates from meta-analyses[4,5] that included studies with exposure based on pharmaceutical records argues against the presence of misclassification bias.

Immortal time bias occurs when the exposed and unexposed groups differ in their time at risk for an event (one having immortal time advantage).[6] In our study, there was no period of follow-up time when an event could not occur because of exposure definition; the median follow-up time (time at risk) for all three categories of exposure (never, infrequent and frequent) for both aspirin and NSAIDs was similar (approximately 2·8 years). We therefore contend that our findings are not influenced by immortal time bias.

Observational studies have limitations for pharmacoepidemiological analyses, as we have acknowledged in our work. Ideally, randomized controlled trials would answer the question definitively. Given the modest benefits and the potential for harm, it is unlikely that such trials will ever be conducted for KC end points. We must therefore rely on data from observational studies to fill the knowledge gap.

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Obituary

Obituary: Professor Marcel F. Jonkman: 1957–2019

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Over the past 30 years, with unbridled energy and commitment, Marcel Jonkman established himself as a respected doctor, dermatologist, scientist, teacher, trainer, professor and head of the department of dermatology at the University Medical Centre Groningen, the Netherlands. He was a thinker and an innovator, yet immensely pragmatic.

Marcel graduated in medicine from the University Hospital Groningen in 1984. He was awarded his PhD on epidermal wound healing by the same university in 1989. He then undertook residency

Photo by Marjolein Annegarn (www.garn.nl).

in the dermatology department in Groningen, becoming a staff member on completion in 1992. In 2002, he accepted a professorship in blistering diseases, giving an inaugural lecture entitled 'Broken Contacts', referring to the broken cell contacts in blistering diseases. In 2003 Marcel was named Chair of the Department of Dermatology at the University Medical Centre Groningen.

Marcel's interest in blistering diseases began early in his academic career. In 1995 he discovered that deficiency of type XVII collagen was the cause of a subtype of junctional epidermolysis bullosa (EB). In 1996 he discovered revertant mosaicism in EB, the phenomenon in which a naturally occurring somatic 'second hit' corrects the effect of a disease-causing gene mutation. This was the key to understanding the genetic mechanism behind the natural gene therapy in skin of patients with EB, and resulted in widely cited publications. He remained dedicated to the pursuit of a cure for EB for the remainder of his career.

In addition to genetic forms of blistering diseases, Marcel made significant contributions in the domain of autoimmune blistering disorders. His book '*Autoimmune Bullous Diseases*' was published in 2016, aiming to improve diagnostics and treatment in everyday practice. Science was his passion, but patient care was his vocation, and for him the most rewarding aspect of his professional life. He was an empathic and respected doctor. He founded the centre of expertise in genetic and autoimmune blistering diseases for the Netherlands, a reference centre in Groningen, equally renowned for its excellent diagnostic and research laboratory as for its patient care. Marcel also was cofounder of the Dutch Association for Experimental Dermatology in 1998 to promote a high scientific level of dermatological research in the Netherlands.

Although illness robbed him of the time necessary to complete his professional ambitions, he inspired many followers who, driven by his knowledge, innovative ideas, passion and perseverance, will continue his important work. During his 26-year academic career, he supervised 21 doctoral students. Those he taught and mentored described him as a visionary and passionate supervisor, whose attention to structure and detail was never at the cost of trust and scientific freedom.

In his free time, Marcel was a reader and a connoisseur of national and international literature. During his final illness he donated a book from his extensive library to every visitor, with a personalized message. He also was a passionate sailor, skier and tennis and golf player. While attending conferences, it was on the golf course you would find him at 6:30 in the morning, squeezing in a few holes prior to lectures. Above all Marcel was a family man. He enjoyed travelling with his wife, daughter and two sons.

Marcel Jonkman died on 14 January 2019, 5 months after being diagnosed with metastatic pancreatic carcinoma. He accepted his inevitable fate with admirable bravery. One of his quotes in this period was, 'There is fortune and there is randomness. You shouldn't pretend that you can change everything.' He will be greatly missed.

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News and Notices

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2019 Ichthyosis Research Program

The Foundation for Ichthyosis & Related Skin Types ® (FIRST) is now accepting letters of intent for the 2019 Research Grant Program for detailed investigations into all ichthyosis research. Awards will be offered for up to $50,000 for year one, with a second year of funding renewed with adequate progress and available funds.