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Atzori L.

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COMMENTARY

Atopic dermatitis and cancer risk – new insights from Mendelian randomization?

Atopic dermatitis (AD) is a complex disease, whose definition is still problematic, behind the undeniable progress of the pathogenetic knowledge and treatment approaches.1 A common denominator of the multiple phenotypes and endotypes remains an exaggerated inherited hypersensitivity reaction to normally well tolerated stimuli, as the etymology suggest, from the ancient Greek ἄτοπος (átopos), made of ἀ- (alpha-privative) + τόπος (tópos, “place”), meaning the “state of being out of place”. Onset on childhood and young adults, together with chronicity and the absolute need of treatment interfering with the immune system for very long periods of each patient’s life are variables that inevitably affect the risk of comorbidities development, including cancers. The extent of the public health concern correlates with the increasing incidence of AD worldwide, and the prevalence, affecting about 20% of children and 10% of adults .2

In the last 2 decades, epidemiological studies have supported growing evidence of a link between AD and the development of cancer at several sites, although a protective effect has been postulated for others, such as brain and gastric cancer. The most controversial issue is the association of AD with primary cutaneous lymphomas, especially mycosis fungoides early stages, which arouses concerns on the safety of novel AD treatments, that might induce a progression of the hematologic neoplasm.3

In such a context, discerning between the background cancer risk in patients with AD, the risk due to chance or other environmental independent risk factors, and the long-term effects of the treatment use is a sort of conundrum.

The work of Liu Q et al.4 offers a new perspective and opens a window into such uncertain field, thanks to the power of numbers, collecting data from major international biobanks and cancer association consortia, and the rigor of a new statistical analysis, named Mendelian randomization (MR), for the first time applied to AD. This methodology is becoming very popular in medicine, to obtain unbiased estimates of the causal relationship between risk factors and diseases using data from observational studies, with the same power of randomized controlled trials (RCT).5 Randomization in clinical trials guarantees the independence of the treatment, considered an exposure, from both measured and unmeasured confounders. In MR, randomization

consists of the random distribution of genetic variants during meiosis, analogous to the random assignment of treatments in clinical trials. If a genetic variant satisfies the assumptions of an instrumental variable, it can be used for estimating the causal effect of the exposure on the outcome, which in the present context is the occurrence of cancer. The many publicly available large-scale genome-wide association study (GWAS) provided the measurable genetic trait, selecting the specific single-nucleotide polymorphisms (SNPs) associated with AD to enable the investigation of the potential link between genetic susceptibility to AD and cancer risk. The study exploited the overall cancer risk, as well as the risk for 14 site-specific cancers, including breast cancer, prostate cancer,

non-melanoma skin cancer, colorectal cancer and lymphomas. An extensive review of all available systematic review and meta-analysis on the topic is also provided, to critically compare the study findings with previous observational data.

Results from this innovative analysis are ambivalent, reassuring in the fact that no strong evidence were found of a causal relationship between AD and overall cancer risk or any site-specific cancers. However, alarming is the suggestion that AD treatment could increase the life-time chance of developing cancer.

The medical community should once more be aware of

the role of pharmacovigilance monitoring, specially of post-marketing observational reports. The impact of new and emerging therapies on tissues microenvironment, and immune system surveillance potentially increasing the risk of cancer occurrence, should never been undervalued. Alert on the use of topical calcineurin inhibitors (TCIs), as well as the selective anti-interleukins 4/13 dupulimab has recently raised in the literature. The new registration of small molecule inhibitors (i.e. upadacitinib, baricitinib, abrocitinib) in the treatment of AD requires careful long-term surveillance, especially in light of the FDA warning on tofacitinib. In conclusion, big data evidence suggests AD patients do not present an increased cancer risk, intrinsically related to the disease, but the chance of developing cancer as consequence of medical intervention is an ethical issue, which remains in our hands to balance.

Conflicts of interest

None to declare

Founding source

None to declare

L Atzori

Dermatology Clinic

Department Medical Sciences and Public Health

University of Cagliari (Italy)

Email: atzoril@unica.it

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