Injecting carcinogenic chemicals into your skin and the possible consequences

*Significant connection between skin cancer and tattoos through epidemiology is admitted reluctantly**

The increased popularity of tattooing in the so-called Western countries was discussed on this blog some time ago (1). The warning that time, that the skin should not be a canvas to express one's personality, was meant to be a reminder that the skin is an organ, necessary for survival, like the heart, the liver, and the kidneys. This should be considered before adopting Western habits more extensively.

Frequency of tattooing

An epidemiologic assessment of tattooing in Thailand seems to be missing. A review about the epidemiology of tattoos in industrialised countries published in 2015 estimated the overall tattoo prevalence in overseas and Europe between 15 to 25%, varying between countries (2). More recent assessments in Sweden reported an overall tattoo prevalence of 20% and pointing out that more than 30% of individuals below the age of 40 are tattooed (3). In Germany, at age 18, individuals are of legal age, and whether they revolt against their parents, who forbid them to be tattooed as long as they could, plays a role or not, the majority of people get their tattoos between 18 and 35 years, and 20% are even younger (4).

The young should consider that the tattoo could cause a risk live long

The tip-off that a high proportion of the younger population is sporting tattoos is essential as it implies a potential lifelong effect of tattoos on skin integrity and tolerance. That the subcutaneous inclusion of substances evokes a reaction should not come as a surprise. Adverse reactions, from skin irritations such as eczema up to life-threatening diseases, have been mentioned in the foregoing overview, including skin cancer (1). The latter are of particular interest because many substances used in the tattoo business are carcinogenic, and the potential development of skin cancer throughout a lifetime cannot be excluded.

Studies point towards the risk of tattoos for skin cancer and lymphoma

Researching the literature about cases of skin cancers with a possible link to tattoos reports about 50 cases, including 23 cases of squamous-cell carcinoma, 16 cases of melanoma, and 11 cases of basal-cell carcinoma. The authors concluded that the number of cases is too low to establish a causal association with the metallic salts and organic dyes used in tattoo creation, and that the development of cancer at the tattoo site could be coincidental (5). Recently, a Danish study of twins, however, shows a more convincing risk pattern of tattooing for skin cancer and lymphoma throughout a lifetime.

The Danish twin study

Using the data of the Danish Cancer Registry and a Danish Twin Tattoo Cohort study of 2.367 randomly selected twins, a case-controls study of 316 twins born between 1960 up to 1996, resulted in a Hazard Ratio of 1.62 (CI: 1.08-2.41) for skin cancer, with the exception of basal-cell carcinoma for tattooed individuals. A twin-matched analysis of 14 pairs, tattooed versus tattoo-free, yielded an overall HR of 1.33 (95% CI: 0.46-3.84). Taking the size of the tattoos into consideration, tattoos larger than the palm of a hand the HR significantly increased to 2.37 (95% CI: 1.11-5,06) for skin cancer and to 2.73 (95% CI: 1.33-5.60) for lymphoma. For the cohort study type of assessment, an HR of 3.91 (95% CI: 1.42-10.8) for skin cancer and of 2.83 (95% CI: 1.30-6.16) for basal-cell carcinoma was identified (6).

Cutaneous melanoma

Among skin cancers, cutaneous melanoma is among the best-known ones. For the year 2020, 325.000 new melanoma cases and 57.000 deaths were estimated. The incidence rate for males with 42/100.000 person-years exceeded that of females with 31/100.000 person-years for Australia and New Zealand, two countries well known for their increased risk of radiation-related disease. This is especially true for Australia, where major cities are near beaches along the Pacific Ocean and have high levels of outdoor activity (3, 7).

UV radiation and carcinogenic chemicals in tattooing

UV radiation, sun beds, or laser treatment could increase the risk for melanoma, together with carcinogenic chemicals in tattoo ink. Removing tattoos via laser treatment may also be risky. As a result, substances are released and accumulate in the lymphatic system, increasing the risk of lymphoma (8).

Among the chemicals used in tattooing, there are azo compounds, which are cleaved under intense UV exposure into toxic substances such as 2-methyl-5-nitroaniline, 2,5-dichloraniline, and 4-nitrotoluene. The European Union (EU), draw attention to 4.000 chemicals, including those in tattoo ink. The regulation is called ‘REACH, standing for registration, evaluation, and authorization of chemicals. Whether the regulation affects the chemicals in use in the tattoo industry in the EU remains uncertain, let alone in Thailand (9). Chemicals suspected of being carcinogenic are used for black and colored tattoos (10).

The black color is similar to soot, which is obtained after the incomplete burning of organic matter. This most likely contains hazardous polycyclic aromatic hydrocarbons (PAHs). PHAs remain lifelong in the skin, which has the potential to absorb UV radiation. Radiation, in general, produces singlet oxygen, also called deoxygenated oxygen, because it contains two oxygen atoms. The concentration of singular PAHs was measured by High-

Performance Liquid Chromatography (HPLC) and mass spectrometry for 19 inks usually used for tattooing. Substantial concentration of benz(a)pyrene, phenol, and PAHs, as Phi(Delta), was identified. The effect on cells was tested by incubating keratinocytes with different ink extracts, which resulted in decreased mitochondrial activity. It was concluded that phenol and PAHs in the skin, exposed to the sunshine, could be risky for skin cancer (11). To improve the tattoo impression, titanium dioxide is applied. The chemical was banned in the EU for whitening certain foods and is classified as potentially carcinogenic (12).

Metals and pigments

Additional ingredients in tattoo inks include metals and pigments, among others, to add color to tattoos and, at the same time, increase the risk of allergic contact dermatitis. Of seventy-three tattoo inks on the market, 93% violated EU legal requirements, and 50% declared at least one pigment incorrect. Substances used in various inks included iron, aluminum, titanium, and copper (as the main metals) for green and blue pigments. Almost all samples contained chromium and nickel, and lead and arsenic were also added (13).

Of particular interest is red tattoo ink, which should not be used on humans, since it contains the potential carcinogen 2-anisidine. Its carcinogenic effect was tested in a hairless mouse strain that was tattooed on its back. Half of the mice were exposed to UV radiation three times weekly. All of the irradiated animals developed squamous cell carcinoma. The red-tattooed group developed carcinoma earlier than the controls. The authors downplayed the importance of their own results, concluding that the effect was weak and unlikely to be clinically relevant (14).

The Swedish epidemiological study about tattoos and cutaneous melanoma

A recent Swedish investigation, which focused on the important skin disease cutaneous melanoma and used straightforward epidemiological and statistical tools, allows a more straightforward assumption (9). For a population-based case-control study, cases of cutaneous melanoma in situ or invasive, as well as nevus with severe atypia, diagnosed in 2017 in patients aged 20 to 60 years, were selected from the Swedish National Cancer registry. The coverage of this cancer amounts to 99%, and practically all cases are morphologically confirmed. From the Total Population Registry on the index date, three matched controls for the same sex and age were randomly sampled.

Tattoos, as the exposure variable, were assessed using a structured questionnaire, explained in detail in a previous publication (3). Tattoos were defined as ‘permanent motifs obtained for decorative, cosmetic (i.e. permanent or semi-permanent makeup and microblading), or medical (i.e. in reconstruction of skin after surgery) reasons.’ The questionnaire also included asking for removed tattoos. The area of the body surface tattooed was scaled as less than one palm, one to five, and more than five palms. Data at which age the tattoo was obtained, as well as the characteristics of the tattoo, including

colors, anatomical location, and the geographical location of the tattooist, who might have been a professional or nonprofessional ((9) see page 2). A skin phenotypic risk index was created considering the reaction of skin to sun exposure and the skin tone as well as eye color, and possible confounders were considered as well (for details see Table 3 page 6).

The relative risk ratio of cutaneous melanoma in tattooed compared to nontattooed individuals was evaluated by a multivariate logistic regression in 'rendering' the incidence rate ratio (IRR). Adjustment variables, besides age and sex, included education, household income, marital status, phenotypic risk index, UV-exposure index, and smoking.

From 1602 cases, ten were dead, and the controls amounted to 2288 individuals. Twenty-two percent of the cases and twenty percent of the controls were tattooed. Details of the matched and unmatched analyses are provided in Table 6 on page 9 of the publication (9). For those less interested in the subtleties of statistics, the adjusted relative risk of becoming a patient with the serious and life-threatening skin cancer cutaneous melanoma is 1.29 (95% CI: 1.07-1.56). The IRR in the matched analysis accounts for 1.31 (CI: 1.05-1.68) for tattoos covering more than 1 palm, and the rate in the unmatched analysis is slightly lower but still significant. Exposure to the invasive and in situ melanomas for 5 to 10 years is substantial, as illustrated in Fig. 2. The number of individuals with tattoos for more than 15 years is slightly above one and not statistically significant, given the small sample size.

Conclusion:

Even in cases of mistrust of statistical results indicating a behavioral risk, common sense might lead us to conclude that injecting carcinogenic substances into the skin is unlikely to benefit health. It's the role of public health to point towards genuine health risks. In this case, the risks remain lower for Thais and higher for sun-hungry tourists, especially Caucasians from the West. Admiring the West, particularly among younger Thais, might in the future lead to the tattooing trend gaining greater traction in Thailand. Therefore, warning against tattoos might be beneficial.

The investigators' obvious reluctance to clearly position themselves against the habit, when the risk involves cancer, is obvious. Also, the Swedish publication scales down their own results. This is echoed by the IARC monographs. They are overly extensive and difficult to comprehend, avoiding a clear conclusion (10, 12). Some online links to journal article summaries of the monographs don't work. It seems politically inopportune, especially in the West, to argue against individual rights to self-determination, regardless of the health risk.

* Using EndNote 20, a temporary warning against the Swedish tattoo study (9) appeared, indicating that the publication was retrieved. Google research explained that the pre-

publication in an e-journal, was criticized by IARC, and after considering the comments published by the European Journal of Epidemiology.

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Grammarly software was used to improve English, but the AI function was disabled.