Beyond leukaemia and nuclear power: Swiss health sciences need a mega-cohort

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Kuehni and Spycher have provided a timely discussion about the association between ionising radiation from nuclear power plants (NPPs) and leukaemia in children [1]. Whereas some studies observed such associations, others were unable to refute the null hypothesis of no effect. This was also encountered in the census- and registry-based Swiss CANUPIS study [2]. The inability to refute the null hypothesis is, of course, not proof of the null hypothesis and – as mentioned by Kuehni and Spycher – scientists agree that ionising radiation causes cancer with no "threshold of no effect". Thus, the question is why the plausible hypothesis of a carcinogenic effect of NPP-related radiation remains unproven.

Observing and, thus, quantifying those effects in humans under real-life conditions poses a major scientific challenge. Exposure differences between those living close to a NPP and the rest of the population are, under normal operation, very small. Thus, the methodological challenge is comparable to a hypothetical study about the health effects of smoking assuming only two study groups, namely one smoking three cigarettes and one smoking four cigarettes per day. This setting would jeopardise the ability to establish the well-known dose-response without threshold unless the study populations were extremely large. Related to NPPs, all one can conclude at this stage is the cautious statement that if NPP-related radiation causes early-life leukaemia, the excess risk among the exposed as compared with the not exposed may be relatively small and the proportion of cases attributable to NPPs is expected to be small too as long as only a minor fraction of the population is living close to NPPs.

Interestingly, despite several decades of research, the aetiology of childhood leukaemia remains in general rather unclear and the short list of established causes may explain only some 10% of all cases [3]. Inconsistent findings may not only indicate that the relative risks are most likely not very large across the range of exposure, but also point toward complex aetiological pathways and interactions among a range of factors and mechanisms – a phenomenon very well known in chronic disease epidemiology [4]. To detect relatively small effects at low levels and across small differences in exposure, and to separate those effects from the role of other cofactors, is a challenge. Although epidemiology is the key science to enlighten the complex "web of causation", epidemiologists cannot guarantee to achieve this goal; thus, Kuehni and Spycher are right to call for further and better research to investigate properly the role of low-level ionising radiation on childhood cancer. Though I agree with their general suggestions, a few issues may need some further specification.

The role of meta-analyses is well emphasised. Meta-analyses should, though, exclude purely ecological analyses – studies that only provide correlations across aggregated data. There is clear methodological proof and applied evidence showing that correlations in aggregate data cannot reliably estimate individual-level associations [5]. It is not only impossible to control individual-level confounders in ecological analyses, but it is of particular concern that one cannot predict the direction of the biases possibly present in the ecological correlations, nor properly analyse interactions or adjust for confounders in any reliable way [6–8]. A scholarly literature in the field of ionising radiation due to natural radon and lung cancer underscores how ecological correlations may mislead in indicating "protective effects" of radon at low doses [9]. Although this was observed in several ecological analyses, prospective cohort data have clearly disqualified those findings with analyses based on individual data [10, 11]. A simulation of Brenner et al. illustrated the very serious unpredictability of the bias in ecological associations between the community-level prevalence of smoking and lung cancer mortality rates. Depending on the (by default unknown) specificity and sensitivity of the aggregated exposure data, the ecological associations may indicate smoking to be protective against lung cancer [12].

The best meta-analytic estimate is one based solely on aetiologically sound research with individual-level data available on the outcome, the exposure to radiation, as well as on all relevant covariates. In light of the highly multifactorial nature, the list of individual level covariates should not be too short but include at least all factors and exposures possibly related to leukaemia, such as tobacco smoke, benzene and other air pollutants, solvents and other chemicals, ionising and nonionising radiation, pesticides,

immunological and dietary factors, markers of genetic susceptibility and socioeconomic conditions [3]. One should have information about these factors both during pregnancy and in early life. The well-done Swiss CANUPIS study discussed by Kuehni and Spycher provides an example of the challenges faced with individual-level registry- and census-based data where none of these covariates may be available on the individual level. It is very unlikely, that one will conclusively unravel the NPP-leukaemia hypothesis with studies with a similar lack of individual-level data.

My conclusion is that we must clearly go beyond registry- and census-based research to promote conclusive knowledge in the fields of complex multifactorial diseases. Without large-scale prospective studies with individual-level information about phenotypes, and functional, structural and biological data complemented with solid data about all other aetiologically essential dimensions of health (social, environmental, cultural), the complex "web of causation" of health and disease will not be uncovered. We need to call for a very large, prospective long-term study platform – namely a Swiss mega-cohort, including not only patients but also subjects from the general population. Such a mega-cohort with its inherent biobank needs to include not tens but hundreds of thousands of subjects from all sociocultural backgrounds, to be followed up for decades. Switzerland with its 7 million inhabitants and a highly successful record in research cannot leave such life science platform initiatives to other countries such as Sweden, the United Kingdom, Germany and many others, where cohorts (with biobanks) of several 100,000 subjects are already established or initiated (see, e.g., the pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) – http://bbmri-eric.eu/ [13].

Indeed, promising steps have been taken in recent years, including the Swiss National Science Foundation (SNF) investment into smaller cohort studies and its most recent decision to invest in a Swiss biobank platform, where the two pillars of patient-based (led by Vincent Mooser, Lausanne) and population-based cohorts (Nicole Probst-Hensch, SwissTPH Basel) lay essential ground for the journey toward a Swiss mega-cohort [14]. It is crucial that all stakeholders – including the Federal and Cantonal agencies – continue to pull in the same direction to establish a well-standardized national mega-cohort, targeted to the research needs of the Swiss healthcare system, personalised medicine as well as personalised prevention and health promotion [14].

Kuehni and Spycher are right that prospective cohorts will be inefficient to investigate the NPP-leukaemia hypothesis given the low incidence [1]. However, this research – like almost any other health-relevant research – will greatly profit from a large-scale prospective population-based mega-cohort. Population-based controls could be sampled from such platforms – which can be linked to census and registry data [15] – thus providing ample information on a whole range of relevant personal data, including biomarkers, disease histories and past exposures in order to unravel the complexity of pathways and susceptibilities that underlie the NPP hypothesis [16, 17].

Last but not least, I agree with Kuehni and Spycher that leukaemia should not be seen as a priority in the political discussion about the future role of NPPs in energy policies. NPPs come with societal challenges and risks far beyond their possible link with leukaemia and, thus, need to be judged in the broader context, including the fact that catastrophic accidents can occur and that the technology leaves behind hazardous nuclear waste as a legacy for thousands of generations to come.

In sum, future research on the biological, life-style, sociocultural and environmental drivers of personal health and disease will need a Swiss national mega-cohort with its biobank. Switzerland has long-standing experience in running highly successful cohorts. The time has come to scale the national expertise up to a concerted Swiss national mega-Cohort.

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