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EDITORIAL

Transient caloric restriction and cancer risk (The Netherlands)

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Abstract Over the past century, many animal experiments have shown that caloric restriction can reduce the risk of cancer, a finding that proved to be highly reproducible. Many papers have been published on its potential for human health, but until know little evidence is available on its actual effects in humans. In Utrecht, The Netherlands, we have been investigating the effects of the 1944–1945 Dutch famine on breast cancer risk factors and breast cancer risk, and paradoxically the relatively short-term famine seemed to be related to increased breast cancer risk in later life. One of the differences between the famine situation and the large body of evidence from animal experiments is the duration of caloric restriction. Almost all animal experiments investigated sustained caloric restriction and information on the effects of short-term transient caloric restriction is very scarce. A search in the literature identified some animal experiments on short-term transient caloric restriction and these seemed to be at least supportive to the famine findings. Because caloric restriction in humans for preventive health measures would be mostly short-term, it is important to extend animal research on short-term caloric restriction.

Keywords Caloric restriction · Transient · Cancer · Risk · Famine · Human

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During the 20th century, a large body of experimental evidence has been accrued signifying that caloric restriction protects against cancer. Rodent data are abundant and consistently show (i) that caloric restriction lowers the incidence of a variety of spontaneous as well as induced or transplanted tumours; (ii) that this effect is directly proportional to the amount of caloric restriction; (iii) that the effects can largely be ascribed to caloric restriction per se, and not merely to the decrease in one or more dietary components; (iv) that caloric restriction initiated in early life as well as in later life is effective in cancer prevention; (v) that caloric restriction prolongs life [1–5]. A pooled quantification of the inhibitory effects of caloric restriction on spontaneous mammary tumour incidence in mice showed that caloric restriction lowered the incidence with 55% [6].

Preliminary reports on energy restriction in non-human primates appear to be consistent with findings in rodents [7, 8]. What about humans? Obviously, this is difficult to investigate, but can lead to important insights in cancer aetiology and to opportunities for prevention. The 1944–1945 Dutch famine, a relatively short severe famine during World War II [9, 10], could shed some light on this issue, and has been used before as an ''experiment of history'' [11–13].

During the past years, we have conducted several studies on the effects of the 1944–1945 Dutch famine on breast cancer risk factors and breast cancer risk in Utrecht, The Netherlands. For these studies we used data on women who were between 2 and 33 years of age during the famine. Therefore we were not only able to investigate the long-term effects of caloric restriction, but could also relate those effects to specific time-windows in female development. Women were

classified to their degree of famine experience on an individual basis, leading to a three-point famine score ('absent', 'moderate', or 'severe' exposure) that enabled dose-response evaluation [14].

In brief, we found that the famine is associated with subsequent reduced reproductive ability in women who were exposed during childhood. This is manifested by decreased chance of childbirth and an earlier mean age at menopause [15, 16]. Strikingly, research on moderate early life diet restriction in *Drosophila melanogaster* by Tu and Tatar showed also a decrease in adult fecundity [17]. Furthermore, we found that hormone concentrations, measured postmenopausal, seem to be affected by the famine with increases in sex-steroid as well as insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 levels (resulting in unaffected IGF-I to IGFBP-3 ratios) [18, 19]. All our observations showed a dose-response to degree of famine exposure, with smaller but still observable associations in those moderately exposed.

With regard to breast cancer risk, the associations between the famine and the reproductive system would suggest a protective effect of the famine [20]. However, the associations with hormone concentrations would suggest the contrary [21, 22], with the exception of increased IGFBP-3 that may relate to decreased breast cancer risk [23].

When we actually determined the effect of famine on breast cancer risk in this population, we found that the famine is related to increased risk, again in a dose response manner—a finding that was stronger in women who were children during the 1944–1945 winter [24]. Body mass index at later ages did not confound this relation nor modified it (last data unpublished), suggesting that catch-up growth after the famine did not play an important role. Total cancer risk, exclusive of breast cancer, seemed not to be affected by the famine [25], which does not preclude that famine may have affected risk of specific types of cancer, but the numbers in our study are presently too small for analysis with more detail. Another famine study by Dirx et al. on breast cancer risk could not detect a protection against breast cancer from the famine either, and if anything, showed a moderate increase in risk in women that were exposed at young ages [11]. In addition, Dirx et al. showed that the famine was, non-significantly, associated with increased prostate cancer and decreased colon cancer risk [12, 13]. In these studies, Dirx et al. used place of residence as a measure of famine exposure whereas we used individual exposure data, based on recall.

These findings are not in line with the animal experiments consistently showing caloric restriction to prevent cancer. Several differences between the usually adopted caloric deprivation strategy in animal experiments and the 1944–1945 Dutch famine may explain these differences, such as the amount of restricted calories. The exact degree of caloric restriction during the 1944–1945 Dutch famine is difficult to ascertain, but rations dropped to about 30% of desired norms for adults and to about 50% for young children. The relative amounts of carbohydrates, fats and proteins remained more or less balanced, and supplementations to the rations were sometimes clandestinely available. Young children were relatively protected within families and by charity organisations [9, 10]. Although the amount of caloric restriction during this famine is larger than usually adopted in animal experiments, tumour incidence has been shown to decrease proportionally to degree of caloric restriction in animal experimental settings, amounting to an estimated 62% tumour reduction with 53% caloric restriction [2]. Therefore, it is unlikely that differences in the amount of caloric restriction explain the contradictory results of the famine studies and the animal experiments.

More notably, during the Dutch famine people were transiently exposed for a relatively short duration of time (6 months) [9, 10]. Therefore, this ''experiment of history''—as most current famines due to crop disaster or war—is only similar to experiments in rodents that studied short-term caloric restriction followed by ad libitum feeding, whereas the vast majority of these studies investigated dietary interventions that were sustained throughout the animals entire live.

We were able to identify eight animal experiments that investigated transient and mostly short-term caloric restriction, where after animals were allowed to eat at will [26–33]. Two of these experiments studied the effect of caloric restriction for different time periods during and after the chemically induction of breast cancer in female rats [28, 31]. Sustained caloric restriction dramatically decreased tumour incidence: from 50% in the ad libitum group to 20% in the continuously restricted group [31]. It also seemed that caloric restriction during tumour initiation—from 1 week before until 1 week after 7,12-dimethylbenz-[α]anthracene administration—potently reduced mammary tumour development [28]. However, restriction for any period after tumour initiation followed by ad libitum feeding, if anything, showed no substantial effect, and could even lead to increased breast cancer risk [28]. Furthermore, Kritchevsky noticed that when rats were returned from restricted to ad libitum feeding this resulted in hyperphagia, accelerated weight gain,

transient mammary hypertrophy, and enhanced tumour growth [31].

Four other experiments investigated the effect of caloric restriction for different periods on, amongst others, spontaneous overall tumour incidence in rats [26, 27, 30], and mice [29]. Again, these studies showed that sustained caloric restriction throughout life lowered cancer risk substantially. However, caloric restriction confined to early life did either not affect cancer risk [30], or actually seemed to increase it [26, 27, 29]. This feeding strategy did not materially increase lifespan, so this cannot explain the observed increase in cancer risk. The study of Cheney et al. in female mice provides some evidence that caloric restriction confined to mid-life may also eventually lead to increased cancer burden [29].

Recently, interest was rekindled with two more studies on prolonged but transient caloric restriction and 1-methyl-1-nitrosaurea induced mammary carcinogenesis in rats [32, 33]. These studies both show that upon refeeding tumour incidence increased.

The disparity between our findings in humans after caloric restriction during a short and severe famine and the abundant literature on sustained caloric restriction and cancer risk in rodents may be ascribed to differences in exposure duration, as is corroborated by the abovementioned animal studies on transient caloric restriction that are in line with the famine observations.

From a biological point of view, it may not be surprising that a short and transient period of caloric restriction in early life may increase human cancer risk. During caloric restriction, a range of responses can be seen, most of which could be directly beneficial to overall cancer risk but are unlikely to be of importance once the restriction is discontinued. Proliferation of cells is reduced with both increased rates of apoptosis together with decreased DNA synthesis and increased DNA repair, limiting the number of preneoplastic lesions. Oxidative stress is reduced, resulting in decreased reactive oxygen species that can damage DNA. Furthermore, of interest to hormone associated tumours, levels of a number of hormones and growth factors are altered during caloric restriction: glucocorticoids are increased whereas concentrations of IGF-I (and to a lesser extent IGFBP-3 resulting in decreased bioavailability of IGF-I), insulin, prolactin, estrogens and leptin are decreased [3–5, 34–36].

Changes in leptin levels can interfere with sexual maturation [37, 38], a period in development during which the Dutch famine showed the largest impact on breast cancer risk in our study. It could be that the hypothalamo-pituitary axis, which is not matured in girls until a few years after menarche when regular menses are established [39], has erroneously adapted to the period of paucity, leading to inappropriate set-levels of hormones that could relate to hormone associated cancers [18, 19]. Such erroneous adaptations, also described as a ''thrifty phenotype'' [40], are the subject of the ''foetal and infant origins of adult disease'' hypothesis by Barker and colleagues [41]. Evidence is mounting that such long-lasting effects indeed exist and may contribute considerably to later health [42]. The potential involvement of the hypothalamo-pituitary axis herein has been recognised [43].

In conclusion, the general notion that caloric restriction prevents cancer needs some amendment, even for rodents. Evidence is strong that during caloric restriction, cancer risk is decreased proportionally to the amount of restriction, and such interventions can be effective whether started in early life or later. However, a short and transient period of restriction followed by a ''normal'' diet does not show such effects and could actually be detrimental.

Thompson et al. made a similar plea. If humans are advised to eat less as a means to prevent cancer, this would probably result in repetitive periods of weight loss followed by periods of weight gain. He warned that such weight cycling may be associated with a modest acceleration of the carcinogenic response [44].

Animal experiments on short-term interventions or weight-cycling diets are scarce and their results yet inconclusive. Such animal experiments are nevertheless highly relevant and need further investigation before any preventive strategy is researched in experimental settings, or actually adopted, in humans, as short-term interventions are the most feasible for the human situation but may bring along considerable hazards. It would be of importance to see if our observations can be replicated in such animal experiments and in human studies making use of other famine episodes, e.g. the 1959–1961 Chinese famine [45]. Other human studies may involve for instance children from countries with poor nutrition that are adopted by families in economically prosperous countries. These children have been exposed to adverse nutritional circumstances at young ages for a clearly demarcated period followed by nutritional abundance (in contrast to immigration studies of for example Japanese women to the United States who gradually adapt, often partly, to a Western lifestyle). Indian girls adopted in Sweden have for example been shown to reach menarche at younger ages compared to Indian standards [46]. It would be intriguing to see whether other physiologic changes occur in these children, e.g. with regard to hormonal levels.

Furthermore, studies on cancer risk in patients with anorexia nervosa are also of interest. Two studies have reported on the topic and found a decreased risk of breast cancer [47, 48]. The generalisability of these observations is however troubled as factors underlying this disease may contribute to the decrease in breast cancer risk, so this may not merely be ascribed to a decreased caloric intake per se.

Currently, the relation between famine exposure in early life and risk of other types of cancer than that of the breast is largely unknown. It would be valuable to further investigate these relations to see whether associations are different between cancer types, e.g. comparing hormone to non-hormone associated cancer types. This would give further insight into whether general mechanisms in human cancer aetiology are involved or whether adaptation of hormonal axes leading to harmful hormone concentrations is the potential culprit.

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