

This good evidence suggests the potential for anticoagulation to be used for cancer chemoprevention. But first, additional observational studies and clinical trials are needed to confirm the findings of the Canadian study and to address potential uncontrolled confounding and other biases—ie, safety and efficacy. Second, the principles behind primary chemoprevention should be considered. Because of the relatively low incidence of prostate cancer, the years and numbers of patients needed to be treated to prevent one cancer case will be very high. To ensure adequate compliance, the chemoprevention regimen should have no adverse effects and be easy to administer. Warfarin treatment does not meet these requirements. Progress in cancer biology and in drug development over the next decades might improve our ability to identify high-risk patients for whom the benefit of treatment with warfarin outweighs the risk of bleeding. The study by Tagalakis and co-workers should stimulate further translational research that combines basic biology, and clinical and epidemiological expertise to assess the association between coagulation and cancer. Such efforts will probably lead to improved primary, secondary, and tertiary prevention of cancer.

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The author declared no conflicts of interest

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Cancer caused by x-rays—a random event?

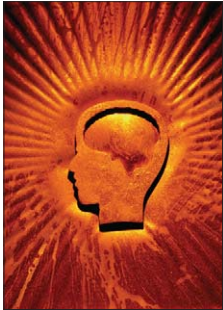
In the years immediately after the establishment of the State of Israel, ringworm of the scalp—tinea capitis—reached epidemic proportions in thousands of immigrant children, many from north Africa. The preferred treatment at the time was to induce temporary epilation by a dose of x-rays. The study by Flint-Richter and Sadetski¹ in this issue of *The Lancet Oncology* documents the incidence of radiation-associated brain tumours in a subset of such individuals, consisting of more than 500 families who have been followed for over 50 years.

This fascinating paper is of substantial interest in itself, but in addition, could have far-reaching and important implications on radiation protection and in every sphere of life in which radiation is used. These areas include diagnostic radiology, radiation oncology, and even the generation of nuclear power. The reason for this possibility is that this study offers solid epidemiological evidence that—at least in this population consisting partly of north-African Jews—radiation-associated cancers are clustered in certain families rather than being

evenly distributed throughout the irradiated population. Specifically, if all of the children irradiated during the treatment of tinea capitis are taken in to account, the risk of developing a radiation-associated meningioma is about 1 in 100. However, in some families the risk is 4 out of 5. This is an incredible concentration of risk. Current standards of radiation protection are based entirely on the assumption that the human population is uniform in radiosensitivity—ie, that radiation carcinogenesis is a stochastic event—so that when a population is exposed to radiation, the small proportion who fall victim to a radiation-induced cancer are randomly distributed. The new data conflict with this paradigm.

Of course, we have realised for some time that a radiosensitive subpopulation might exist. The International Commission on Radiological Protection issued a voluminous report on this topic in 1999,² and the subject was discussed again in the Biological Effects of Ionizing Radiation (BEIR) VII report of The National Academy of Sciences.³ Both reports concluded that certain

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inherited combinations of common low-penetrance genes can result in the presence of subpopulations with substantially different susceptibilities to spontaneous and radiation-associated cancer. This is the view espoused by the researchers of the present study. The vital question is to what extent is the population in the tinea capitis study atypical in having a higher-than-normal load of mutations, and to what extent can the conclusions be extrapolated to more typical populations?

One way to address this question is to compare the tinea-capitis data with a recent analysis of brain tumours (including meningioma) that developed after cranial irradiation in the treatment of childhood leukaemia in the USA.⁴ We have two bases for comparison. First, the ERR/Gy (the excess relative risk per unit dose); this quantity is smaller in the childhood cancer study than in the tinea capitis study, as pointed out by the researchers. However, this in itself does not prove a difference between the two populations, since the doses in the childhood cancer studies were much higher (up to 50 Gy) and were delivered in multiple daily fractions. This difference would be expected to result in a lower ERR/Gy.⁵ Second, the overall incidence of meningiomas is substantially higher in the tinea-capitis study than in the childhood-cancer study (24 of 1835 [1%] vs 66 of 14361 [0.5%], respectively), despite the much lower radiation doses involved (1–6 Gy vs 16–50 Gy, respectively). This finding would argue in favour of a larger sensitive subpopulation in the tinea-capitis study, but it does not in any way discredit the conclusion that the clustering of cancers in families that was recorded indicates a sensitive subpopulation.

The Israeli dataset is unique because it consists of a large number of families each with many siblings (mean 5.7, SD 2.7 [range 0–13]), while at the same time, tinea capitis is so contagious that if one child was affected, all siblings probably would be, and so all were irradiated.

This coincidence of factors makes identification possible of the clustering of multiple cases of radiation-associated meningioma in given families. When such an important finding is noted, the urgent need is to repeat it, but the Achilles heel of this report is that the scientific community will be hard-pressed to find another dataset that will yield the confirmation needed. Instead, the only way forward is to identify the genetic defects in the affected families—a solution that seems difficult to reach because it is already more than 10 years since the founder mutation in the *ATM* gene was identified in this population.⁶

We should delay any final judgment on the wider importance of this study until we can prove the existence in the general population of a subgroup that carries a combination of low-penetrance genes that confer susceptibility to radiation-associated cancer, albeit a smaller subgroup than is present in the tinea-capitis study. If and when the existence of such a group is proven, some re-thinking of the basis of radiation protection will be needed.

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The author declared no conflicts of interest

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Fresh frozen plasma as a complement source

I read with great interest the recent Case Report by Klepfish and colleagues,¹ in which they reported that infusion of fresh frozen plasma along with rituximab gave an enhanced clinical response in the treatment of a patient with chronic lymphocytic leukaemia (CLL). In 2004, we predicted that, with respect to the treatment of CLL, fresh frozen plasma as a complement source

might enhance the action of rituximab in patients with reduced or depleted complement concentrations.² The basis of this prediction derives, in part, from the work by our laboratory and that of several others. The in-vitro solution-phase killing of CD20-positive B cells by rituximab needs a source of complement, in the absence of which, little, if any, killing of targeted cells occurs.^{2–5}