Are haemophiliacs protected against cancer development? Prospective controlled studies are needed

Dear Editor:

We read with interest the recent article by Brüggemann and colleagues [1]. In a murine (B16F10 murine melanoma cell line) experimental study, the authors have demonstrated that congenital prothrombotic disorders, like factor V Leiden, ease the metastatic capacity of cancer, whereas congenital bleeding tendencies, like haemophilia A, impede metastasis. These results are in agreement with those previously reported by Langer and colleagues [2], who demonstrated that replacement substitution therapy with factor VIII in the haemophilic mice enhances the formation of lung metastasis. Although these findings from the bench suggest that factor VIII plays a critical role in the early blood-borne phase of the metastatic cascade, they could also explain bedside observations on haemophilia patients found by some investigators.

A number of studies have reviewed the causes of death among the haemophilia population [3], but their results were strongly biased by the dramatic influence of the HIV and hepatitis C virus (HCV) epidemics transmitted by non-virus inactivated clotting factor concentrates. These viruses were responsible for the great majority of deaths (*i.e.* acquired immunodeficiency syndrome, HIV-related lymphomas, end-stage liver diseases, including HCV-related hepatocellular carcinoma) during the 1980s, decimating the haemophilia population and clouding the true evaluation of other causes of death. Thanks to considerable improvement in the quality and safety of replacement therapy, the life span of haemophiliacs has substantially increased over the last decade and is now approaching that of males in the general population. However, in parallel with the increased life expectancy, haemophiliacs now develop medical and surgical diseases, such as cardiovascular diseases and cancers, not previously seen in this group [4]. To date, only few studies have analysed the causes of deaths in haemophiliacs after excluding those related to HIV or HCV infections.

Walker and Julian, on behalf the Association of Hemophilia Clinic Directors of Canada, analysed the causes of death in Canadians with haemophilia during the years 1980–1995 [5], reporting a marked increase of deaths from liver cancer and lymphoma in patients with HCV or HIV with respect to the general population. Besides this rather obvious observation, the authors found an unexpected lower (0.3) standardized mortality ratio (SMR, the ratio of the total observed number of cause-specific deaths in the study population to the expected number of deaths based on the reference population) in HIV-negative haemophiliacs for other cancers. However, this finding did not appear to influence the overall death rate in this subgroup of patients (SMR 0.9). Darby and colleagues on behalf the UK Hemophilia Centre Doctors' Organization, more recently analysed mortality rates and causes of death in 6018 HIV-uninfected people with haemophilia during the period 1977–1998 [6]. Although the mortality caused by neoplasm in overall haemophilia population was not significantly different of that in the general population (SMR 0.90), the authors observed a progressive reduction of the incidence of cancer with the increase of severity of haemophilia. Indeed, while the SMR for neoplasms different from liver cancers or lymphomas was 0.95 in patients with mild/moderate haemophilia, it decreased to 0.65 in patients with severe haemophilia. Unfortunately, the two studies did not analyse cancer metastases, so that the *in vitro* observations by Brüggemann and colleagues cannot be confirmed directly *in vivo* in these haemophilia patients. However, this category of patients could represent a unique model for studying the *in vivo* interaction between cancer and coagulation system. Furthermore, if these preliminary findings will be confirmed by further prospective trials on large population of patients, they could pave the way for the development of new pharmaceutical agents targeting the blood coagulation cascade to inhibit cancer cell metastasis or, better, relapse.

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