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Temporal distribution of radiation induced leukaemia [2]

Abstract

The temporal distribution of radiation induced leukaemia shows no continuous pattern but distinct groups. The composition of these groups is influenced by age, sex, diagnosis, city and age at time of bombings. Therefore, estimating risk factors using models with constant risk as models with a wave function of time since exposure effect underestimate the risk at time of incidence peaks. About half of the cases of ALL appear in a time of three years.

Introduction

The temporal distribution of radiation induced leukaemia is often described as wave function [5, 6] in a shape which was observed similarly in humans only on the osteosarcoma after administration of Ra-224 [9]. Mays and Spiess compared the temporal distribution of the osteosarcoma cases with that of the leukaemia of the atomic bomb survivors as described by Bizzozero et al. [2] overlooking the time course presenting several peaks. This wave function was observed by Stewart and co-workers in childhood leukaemia after obstetric X-ray with a peak at about three years after exposure, too [12]. The time of observation in these cases was limited to ten years.

After the dose revision in the atomic bomb survivors only in males suffering from CML[3] it was possible to get a good fit of wave functions to the temporal distribution of the onset of disease. It seems that in

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younger males at the time of the bombings there was a reduction of time to onset with increasing dose or, alternatively, in the high dose range the time to onset increases with increasing age at the time of the bombings (ATB).[4]

The calculation of dose response functions can give erroneous results if there exist subgroups with very different radiation sensitivity in the collective investigated and the time since exposure (TSE) effect is an expression of sensitivity.

For example, Thompson and co-workers described a subgroup of young females of the atomic bomb survivors with a very short time to onset of breast cancer and a relative risk which was about tenfold greater than the mean [13].

Therefore, I will risk a glimpse on the inhomogeneity of the temporal distribution of leukaemia incidence.

Time Since Exposure Effect in Atomic Bomb Survivors

Analysing the time pattern somewhat more in detail, I use the data presented by Ishimaru and co-workers with a table of the month and year of the onset of leukaemia [5]. The diagnoses and the doses are from the time before revision after FAB resp. DS86. Some diagnoses in Nagasaki could be revised [8]. The unrevised diagnoses were classified in the same manner as done by Preston et al. [11].

The diagnosis of chronic granulocytic leukaemia (CGL after Ishimaru et al. [5]) can be attributed to CML (FAB) with a small erroneous. We see that the wave function is broken up by distinct peaks (cf. fig. 1, p. 3).

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[3] Abbreviations: AL: **a**cute **l**eukaemia; ALL: **a**cute **l**ymphatic **l**eukaemia; AGL: **a**cute **g**ranulocytic **l**eukaemia; AML: **a**cute **m**yeloid **l**eukaemia; ASL: **a**cute **s**tem cell undifferentiated **l**eukaemia; ATB **a**t **t**ime of **b**ombings; CGL: **c**hronic **g**ranulocytic **l**eukaemia; CML: **c**hronic **m**yeloid **l**eukaemia; DS 86: **D**osimetry **S**ystem 1986; FAB: **F**rench **A**merican **B**ritish classification of leukaemia; MDS **m**yelo**d**ysplastic **s**yndrome; TSE **t**ime **s**ince **e**xposure
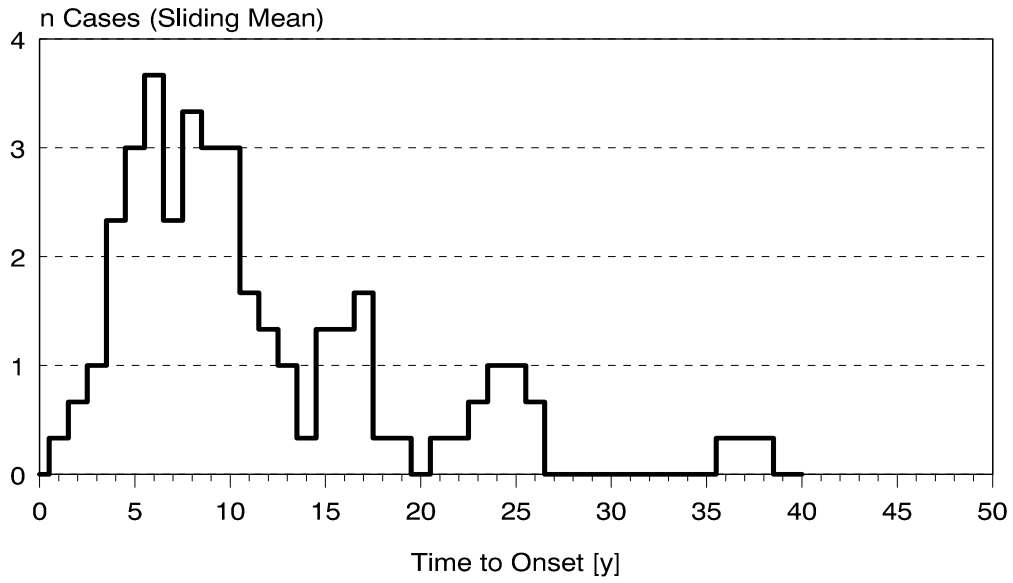
Fig. 1: Time to onset of disease of CGL (after Ishimaru et al. [5]), attributed to CML (FAB). Sliding mean with a window width of 3 years.

Acute granulocytic leukaemia (AGL after Ishimaru et al. [5]), acute myeloid leukaemia (AML after Ishimaru et al.), and one case of erythroleukaemia (Erythr. after Ishimaru et al. [5]) I have summarised and interpreted as AML (FAB). Again three clearly separated peaks can be recognised (cf. fig. 2, p. 3).
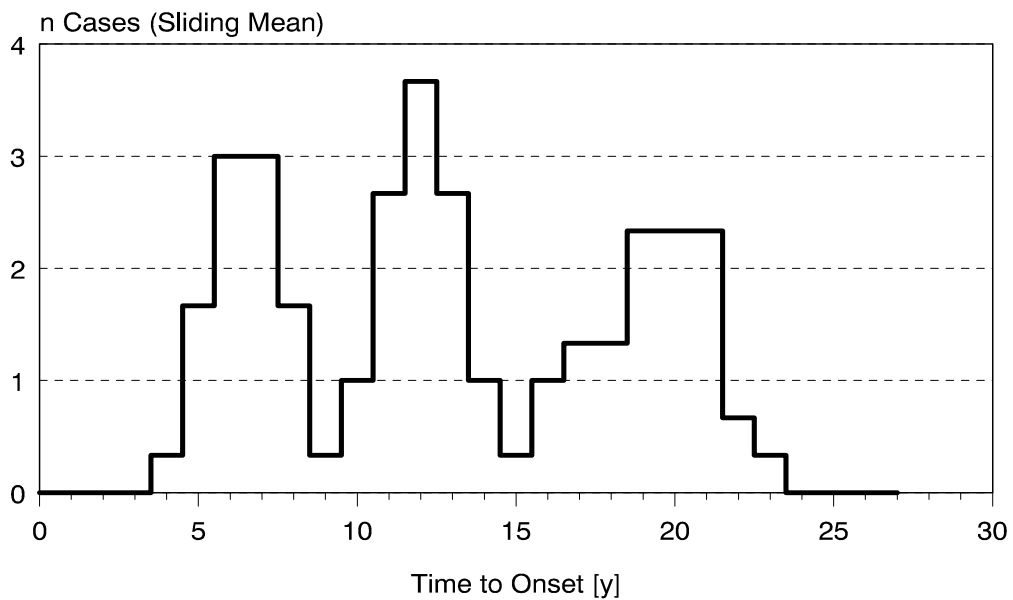

Fig. 2: Time to onset of disease of AGL (after Ishimaru et al. [5]), AML (after Ishimaru et al. [5]), and Erythroleukemia (after Ishimaru et al. [5]), attributed to AML (FAB). Sliding mean with a window width of 3 years.

A similar picture is presented analysing the acute leukaemia (AL after Ishimaru et al.) and acute stem cell leukaemia (ASL after Ishimaru et al. [5]) (cf. fig. 3, p. 4).
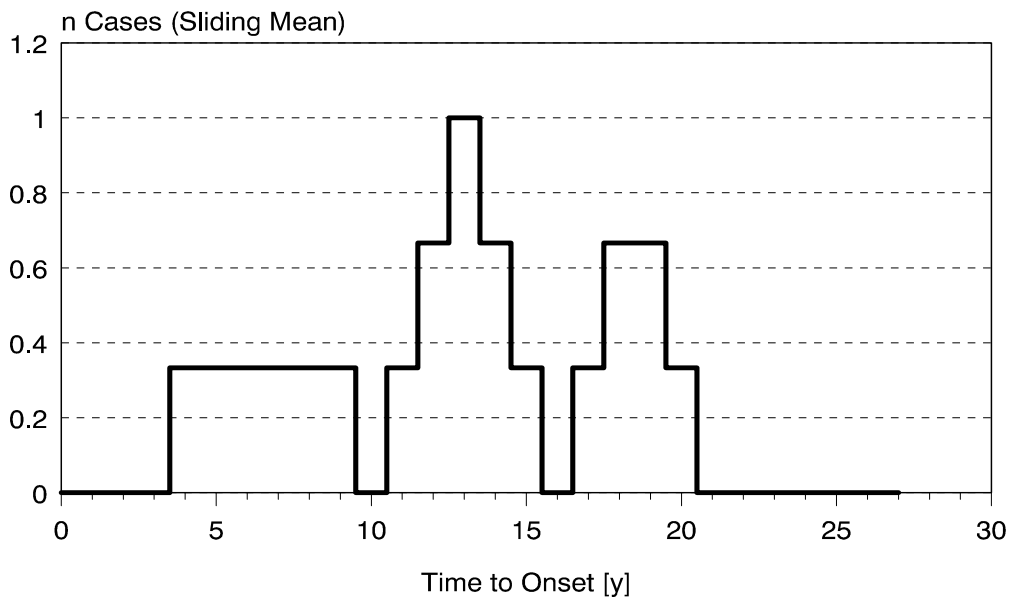

Fig. 3:   Time to onset of disease of AL (after Ishimaru et al. [5]) and ASL (after Ishimaru et al. [5]), attributed to AL (FAB). Sliding mean with a window width of 3 years.

The acute lymphocytic leukaemia (ALL after Ishimaru et al. [5]) was interpreted as ALL (FAB). This is not done without some error because of some diagnoses have been changed by the new FAB-classification to AML and vice versa in Nagasaki [8]. The distribution of the onset shows the best similarity with a wave function (cf. Fig. 4, p. 5), but with a very high peak. About half of the cases of ALL appear in a time of three years.
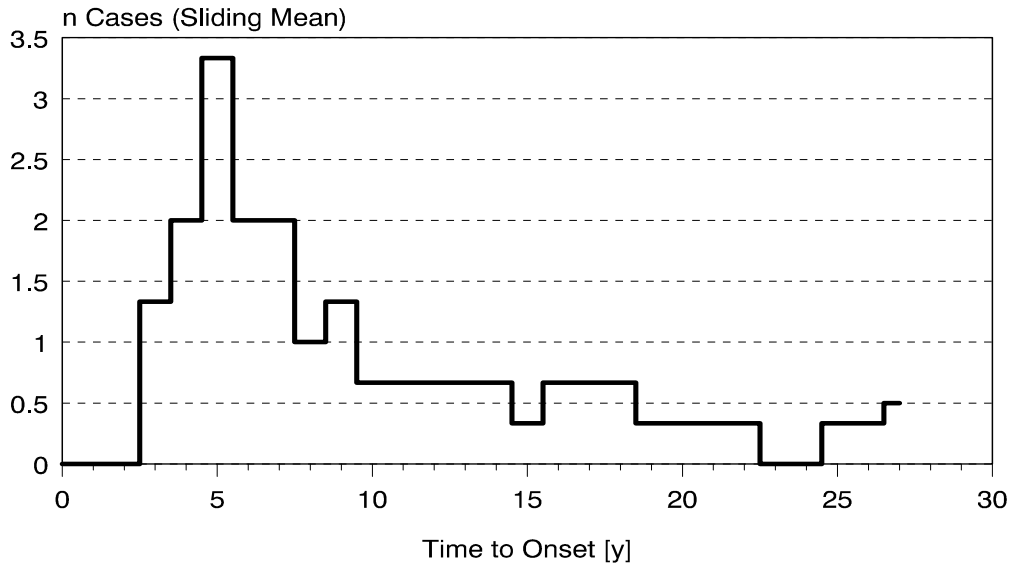
Fig. 4:   Time to onset of disease of ALL (after Ishimaru et al. [5]), attributed to ALL (FAB). Sliding
           mean with a window width of 3 years.

In secondary leukaemia after chemotherapy with alkylating pharmaceuticals [1, 3, 10], mainly AML, we
see a quite other time response pattern as AML and AL of the atomic bomb survivors, but more similar
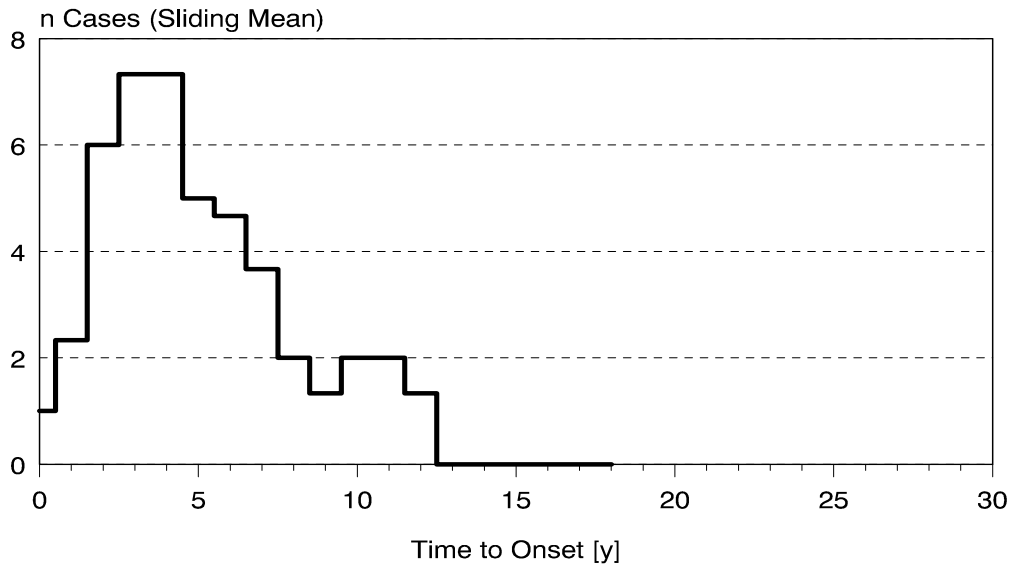to a wave function with an very early peak (cf. fig. 5, p. 5).

Fig. 5:   Time to onset of secondary leukaemia after chemotherapy (data: [1, 3, 10]). Sliding mean
           with a window width of 3 years.

Multidimensional Analysis

Now we are prepared to examine one dimension more. The columns show the time from age at the time of bombings (ATB) to onset of the disease. In fig. 6 (p. 6) the cases attributed to CML are sorted and ranked by dose .
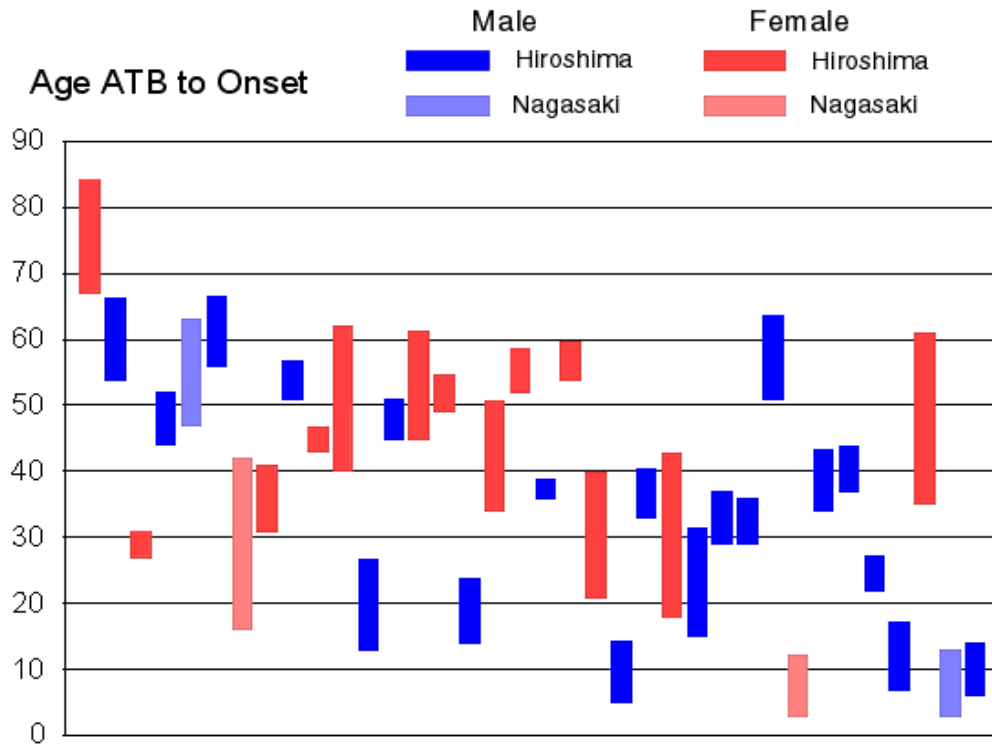

Fig. 6:   Columns from age ATB to onset of CGL (after Ishimaru et al. [5]), attributed to CML (FAB). Cases are sorted and ranked by dose (no quantitative scale!) and discriminated by sex and city.

We see the general trend: The lower the dose - the older the persons must be at exposure for falling ill. It seems that an accumulation of irritation of the genom during life enhanced the sensitivity inducing a CML. Furthermore we see subgroups, more males than females, in which CML can be induced in younger age.

Sorted by TSE we see that short time periods to onset are to find in Hiroshima only and mainly in the age group among 30-60 (cf. fig. 7, p. 7). In the group of very long time periods we recognise with one exception only females. CML was seen very seldom in Nagasaki.
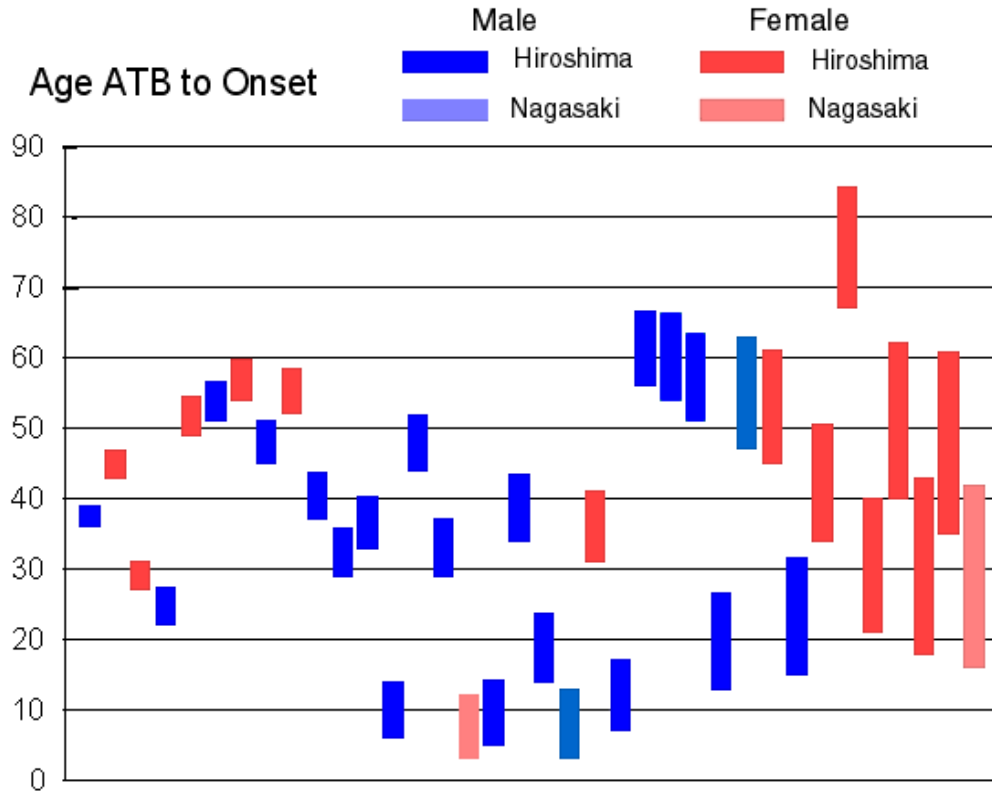

Fig. 7: Columns from age ATB to onset of CGL (after Ishimaru et al. [5]), attributed to CML (FAB). Cases are sorted and ranked by TSE (no quantitative scale!) and discriminated by sex and city.

In cases attributed to AML sorted by dose the first impression is that Nagasaki cases are more frequent than in case of CML and distributed equally over the dose range. We see again two groups with the tendency to older ages ATB with decreasing dose. Male and female appear with about the same frequency, but in the age of less than 20 ATB with eleven persons we find only three males (cf. fig. 8, p. 8).
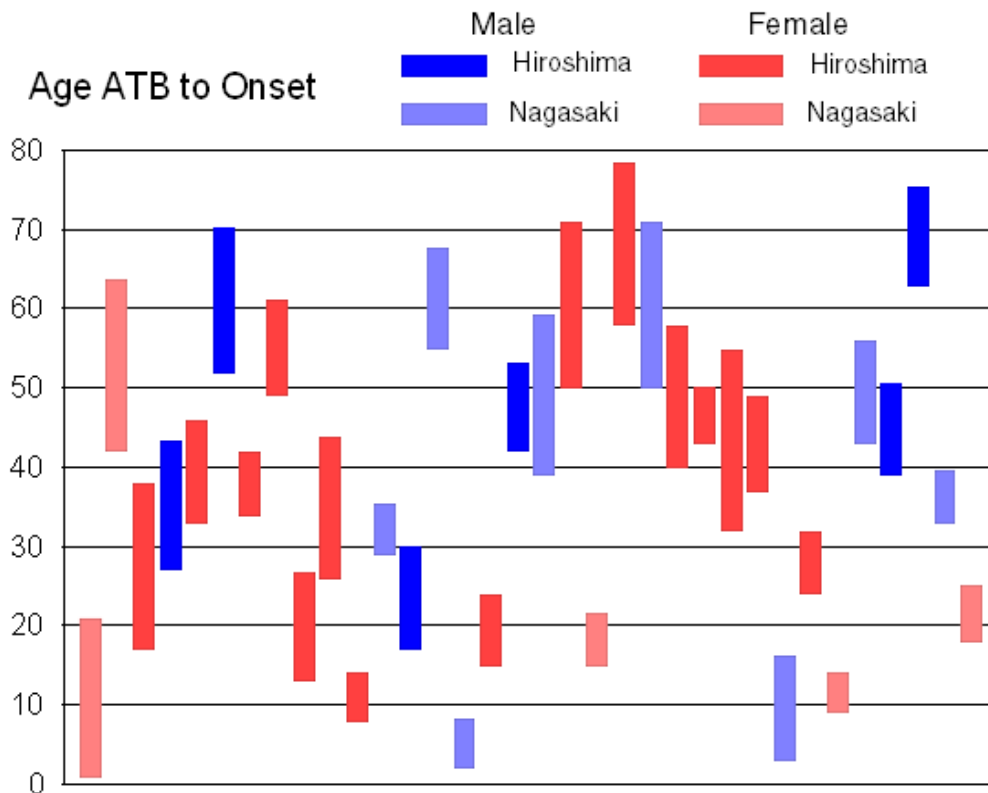

Fig. 8: Columns from age ATB to onset of AGL (after Ishimaru et al. [5]), AML (after Ishimaru et al. [5]), and Erythroleukemia (after Ishimaru et al. [5]), attributed to AML (FAB). Cases are sorted and ranked by dose (no quantitative scale!) and discriminated by sex and city.

Where are the males? Died by infectious complications in the preleukaemic phase of AML (MDS)? Also, in the groups combining the effect of dose and age ATB we see only half as many males as expected in the left lower range one.

Sorted by TSE we see again in the groups with long time periods predominantly females as in CML (cf. fig. 9, p. 9). In contrast to CML longer TSE corresponds to older age in ATB. In Nagasaki we find a small group of young people with short time to onset.
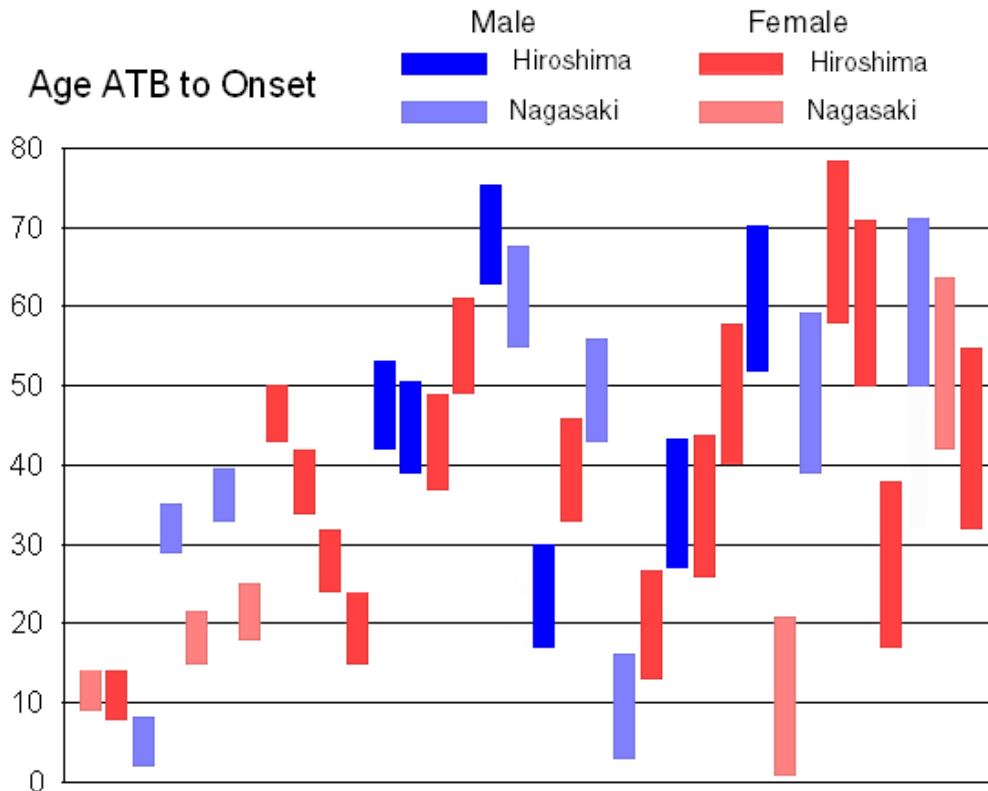

Fig. 9: Columns from age ATB to onset of AGL (after Ishimaru et al. [5]), AML (after Ishimaru et al. [5]), and Erythroleukemia (after Ishimaru et al. [5]), attributed to AML (FAB). Cases are sorted and ranked by TSE (no quantitative scale!) and discriminated by sex and city.

ALL exhibits that in children the underrepresentation of male, seen in AML, can not be recognised (cf. fig. 10, p. 10).
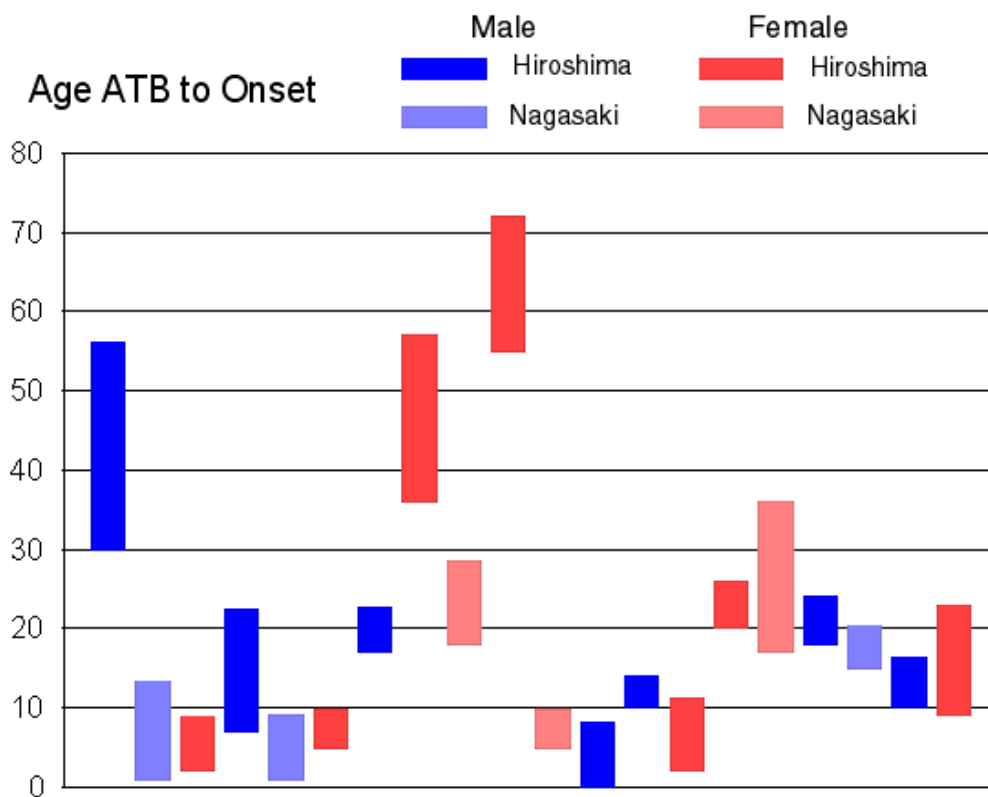

Fig. 10:   Columns from age ATB to onset of ALL (after Ishimaru et al. [5]), attributed to ALL (FAB).
            Cases are sorted and ranked by dose (no quantitative scale!) and discriminated by sex and
            city.

Sorted by dose very few cases are observed in elder people, which occur in low dose range and were correlated with unusual high values of TSE (cf. fig. 11, p. 11). It cannot be excluded that this kind of inhomogeneity is due to false classification of the diagnose.
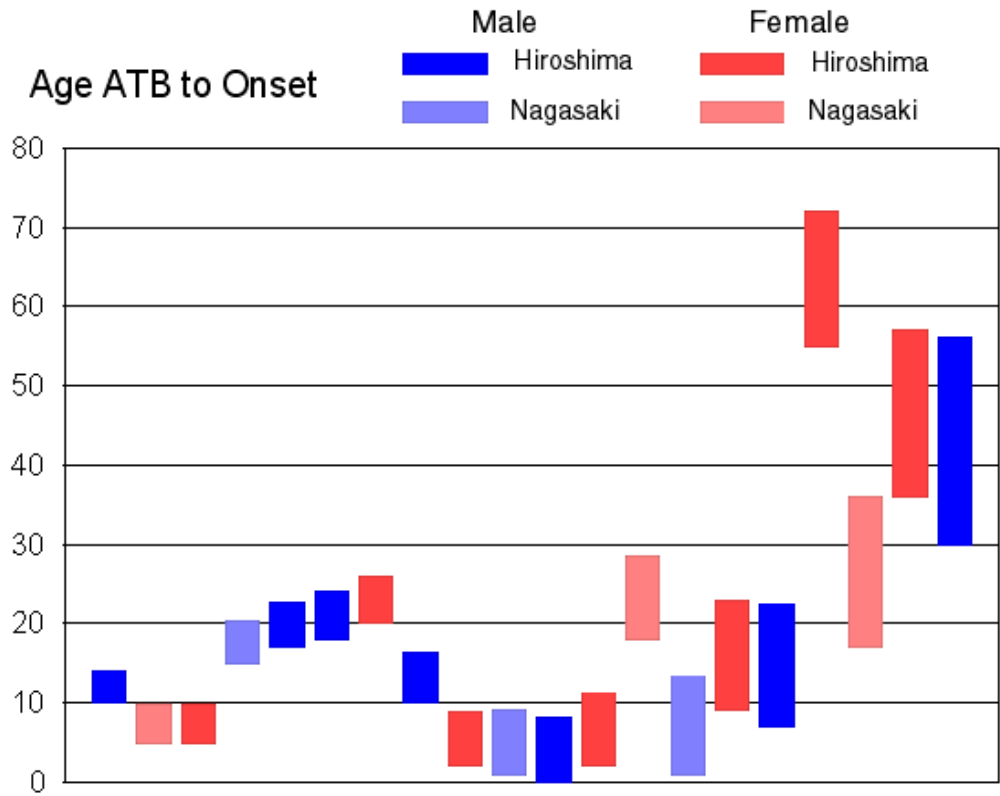
Fig. 11:   Columns from age ATB to onset of ALL (after Ishimaru et al. [5]), attributed to ALL (FAB). Cases are sorted and ranked by TSE (no quantitative scale!) and discriminated by sex and city.

I think the effort is justified to repeat such analysis with the revised doses and diagnosis and the cases up to the eighties.

Finally I will show you the time pattern of leukaemia, for better statistics all types combined and smoothed with a broad window, related to age ATB (cf. fig. 12, p. 12).
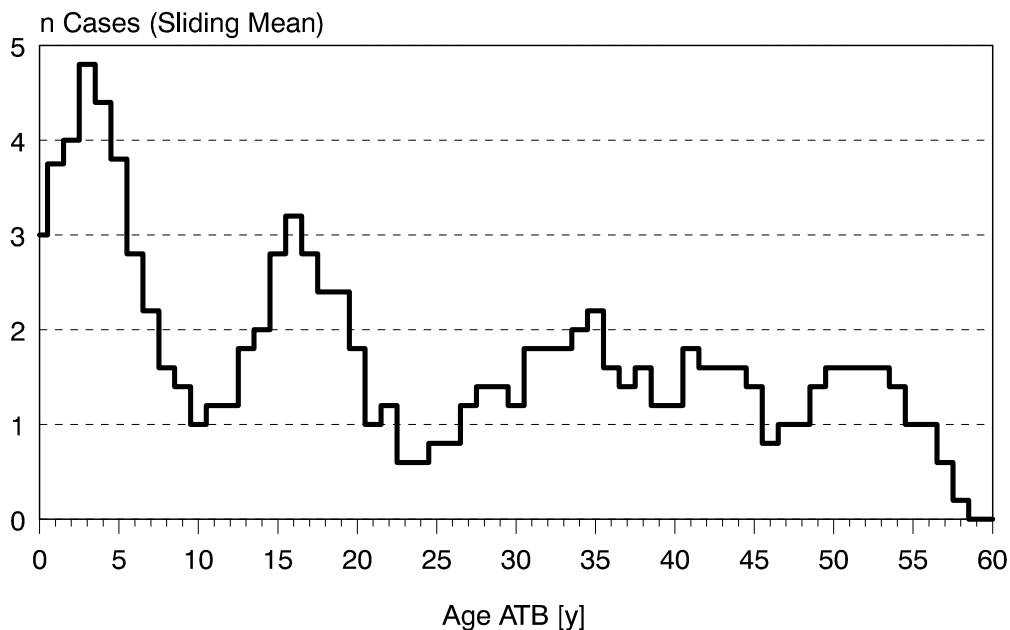

Fig. 12:   Time to onset of disease of all kinds of leukaemia together (CGL, AGL, AML, AL, ALL ASL and Erythroleukemia. (after Ishimaru et al. [5]). Sliding mean with a window width of 5 years.

This is suggesting an extrinsic factor of influence. Observing the time distance of the peaks I remember the paper of Juckett and Rosenberg [7] presenting a correlation of human longevity oscillations with sunspot cycles. However, beside the possible effect of cosmic neutrons with a dose rate of half the value in our geomagnetic latitude, we have to consider that virus infections show epidemic peaks with similar patterns, too. Perhaps a virus vector is transferred to the human genom causing enhanced radiation sensitivity for initiation of malignant transformation.

Conclusion

There is no doubt that the constant risk model is not valid describing the temporal distribution of radiation induced leukaemia. Also the time pattern of incidence cannot be approximated by a continuous wave function without erroneous results because of time periods interposed with incidence rates well below the mean course of incidence. In time periods of peaks of incidence the excess risk is strongly underestimated.

Acknowledgement

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