Vedlegg 1

Fagfelleuttalelse fra Paolo Boffetta

I have examined the two reports on the cancer cluster at NTNU prepared by Kristensen et al. (so-called Rosenberg 1 , dated 14 February 2007, and Rosenberg 2, dated 12 December 2007) and the Norwegian Official Report submitted by the Investigation Committee to the Ministry of Justice on 16 August 2007. Since the latter Report addresses mainly legal and procedural issues, but does not add scientific information, I will restrict my comments to Rosenberg 1 and Rosenberg 2 reports.

1. The reports provide a comprehensive, balanced and evidence-based review of the main scientific issues concerning the evaluation of cancer clusters and summarizes adequately the main issues relevant to the assessment of the cluster at NTNU.

2. Based on the information provided in the reports, the conclusions and the recommendations of the Advisory Group appear to be well justified.

3. The methods used in the study are fully adequate. The statistical analysis is correct. The use of high-quality registration data available in Norway adds to the validity of the study. The results are presented in a clear and logical way. I have no specific comments on these aspects of the study.

4. The main limitation of the study, namely the lack of specific information on the exposure experienced by study subjects, is adequately addressed in the discussion and its implications are properly taken into consideration.

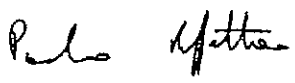
5. The ability of the authors of the reports to distinguish between the different types of lymphohaematopoietic neoplasms is particularly valuable, since the lack of this information was a major limitation of the preliminary report.

5. The conclusions of the reports, namely that (i) there was no excess risk of lymphohaematopoietic neoplasms beyond the initial cluster, (ii) the excess is confined to employees and PhD students, in particular those involved in the chemistry cluster, and (iii) an etiological role of benzene exposure is possible but cannot be proven, are

endorsed. Similarly, recommendations for future action, in particular an attempt to improve the assessment of exposure to benzene and other chemicals, are supported.

6. The analysis of melanoma and non-melanoma skin cancer is also of interest and adds to the interpretation of the results.

7. Finally, I would like to express my satisfaction for the changes made by the Expert Group' in the final report in response to my comments to the draft report. All my comments have been adequately taken into consideration in the final report.



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28 April 2008

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Re. normal and increased incidence rates of haematological cancers in the Rosenborg cohort

Throughout the last years investigations, press announcements and media focus, everyone involved in this case, has had a difficult task to deal with. It has both been necessary to try to reassure a large proportion of the former students, as well as trying to explain and understand a substantially increased rate of haematological cancers in the Rosenborg population. In relation to this, both misleading and wrong claims like; 'a certain increased incidence' or 'probably a coincidence' has been pronounced and published. We wish to emphasise that the totality of the findings in STAMI's Rosenborg 1 and 2 reports (Kristensen et al. 2007), shows a substantially increased incidence for certain cancers. To the degree that it is possible, this should be explained, not minimized. In this context we want to focus on the following:

In IARC,'s (International Agency for Research on Cancer) list of known carconigenic agents, benzene seems to be the most certain carcinogenic agent.
In Ekspertgruppens preliminary report from June 2007 it is estimated that only 3.5 litres of benzene was used annually. This figure formed part of an argument where benzene was deemed an unlikely cause of the haematological cancers found in the cohort. We want to point out here that several people, with a connection to the laboratories at Rosenborg, questioned this estimate for amount of benzene used.
[PB: In my reading of the reports, the possibility of an increased risk of cancer due to benzene exposure is clearly mentioned and arguments in favour and against this hypothesis are discussed.]

WHO subtypes and subgroups of leukemia and lymphoma:
It is well documented that subgroups of leukaemia are strongly associated with exposure to benzene. In the commission appointed by Justisdepartementet in the spring of 2007 (Department of Justice, Ersdalutvalget, NOU 2007:9) it is also pointed out in item 7.1 that the WHO subtypes of Non-Hodgkin's lymphoma can be important when trying to establish causal links. It is therefore very important that subgroups and WHO subtypes are evaluated in the Rosenborg cohort. The Norwegian Cancer Registry has in this cohort grouped the haematological cancers into two non-standard collective codes ICDO3 206 and 207. If one exclusively look at the collective codes one will miss the opportunity to interpret the increased incidence of haematological cancers in relation to causality, and risk will be underestimated.
[PB: This is correct although to my understanding information on WHO types is not routinely available at the Cancer Registry, which means that the expected number of cases cannot be calculated. Furthermore, one should consider the statistical power of analysis of subtypes of lymphoma and leukemia: although the relative risk might be higher, this is based on a small number of cases. Finally, I understand that access to detailed clinical and pathological information might clash with data protection regulations.]

The investigated Rosenborg cohort is mainly students between the ages of 18-35 (60% are born after 1970). This fact demands that the assumed normal incidence rate for this group follows the group precisely.
[PB: I am not sure I understand this comment. However, the follow-up of the cohort has been performed using state-of-the-art methods.]

According to the Norwegian Cancer Registry the incidence rate of leukaemia and Non-Hodgkin's lymphoma is 7-8 and 6-8 respectively per 100 000 person years for the age group 30-35 and follows a curve that increases till you reach 80.
There has also been a general increase in the rate of these cancers in the population as a whole since the 1970s.
[PB: The increase in incidence during the last part of the 20th century has concerned NHL, not leukemia. Furthermore, there is evidence that the increase has stopped in the last decade. In general, I do not see how this phenomenon would affect the results of this study.]

The incidence rate for the sub-diagnosis shows, to some extent, a very different age distribution from average leukaemia/ lymphoma incidence rates. A well-known difference exists between Hodgkin and Non-Hodgkin's lymphoma and for the incidence of myelogenous leukaemias in younger age groups. Several sub-diagnoses such as follicular lymphoma, marginal zone lymphoma, and CLL/SLL has incidence rates close to one per million in the age group 30-35, and is virtually non-existent before the age of 30. These are sub-diagnoses that have a median age of 60-65 and do not exist amongst children and adolescents. (See tables and charts below).
[PB: Again, this is correct but the differences are taken into consideration in the analysis of the data performed on this cohort.]

Sub-diagnosis and carcinogenic exposure:
It is known that several of the cases of leukaemia and lymphoma in the Rosenborg cohort belong to the above-mentioned categories, which are normally found amongst the elderly. We want to emphasize that this represents an age displacement that statistically diverges from normal incidence rates. This is not apparent in the statistical material presented by STAMI. The over representation of males in the group is also worth noting and demands further investigation; 75% men can be an indication of exposure to carcinogens. There were 45% males in the cohort.
[PB: Some random fluctuations is expected in all observational studies, and methods have been developed to assess the likelihood of departure of results from what is expected just by chance. These methods have been applied in the analysis of the data on the cancer cluster at Rosenberg.

We therefore want to stress that when you find even a few cases of haematological cancers, that are not age typical, not gender typical, and not sub-diagnosis typical, it is likely to indicate carcinogenic exposure.
[PB: I disagree with this statement. Although occasionally cancer clusters indicate the effect of a carcinogenic exposure, in most instances they are just the product of chance.]

A distinctive feature of the haematological cancers is the different chromosomal translocations. It is shown that the translocation t(14;18) appears with increased frequency as a result of carcinogenic exposure. In CML there is a direct correlation between age and incidence of the chromosomal translocation. The translocation is also a direct cause of the cancer, and no further genetic predispositions or mutations are necessary in order to cause the cancer. (See table below) (ref. Roulland S, Lebailly P, Lecluse Y, Briand M, Pottier D, Gauduchon P. Characterization of the t(14;18) BCL2-IGH translocation in farmers occupationally exposed to pesticides. Cancer Res. 2004 Mar 15;64(6):2264-9, Zhang L, Rothman N, Li G, Guo W, Yang W, Hubbard AE, Hayes RB, Yin S, Lu W, Smith MT. Aberrations in chromosomes associated with lymphoma and therapy-related leukemia in benzene-exposed workers. Environ Mol Mutagen. 2007 Jul;48(6):467-74).

[PB: The association between t(14;18) and exposure to specific agents is still a hypothesis. Other studies have failed to detect it.]

One the basis of what we have said above, it is extremely important, if a possible cause is to be found, that the sub-diagnoses are presented in their totality. According to our information, the Norwegian Cancer Registry can supply the data for this, but have not been asked by Ekspertgruppen.

Exposure:
The incidence of haematological cancers increases amongst the students at Rosenborg following the number of study courses attended, from 6.3 to 20 (per 100 000 person years, Kristensen et al. 2007). Another peculiar finding is that the incidence rate for non-PhD sudents without the organic chemistry course K2/20 is half the expected rate. This can also indicate causality, and indicate the need to use students from e.g. social sciences studies at NTNU as a reference.
[PB: I think it is not good practice to change the comparison group (or in general the strategy for the statistical analysis) after having seen the results.]

In the preliminary report from Ekspertgruppen (June 2007) it was indicated that the exposure to benzene was very small. We have already pointed out that the estimate of 3.5 litres per year might be wrong. During the presentation of Rosenborg 2 this was pointed out. We also want to emphasize that even exposure to low doses has a carcinogenic potential. Ref. (Kristensen P, Hilt B, Svendsen K, Grimsrud TK. Incidence of lymphohaematopoietic cancer at a university laboratory: a cluster investigation. Eur J Epidemiol. 2007 Nov 6, Bollati V, Baccarelli A, Hou L, Bonzini M, Fustinoni S, Cavallo D, Byun HM, Jiang J, Marinelli B, Pesatori AC, Bertazzi PA, Yang AS. Changes in DNA methylation patterns in subjects exposed to low-dose benzene. Cancer Res. 2007 Feb 1;67(3):876-80).

During the interviews (1-2nd November 2007) with the people affected by this case, Ekspertgruppen was made aware of the fact that Professor Thorleif Anthonsen (Institute of Chemistry NTNU) had important information regarding the use of embedding resin monomers (e.g. acrylic and epoxy plastics) for electron microscopy used at Rosenborg. In his view, this could have been a contributing factor to the increased rate of haematological cancers. We cannot see that Ekspertgruppen have followed this lead. We also want to point out that several of the materials used in electron microscopy are known carcinogenic agents. It is clearly noted in the Department of Justice's investigation of the so-called Rosenborgsaken (NOU 2007: 9) that this work took place in laboratories with defective or switched off ventilation systems, that redistributed the fumes to other parts of the building.
[PB: I am not aware of a carcinogenic potential of these agents.]

Omitted cases:
We have understood from conversations with Bjørn Hilt and Petter Kristensen that a further two cases of haematological cancer, in addition to the 25 reported in Rosenborg 2, were found. The first case was not included because of an administrative error. We do not know his diagnosis. The second, Einar Jenssen, was excluded because he had emigrated and it was therefore a concern that he could be identified. Einar Jenssen was diagnosed with CML in 1993. (8 out of the 27 cases are CML). The incidence rate for CML in the age group 25-45 is very low, so it is important for further statistical calculations that he is included.

One further case of CML in this population was also excluded because Rosenborg 1 only included cases reported before 31/12 2005 (and data up to 2008 is now available).
[PB: In such investigations, it is crucial that the numerator (observed cases) and the denominator (expected cases based on a comparison population) are consistent. The observations above would inflate the numerator without modifying the denominator.]

Rosenborg was closed and demolished in 1999, yet despite this fact, students enrolled up to the summer of 2004 are included in the statistical calculations for expected rates of cancer in this population. No one was exposed to anything at Rosenborg after 1999 and should not have been included.
[PB: This is not likely to have affected the results to a large extent because of the limited contribution of this additional individuals to the follow-up.]

The known number of haematological cancers in this population (Rosenborg 1 and 2) is at least 28, as opposed to 21 expected. (Adjusted for students post 1999, but not for age typical sub-diagnosis and gender)

With reference to statements made by the Minister of Education and Research, Øystein Djupedal, who initiated this investigation, we ask that Ekspertgruppen takes note of our communication.

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