Interaction of Pathology and Molecular Characterization of Thyroid Cancers

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Abstract. This paper presents the results of joint studies of thyroid cancer in children under 15 years of age between departments in Cambridge, Brussels, Naples and Munich in the European Union, and departments in Minsk, Kiev and Obninsk in the newly independent states of Eastern Europe.

The pathology of 264 cases of childhood thyroid cancer out of 430 that have occurred since 1990 in the 3 countries in which high levels of fallout from the Chernobyl accident occurred has been restudied by NIS and EU pathologists. The overall level of agreement reached was about 97%. The diagnosis was supported by immunocytochemistry and ISH for the differentiation markers, thyroglobulin and calcitonin, and the tumours were classified according to the WHO, with papillary carcinomas being further subclassified. 99% of the 134 Belarussian cases were papillary carcinomas, as were 94% of the 114 Ukrainian tumours. All 9 of the Russian cases available for study were papillary in type. 76 of 154 cases of childhood thyroid cancer reviewed over a 30 year period in England and Wales and were also studied, 68% of these were papillary carcinoma. Histological study showed that a subtype of papillary carcinoma, rarely found in adults, with a solid/follicular architecture occurred in children. It was found in 72% of the Belarussian papillary carcinomas, 76% of the Ukrainian cases, but only 40% of the England and Wales cases.

Molecular biological studies showed that the proportion of cases of papillary carcinoma expressing the ret gene was not significantly different in the exposed and the unexposed tumours, studies of the type of translocation leading to ret gene expression are not yet conclusive. Ras gene mutations were found as expected in follicular carcinoma, but were absent from any papillary carcinoma, whether from exposed or unexposed cases. TSH receptor mutations, normally found in follicular tumours were not found in any papillary carcinomas, nor were any p53 mutations identified. All these results conform to the proposal that papillary carcinomas only are associated with ret translocation and that ras and TSH receptor mutations occur in follicular tumours, and p53 mutations in undifferentiated carcinomas. The results support the diagnosis of nearly all of these cases as papillary carcinoma.

The major differences between the tumours from the exposed areas and those from England and Wales, lie in their frequency, the proportion of papillary carcinomas, and within these the proportion of the solid / follicular subtype. The high level of agreement between the different centres in establishing the diagnosis allows all the data to be studied. The number of

tumours shows a very great increase, particularly noticeable in Southern Belarus and Northern Ukraine. The birth dates show that virtually all children with thyroid carcinoma in the areas exposed to fallout were born before the accident, very few occurred in children born after the accident. Analysis of the age at operation showed that it differed greatly in the exposed children as compared to children in England and Wales, and further analyses suggest that there is a very great increase in sensitivity relating to the age at exposure with the youngest children showing the greatest sensitivity. Overall the findings suggest that the great increase reported in childhood thyroid carcinomas in the areas exposed to fallout from Chernobyl is currently reported, that it is not due to over-ascertainment, that the incidence is almost certainly due to exposure to fallout from Chernobyl with the most likely cause being isotopes of iodine, and that this exposure to radiation has led to the development of an unusual subtype of papillary carcinoma.

1. Introduction

It is now generally accepted that cancer is derived by an interactive process of somatic mutation and clonal selection, and that a number of steps are involved, perhaps 6 or more in many cancers. The interaction of the consequences of these mutations with each other, and with the pattern of expression of the genome of the cell of origin of the cancer determine the structure and behaviour of the tumour; both would be expected to correlate with the somatic mutations present. In studying such correlations it must be remembered that, particularly in slowly growing tumours such as thyroid carcinoma, clones with different mutations may coexist, and a mutation conferring malignancy in a small clone is unlikely to produce instant metastases. Correlation of the structure of a tumour and of its behaviour is based upon a very large body of accumulated knowledge, and it is now important to correlate structure with molecular biological changes, to build upon and add to the ability to predict behaviour and determine appropriate treatment. Different mutagens are known to produce differing spectra of mutations, for example liver cancer induced by aflatoxin is characterized by a particular mutation in the p53 oncogene (1) and radiation is known to be more likely to induce translocations and deletions than point mutations, in contrast to some chemical mutagens which produce point mutations (2, 3).

The accident in the nuclear power station at Chernobyl in April 1986 led to the exposure of large numbers of the population in southern Belarus, northern Ukraine, and adjacent western areas of the Russian Federation to high levels of radioactivity in fallout. The radioactivity released from the reactor contained large amounts of isotopes of iodine, mostly ^{131}I, but the population was also exposed to significant amounts of short lived isotopes, including ^{133}I and ^{132}I. The distribution of the dose from these isotopes is not known with precision, and is likely to have diminished more rapidly with distance from the reactor than did the dose from ^{137}Cs. An increased incidence of childhood thyroid cancer in Belarus and the Ukraine was first noticed in 1990, four years after the accident, it was drawn to the attention of the West in 1992 (4, 5) and has

continued up to the present. The purpose of the present paper is to describe the pathomorphology of the tumours in the three countries exposed to high levels of fallout from Chernobyl, to correlate these findings with a study of the molecular biology of selected oncogenes in thyroid cancer from the exposed population, and to compare and contrast both the pathological and the molecular biological findings with studies in a series of childhood thyroid cancers from an unexposed population in England and Wales.

2. Pathomorphology - general

430 cases have been diagnosed as childhood thyroid cancer in the three republics of Belarus, Ukraine and the Russian Federation since 1990; 266 of these have been studied jointly with pathologists in the UK, and a total of 76 cases of childhood thyroid cancer diagnosed in the UK have been studied jointly with pathologists from the CIS countries. The overall level of agreement in the diagnosis of malignancy has been high, 97% in the CIS countries and 96% in the UK. The tumours from all 4 countries could be divided into the major groups of papillary, follicular and medullary carcinomas, and the papillary carcinomas subdivided into classic, solid follicular, diffuse sclerosing and other types. The follicular and medullary carcinomas showed the expected features, all medullary carcinomas were confirmed by calcitonin immunocytochemistry and all follicular carcinomas showed capsular or vascular invasion with one exception in which invasion was not seen in the section available, but metastasis occurred. The classic papillary carcinomas showed the typical branching papillary architecture commonly found in adult papillary carcinomas, and the typical ovoid grooved nuclei, together with intranuclear cytoplasmic inclusions. The solid follicular papillary carcinomas were characterized by a solid and/or small follicular pattern, occasionally with a minor papillary component. They commonly contained psammoma bodies, but in general showed irregular round nuclei, lacking prominent nuclear grooving. Diffuse sclerosing papillary carcinomas showed a diffuse pattern of invasion through thyroid tissue, usually the whole of one lobe, with a marked fibrous and lymphoid response. The distinction between these subtypes was not absolute, and some cases showed features of more than one type. These were classified by the dominant pattern in the primary tumour.

2.1 Belarus

298 cases of thyroid cancer have been diagnosed in children under the age of 15 in the Pathology Institute in Minsk between 1990 and 1994 inclusive. A total of 134 of these (45%) have been seen also in Cambridge, and the diagnosis agreed in consultation with pathologists from Minsk. Agreement was reached in 98% of cases. The cases included 67 from the first 100 cases seen during the period, and 65 from the last 100, the selection being made on the basis of those cases where blocks were available for study. There was no change in the level of agreement in the diagnosis between the two periods, with disagreement between the original and the revised diagnosis present in only 1 case from each period. Virtually all of the Belarussian cases (99%) were papillary carcinomas, with 1 medullary carcinoma seen in the cases available for study. Because of the very high level of agreement on diagnosis in the sample examined from the earlier and from the later cases, the sex and age data from the whole series has been

examined. There was an overall peak age of 9 years, with a mean age of 10.4 years, and a sex ratio of 1.7:1 F:M. When the cases occurring in the early part of the outbreak were compared with the last group seen there was a change in both peak and mean age from 8 years with a mean of 9.1, to 9 years with a mean of 10.9 years (Fig. 1). The diagnoses in the whole group of 298 were 293 papillary carcinomas (98%), 4 follicular carcinomas (1.3%) and 1 medullary carcinoma (0.3%). Of the 134 cases studied histologically in Cambridge, 2 were excluded because on the material available the diagnosis could not be confirmed, 4 were papillary microcarcinomas, and 2 were malignant but unclassifiable. 124 papillary carcinomas were subclassified, 72% were of the solid follicular type, 14% were classic, 8% diffuse sclerosing and 6% others. The sex ratio, F:M was 1.2:1 for the solid follicular type, 1.25:1 for the classic type and 8:1 for the diffuse sclerosing tumours.

Because of the high level of agreement with the diagnosis from the Pathology Institute in Minsk, the figures for all 298 cases were used to demonstrate the changes in age at operation with time (Fig. 2). It can be seen that there is a sharp cut off in the number of younger patients, but that this increases with time, and corresponds closely to the age of a child born 6 months after the Chernobyl accident. The data has also been analysed by cohorts based on the age of the child at the moment of the accident (Fig. 3). It can be seen that overall the number of cases within each cohort continues to rise with time.

2.2 Ukraine

122 cases of thyroid cancer have been diagnosed in children under the age of 15 at the Institute of Endocrinology in Kiev between 1990 and 1994 inclusive. 114 of these cases have also been studied in Cambridge, and the diagnosis agreed in correlation with pathologists from Kiev. The diagnosis of malignancy was agreed in 97.4% of the cases, with the small number of disagreements probably being due to lack of appropriate material for restudy. The great majority (94%) of the cases were papillary carcinomas, there were 2 medullary carcinomas and 5 follicular carcinomas. The papillary carcinomas could be subdivided into 80 of the solid follicular type (76%) 7 classic papillary carcinomas (7%), 9 diffuse sclerosing carcinomas (9%) and 7 others (7%) 1 occult papillary carcinoma is excluded. The sex ratio (M:F) for the different types was 1.2:1 for the solid follicular type, 2.3:1 for the classic type, and 3:1 for the diffuse sclerosing variant. The peak age for the Ukraine cases was 8 years, and the overall sex ratio F:M was 1.2:1. The age at operation rose with time, (Fig. 4) and the change in the lower limit corresponded to the age of a child born 6 months after the Chernobyl accident.

2.3 Russian Federation

Study of the thyroid carcinomas that have occurred in children in the exposed areas of the Russian Federation is more difficult than studies in Ukraine or Belarus because the exposed areas form only a relatively small part of the very large Federation, and because no single central hospital has treated all or the great majority of the cases. Pathological material has been made available from 10 cases of childhood thyroid cancers by the RAMS Institute in Obninsk, from material originally treated and diagnosed in different hospitals serving the

contaminated areas. The diagnosis of malignancy was confirmed in 9 of the 10 cases, the tenth contained no tumour in the material available in Cambridge. All 9 cases were papillary carcinomas, 5 were of the solid follicular type, 2 were classic papillary carcinomas and 2 oxyphil carcinomas. The overall sex ratio was 0.7:1, F:M., the mean age was 11 years. One of the classic papillary carcinomas was 3 mm in diameter in the section available. None of the children were born after the Chernobyl accident, and all came from contaminated regions in Bryansk, Kaluga or Tula Oblasts.

2.4 England and Wales

The occurrence of thyroid carcinomas in children in England and Wales was studied over a 30 year period, 1963 to 1992 (6). Information was obtained from the United Kingdom Childhood Cancer Registry, which had recorded 154 cases of thyroid cancer in children under the age of 15 during the study period. Tissue blocks were requested for all cases, and material was made available for 81 of the cases. The review diagnosis confirmed the original diagnosis of malignancy in 76 of the cases (94%); the cases where there was a disagreement included several earlier cases when the diagnosis of papillary carcinoma was made on the basis of architecture rather than cytology. One case of malignant lymphoma of doubtful primary origin in the thyroid was excluded. The remaining 75 cases included 1 teratoma, 53 papillary carcinomas, 8 follicular carcinomas, 12 medullary carcinomas and 1 other. The 53 papillary carcinomas were divided into 21 solid follicular tumours, 27 classic papillary carcinomas, and 5 of the diffuse sclerosing variant. The sex ratio (F:M) for these tumours was 6:1 for the solid follicular carcinomas, 3.5:1 for the classic papillary carcinomas, and 4:1 for the diffuse sclerosing carcinomas.

The overall sex incidence for the whole series was 2.3:1 F:M, and the age incidence rose rapidly with age, and was still rising at the age of 14 (Fig. 5).

3. Immunocytochemical and Molecular Biology studies

Immunocytochemical investigations have been carried out on the great majority of these tumours from all 4 countries. They have included studies of the differentiation markers thyroglobulin and calcitonin which were used to confirm the cell type in all the carcinomas studied, and were in most cases used together with *in situ* hybridisation to demonstrate the specific mRNA. No specific changes were seen between the tumours from the different countries with these techniques. Immunohistochemical techniques have also been used to demonstrate the presence of ret and met peptides in the tumours. The great majority of papillary carcinomas were positive for ret, using two antibodies. In most the distribution of the peptide was unusual, presenting as a dot-like deposit of reaction product between the nucleus and the basement membrane. The distribution of the met oncogene product (the hepatocyte growth factor receptor) was mostly on the cell membrane, it was found in approximately 80% of the papillary carcinomas, but was absent from the follicular carcinomas.

Molecular biological studies were carried out in a collaboration between the CIS countries and groups from Cambridge, Brussels, Naples and Munich.

The three ras genes have been studied by PCR and direct sequencing in formalin fixed material from 14 childhood papillary carcinomas from the CIS. No mutations have been observed in the commonly mutated codons (12,13 and 61). Similar studies carried out on a control group of childhood thyroid papillary carcinomas from England and Wales also showed no mutation at these sites. However, mutations of these genes have been identified in 3 of 10 adult follicular carcinomas using the same approach. This suggests that ras gene mutation is probably not normally involved in the genesis of thyroid papillary carcinomas, whether induced by radiation or not.

Expression of the ret gene has been studied using RT-nPCR for a 90 base pair sequence within the tyrosine kinase domain and direct sequencing. Ret expression was identified in 6 of 18 (33%) Chernobyl associated childhood papillary carcinomas so far studied. This was a significantly lower frequency than that found in a study which used the same technique on adult papillary carcinomas from England and Wales, and was also lower than the frequency observed in 20 childhood papillary carcinomas from England and Wales. However, due to the smaller number of carcinomas from children so far studied, it is not yet possible to say whether the irradiated series shows a significant reduction in the frequency of ret expression. A small study carried out on frozen material from the Ukraine showed ret expression in a similar proportion (3/11) of childhood thyroid papillary carcinomas, suggesting that the low frequency found in the paraffin embedded material was not due to a decreased sensitivity of the system. There does not appear to be a correlation between the expression of the ret oncogene as observed by RT-nPCR analysis and morphological subtype of papillary carcinoma. Positivity for actin amplification was used as a control for quality of the RNA extracted from the sections.

Twenty five cases of childhood thyroid carcinomas from the CIS have been used in a study of the type of ret gene translocation; only 11 yielded sufficient RNA for further analysis. Two controls for RNA quality were used: amplification of actin mRNA by RT-PCR and Northern blot with an 18S RNA probe. Using primers which allow detection of the three individual translocations of the ret oncogene so far identified, three papillary carcinomas with ret translocation have so far been identified by PCR and Southern blotting. All 11 cases which provided sufficient RNA have been analysed for the PTC1 translocation; only one case was positive. Two of the 7 cases so far analysed have been found to be positive for the PTC3 translocation. Analysis of the presence of PTC1 in a small series of adenomas from the Ukraine has also been carried out and shown to be absent. Interestingly one of the carcinomas found to be positive for ret expression by RT-PCR was not found to possess one of the 3 known translocations. Further studies on the remaining papillary carcinomas for PTC2 and PTC3 expression and to identify other translocations involving the ret oncogene are underway.

As part of a study of TSH receptor mutations in thyroid carcinogenesis, DNA extraction has been performed on material from 41 cases of childhood thyroid carcinoma from the CIS and regions of interest in exon 10 of the TSH receptor have been amplified using PCR. The regions studied include the third intracellular loop and the third transmembrane segment of the TSH receptor

gene. Single stranded conformational polymorphism (SSCP) in all cases followed by sequencing (in 15 papillary carcinomas) has been used to identify TSH receptor mutations in exon 10. So far no mutations have been observed in 41 cases of papillary thyroid carcinoma or in 18 follicular adenomas and 3 follicular carcinomas from children and adolescents from the radiation exposed population. Cases known to be positive for mutations in exon 10 have been used as control for the technique used. The absence of mutations in the TSH receptor correlates with the morphological observations that the childhood thyroid tumours identified in the Ukraine after Chernobyl are of the papillary subtype.

P53 is a gene which is widely involved in human neoplasia, and although it is not usually involved in the early stages of thyroid carcinogenesis, a study has been performed to look for p53 mutations in possible radiation induced tumours. Exons 5 and 7 and 8 have been successfully amplified from 23 papillary carcinomas using nested PCR. SSCP analysis under four different running conditions has so far been applied to all 23 samples, but no aberrant cases have been found. p53 mutation involvement in thyroid carcinoma is usually a late phenomenon, at the interface between differentiated and undifferentiated carcinoma. None of the tumours so far studied has been un-differentiated and none show widespread positivity for p53 on immunocytochemistry. However, exposure to radiation has been reported to increase the frequency of mutation in the p53 gene in other tumours. From the results presented here p53 mutation does not appear to play a major role in papillary thyroid carcinogenesis post Chernobyl.

4. Discussion

These studies have involved cases of childhood thyroid cancer from Belarus, Ukraine, the Russian Federation, and England and Wales. The countries obviously differ in that parts of the first three were exposed to high levels of fallout from Chernobyl, while in England and Wales only very small amounts of fallout took place, and the cases can effectively be regarded as unexposed. England and Wales differ from the CIS countries in other ways, particularly in that they show no significant iodide deficiency, while mild iodine deficiency is prevalent in parts of the CIS. The rate of occurrence of childhood thyroid carcinomas in England and Wales is about 0.5/million children/year(6), a rate that is towards the lower end of the spectrum of figures for childhood thyroid carcinoma. Most countries would expect to have a rate of about 1/million/year, and a few rise as high as 3/million/year. The rates calculated for Belarus and the Ukraine are very much higher than any of the reported international figures, and this study has confirmed the diagnostic accuracy on which the figures are based, and excluded papillary microcarcinoma as a significant contribution. There are major differences between the findings in the CIS countries and those in England and Wales (Tables 1 & 2).

Table 1:

Childhood thyroid carcinoma in Belarus, Ukraine and England and Wales

	Belarus	Ukraine	England and Wales
Total no. of carcinomas registered (years studied)	298 ('90-'94)	122 ('90-'94)	154 ('63-'92)
Numbers available for review	134 (45%)	114 (93%)	81 (53%)
% of diagnosis confirmed	98%	97.4%	96%
% of papillary carcinomas in reviewed cases	99%	96%	68%

In this discussion the figures from Belarus and the Ukraine will be used, the numbers available for study from the Russian Federation are currently too few for adequate comparisons. The most obvious difference between the CIS tumours and those from England and Wales lies in the proportion of papillary carcinomas and the different subtypes of papillary carcinoma. Well over 90% of the CIS tumours were papillary carcinomas, as compared to 68% of the England and Wales tumours. Within the papillary carcinoma group over 70% of the CIS tumours were of the solid follicular type compared to only 40% in England and Wales. The difference was even more marked with the classic type of papillary carcinoma, which formed over half the England and Wales series, but only 12% of the CIS cases. There was no significant change in the proportion of the different type of papillary carcinoma between the earlier and the later cases, or between the younger and the older CIS cases. These findings suggest that the aetiological agent causing the increase in thyroid cancer in children in the CIS countries is specifically leading to an increase in papillary carcinoma of the solid follicular type.

Table 2:

Subtypes of papillary carcinoma of the thyroid in Belarus, Ukraine and England and Wales

	Belarus	Ukraine	England and Wales
Solid/follicular papillary carcinoma	72%	76%	40%
Classic papillary carcinoma	14%	7%	51%
Diffuse scelerosing variant	8%	9%	9%

Mutations in the ras oncogenes were absent from both the exposed and the non-exposed childhood papillary carcinomas, and from the non-exposed adult papillary carcinomas. Recent work suggests that in the thyroid ras mutations are much more restricted to follicular carcinomas than was previously thought (7) and this study confirms this. It shows that the exposed group of tumours do not differ from non-exposed in their lack of ras gene mutations. The study of the

TSH receptor gene gives a similar negative result; mutation in this gene is generally found in follicular rather than papillary tumours, and the papillary tumours from the exposed population show the lack of TSH receptor mutation expected in non-exposed areas. The position with the ret gene is more complex. There are at least 3 translocations of the ret oncogene in papillary carcinoma in adults; the commonest is PTC1. The papillary carcinomas in the exposed group could differ from unexposed tumours in their overall frequency of ret translocation, or in the type of ret translocation involved. These studies show that there is no increase in the overall frequency of ret activation in these tumours, but that compared to adults there may be a reduction in the cases due to PTC1. However the frequency of the various ret translocations in childhood thyroid carcinoma is not yet known, so that no conclusion can yet be drawn from these or from other results suggesting an increase in PTC3 in these cases. The p53 results again conform to the result expected in non radiation exposed papillary carcinomas.

The age and sex structure is interesting. In England and Wales there were more males in the younger but not the older age group. In the CIS countries the female to male sex ratio was closer to equality than it was in the England and Wales, and the difference was not solely due to the younger age of the cases. There was a marked difference in the age structure of the children with thyroid cancer in the CIS compared to England and Wales. The Chernobyl related cases showed a peak age of about 8-9, while in England and Wales the incidence continued to rise with increasing age. The peak age in Belarus showed a change with time, suggesting that there might be a cohort affect, with one group of children showing a higher sensitivity than others. Analysis by age at exposure to the accident shows that the cohorts showed a continuing increase in incidence with age. When this is compared with the expected incidence derived from the England and Wales figures, it can be seen that there is a great increase in observed as compared to expected tumours in the youngest cohort at exposure, and a steady drop in sensitivity with increasing age (Fig. 6).

These results lead to a number of conclusions. The pathological diagnosis and number of cases reported from Belarus and the Ukraine have been broadly confirmed, and the number of microcarcinomas shown to be very small. The relation of the tumours to exposure to fallout from the Chernobyl accident is strongly supported by the great reduction in the numbers of tumours operated on from children born more than a few months after the accident; the rapidity of the drop in the number of cases suggests that the causative agent did not persist at high levels in the environment. This, together with the apparent restriction of the increase in malignancy to thyroid carcinomas strongly suggests that exposure to isotopes of iodine from fallout is the major, if not the only cause of the increase.

The molecular biology results do not distinguish the papillary carcinomas in the exposed children from those in an unexposed population. It is possible that the ret oncogene translocations differ in type, or perhaps in the exact break points of the translocation, although these are difficult to ascertain because they take place in an intron. Although there is not a relative increase in the proportion of

papillary carcinomas with a ret translocation in the CIS cases, as increase is almost exclusively in papillary carcinoma, there is a very large absolute increase in cases with translocation of the ret oncogene. The genes involved in the ret negative papillary carcinomas are not known, except for trk, which is translocated in a small proportion of adult papillary carcinomas. Radiation is known to give rise to more translocations than point mutations.

The age structure of the children with thyroid carcinoma in the CIS and a comparison with cases in England and Wales suggest that the children aged under 1 at the time of the Chernobyl accident have shown the greatest susceptibility to the carcinogenic effect on the thyroid of exposure to fallout, and that older children have a gradually reducing sensitivity. In summary these results overall lead to the hypothesis that the great increase in thyroid carcinomas recorded in CIS countries is due to exposure to radiation from isotopes of iodine causing translocation of the ret oncogene and translocation or other mutational events in other genes, leading to the development of papillary carcinoma of the thyroid. The chance of developing cancer is heavily influenced by age at the time of exposure, leading to a cohort which carries a much greater risk than the other exposed population.

Figure 1: Change in age distribution of cases of childhood papillary carcinoma in Belarus with time

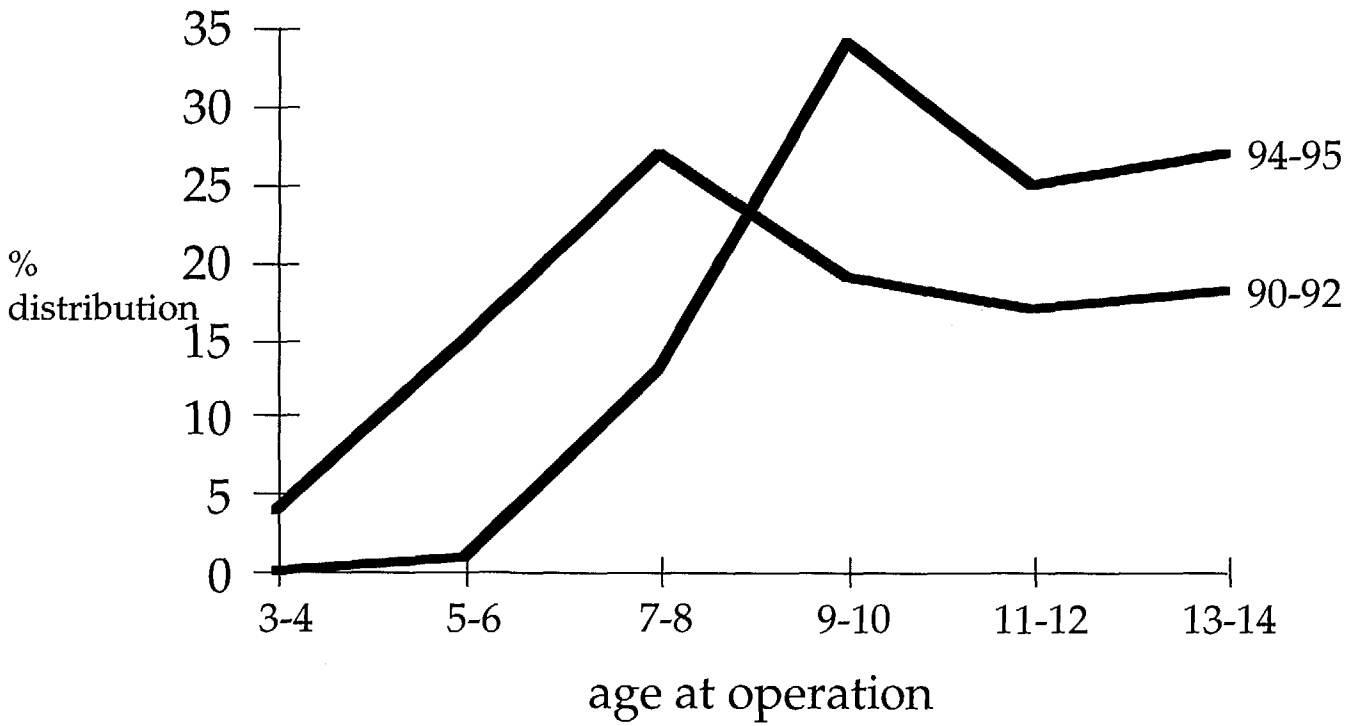
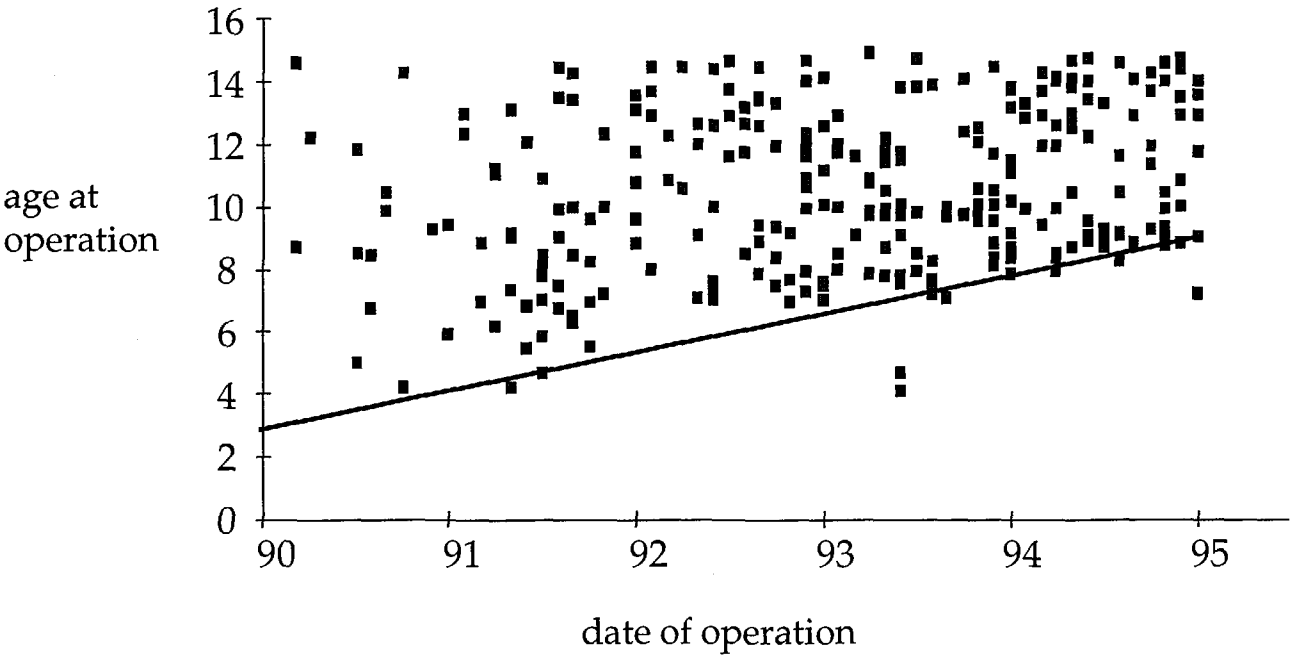


Figure 2

Childhood thyroid cancer in Belarus Jan 1990 - Dec 1994



The line corresponds to the age of a child born on November 26th 1986 - that is 3/12 intrauterine age at the time of the Chernobyl accident

Figure 3

Relationship between age at exposure and age at operation for childhood thyroid carcinomas occurring in Belarus between 1990-1994

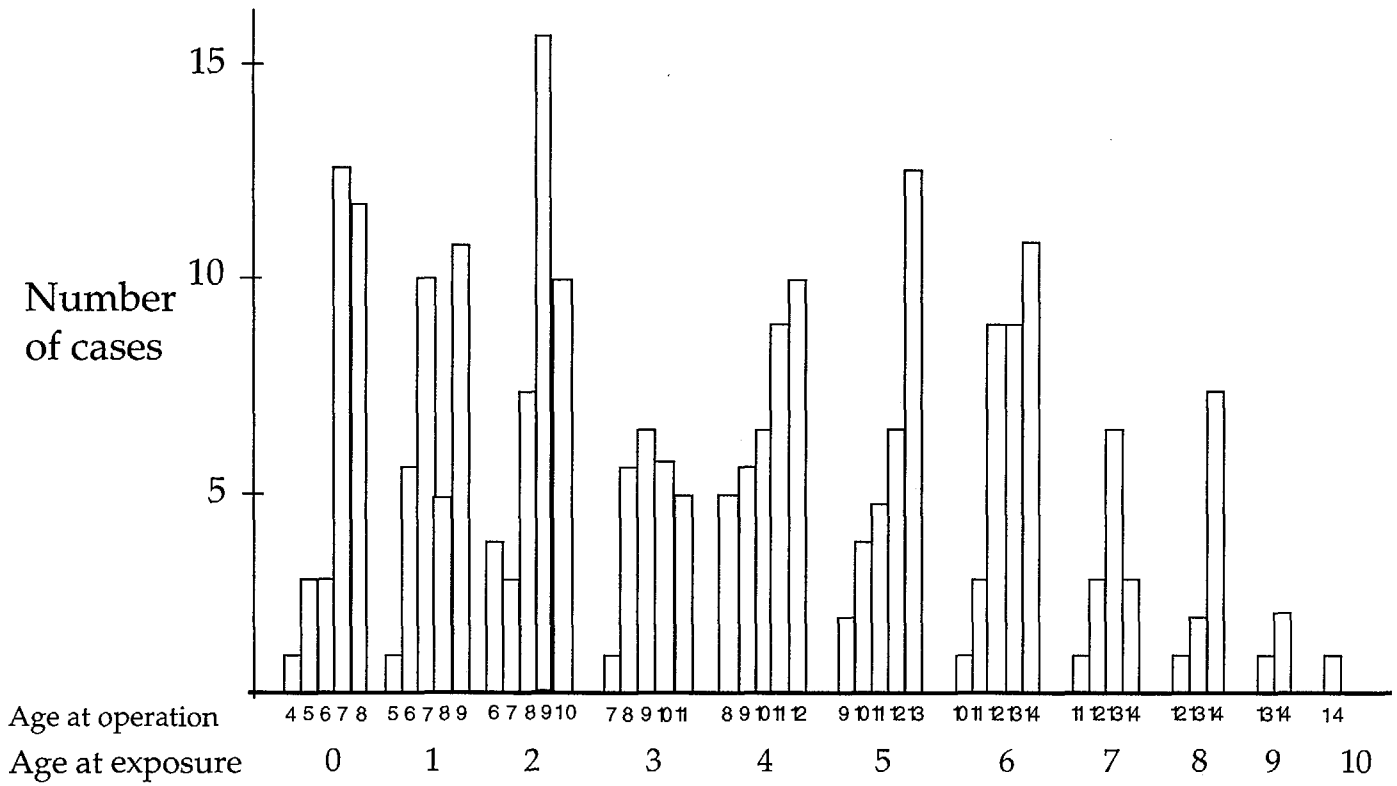
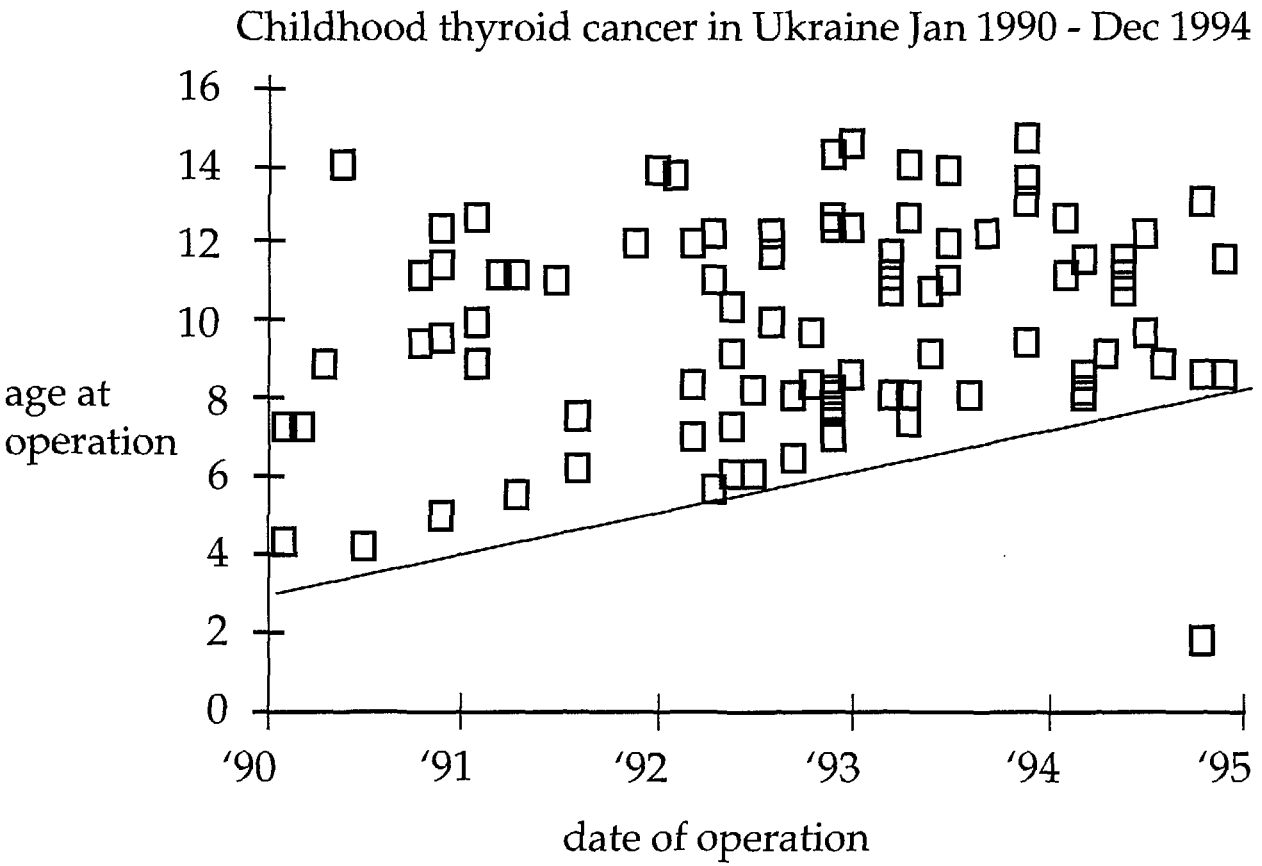


Figure 4



The line corresponds to the age of a child born on November 26th 1986 - that is 3/12 intrauterine age at the time of the Chernobyl accident

Figure 5

Age Distribution of thyroid tumours in children aged 15 and under at the time of operation in England and Wales 1963-1992

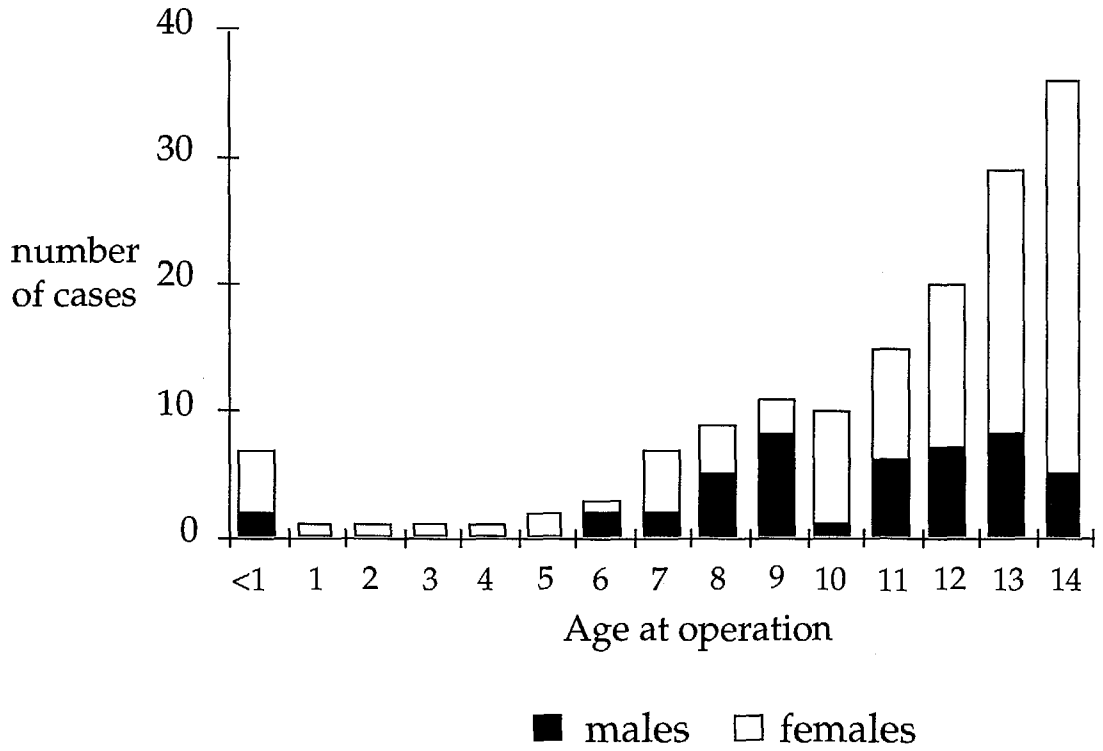


Figure 6

Risk of development of thyroid carcinoma relative to age at exposure.
Acomparison of rates in Belarus and rates in England and Wales